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Medication adherence of bisphosphonate weekly or monthly regimens in patients with osteoporosis using a nationwide large claims database

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Bisphosphonate (BPN) therapy, which mainly targets osteoporosis, evolves rapidly, leaving patients and physicians with a substantial collection of BPN regimen options. In this study, we aimed to clarify BPN medication adherence between weekly and monthly regimens using a nationwide claims database in Japan. We analyzed 5,016 patients with a screening period of 3 months and a 12 month observation period who started using BPN. We used propensity score matching with baseline patient background after dividing the patients into two groups: weekly and monthly BPN users. Medication adherence was calculated using proportion days cover (PDC). A PDC of > 80% was 55.9% and 52.5% in monthly and weekly formulas, respectively, during the 12 months after initiating BPN treatment. PDC-based BPN medication adherence was higher in monthly regimens than in weekly regimens (66.3±34.0 vs. 64.1±36.8%). No differences were found in the proportion of patients with > 80% medication adherence between the monthly and weekly regimens after stratifying patient background using propensity score matching. Our clinical findings highlight the importance of closely monitoring BPN medication adherence, particularly during the initial year of therapy. Notably, half of the patients with osteoporosis exhibited low medication adherence. Therefore, prioritizing monthly regimens over weekly regimens is crucial to promote BPN adherence and ensure optimal treatment outcomes.

1. Introduction

The main target group for bisphosphonate (BPN) therapy, patients with osteoporosis, present decreasing bone density and microstructure collapse that results in vulnerability and is typically observed in the femoral head and ulnar and distal radii fractures (Manolagas 2000). Globally, the prevalence of osteoporosis is consistently high in women and the elderly (Chen et al. 2018; Hernlund et al. 2013; Khosla et al. 2011; Wright et al. 2014; Yoshimura et al. 2022).

BPN medication adherence strongly relates to vertebral fracture reduction (Kim et al. 2022; Siris et al. 2006), and by following this finding, higher BPN medication adherence would likely lead to less vertebral fractures (Kim et al. 2022). However, in terms of long term BPN administration, physicians are considering recommending "drug holidays" to balance the risk and benefit effects, considering fracture risks and medical cost (Wang et al. 2022). Previously, the adequate period for BPN administration was reconsidered to include a "drug holiday" after approximately five years of treatment (Adler et al. 2016; Anagnostis et al. 2017; National Osteoporosis Guideline Group, 2021). In contrast, clinical trial evidence indicated that health resource use induced a protective effect for fractures following BPN discontinuation, but was not sufficient to reduce medical cost burdens (Ferguson et al. 2016). In fact, switching from BPNs to placebo did not enhance fracture risk without high risk women (Black et al. 2006, 2012). Any researchers agreed with short-term BPN medication adherence that provides desirable outcomes, including medical costs for only one year (Black et al. 2000). Furthermore, the National Osteoporosis Guidelines Group UK (NOGG) recommended BPN medication adherence assessment for one year after initiating BPN (National Osteoporosis Guideline Group, 2021).

BPNs use is facilitated by several dosing regimens, such as daily, weekly, monthly, half yearly, and annually based on improving medication adherence. It was reported that monthly regimens exhibited high medication adherence compared to daily or weekly regimens in 2015 using medical information from a national university in Japan (Kishimoto and Maehara 2015) Kosaka et al. (2021) further reported that longer regimens have higher BPN medication adherence in > 60 years old postmenopausal women, based on medication information in the Tokyo metropolitan area of Japan between October 2012 and January 2018. BPN medication adherence is changing over time (Laius et al. 2017) as it is affected by complexation among various regimens (drug formulas), new drug use, changing medication cost including generic drugs, or other patients background factors. Conclusively, previous research indicates that daily regimens are associated with low BPN medication adherence.

However, studies that compare weekly and monthly regimens with well-balanced co-variables and use a nationwide research database are lacking. Therefore, we aimed to clarify BPN medication adherence, focused on weekly and monthly regimens, using a nationwide claim database in Japan.

