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Effects of Osteoporosis Medication Use on Reprocedure Rates Following Vertebral Augmentation: A Nationwide Cohort Study

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Background: In this study, we aimed to investigate the effects of osteoporosis medication use and prescription duration on the rates of reprocedures for re-fractures in patients who underwent vertebral augmentation (VA).

Methods: This retrospective cohort study was conducted using data collected from the National Health Insurance Service database of South Korea. Patients aged 50 years or older who underwent VA in 2012 were included in this study. A reprocedure was defined as an additional VA performed for re-fractures during a follow-up period of up to 5 years. Patients were categorized based on medication type (bisphosphonates, selective estrogen receptor modulators [SERMs], calcium supplements, or vitamin D supplements) and prescription duration (incomplete, complete, or absolute complete). The results were statistically analyzed using Cox regression and Kaplan-Meier survival analyses.

Results: Among 9,070 patients included, 678 patients (7.5%) underwent reprocedures for re-fractures, with 41.0% of reprocedures performed within 6 months after VA. The reprocedure rate was higher in patients prescribed calcium or vitamin D supplements (13.3%) than in those prescribed bisphosphonates (7.7%) or SERMs (8.6%). Multivariate analysis revealed that prolonged prescription duration was associated with higher reprocedure rates, reflecting greater disease severity. The absolute complete prescription group showed a 9.07 times higher hazard ratio for reprocedure than the no-medication group.

Conclusions: These findings highlight the potential of osteoporosis medication use and prescription duration as predictive factors for reprocedure rates after VA. Although patients with more severe osteoporosis require longer treatment, adherence to therapy may help reduce the risk of additional interventions over time.

Keywords: *Vertebral augmentation, Medication, Osteoporosis, Vertebral fractures, Reoperation*

Osteoporotic vertebral compression fractures (OVCFs), which are common in older individuals, lead to pain, spinal deformities, and a decreased quality of life.[1] The primary treatment options for OVCFs include conservative management and vertebral augmentation (VA). Among these options, VA, comprising percutaneous vertebroplasty (PVP) or percutaneous kyphoplasty (PKP), is widely used because of its ability to rapidly relieve pain and restore vertebral height.[2] However, it is associated with complications such as re-fracture of the treated vertebrae and subsequent fractures in the adjacent vertebrae.[3,4]

Studies have investigated the incidence of and risk factors for subsequent fractures after the initial OVCF, focusing on factors such as low bone mineral density (BMD), advanced age, cement leakage, and insufficient postoperative management of osteoporosis.[5-7] These studies have

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highlighted the importance of effective osteoporosis treatment to reduce the risk of subsequent fractures. Osteoporosis medications such as bisphosphonates (BP) and selective estrogen receptor modulators (SERMs) lower fracture risk by improving bone strength. Although the role of these medications in preventing fractures has been explored, it is not clear how these treatments affect the likelihood of requiring additional interventions after the initial VA.

Studies focusing on the incidence of and risk factors for reprocedures after VA are scarce.[8] Additionally, there is a lack of consensus regarding reprocedures following VA; however, some studies suggest that inadequate management of osteoporosis, poor adherence to prescribed medications, and advanced disease severity may contribute to higher reprocedure rates.[1,9] Additionally, robust data regarding how the type and duration of osteoporosis treatment influence reprocedure rates are scant. Despite the widespread use of VA in South Korea, a substantial proportion of patients with OVCF do not receive adequate anti-osteoporotic therapy after a procedure, and adherence rates remain low among those prescribed medications.[10] Thus, there is an urgent need for targeted interventions to optimize postoperative care and reduce the burden of additional procedures.

The aim of this study was to investigate whether the use of osteoporosis medications and the duration of therapy affect the rates of reprocedures for subsequent fractures at the adjacent level or re-fracture in patients who had undergone VA. We hypothesized that the type of osteoporosis medication and the duration of treatment substantially affect the incidence of subsequent fractures, necessitating additional surgical interventions.

