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Original article

Adherence of bisphosphonate and decreased risk of clinical vertebral fracture in osteoporotic patients: A propensity score matching analysis

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ABSTRACT

Objectives: Bisphosphonate is associated with a decreased risk of vertebral fractures due to osteoporosis. However, there are limited studies on how poor compliance with bisphosphonate affects the risk of vertebral fractures in a nationwide cohort. We aim to evaluate whether adherence to bisphosphonate affects the risk of fracture in osteoporosis patients.

Methods: We used the data of the Korean National Health Insurance Service Senior Cohort. A total of 33,315 (medication possession ratio [MPR]: 50) osteoporosis patients were matched using the propensity score matching method: those who received low-dose bisphosphonate and those who received high-dose bisphosphonate. Twenty-two confounding variables, including age, socioeconomic status, medications prescribed, and underlying diseases that may affect the risk of fracture were adjusted for propensity score matching. The risk of vertebral fracture was assessed by Cox proportional hazards regression.

Results: Patients with a higher MPR showed a decreased vertebral fracture risk than those with a lower MPR (MPR 50 = hazard ratio [HR] 0.909; 95% confidence interval [CI] 0.877–0.942 $P < 0.001$; MPR 70 = HR: 0.874, 95% CI: 0.838–0.913, $P < 0.001$; MPR 90 = HR: 0.822, 95% CI: 0.780–0.866, $P < 0.001$). MPR was associated with a decreased vertebral fracture risk in both groups with or without history of fracture. In the subgroup analysis, MPR was associated with a decreased vertebral fracture risk in women, in all ages, with or without T2DM, and with or without hypertension.

Conclusions: Higher MPR is associated with a lower vertebral fracture risk.

1. Introduction

Osteoporosis causes vertebral fracture or all-cause fracture, which affects the patient's quality of life and is an increasing burden to the society [1–3]. In 2000, 9.0 million new cases of osteoporotic fractures were registered worldwide, of which 1.6 million were hip fractures, 1.7 million were distal forearm fractures, and 1.4 million were clinical vertebral fractures [4].

In the United Kingdom, Sweden, Australia, and the United States, the lifetime risks of vertebral fracture at the age of 59 years have been estimated to be 39.7%–53.2% in women and 13.0–22.4% in men [1]. Osteoporosis requires careful management because this condition and the related fractures are important public health issues that increase the personal healthcare costs and economic burden on the healthcare system [2]. An increase in the mortality rate after vertebral fractures has been reported in several studies [1]. A vertebral fracture is the most common fracture due to osteoporosis, and damage to the spinal nerve and spinal cord is a more serious problem than the fracture itself [1–3]. In addition, patients with high bisphosphonate adherence have lower socioeconomic status than those with low bisphosphonate compliance [5–7]. Thus, treatment of osteoporosis is a very important issue for postmenopausal women, which is required to prevent fractures and chronic disability.

Bisphosphonates are generally the first-line treatment for osteoporotic vertebral fractures; a number of studies have already

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evaluated this class of drugs and they are known to be inexpensive, are cost-effective, and have relatively fewer side effects. Several studies have shown that bisphosphonates decrease vertebral and femur fractures.

However, although osteoporosis is asymptomatic in the early stages, adverse reactions such as upper gastrointestinal tract disorders, musculoskeletal pain, hypocalcemia, and eye inflammation have been reported. In particular, when bisphosphonates are taken orally, esophagitis, esophageal ulcers, and gastric ulcers may occur [8–13].

A number of studies have reported that compliance and persistence with bisphosphonates affect the risk of vertebral fractures following osteoporosis. However, in clinical practice, there is limited evidence showing the rate of adherence to this medication, where the compliance and persistence rates are likely to be different from those in clinical trials. In addition, a few studies have examined the association between poor adherence and the risk of fractures in real-world practice [14]. In addition, previous studies reported varied opinions on the dose of bisphosphonate drugs that should be used to help prevent fractures. Most studies report a medication possession ratio (MPR) of 80% or more [15–19] as good compliance, despite the fact that the number of patients who adhere to the drugs is significantly lower than the adherence level [20].

In addition, although many existing studies report an MPR of 80% or higher as the optimal drug adherence, low drug adherence has been reported in actual clinical practice. According to the study by Cheng et al [19] 61.9% of patients used the drug for 1 year as maintenance treatment after taking bisphosphonates, while Soong et al [21] reported that 50% of patients were non-adherent to bisphosphonate treatment. At 1 year, only 30% of the patients reported good drug compliance. In the study by Sampalis et al [22], 49.9% of patients had an MPR of 80% or higher between 0 and 2 years. Therefore, considering the actual clinical situation, it will be helpful to provide the appropriate MPR to prevent fracture for 1 year.