2. Investigations and results

2.1. Patient background

Two sets of patients (n=2,772; female/male: 2,155/617; age: 56.9±9.9 years old and n=2,244; female/male: 1,942/302; age: 59.6±8.5 years old) received BPN weekly and monthly respectively. In these patients, insured individuals were 42.7% (n=1,184) and 35.2% (n=789), respectively. Comorbidities, including

diabetes mellitus, rheumatoid arthritis, and chronic kidney disease, were higher in the weekly BPN group. Standard differences ranged from 0.01–0.30 (Table 1). After 1:1 propensity score matching, the standard differences were within 0.03 in both groups. Briefly, the average age for weekly and monthly group for 59.4 and 59.3 years old, and female was 85.7% in both groups. Insured individuals were 35.8 and 35.9%. Nine comorbidities were comparable between weekly and monthly BPN groups.

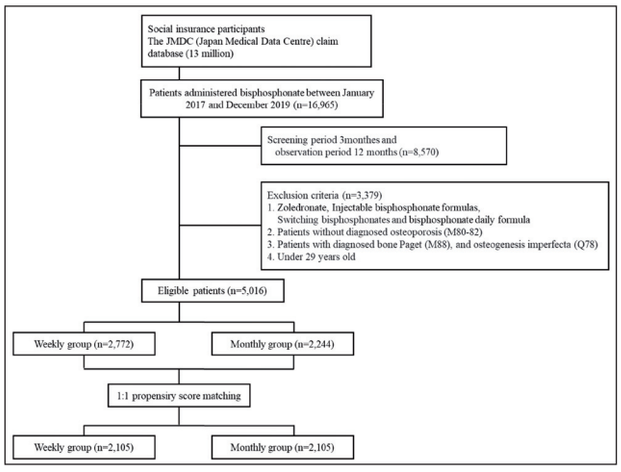

Fig. 1: Patients identification workflow for patients starting weekly or monthly bisphosphonate treatment.

stratification. The prevalence rate ratio with 95% CI for > 80% PDC, were 1.06 (0.98–1.15) for males and 1.08 (0.86–1.30) for females, respectively, using the weekly regimen as reference. There were no differences in age, insurance status, or comorbidities between the weekly and monthly regimens.

3. Discussion

We clarified differences of BPN medication adherence between weekly and monthly regimens using a geographically-low biased dataset of patients treated with BPN in Japan.

The proportion of high BPN medication adherence > 80% was higher in monthly regimens compared to weekly regimens after propensity matching using PDC (55.9% vs. 52.5%) (Table 1, Fig. 2). The trend of higher medication adherence in monthly regimens was higher than in weekly or daily regimens in previous reported data in Japan and France (Cotté et al. 2010; Kishimoto and Maehara, 2015; Kosaka et al. 2021). Low BPN medication adherence was intensively correlated with hip or vertebral fractures (McCombs et al. 2004). The fracture prevalence was 16% lower for > 80% BPN medication adherence compared to < 80% (Caro et al. 2004). These findings suggest that half of osteoporosis patients still face the risk of fracture and should maintain BPN medication adherence from the initiation of the medication. The reasons for BPN discontinuation were reported as gastroenterologically related, including adverse events, low motivation, safety concerns, or medication cost, by the questionnaire survey (Carr et al. 2006; Rossini et al. 2006). This suggests that patients may partially prefer low frequency BPN administration, such as monthly compared to weekly regimens, because of the lower chance of oral intake