METHODS

This study was approved by our Institutional Review Board and Ethics Committee of Yonsei University College of Medicine (IRB No. 3-2019-0053), which waived the requirement for patient consent. All experiments were performed in accordance with relevant guidelines and regulations.

Data Acquisition

The National Health Insurance Service (NHIS) is a public medical insurance system in the Republic of Korea covering most of the Korean population (over 50 million) receiving various treatments; however, it does not cover cosmetic surgeries and service claims through specific insurance for traffic or industrial accidents. The NHIS established the National Health Insurance Sharing Service (NHISS) to improve the convenience of access and utilization of data for users, via an application for National Health Information data provision to share research results. The NHISS supports research in various fields such as society, economy, environment, and industry, as well as policy and academic research in the health and medical fields based on evidence, by providing sample research databases, customized research of the databases, and disease indicators.[11] Information regarding diagnoses, prescriptions, and procedure codes based on the International Classification of Diseases, 10th Revision (ICD-10) can be specified and recorded as per an individual's unique identification number; through this approach, information can be followed up within a set period. We used the NHIS cohort database to extract information on patients diagnosed with vertebral fractures requiring VA, such as PVP and PKP, between January 1, 2006, and December 31, 2017.

Enrolled Patients' Definition

This retrospective cohort study was conducted to investigate subsequent vertebral fractures requiring reprocedures in patients aged 50 years or older who experienced their first vertebral fracture in 2012. The wash-out period was defined from January 1, 2006, to December 31, 2011, during which patients who met any of the following criteria were excluded from the study: patients with procedure codes for PVP or PKP (N0471, N0472, N0473, and N0474); patients with diagnosis codes for vertebral fractures (S220, S221, S320, M484, and M485); and patients prescribed medications for osteoporosis at least once.

Subsequently, patients who underwent PVP or PKP for vertebral fractures between January 1, 2012, and December 31, 2012, were enrolled in the study if they satisfied all of the following criteria: patients aged ≥ 50 years with diagnosis codes for vertebral fractures (S220, S221, S320, M484, and M485); patients with at least 1 prescription code for magnetic resonance imaging (HE110, HE210, HE501, HE111, and HE511); patients with procedure codes for PVP or PKP (N0471, N0472, N0473, and N0474); and patients without diagnosis codes for pathological fractures (M800, M808, Z87.311, M844, M845, and M846) or multiple myeloma (C900, C901, C902, and C903). Patients who met these criteria were defined as those diagnosed with a vertebral fracture and who underwent VA for the first time in 2012.

Definition of Reprocedure and Classification of Patients

Based on ICD-10 diagnosis codes, during the follow-up of patients who underwent PVP or PKP for vertebral fractures, if a subsequent vertebral fracture occurred that required another PVP or PKP procedure, the event was

Table 1. Baseline Characteristics of the Study Participants According to Medication Use after Index Vertebral Augmentation