There are many and various drugs that can be used to treat osteoporosis, but bisphosphonates are frequently used in Korea (approximately 80%); it is the first-line treatment for osteoporosis. Denosumab was covered by health insurance since 2019, while teriparatide was covered by health insurance since 2017; therefore, it was not included as the target drug in this study, and selective estrogen receptor modulators (SERMs) were used in less than 20% of cases in Korea. According to the 2018 Intercontinental Medical Statistics Health Sales data, the prescription for bisphosphonate was still overwhelmingly high at 80.0%; SERM, 13.9%; denosumab, 4.7%; teriparatide, 0.8%; and calcitonin, 0.7% [23]. Therefore, we focused on investigating the efficacy of bisphosphonate treatment.

This study aims to investigate the relationship between adherence to bisphosphonates and the risk of vertebral fracture in osteoporotic patients in a large population-based real-world cohort. In addition, this study aimed to determine the difference in fracture risk according to the levels of drug adherence.

2. Methods

2.1. Study design

The nationwide cohort study used the propensity matching methods. This study was reviewed and approved by the institutional review board of Ajou University Hospital (AJIRB-MED-EXP-17-475). These data are secondary data using the Korean National Health Insurance Service data, and information disclosed to the general public was used, and as research or research that does not collect and record personally identifiable information, it was exempted from the IRB review.

2.2. Data source

The data of the Korean National Health Insurance Service Senior Cohort (ver. 3.0, January 1, 2002, to December 31, 2015) were used in the study, which included 10% of the random anonymized sample of the entire South Korean senior population in 2002 (550 000 patients). The abovementioned data were extracted from the Korean National Health Insurance Service, which covers 98% of the South Korean population using a stratified random sampling method with 1476 strata; therefore, the dataset represents the entire South Korean senior population [24].

2.3. Inclusion and exclusion criteria

Patients who had been prescribed with bisphosphonates after the diagnosis of osteoporosis were enrolled (Fig. 1). The enrollment date was January 1, 2002. We enrolled patients with osteoporosis (International Classification of Diseases, 10th revision [ICD-10] codes: M80 and M81]. The bisphosphonate drugs included alendronate, risedronate, ibandronate, pamidronate, zoledronic acid, etidronate, and clodronate, with an ATC code M05B3. The washout period was 1 year (365 days), and the index dates were from January 1, 2003 to December 31, 2014. Since we focused on the effect of taking bisphosphonates on fractures, patients diagnosed with fracture (ICD-10 codes: S320, S220, S221, M8008, M8098, and M485) were excluded. Also, Paget's disease (ICD-10 code: M88), or prescriptions for cancer (ICD-10 codes: Cx) before the index date (from January 1, 2003, to December 31, 2014) were excluded. Patients who were lost to follow-up are presented in Fig. 1. The Korean National Health Insurance Service Senior Cohort consisted of patients aged 60 years or older.

2.4. MPR

Bisphosphonate treatment adherence was calculated using the medication possession ratio (MPR), which is the proportion of days of bisphosphonate treatment within a fixed duration (a value ranging from 0% to 100%). Patients were classified into two groups according to their MPR: MPR of $< 50\%$ or $\geq 50\%$, MPR of $< 70\%$ or $\geq 70\%$, and MPR of $< 90\%$ or $\geq 90\%$. We calculated the MPRs within 12 months after the index date to test the following hypothesis: that a longer period of high adherence to bisphosphonate treatment was associated with a lower risk of vertebral fracture in osteoporotic patients.

2.5. Study outcome and subgroup analysis

The primary outcome was vertebral fracture (ICD-10 codes: S320, S220, S221, M485, S720, S721, S442, S525, and S526). We also analyzed patients with or without fracture at the index date (ICD 10 codes: M80 vs. M81) separately. Subgroup analyses were performed according to sex, age (< 75 and ≥ 75 years), and the presence of type 2 diabetes mellitus or hypertension.

2.6. Statistical analysis

All statistical analyses were performed using R software (ver. 3.3.3; R Development Core Team, Vienna, Austria) and SAS (SAS ver. 9.4; SAS Institute, Cary, NC, USA). All values were expressed as mean ± standard deviation. The disparity between patients with and without bisphosphonate treatment was adjusted with a likelihood score corresponding to the probability scale using the nearest-neighbor technique with a caliper of 0.1. Age, sex, and socioeconomic status were set based on the index date, diagnosis was set at 1 year before the index date, and prescribed medications