Table 1: Patient characteristics

	Before propensity score matching				After propensity score matching			
	Weekly group n=2,772	Monthly group n=2,244	*P* value	Std diff	Weekly group n=2,105	monthly group n=2,105	*P* value	Std diff
Sex (female), n (%)	2,155 (77.7%)	1,942 (86.5%)	< 0.0001	0.23	1,803 (85.7%)	1,803 (85.7%)	1.0000	0.00
Age (year), average (±SD)	56.9 (9.9)	59.6 (8.5)	< 0.0001	0.30	59.4 (8.4)	59.3 (8.6)	0.8377	0.01
Insured individual, n (%)	1,184 (42.7)	789 (35.2)	< 0.0001	0.16	754 (35.8%)	755 (35.9%)	0.9744	0.00
Comorbidity								
Neoplasms (C00-D48), n (%)	619 (22.3%)	502 (22.4%)	0.9728	0.00	459 (21.8%)	461 (21.9%)	0.9405	0.00
Hypertensive diseases (I10-I15), n (%)	813 (29.3%)	743 (33.1%)	0.0040	0.08	650 (30.9%)	664 (31.5%)	0.6415	0.01
Diabetes mellitus (E10-E14), n (%)	1,134 (40.9%)	775 (34.5%)	< 0.0001	0.13	743 (35.3%)	747 (35.5%)	0.8974	0.00
Disorders of lipoprotein metabolism and other lipidaemias (E78), n (%)	950 (34.3%)	883 (39.3%)	0.0002	0.11	780 (37.0%)	788 (37.4%)	0.7987	0.01
Other rheumatoid arthritis (M06), n (%)	526 (19.0%)	360 (16.0%)	0.0068	0.08	333 (15.8%)	344 (16.3%)	0.6444	0.01
Hyperparathyroidism and other disorders of parathyroid gland (E21), n (%)	75 (2.7%)	84 (3.7%)	0.0370	0.06	61 (2.9%)	73 (3.5%)	0.2921	0.03
Chronic kidney disease (N18), n (%)	115 (4.1%)	54 (2.4%)	0.0007	0.10	54 (2.6%)	54 (2.6%)	1.0000	0.00
Atherosclerosis of aorta (I70), n (%)	171 (6.2%)	158 (7.0%)	0.2147	0.04	141 (6.7%)	145 (6.9%)	0.8065	0.01
Other chronic obstructive pulmonary disease (J44), n (%)	30 (1.1%)	22 (1.0%)	0.7232	0.01	21 (1.0%)	20 (1.0%)	0.8753	0.00

Std diff, standard differences

2.2. Primary and secondary endpoints

A primary endpoint of the proportion for the number of patients with > 80% of BPN medication adherence using PDC after propensity score matching was 52.5% and 55.9% in weekly and monthly BPN groups (p=0.0239), respectively, within the 12-month observation periods (Fig. 2). The proportion was suppressed but exhibited a consistent trend compared to that before propensity score matching (51.9% and 56.1%, p=0.0034). The secondary endpoint for average PDC after propensity score matching was higher in monthly regimens than in weekly regimens (66.3±34.0 and 64.1±36.8%, respectively, p=0.0313).

We conducted several sub-group analyses by stratifying baseline covariates (Table 2). Overall, our findings did not show a difference in the proportion of patients with high medication adherence (> 80% PDC) between the monthly and weekly regimens following

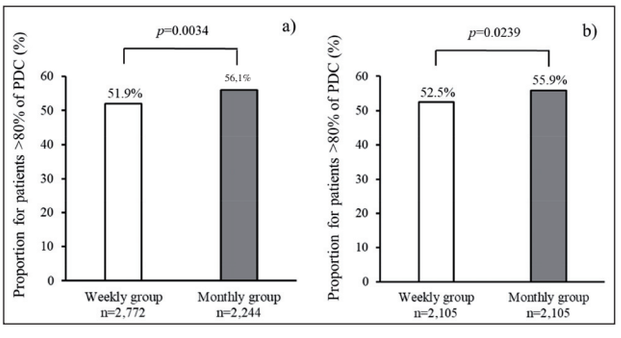

Fig. 2: Study patient proportion with > 80% of days covered that started weekly or monthly bisphosphonate treatment with propensity score matching. a) Before and b) After propensity matching. PDC, proportion days cover.