Variable	Total (n=9,070)	No medication (n=3,289)	BP (n=5,125)	SERM (n=326)	Teriparatide (n=36)	Calcium or vitamin D (n=294)	*p*-value
Age (yr)	74.81 ± 9.45	74.90 ± 10.04	74.80 ± 9.04	74.42 ± 9.15	76.00 ± 7.45	74.29 ± 10.10	0.279
Age group (yr)							< 0.001*
50–59	668 (7.36)	292 (8.88)	324 (6.32)	21 (6.44)	1 (2.78)	30 (10.20)	
60–69	1,834 (20.22)	656 (19.95)	1,044 (20.37)	72 (22.09)	4 (11.11)	58 (19.73)	
70–79	3,395 (37.43)	1,099 (33.41)	2,042 (39.84)	130 (39.88)	22 (61.11)	102 (34.69)	
≥ 80	3,173 (34.98)	1,242 (37.76)	1,715 (33.46)	103 (31.60)	9 (25.00)	104 (35.37)	
Sex							< 0.001*
Male	3,230 (35.61)	1,177 (35.79)	1,955 (38.15)	0	9 (25.00)	89 (30.27)	
Female	5,840 (64.39)	2,112 (64.21)	3,170 (61.85)	326 (100.00)	27 (75.00)	205 (69.73)	
Charlson Comorbidity index (score)	2.92 ± 2.46	3.09 ± 2.59	2.80 ± 2.36	2.89 ± 2.40	2.67 ± 2.11	3.25 ± 2.57	0.122
Myocardial infarction	380 (4.19)	150 (4.56)	205 (4.00)	12 (3.68)	3 (8.33)	10 (3.40)	0.435
Congestive heart failure	1,092 (12.04)	425 (12.92)	575 (11.22)	40 (12.27)	4 (11.11)	48 (16.33)	0.029*
Peripheral vascular disease	2,047 (22.57)	762 (23.17)	1,135 (22.15)	73 (22.39)	6 (16.67)	71 (24.15)	0.673
Cerebrovascular disease	2,041 (22.50)	815 (24.78)	1,093 (21.33)	60 (18.40)	7 (19.44)	66 (22.45)	0.002*
Dementia	1,217 (13.42)	473 (14.38)	655 (12.78)	41 (12.58)	8 (22.22)	40 (13.61)	0.134
Chronic obstructive pulmonary disease	3,739 (41.22)	1,345 (40.89)	2,122 (41.40)	130 (39.88)	17 (47.22)	125 (42.52)	0.878
Rheumatologic disease	8 (0.09)	3 (0.09)	5 (0.10)	0	0	0	0.959
Peptic ulcer disease	3,365 (37.10)	1,207 (36.70)	1,895 (36.98)	133 (40.80)	15 (41.67)	115 (39.12)	0.557
Mild liver disease	3,162 (34.86)	1,225 (37.25)	1,719 (33.54)	107 (32.82)	11 (30.56)	100 (34.01)	0.011*
Diabetes without chronic complication	3,243 (35.76)	1,224 (37.21)	1,757 (34.28)	123 (37.73)	11 (30.56)	128 (43.54)	0.002*
Diabetes with chronic complication	967 (10.66)	357 (10.85)	522 (10.19)	45 (13.80)	4 (11.11)	39 (13.27)	0.145
Hemiplegia or paraplegia	152 (1.68)	63 (1.92)	73 (1.42)	6 (1.84)	0	10 (3.40)	0.059
Renal disease	294 (3.24)	131 (3.98)	125 (2.44)	12 (3.68)	1 (2.78)	25 (8.50)	< 0.001*
Any malignancy including leukemia and lymphoma	1,047 (11.54)	402 (12.22)	578 (11.28)	31 (9.51)	2 (5.56)	34 (11.56)	0.352
Moderate or severe liver disease	95 (1.05)	54 (1.64)	37 (0.72)	2 (0.61)	0	2 (0.68)	0.001*

Table 1. Continued

Variable	Total (n=9,070)	No medication (n=3,289)	BP (n=5,125)	SERM (n=326)	Teriparatide (n=36)	Calcium or vitamin D (n=294)	*p*-value
Metastatic solid tumor	164 (1.81)	76 (2.31)	78 (1.52)	5 (1.53)	0	5 (1.70)	0.097
Acquired immune deficiency syndrome/HIV	4 (0.04)	2 (0.06)	2 (0.04)	0	0	0	0.971
Boby mass index (kg/m^2)	23.67 ± 3.49	24.05 ± 3.47	23.41 ± 3.45	24.22 ± 3.55	22.68 ± 3.99	23.70 ± 3.68	< 0.001*
Current smoking	799 (8.81)	253 (7.69)	501 (9.78)	8 (2.45)	4 (11.11)	33 (11.22)	< 0.001*
Heavy drinking	589 (6.49)	218 (6.63)	335 (6.54)	8 (2.45)	1 (2.78)	27 (9.18)	0.010*
Walking over 3 days a week	3,056 (33.69)	1,127 (34.27)	1,752 (34.19)	96 (29.45)	14 (38.89)	67 (22.79)	0.001*
Duration of medication (mo)	10.31 ± 3.94	0.00 ± 0.00	10.76 ± 4.13	7.20 ± 9.47	1.0 ± 0.9	10.78 ± 4.41	< 0.001*