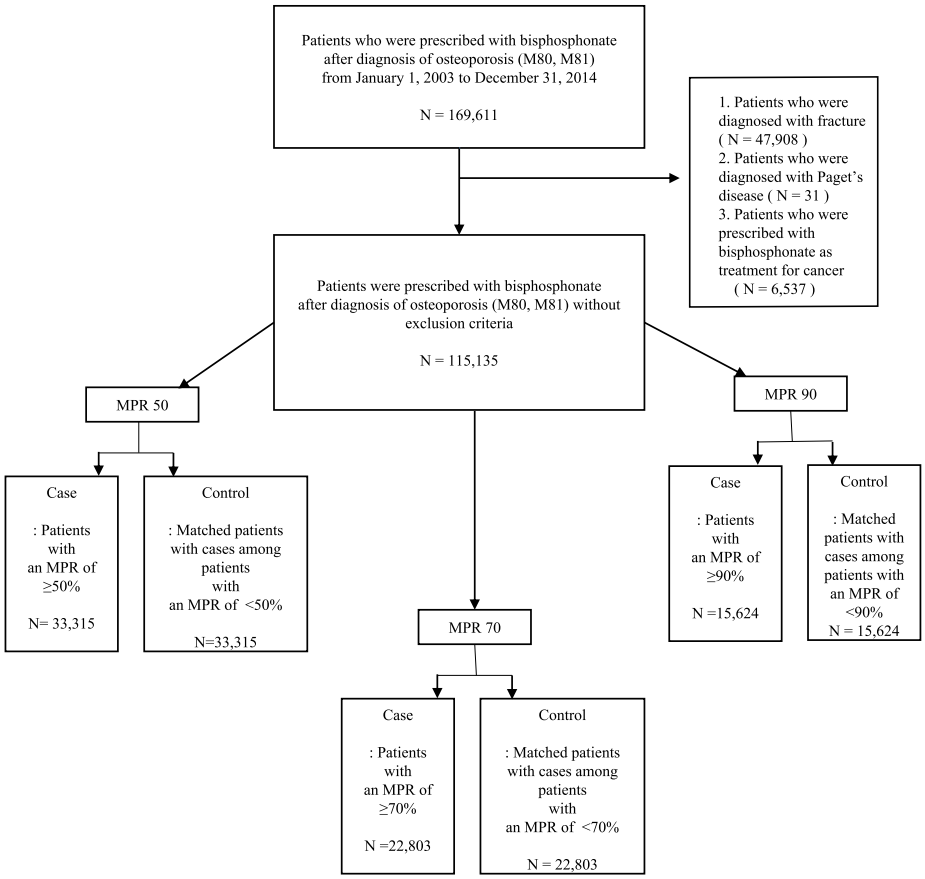

Fig. 1. Flow chart of the sample selection process.

were set at 180 days before the index date, which were specified as confounding variables (all variables presented in Table 1) and were used to obtain the propensity scores [25]. Using standardized differences, the balance achieved by matching the propensity score was assessed; an absolute standardized difference between groups of < 0.1 was considered negligible. The case and control groups were matched on a one-to-one basis. In the analysis the ICD 10 code, we matched cases and controls based on the ICD 10 codes (M80 vs M80, and M81 vs M81). The Kaplan-Meier curve and Cox proportional hazard model were used to measure the fracture risk following the propensity score matching method. We checked the proportionality assumption with log minus log plots and confirmed that the model was suitable. Since the likelihood score matching was balanced for all confounding variables, 1 minus the Kaplan-Meier estimate and univariable Cox regression analysis were performed.

3. Results

A total of 169,611 patients were included in the study. After propensity score matching, 33 315 (MPR 50), 22 803 (MPR 70), and 15 624 (MPR 90) patients were included in both groups (Fig. 1). The baseline characteristics of the matched group are presented in Table 1; all absolute values of standardized differences were less than 0.1; thus, all confounding variables were considered to be properly adjusted by propensity score matching. The mean follow-up periods of MPR 50 match were 4192.5 days, MPR 70 match were 4209.8 days, and MPR 90 match were 4211.5 days. During the study period, 115,135 patients were newly diagnosed with osteoporosis. Patients with high MPR showed a decreased risk of all-cause vertebral fracture compared with those in the following MPR groups: MPR50 (hazard ratio [HR]: 0.909; 95% confidence interval [CI]: 0.877–0.942; P < 0.001), MPR70 (HR: 0.874; 95% CI: 0.838–0.913; P < 0.001), and MPR90 (HR: 0.822; 95% CI: 0.780–0.866; P < 0.001; Table 2, Fig. 2). In the analysis of MPR 70 by ICD 10 code, the patients were divided by fracture history at index date according to the ICD 10 code, including those with or without fracture at the index date (Table 3). Patients in the M80 group showed a decreased risk of all-cause vertebral fracture compared with those in the MPR50 (HR: 0.904; 95% CI: 0.842–0.971; P < 0.001), MPR70 (HR: 0.901; 95% CI: 0.827–0.982; P < 0.001), and MPR90 groups (HR: 0.789; 95% CI: 0.709–0.877; P < 0.001; Table 3, Fig. 3). Patients in the M81 group showed a decreased risk of all-cause vertebral fracture compared with those in the MPR50 (HR: 0.863; 95% CI: 0.829–0.898; P < 0.001), MPR70 (HR: 0.863; 95% CI: 0.821–0.906; P < 0.001), and MPR90 groups (HR: 0.809; 95% CI: 0.762–0.859; P < 0.001; Table 3, Fig. 3).