Table 2: Propensity score-matched prevalence rate ratios (PRRs) for > 80% of PDC stratified by patient characteristics

	Weekly group	Monthly group	PRR (95% CI)	*P* for interaction
	No. of events/total No (%)	No. of events/total No (%)		
Sex				
Male	154/302 (51.0%)	166/302 (55.0%)	1.08 (0.86—1.30)	0.9155
Female	950/1,803 (52.7%)	1,011/1,803 (56.1%)	1.06 (0.98—1.15)	
Age (year)				
30-44	59/120 (49.2%)	82/134 (61.2%)	1.24 (0.91—1.58)	0.6047
45-59	399/816 (48.9%)	426/810 (52.6%)	1.08 (0.94—1.21)	
60-74	646/1,169 (55.3%)	669/1,161 (57.6%)	1.04 (0.93—1.15)	
Insured person				
Insured individuals	378/754 (50.1%)	414/755 (54.8%)	1.09 (0.95—1.23)	0.6561
Insured individuals' family	726/1,351 (53.7%)	763/1,350 (56.5%)	1.05 (0.95—1.15)	
Comorbidity				
Neoplasms (C00-D48)	261/459 (56.9%)	282/461 (61.2%)	1.08 (0.91—1.24)	0.9032
Hypertensive diseases (I10-I15)	378/650 (58.2%)	401/664 (60.4%)	1.04 (0.90—1.18)	0.6629
Diabetes mellitus (E10-E14)	413/743 (55.6%)	424/747 (56.8%)	1.02 (0.89—1.16)	0.4344
Disorders of lipoprotein metabolism and other lipidaemias (E78)	445/780 (57.1%)	453/788 (57.5%)	1.02 (0.89—1.16)	0.2807
Other rheumatoid arthritis (M06)	202/333 (60.7%)	205/344 (59.6%)	0.98 (0.79—1.18)	0.3669
Hyperparathyroidism and other disorders of parathyroid gland (E21)	45/61 (73.8%)	44/73 (60.3%)	0.82 (0.40—1.23)	0.2032
Chronic kidney disease (N18)	36/54 (66.7%)	36/54 (66.7%)	1.00 (0.54—1.46)	0.7825
Atherosclerosis of aorta (I70)	71/141 (50.4%)	90/145 (62.1%)	1.23 (0.92—1.54)	0.3416
Other chronic obstructive pulmonary disease (J44)	15/21 (71.4%)	14/20 (70.0%)	0.98 (0.25—1.71)	0.8192

that directly impairs gastroenterological adverse events. However, controversial effects are reported associated with BPN injectable formulas, considering the low gastrointestinal adverse events and without directly impairing the esophagus, such as high and low persistence as compared to that of starting oral BPN formula in over middle age women (Durden et al. 2017; Modi et al. 2017) and from meta-analysis (Bastounis et al. 2022). Although the discrepancy is unclear, the advantages and disadvantages of high medication adherence in BPN may be complex. Our results could not reveal characteristics for high medication adherence or patient background in the sub-group analysis (Table 2). However, as mentioned above, the criteria for medication adherence should be updated and combined with patient knowledge or beliefs in future studies.

Our study patients exhibited that BPN medication adherence (as assessed by PDC) was 64% and 66% in weekly and monthly formulas, respectively. This finding was lower than that of previous studies that assessed the medication possession ratio (MPR) for 64–79.4% (weekly) and 70–84.5% (monthly) BPN formulas (Cotté et al. 2010; Kishimoto and Maehara, 2015; Kosaka et al. 2021). The MPR calculation estimates a higher trend if patients have overlapped medication refills (Loucks et al. 2022). This is one possible reason for the difference between the PDC values calculated for our patients and other studies for MPR. We confirmed that BPN medication adherence in weekly regimens is consistently low. Rabenda et al. (2008) reported that a 1% decrease in BPN medication adherence was associated with an increase of 0.4% in hip fracture occurrence, as assessed by MPR (Rabenda et al. 2008). It is essential that medical staff is aware that approximately 50% of patients with osteoporosis have low medication adherence. Therefore, it is crucial to prioritize efforts toward promoting and improving medication adherence, as well as staying updated on information regarding BPN medication adherence.

This study has several limitations. First, analyses were performed using propensity score matching. This analysis provides matching in both groups for weekly and monthly BPN formulas. In other words, patients that do not match are removed from our analysis as a propensity score matching-dependent limitation. Secondly, the JMDC dataset includes patients of < 74 years old. Although our data mainly covered the middle aged patients with osteoporosis, evidence for < 74 years old is also important as a healthy life expectancy is 73 and 75 years old for males and females, respectively (Ministry of Health, Labour and Welfare, 2021).