Values are presented as mean ± standard deviation or number (%).
BP: bisphosphonate, SERM: selective estrogen receptor modulator.
*Statistical significance with a *p*-value < 0.05.
The *p*-values were calculated using the Student *t*-test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate.

termed a reprocedure. We defined patients who met all of the following criteria as patients with re-fracture requiring reprocedure and followed them for up to 5 years, until December 31, 2017: patients with at least 1 diagnosis code for vertebral fractures (S220, S221, S320, M484, and M485) after the index date; patients with at least 1 prescription code for magnetic resonance imaging (HE110, HE210, HE501, HE111, and HE511) after the index date; patients with additional diagnosis codes for PVP or PKP (N0471, N0472, N0473, and N0474) after the index date; and patients who underwent BMD testing within 1 month of the index date. The date of the first VA, such as PVP and PKP, for vertebral fractures served as the index date for the retrospective cohort. Conversely, patients with diagnosis codes indicating pathological fractures (M800, M808, Z87.311, M844, M845, and M846) or multiple myeloma (C900, C901, C902, and C903) were excluded.

Patients who did not receive osteoporosis medications within 6 months of the index date were included in the no osteoporosis medication group. It was assumed that patients in this group did not have sufficiently low BMD levels to warrant the prescription for osteoporosis medications. Additionally, data regarding baseline characteristics such as age, sex, body mass index (BMI), smoking behavior, walking exercise frequency, and Charlson Comorbidity Index (CCI) as variables were collected.

Definition of Prescription Duration for Osteoporosis Medication

Patients were categorized based on the duration of osteoporosis medication prescriptions from the index date until the time of reprocedure for re-fracture. The "incomplete prescription group" comprised patients prescribed medications for less than 50% of the period, the "complete prescription group" comprised those prescribed medications for 50%–90% of the period, and the "absolute complete prescription group" comprised patients prescribed medications for more than 90% of the period. Here, a stricter definition of prescription duration indicated that patients with more severe osteoporosis likely required more intensive management, resulting in a higher frequency of medication prescriptions.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 21.0 (IBM Corp.). Differences in continuous and non-continuous variables between the groups were analyzed using Student *t*-test and chi-square test. Associations of osteoporosis drug use and prescription duration with various factors such as age, sex, CCI, and BMI were evaluated using Cox regression analysis. Kaplan-Meier curves were

used to assess cumulative survival rates. Statistical significance was set at $p < 0.05$.

RESULTS

Demographic Data and Reprocedure Rates According to Osteoporosis Medications

Of the 9,070 patients included in the study, 3,289 (36.3%) did not receive osteoporosis medications. Significant differences in osteoporosis medications used after VA were observed according to age, sex, and certain CCI items (Table 1). A total of 36 patients received teriparatide; the reprocedure rate was 16.7% (6 patients), with 4 patients (11.1%) undergoing reprocedures within 6 months. The average treatment duration was only 0.1 month. Given this extremely short treatment duration, it was difficult to include teriparatide users in a meaningful cohort-based comparison with other osteoporosis medications. Therefore, this group was excluded from the main analysis. Among patients who did not receive osteoporosis medications, the reprocedure rate was 6.5%. For patients who received BPs, SERMs, or calcium or vitamin D supplements, the reprocedure rates were 7.7%, 8.6%, and 13.3%, respectively. Significant differences were observed in the reprocedure rates according to administered osteoporosis medications (Table 2). In the comparison of the cumulative incidence rates of reprocedures, no significant difference was observed between patients who received BPs or SERMs and those who did not receive osteoporosis medications. However, patients who received calcium or vitamin D supplements had significantly higher cumulative incidence rates ($p < 0.001$) (Fig. 1).