In the subgroup analysis of the MPR70 group, patients with high MPR showed a decreased risk of vertebral fracture irrespective of age, type 2 diabetes mellitus status, or hypertension status. A higher MPR was associated with a decreased risk of vertebral fracture in women but not in men (Table 4).

4. Discussion

This population-based retrospective cohort study showed that patients with a high MPR had a lower risk of total vertebral fracture using the propensity score matching method with large cohort data. The HRs of fracture were 0.909 for MPR above 50, 0.874 for MPR above 70, and 0.822 for MPR above 90. The trend of the HR of

Table 1
Baseline characteristics of the matched pairs.

	Control	Case	P-value	SMD
MPR 50				
N	33,315	33,315		
Age (SD)	71.9245 (5.7696)	71.9472 (5.8689)	0.616	0.004
Sex (male, percent)	1.9187 (0.2734)	1.9186 (0.2735)	0.977	<0.001
Socioeconomic status (n, (%))			<0.001	0.036
0	10,075 (30.2)	9949 (29.9)		
1	9480 (28.5)	10,015 (30.1)		
2	13,760 (41.3)	13,351 (40.1)		
Alcohol	0.0098 (0.0986)	0.0094 (0.0963)	0.551	0.005
Smoke	0.0001 (0.0077)	0.0001 (0.0077)	1	< 0.001
Asthma	0.1624 (0.3688)	0.1633 (0.3697)	0.745	0.003
COPD	0.1116 (0.3149)	0.1132 (0.3168)	0.516	0.005
Hypertension	0.6082 (0.4882)	0.6039 (0.4891)	0.257	0.009
Heart disease	0.1054 (0.3070)	0.1067 (0.3087)	0.571	0.004
Type 2 DM	0.2436 (0.4293)	0.2454 (0.4303)	0.607	0.004
Type 1 DM	0.0211 (0.1437)	0.0223 (0.1476)	0.3	0.008
CRF	0.0157 (0.1243)	0.0153 (0.1227)	0.661	0.003
ESRD	0.0081 (0.0898)	0.0083 (0.0906)	0.83	0.002
Rheumatic arthritis	0.1133 (0.3170)	0.1103 (0.3132)	0.214	0.01
Ankylosing spondylitis	0.0092 (0.0957)	0.0097 (0.0978)	0.575	0.004
Hypothyroidism	0.0323 (0.1769)	0.0317 (0.1753)	0.66	0.003
Thyrotoxicosis	0.0441 (0.2052)	0.0424 (0.2015)	0.286	0.008
Hyperprolactinemia	0.0003 (0.0164)	0.0003 (0.0164)	1	< 0.001
Hyperparathyroidism	0.0007 (0.0268)	0.0006 (0.0251)	0.655	0.003
Cushing syndrome	0.0058 (0.0759)	0.0051 (0.0715)	0.248	0.009
Paget's disease	0.0000 (0.0000)	0.0000 (0.0000)	NaN	< 0.001
Cancer	0.0000 (0.0000)	0.0000 (0.0000)	NaN	< 0.001
Thiazolidinedione	0.0182 (0.1337)	0.0181 (0.1334)	0.931	0.001
Warfarin	0.0106 (0.1022)	0.0094 (0.0963)	0.119	0.012
Steroid	0.0364 (0.1874)	0.0343 (0.1820)	0.136	0.012
MPR 70				
N	22,803	22,803		
Age (SD)	71.8987 (5.7943)	71.9039 (5.8492)	0.923	0.001
Sex (male, percent)	1.9196 (0.2719)	1.9222 (0.2678)	0.298	0.01
Socioeconomic status (n, (%))			0.008	0.029
0	6648 (29.2)	6736 (29.5)		
1	6559 (28.8)	6787 (29.8)		
2	9596 (42.1)	9280 (40.7)		
Alcohol	0.0093 (0.0957)	0.0087 (0.0930)	0.552	0.006
Smoke	0.0000 (0.0066)	0.0000 (0.0066)	1	< 0.001
Asthma	0.1584 (0.3652)	0.1598 (0.3665)	0.682	0.004
COPD	0.1098 (0.3126)	0.1104 (0.3134)	0.822	0.002
Hypertension	0.6139 (0.4869)	0.6024 (0.4894)	0.012	0.023
Heart disease	0.1080 (0.3103)	0.1069 (0.3090)	0.705	0.004
Type 2 DM	0.2514 (0.4338)	0.2526 (0.4345)	0.763	0.003
Type 1 DM	0.0210 (0.1436)	0.0208 (0.1427)	0.844	0.002
CRF	0.0177 (0.1318)	0.0168 (0.1287)	0.494	0.006
ESRD	0.0094 (0.0966)	0.0098 (0.0986)	0.666	0.004
Rheumatic arthritis	0.1170 (0.3214)	0.1143 (0.3182)	0.372	0.008
Ankylosing spondylitis	0.0089 (0.0939)	0.0090 (0.0944)	0.921	0.001
Hypothyroidism	0.0347 (0.1831)	0.0333 (0.1795)	0.409	0.008
Thyrotoxicosis	0.0462 (0.2099)	0.0457 (0.2089)	0.823	0.002
Hyperprolactinemia	0.0004 (0.0187)	0.0003 (0.0175)	0.796	0.002
Hyperparathyroidism	0.0010 (0.0310)	0.0007 (0.0265)	0.33	0.009
Cushing syndrome	0.0064 (0.0795)	0.0058 (0.0759)	0.433	0.007
Paget's disease	0.0000 (0.0000)	0.0000 (0.0000)	–	< 0.001
Cancer	0.0000 (0.0000)	0.0000 (0.0000)	–	<0.001
Thiazolidinedione	0.0193 (0.1376)	0.0184 (0.1343)	0.469	0.007
Warfarin	0.0109 (0.1037)	0.0116 (0.1072)	0.45	0.007
Steroid	0.0391 (0.1938)	0.0369 (0.1885)	0.221	0.011
MPR 90				
N	15,624	15,624		
Age (SD)	71.8332 (5.7685)	71.8157 (5.8328)	0.79	0.003
Sex (male, percent)	1.9187 (0.2734)	1.9188 (0.2731)	0.95	0.001
Socioeconomic status (n, (%))			0.065	0.026
0	4378 (28.0)	4266(27.3)		
1	2261 (28.6)	4643 (29.7)		
2	6785 (43.4)	6715 (43.0)		
Alcohol	0.0089 (0.0939)	0.0094 (0.0965)	0.635	0.005
Smoke	0.0001 (0.0080)	0.0000 (0.0000)	0.317	0.011
Asthma	0.1560 (0.3628)	0.1525 (0.3595)	0.389	0.01