In conclusion, we elucidated the disparity in BPN medication adherence between weekly and monthly regimens for the first year of treatment. Our clinical data analysis for up to 2019 highlights the importance of closely monitoring BPN medication adherence, particularly during the initial therapy year. Notably, half of the patients with osteoporosis exhibit low medication adherence. Accordingly, prioritizing monthly regimens over weekly regimens presents a viable alternative to promote BPN adherence and ensure optimal treatment outcomes.

4. Experimental

4.1. Data source

The Japan Medical Data Centre (JMDC) claims its database contains anonymized patient data. The cumulative dataset contains approximately 13 million individuals (inpatients, outpatients, and pharmacy claims), covering approximately 90% of hospitals in Japan (as of September 2021). All patients in the JMDC database have "social insurance" that covers the working person and their family. As of September 2021, the database represents 10.0% of the Japanese population (Nagai et al. 2021).

4.2. Patient identification

We identified patients who started BPN among approximately 13 million social insurance participants. Of these, we obtained participants from January 2017 and December 2019 from the JMDC database, of whom 16,965 patients were treated with BPN. A retrospective cohort was set up for 3 months of screening and a 12-month observation period (n=8,570). We also set the following exclusion criteria: 1) patients that received zoledronate administration, 2) patients who received injectable BPN formulas, 3) patients who received daily BPN formula at the index month (month 0), 4) patients who switched BPN components during the observation periods, 5) patients that were not diagnosed with osteoporosis (M80-82), 6) patients with diagnosed Paget's disease of bone (M88) and osteogenesis imperfecta (Q78), and 7) patients of age ≤ 29 years (n=3,554). As a result, 5,016 patients were analyzed in this study (Fig. 1, Supplementary Table 1, Supplementary Figure 1).

Briefly, "month 0" refers to the index month when patients were prescribed BPN for the first time. Baseline data refers to the following information: 1) patient characteristics such as sex, age, and monthly or weekly BPN regimen (month 0=index month) and 2) comorbidities (month -3 to month 0). The screening period refers to month -3 to 1 from the index month as a washout window for BPN administration. The observation period shows up to month +11 from the index month.

4.3. Study definitions

BPN exposure was assessed using the proportion days covered (PDC) (Loucks et al. 2022). PDC was derived by dividing the number of BPN supply days by the number of observation days (365 days), capped at 1 in each patient (Supplementary Table 2). Weekly and monthly BPNs are defined according to the indication in the package inserts such as weekly formula as "weekly" and monthly formula or 4 weeks formula

as "monthly" in this study. BPNs are defined as anatomical therapeutic chemical (ATC) code at index month and comorbidity for the International Statistical Classification of Diseases and Related Health Problems (ICD) 10 code screening period (month -3 to 0) (Supplementary Table 1). Good medication adherence was defined as 80% of BPN PDC (Naranjo et al. 2022) during the 12- month observation period (month 0 to +11).

4.4. Primary and secondary study endpoints

The primary endpoint of this study was to establish a PDC of > 80% for patients who started with weekly or monthly BPNs (Siris et al. 2006, Naranjo et al. 2022). The secondary endpoint was to assess average PDC between weekly and monthly BPNs following propensity score matching.

4.5. Statistical analysis

Univariate analyses (Student's t-test, Mann–Whitney U-test, chi-square test, and Fisher's exact test) of the groups for "PDC > 80%" and "PDC < 80%" for 12-month observation were performed using the patient demographics of 5,016 patients.

The propensity score was calculated using sex, age, insured individual or their family, and comorbidities in the study patients divided between the < 80% and > 80% PDC groups. Matching was used to conduct 1:1 nearest-neighbor matching. The caliper value (caliper width) for the nearest neighbor matching was set to 0.2 times the standard deviation of the log of the propensity scores. The standardized difference (d) was calculated to compare patient backgrounds between > 80% and < 80% of PDC groups before and after matching. The difference in backgrounds after matching was considered negligible if d < 0.1.

Stratified analysis for each baseline parameters, such as sex, age, insured individual or their family, and comorbidities after propensity score matching, were compared for the number of patients with a PDC of > 80% between weekly and monthly regimens. Prevalence rate ratio (PRR) and 95% confidence interval (CI) were calculated as reference in the weekly group.