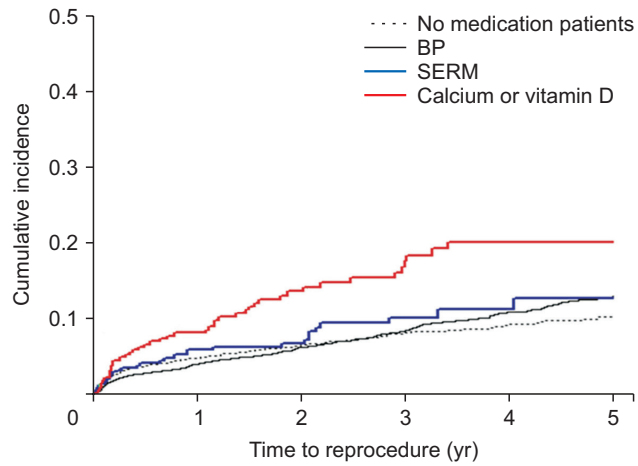

Fig. 1. Cumulative incidence graph of reprocedure rates by osteoporosis medication. BP: bisphosphonate, SERM: selective estrogen receptor modulator.

Table 2. Reprocedure Rates According to Osteoporosis Medication Use after Index Vertebral Augmentation

Variable	Total (n = 9,034)	No medication (n = 3,289)	BP (n = 5,125)	SERM (n = 326)	Calcium or vitamin D (n = 294)	*p*-value
Reprocedure						< 0.001*
No	8,356 (92.5)	3,074 (93.5)	4,729 (92.3)	298 (91.4)	255 (86.7)	
Yes	678 (7.5)	215 (6.5)	396 (7.7)	28 (8.6)	39 (13.3)	
Reprocedure time						< 0.001*
No	8,356 (92.5)	3,074 (93.5)	4,729 (92.3)	298 (91.4)	255 (86.7)	
< 6 mo	278 (3.1)	115 (3.5)	133 (2.6)	14 (4.3)	16 (5.4)	
6–< 12 mo	78 (0.9)	26 (0.8)	45 (0.9)	4 (1.2)	3 (1.0)	
12–< 24 mo	131 (1.4)	37 (1.1)	81 (1.6)	2 (0.6)	11 (3.7)	
24–< 36 mo	97 (1.1)	25 (0.8)	61 (1.2)	6 (1.8)	5 (1.7)	
36–< 48 mo	58 (0.6)	8 (0.2)	45 (0.9)	1 (0.3)	4 (1.4)	
48–< 60 mo	29 (0.3)	4 (0.1)	24 (0.4)	1 (0.3)	0	
≥ 60 mo	7 (0.1)	0	7 (0.1)	0	0	

Values are presented as number (%).
BP: bisphosphonate, SERM: selective estrogen receptor modulator.
*Statistical significance with a *p*-value < 0.05.
The *p*-values were calculated using the chi-square test or Fisher's exact test for categorical variables, as appropriate.

Reprocedure Rate According to the Prescription Duration of Medications

In the comparison of reprocedure rates according to the duration of osteoporosis medication prescriptions, 22% of the patients in the absolute complete prescription group, 11% in the complete prescription group, and 7.8% in the incomplete prescription group underwent reprocedures, showing significant differences. Moreover, when the follow-up period was further divided, patients in the incomplete prescription group continued to undergo reprocedures owing to re-fractures even after 2 years (Table 3). Upon reviewing the cumulative incidence rates of reprocedures, the complete and absolute complete prescription groups had significantly higher reprocedure rates (p = 0.009 and $p < 0.001$, respectively) (Fig. 2).

Multivariate Analysis

Examination of the hazard ratios for variables showing significant differences in demographic data and osteoporosis medications revealed that patients who received BPs had a 1.21 times higher probability of undergoing a reprocedure for re-fractures than those who did not receive osteoporosis medications. Patients who received SERMs and those who received calcium or vitamin D supplements had 1.22 and 2.74 times higher probability of undergoing reprocedures, respectively. Regarding prescription duration, the hazard ratio was 1.22 for the incomplete prescription group and 1.89 for the complete prescription group, with the absolute complete prescription group showing a 9.07 times higher hazard ratio (Table 4).