(*continued on next page*)

Table 1 (*continued*)

	Control	Case	P-value	SMD
COPD	0.1064 (0.3084)	0.1072 (0.3094)	0.826	0.002
Hypertension	0.6250 (0.4841)	0.6174 (0.4860)	0.165	0.016
Heart disease	0.1081 (0.3105)	0.1102 (0.3131)	0.562	0.007
Type 2 DM	0.2567 (0.4368)	0.2560 (0.4364)	0.887	0.002
Type 1 DM	0.0206 (0.1421)	0.0200 (0.1401)	0.718	0.004
CRF	0.0194 (0.1379)	0.0192 (0.1372)	0.902	0.001
ESRD	0.0100 (0.0994)	0.0108 (0.1031)	0.503	0.008
Rheumatic arthritis	0.1161 (0.3204)	0.1134 (0.3171)	0.456	0.008
Ankylosing spondylitis	0.0083 (0.0905)	0.0088 (0.0936)	0.58	0.006
Hypothyroidism	0.0374 (0.1898)	0.0381 (0.1916)	0.744	0.004
Thyrotoxicosis	0.0499 (0.2178)	0.0454 (0.2083)	0.063	0.021
Hyperprolactinemia	0.0004 (0.0212)	0.0003 (0.0179)	0.564	0.007
Hyperparathyroidism	0.0011 (0.0330)	0.0010 (0.0320)	0.862	0.002
Cushing syndrome	0.0062 (0.0786)	0.0061 (0.0777)	0.885	0.002
Paget's disease	0.0000 (0.0000)	0.0000 (0.0000)	–	< 0.001
Cancer	0.0000 (0.0000)	0.0000 (0.0000)	–	< 0.001
Thiazolidinedione	0.0198 (0.1392)	0.0188 (0.1359)	0.537	0.007
Warfarin	0.0115 (0.1067)	0.0093 (0.0962)	0.058	0.021
Steroid	0.0388 (0.1931)	0.0364 (0.1872)	0.258	0.013

[a] Confirmed by diagnosis code (International Classification of Diseases, 10th revision).
[b] An absolute standardized difference between groups of < 0.1 (10%) was considered negligible. The standardized mean differences (SMDs) of all covariates were 0.57% (0.73%) an MPR of 50%, 0.59% (0.59%) at an MPR of 70%, and 0.74% (0.71%) at an MPR of 90%.
[c] COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CRF, chronic renal failure; ESRD, end-stage renal disease; SMD, standardized mean difference.
Data are presented as frequencies or means (SD).