Data are expressed as medians with ranges or mean±standard deviations. Data analysis was performed using JMP 16® (SAS Institute Inc., Cary, NC, USA).

4.6. Ethics approval

The commercially available JMDC database used in this study contains anonymized information processed based on Japan's Personal Information Protection Law, and individual informed consent is not required for the provision and use of this information. In addition, according to the ethical guidelines for clinical research in Japan, review by an ethics committee is not required for studies using anonymized information. Therefore, no informed consents were obtained for this study since the patient data were anonymized before access.

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Conflicts of Interest: KM, TS (Showa University), and JMDC Inc. collaborate other project according to the collaborative research agreement; JMDC Inc. did not intervene in the implementation of the data analyzed in this study; KM received honorarium fees for presentations from JMDC Inc.; TS received an honorarium for presentation at Daiichi Sankyo, Nipro, Nichi-Iko, Pfizer, Sandoz, Mylan, and Meiji Seika Pharma; TS is an advisor at Torii Pharmaceutical; KM and TS received travel reimbursement from Abbvie to attend their conference. Department of Hospital Pharmaceutics, School of Pharmacy, Showa University received funding from Ono. with a contract research project according to the collaborative research agreement.

As a potential conflict of interest, KR's kin is employed from Nippon-Shinyaku; KR received honorarium fee from Chugai; KM received honorarium fee from Nippon-Kayaku, Eisai, and Abbvie; Hospital Pharmaceutics received a research grant from Daiichi Sankyo, Mochida Pharmaceutical, Shionogi, Ono Pharmaceutical, Taiho Pharmaceutical, Bayer, and Nippon-kayaku; The other authors declare no conflict of interest.

References

Adler RA, El-Hajj Fuleihan G, Bauer DC, Camacho PM, Clarke BL, Clines GA, Compston JE, Drake MT, Edwards BJ, Favus MJ, Greenspan SL, McKinney R Jr, Pignolo RJ, Sellmeyer DE (2016) Managing osteoporosis in patients on long-term bisphosphonate treatment: Report of a Task Force of the American Society for Bone and Mineral Research. J Bone Mineral Res 31: 16–35.

Anagnostis P, Paschou SA, Mintziori G, Ceausu I, Depypere H, Lambrinoudaki I, Mueck A, Pérez-López FR, Rees M, Senturk LM, Simoncini T, Stevenson JC, Stute P, Trémollieres FA, Goulis DG (2017) Drug holidays from bisphosphonates and denosumab in postmenopausal osteoporosis: EMAS position statement. Maturitas 101: 23–30.

Bastounis A, Langley T, Davis S, Paskins Z, Gittoes N, Leonardi-Bee J, Sahota O (2022) Comparing medication adherence in patients receiving bisphosphonates for preventing fragility fractures: A comprehensive systematic review and network meta-analysis. Osteoporos Int 33: 1223–1233.

Black DM, Reid IR, Boonen S, Bucci-Rechtweg C, Cauley JA, Cosman F, Cummings SR, Hue TF, Lippuner K, Lakatos P, Leung PC, Man Z, Martinez RL, Tan M, Ruzycky ME, Su G, Eastell R (2012) The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: A randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). J Bone Mineral Res 27: 243–254.

Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, Wehren LE, Lombardi A, Santora AC, Cummings SR (2006) Effects of continuing or stopping alendronate after 5 years of treatment: The Fracture Intervention Trial Long-term Extension (FLEX): A Randomized Trial. JAMA 296: 2927.

Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, Nevitt MC, Suryawanshi S, Cummings SR (2000) Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. J Clin Endocrinol Metab 85: 4118-4124.

Caro JJ, Ishak KJ, Huybrechts KF, Raggio G, Naujoks C (2004) The impact of compliance with osteoporosis therapy on fracture rates in actual practice. Osteoporos Int 15: 1003–1008.

Carr AJ, Thompson PW, Cooper C (2006) Factors associated with adherence and persistence to bisphosphonate therapy in osteoporosis: A cross-sectional survey. Osteoporos Int 17: 1638–1644.