DISCUSSION

VA is a minimally invasive treatment method that rapidly reduces pain and stabilizes the vertebral body in patients with vertebral fractures. However, one of the complica-

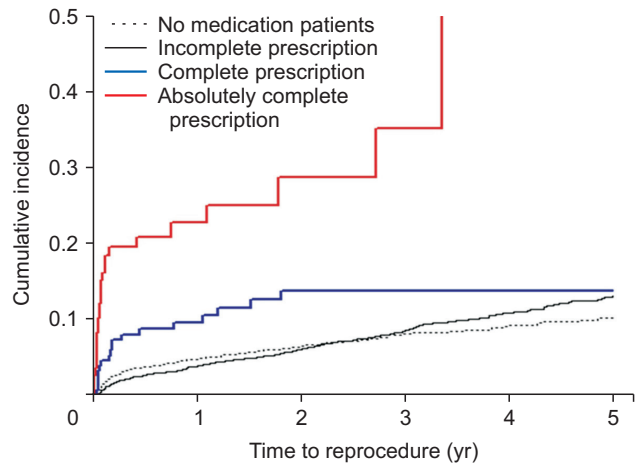

Fig. 2. Cumulative incidence graph of reprocedure rates by prescription compliance.

Table 3. Reprocedure Rate According to Prescription Duration of Medications after Index Vertebral Augmentation

Variable	Total (n = 9,034)	No medication (n = 3,289)	Incomplete (n = 5,492)	Complete (n = 144)	Absolute complete (n = 109)	*p*-value
Reprocedure						< 0.001*
No	8,356 (92.5)	3,074 (93.5)	5,064 (92.2)	130 (89.0)	88 (78.0)	
Yes	678 (7.5)	215 (6.5)	428 (7.8)	14 (11.0)	21 (22.0)	
Reprocedure time						< 0.001*
No	8,356 (92.5)	3,074 (93.5)	5,064 (92.2)	130 (89.0)	88 (78.0)	
< 6 mo	278 (3.1)	115 (3.5)	139 (2.6)	9 (8.3)	15 (17.4)	
6–< 12 mo	78 (0.9)	26 (0.8)	49 (1.0)	2 (1.4)	1 (0.9)	
12–< 24 mo	131 (1.4)	37 (1.1)	89 (1.6)	2 (1.4)	3 (2.8)	
24–< 36 mo	97 (1.0)	25 (0.8)	70 (1.3)	1 (0.7)	1 (0.9)	
36–< 48 mo	58 (0.6)	8 (0.2)	49 (1.0)	0	1 (0.9)	
48–< 60 mo	29 (0.3)	4 (0.1)	25 (0.4)	0	0	
≥ 60 mo	7 (0.1)	0	6 (0.1)	0	0	

Values are presented as number (%).
*Statistical significance with a p-value < 0.05.

Table 4. HRs for Reprocedure Rates by Osteoporosis Medication Use and Prescription Duration after Index Vertebral Augmentation

Variable	Cox proportional hazard model	*p*-value
	Adjusted HR (95% CI)	
Osteoporosis medication		
No medication	1 (Reference)	
BP	1.21 (1.00–1.47)	0.048*
SERM	1.22 (0.75–1.97)	0.042*
Calcium or vitamin D	2.74 (1.88–4.00)	< 0.001*
Prescription duration		
No medication	1 (Reference)	
Incomplete	1.22 (1.01–1.47)	0.042*
Complete	1.89 (1.02–3.49)	0.042*
Absolute complete	9.07 (5.60–14.68)	< 0.001*

HR was adjusted for age, sex, Charlson Comorbidity Index, current smoking, heavy drinking, and walking more than 3 days a week.
HR: hazard ratio, BP: bisphosphonate, SERM: selective estrogen receptor modulator.
*Statistical significance with a *p*-value < 0.05.

tions that can occur after VA is re-fracture in the vertebral bodies adjacent to the one treated with the procedure. According to Jang et al.,[12] although several studies have reported the use of VA for osteoporotic spinal fractures, its effectiveness compared with that of conservative treatment remains controversial. Uppin et al.[13] reported that in 67% of cases, refractures occurred within 1 month after the initial procedure; Li et al.[14] observed that re-fractures primarily occurred within 3 months after the initial procedure and decreased thereafter. Based on data from the NHIS between 2007 and 2018, Kang et al.[9] reported that in patients with OVCF, the cumulative incidence rate of spinal re-fractures over 4 years was 24.4%, with a rapid increase in incidence observed within 3 months after the first fracture. Compared with patients who underwent conservative treatment (22.5%), those who underwent VA (PVP, 36.2%; PKP, 35.8%) had significantly high cumulative incidence rates of re-fractures.[9]