Table 2
Risk of vertebral fracture according to MPR.

	N of both group	Events		HR	Lower CI	Upper CI	P-value
		control	case				
MPR ≥ 50	33,315	12,364		0.909	0.877	0.942	< 0.001
		6437	5927				
MPR ≥ 70	22,803	8423		0.874	0.838	0.913	< 0.001
		4457	3966				
MPR ≥ 90	15,624	5670		0.822	0.780	0.866	<0.001
		3078	2592				

CI, 95% confidence interval; HR, hazard ratio; MPR, number of available medications/total number of days of period; N, number of patients.

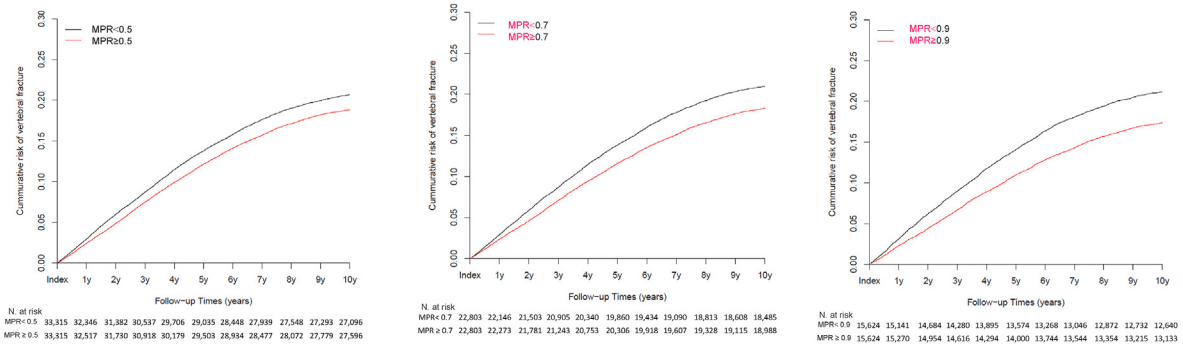

Fig. 2. Kaplan–Meier plots for vertebral fracture risk of MPR 50 (A), MPR 70 (B), and MPR 90 (C) in the M80 and M81 patients.

fracture showed a lower risk according to the level of adherence to bisphosphonate. A decreased risk of vertebral fracture was observed in both the M80 and M81 groups. In the subgroup analysis, there was a decreased risk of vertebral fracture in women, in all age group, with or without type 2 diabetes mellitus, and with or without hypertension compared with the control group.

To our knowledge, this cohort study is the first to use propensity score matching to minimize selection bias in looking at bisphosphonate drug compliance. In addition, our study included the largest number of patients to date with osteoporosis.

Our results agree with those of previous studies, which reported that poor adherence to these drugs increased the risk of fracture [13,15,16,20,26,27]. According to the PHARMO study, after 1 year of persistent bisphosphonate use, the risk of fractures was reduced by 26%; after 2 years, the risk of fractures reduced by 32% [27]. According to the study by Siris et al, the vertebral fracture risks was reduced by 32% in the compliant group, while it reduced by 40% in the persistent group [15]. Women on monthly regimens were 37% less likely to be nonpersistent after correcting for possible confounding variables [20].

We also report that the risk of vertebral fracture gradually decreased as the drug adherence increased. In particular, the risk of

Table 3
Risk of vertebral fracture according to MPR by ICD 10 code.

M80	N of both group	Events		HR	Lower CI	Upper CI	P-value
		Control	Case				
MPR ≥ 50	5474	2997		0.904	0.842	0.971	< 0.001
		1558	1439				
MPR ≥ 70	3890	2076		0.901	0.827	0.982	< 0.001
		1081	995				
MPR ≥ 90	2629	1386		0.789	0.709	0.877	< 0.001
		762	624				
M81							
MPR ≥ 50	27,800	9572		0.863	0.829	0.898	< 0.001
		5099	4473				
MPR ≥ 70	18,907	6347		0.863	0.821	0.906	< 0.001
		3379	2968				
MPR ≥ 90	12,993	4362		0.809	0.762	0.859	< 0.001
		2376	1986				

CI, 95% confidence interval; HR, hazard ratio; MPR, number of available medications/total number of days of period; N, number of patients.