Chen FP, Huang TS, Fu TS, Sun CC, Chao AS, Tsai TL (2018) Secular trends in incidence of osteoporosis in Taiwan: A nationwide population-based study. Biomed J 41: 314–320.

Cotté FE, Fardellone P, Mercier F, Gaudin AF, Roux C (2010) Adherence to monthly and weekly oral bisphosphonates in women with osteoporosis. Osteoporos Int 21: 145–155.

Durden E, Pinto L, Lopez-Gonzalez L, Juneau P, Barron R (2017) Two-year persistence and compliance with osteoporosis therapies among postmenopausal women in a commercially insured population in the United States. Arch Osteoporos 12: 22.

Ferguson S, Feudjo Tepie M, Taylor A, Roddam A, Critchlow C, Iqbal M, Spangler L, Bayly J (2016) The impact of persistence with bisphosphonates on health resource utilization and fracture risk in the UK: A study of patient records from the UK Clinical Practice Research Datalink. J Eval Clin Pract 22: 31–39.

Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, McCloskey EV, Jönsson B, Kanis JA (2013) Osteoporosis in the European Union: Medical management, epidemiology and economic burden: A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos 8: 136.

Khosla S, Melton LJ, Riggs BL (2011) The unitary model for estrogen deficiency and the pathogenesis of osteoporosis: Is a revision needed? J Bone Mineral Res 26: 441–451.

Kim S, Chung YS, Lee Y (2022) Adherence of bisphosphonate and decreased risk of clinical vertebral fracture in osteoporotic patients: A propensity score matching analysis. Osteoporos Sarcopen 8: 98–105.

Kishimoto H, Maehara M (2015) Compliance and persistence with daily, weekly, and monthly bisphosphonates for osteoporosis in Japan: Analysis of data from the CISA. Arch Osteoporos 10: 27.

Kosaka Y, Sugiyama T, Hara K, Kobayashi Y (2021) Adherence to daily, weekly, and monthly dosing regimens of bisphosphonates for osteoporosis treatment in postmenopausal women in Japan: A retrospective study using claims data. Tohoku J Exp Med 255: 147–155.

Laius O, Pisarev H, Maasalu K, Kõks S, Märtson A (2017) Adherence to osteoporosis medicines in Estonia-A comprehensive 15-year retrospective prescriptions database study. Arch Osteoporos 12: 59.

Loucks J, Zuckerman AD, Berni A, Saulles A, Thomas G, Alonzo A (2022) Proportion of days covered as a measure of medication adherence. Am J Health-Syst Pharm 79: 492–496.

Manolagas SC (2000).Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocrine Rev 21: 115–137.

McCombs JS, Thiebaud P, McLaughlin-Miley C, Shi J (2004) Compliance with drug therapies for the treatment and prevention of osteoporosis. Maturitas 48: 271–287.

Ministry of Health, Labour and Welfare. (2021). The 16th Expert Committee for the Promotion of Healthy Japan 21 (Second Stage), "Healthy life expectancy." https://www.mhlw.go.jp/content/10904750/000872952.pdf

Modi A, Sajjan S, Insinga R, Weaver J, Lewiecki EM, Harris ST (2017) Frequency of discontinuation of injectable osteoporosis therapies in US patients over 2 years. Osteoporos Int 28: 1355–1363.

Nagai K, Tanaka T, Kodaira N, Kimura S, Takahashi Y, Nakayama T (2021) Data resource profile: JMDC claims database sourced from health insurance societies. J Gen Fam Med 22: 118–127.

Naranjo A, Molina A, Quevedo A, Rubiño FJ, Sánchez-Alonso F, Rodríguez-Lozano C, Ojeda S (2022) Long-term persistence of treatment after hip fracture in a fracture liaison service. Sci Rep 12: 9373.

National Osteoporosis Guideline Group (2021) Clinical Guideline for the Prevention and Treatment of Osteoporosis, "Summary of Main Recommendations." https://www.nogg.org.uk/full-guideline/summary-main-recommendations

Rabenda V, Mertens R, Fabri V, Vanoverloop J, Sumkay F, Vannecke C, Deswaef A, Verpooten GA, Reginster JY (2008) Adherence to bisphosphonates therapy and hip fracture risk in osteoporotic women. Osteoporos Int 19: 811–818.

Rossini M, Bianchi G, Di Munno O, Giannini S, Minisola S, Sinigaglia L, Adami S (2006) Determinants of adherence to osteoporosis treatment in clinical practice. Osteoporos Int 17: 914–921.

Siris ES, Harris ST, Rosen CJ, Barr CE, Arvesen JN, Abbott TA, Silverman S (2006) Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: Relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clinic Proceed 81: 1013–1022.

Wang M, Wu Y, Girgis CM (2022) Bisphosphonate drug holidays: Evidence from clinical trials and real-world studies. JBMR Plus 6: e10629.

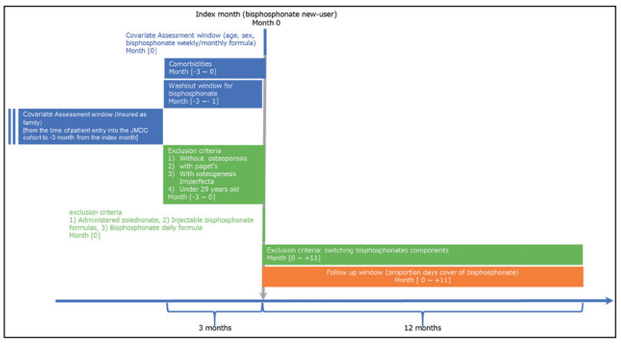
Wright NC, Looker AC, Saag KG, Curtis JR, Delzell ES, Randall S, Dawson-Hughes B (2014) The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. J Bone Min Res 29: 2520–2526.

Yoshimura N, Iidaka T, Horii C, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T, Tanaka S (2022) Trends in osteoporosis prevalence over a 10-year period in Japan: The ROAD study 2005–2015. J Bone Min Metabol 40: 829–838.

Supplementary material

Supplementary Table 1. Definition and categorization of study covariates

Characteristic	Definition/categories
Demographic characteristic	
Sex	Male/female
Age	Measured at index month
Comorbidities	
Neoplasms	ICD-10: C00-D48
Hypertensive diseases	ICD-10: I10-I15
Diabetes mellitus	ICD-10: E10-E14
Disorders of lipoprotein metabolism and other lipidaemias	ICD-10: E78
Other rheumatoid arthritis	ICD-10: M06
Hyperparathyroidism and other disorders of parathyroid gland	ICD-10: E21
Chronic kidney disease	ICD-10: N18
Atherosclerosis of aorta	ICD-10: I70
Other chronic obstructive pulmonary disease	ICD-10: J44
Diagnosis	
Osteoporosis	ICD-10: M80-92
Exclusion criteria	
Bone Paget	ICD-10: M88
Osteogenesis imperfecta	ICD-10: Q78



Supplementary Fig. 1: Study design diagram

Supplementary Table 2: Calculation for proportion days cover for bisphosphonate

Proportion Days Cover (PDC) was derived by dividing the number of supply days of bisphosphonates by the number of observation days (365 days) capped at 1 in each patient calculated below formula;
Formulation for calculating PDC of bisphosphonate

$$PDC = \frac{total\ days\ covered\ by\ bisphosphonate}{observation\ period\ for\ 12\ months} \times 100\ ^{1}$$

The duration of therapeutic effectiveness following the administration of Bisphosphonate formulations was defined as follows, based on the respective package inserts for each formulation.

Component	Formula	ATC code	Days of supply
Alendronic acid	Weekly	M05BA04	Number of tablet × 7 days
Ibandronic acid	Weekly	M05BA06	Number of tablet × 30 days
Minodronic acid	Monthly	M05BA	Number of tablet × 28 days
Risedronic acid	Weekly Monthly	M05BA07	Number of tablet × 7 days Number of tablet × 30 days

Reference

Loucks J, Zuckerman AD, Berni A, Saulles A, Thomas G, Alonzo A (2022) Proportion of days covered as a measure of medication adherence. Am J Health-Syst Pharm 79: 492–496.