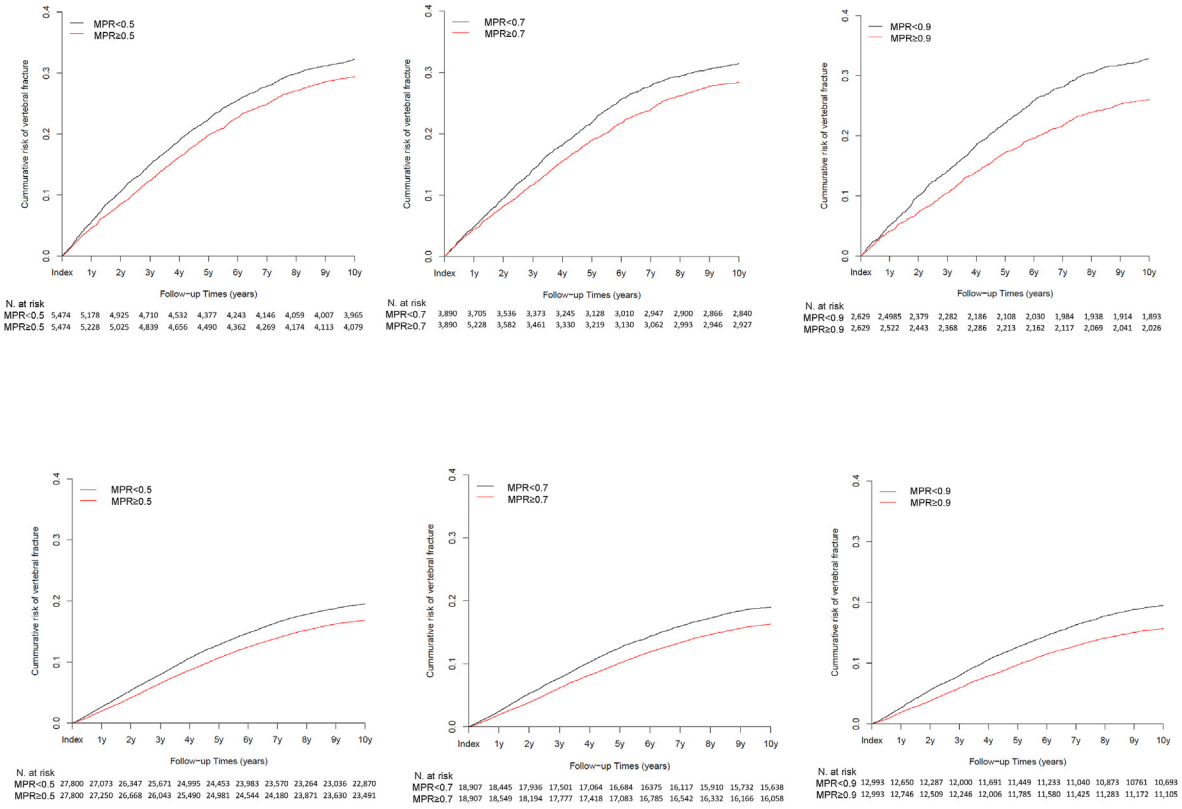

Fig. 3. Kaplan–Meier plots for vertebral fracture risk of i) M80 patients: MPR 50 (A), MPR 70 (B), and MPR 90 (C); ii) M81 patients: MPR 50 (D), MPR 70 (E), and MPR 90 (F).

vertebral fracture was reduced even when the MPR was greater than 50, which is much lower than the criteria used in previous studies that considered optimal MPR levels of 80% and above [26]. The rate of non-compliance to bisphosphonate treatment was 35–65% in previous studies; this finding would be useful in real-world practice [9,28]. The same trend was observed in the subgroup analysis of the ICD 10 codes M80 (with fracture) and M81 (without fracture) at baseline (Table 3). These results indicate that during the course of bisphosphonate treatment, in which adherence is difficult to achieve due to the difficulty in taking this medication and the risk of gastrointestinal side effects, fracture can still be prevented in all osteoporosis patients even if the compliance rate is not as high as that prescribed by the doctor. In particular, the M81 (non-fracture) group benefited from bisphosphonate treatment at MPRs 50 and 70 than the M80 (fracture) group. In the M80 group (fracture group), taking 50% of the dose was less effective in preventing secondary vertebral fractures, but taking more than 90% of the prescribed dose was thought to be effective (Table 3). The absolute fracture incidence rate was high in the M80 (fracture) group at approximately 30% at 10 years, but that in the M81 (non-fracture) group was only 20% at 10 years (Fig. 3).

In another subgroup analysis, all groups except men showed a decreased risk of vertebral risk compared with the control group with a MPR of 70%. Since the male group had a small sample size,

Table 4
Subgroup analyses according to sex, age, type 2 DM status, and HTN status at MPR≥70.

		N	Events	HR	Lower CI	Upper CI	P-value
Male	MPR < 70	1567	155	0.859	0.682	1.082	0.198
	MRP ≥ 70	1559	134				
Female	MPR < 70	17,340	3224	0.862	0.820	0.907	< 0.001
	MRP ≥ 70	17,348	2834				
Patients aged ≥75 years	MPR < 70	5581	944	0.850	0.774	0.934	< 0.001
	MRP ≥ 70	5529	810				
Patients aged <75 years	MPR < 70	13,326	2435	0.867	0.819	0.919	< 0.001
	MRP ≥ 70	13,378	2158				
Patients with T2DM	MPR < 70	4725	720	0.848	0.761	0.944	0.003
	MRP ≥ 70	4754	623				
Patients without T2DM	MPR < 70	14,182	2659	0.867	0.820	0.917	< 0.001
	MRP ≥ 70	14,153	2345				
Patients with HTN	MPR < 70	11,539	1920	0.846	0.792	0.904	< 0.001
	MRP ≥ 70	11,625	1666				
Patients without HTN	MPR < 70	7368	1459	0.887	0.823	0.956	0.002
	MRP ≥70	7282	1302				

CI, 95% confidence interval; HR, hazard ratio; N, number of patients; DM, diabetes mellitus; HTN, hypertension; MPR, number of available medications/total number of days of the period.

further analysis is required using a large sample size.

This study has several strengths. First, to the best of our knowledge, this study is the first to examine all MPRs (50%, 70%, and 90%). In the real world, the rate of adherence to the treatment regimen is reported to be 50%; in our study, the risk of fracture was reduced (HR, 0.921) even at an MPR of 50%. Second, the adherence rate was analyzed using the claims data of a large cohort of older adults, including 10% of the nation's population, for 14 years. Third, we tried to exclude the confounding variables and to minimize selection bias by considering 21 variables through propensity score matching.

However, there are some limitations to consider. First, since this study is retrospective in nature, the information used in the study were obtained from the database; hence, the data on several factors such as BMD measurements, which are necessary for diagnosing osteoporosis; health beliefs; and health system-related factors were limited. Moreover, in 2011, the insurance reimbursement standard has been changed from T score of −3.0 or less to a T score of −2.5 or less, so from 2011 to 2014, it is possible that the effect of medication adherence was somewhat overestimated. We also washed out vertebral fractures (S320, S220, S221, M8008, M8098, and M485) for 1 year prior to the start of the study to examine the effect of bisphosphonate administration on fractures. However, there is a limitation that fracture could not be completely controlled after a one-year washout period. Second, the claims data were analyzed based on the information of the prescribed drug, which is expected to be different from the exact data obtained by the actual patient. For example, in this large administrative database, only patients diagnosed with clinical vertebral fractures were reported, while asymptomatic patients were not reported; therefore, there was an underestimation bias. Moreover, it was not possible to determine the long-term effects of bisphosphonate treatment as the follow-up period was only 1 year. However, the Kaplan-Meier plot consistently reported differences of fracture between groups over a period of 10 years, and it has been reported that bisphosphonate drugs remain in bone tissue for up to 10 years [29]. Third, in this study, detailed analysis according to drug type and administration method could not be performed. Intravenous agents, such as zoledronic acid and ibandronate, may be more effective in reporting strong MPR. However, in Korea, up to 2015, more than 80% of bisphosphonates were prescribed as oral form [30]. Finally, since only the Korean population is included, our results were only generalizable to East Asians.

Despite the abovementioned limitations, our results showed that the higher the drug adherence, the lower the risk of fracture. In addition, we investigated the effects of drugs in patients with an MPR of ≥50%.

In conclusion, high adherence to bisphosphonate was associated with a lower risk of vertebral fracture in a random sample of older Koreans. However, it was not possible to analyze the difference in the risk of fractures according to drug component, administration method (medication, injection, etc), and drug compliance rate based on the dosage frequency. Also, in this study, the effect by generation could not be looked at. In future research, we propose sensitivity analysis with nitrogen-containing and non-nitrogen containing bisphosphonates. In order to develop a strategy that can increase the MPR and lower the fracture risk, various subgroup studies such as each type, generation, and dosage form of bisphosphonates are additionally needed.

CRediT author statement

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Conflicts of interest

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.afos.2022.05.004.

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