Unlike that in a previous study, in this study, we compared and analyzed the data of patients who underwent reprocedures for re-fractures following the initial VA for spinal fractures according to osteoporosis medication administration. As the study utilized NHIS data, it was not possible to retrieve detailed information such as specific tests used, values per patient, the sites of VA, or the occurrence of re-fractures in adjacent areas after VA. However, among patients who underwent VA, 678 (7.5%) underwent reprocedures for refractures, of whom 278 underwent reprocedures within 6 months, accounting for 41.0% of all patients who underwent reprocedures. This finding suggests that active treatment and caution are required in the early stages after stabilization is achieved following VA.[15]

Compliance with medications for osteoporosis and prescription duration are important factors that affect reprocedure rates. According to a study by Ahn et al.,[10] only 33.5% of patients with osteoporosis in South Korea receive osteoporosis medication and only 41.9% of patients diagnosed with osteoporotic fractures receive osteoporosis medication within 12 months. Furthermore, among patients taking osteoporosis medication, the rate of medication adherence of over 80% was just 33.2% over 1 year and 21.5% over 2 years. Siris et al.[16] performed a comparative analysis of studies examining the relationship between osteoporosis medication compliance and fracture rates and concluded that patients with good compliance (medication compliance > 80%) had significantly reduced fracture rates.

One of the most challenging aspects of this study was addressing the issue of medication adherence. Given the inherent limitations of NHIS data, it was not possible to determine the actual level of patient compliance with osteoporosis medications. As a result, we had no choice but to classify patients based on the duration of prescriptions recorded by physicians over the study period. This approach involves an unavoidable assumption that patients with longer prescription durations either had more severe osteoporosis or demonstrated better medication adherence, which in turn prompted physicians to continue prescribing treatment. If BMD values had been available within the NHIS data, we could have more accurately controlled for osteoporosis severity and minimized this confounding factor. However, in the absence of such data, we were compelled to interpret the prescription groups as representative of patients with either more severe osteoporosis or those who maintained consistent treatment over time.

In our analysis of reprocedure rates based on prescription duration, the rates of reprocedures within 6 months were higher in the complete (8.3%) and absolute complete (17.4%) prescription groups compared with the incomplete prescription group (2.6%) and the group not prescribed osteoporosis medications (3.5%). Moreover, in the multivariate analysis, the absolute complete prescription group had 9.07 times higher risk of re-fracture. These findings suggest that the higher cumulative reprocedure rates observed in the absolute complete and complete

groups likely reflect the fact that these patients had more severe osteoporosis compared to other groups. However, it is noteworthy that over time, the frequency of reprocedures appeared to decrease more substantially in the absolute complete and complete groups relative to the other groups. This trend suggests that continued osteoporosis management and sustained treatment may help reduce the long-term risk of reprocedures in these patients.

Ongoing studies continue to report the effectiveness of various types of available osteoporosis medications. However, as the effects of osteoporosis medications vary depending on the patient's condition and fracture site, careful consideration is needed before administration. According to the UK National Osteoporosis Guideline Group guidelines, considering cost-effectiveness and patient preference, BPs are recommended as first-line medications for osteoporosis treatment, with denosumab, ibandronate, and raloxifene as alternatives.[17] According to the 2020 American Association of Clinical Endocrinology guidelines, alendronate, risedronate, zoledronate, and denosumab should be considered first-line medications for osteoporosis treatment unless there are specific contraindications, as they are effective for overall fracture prevention.[18,19] While these medications are widely used and considered foundational treatments for osteoporosis, there has been growing interest in anabolic agents such as teriparatide and romosozumab, which directly stimulate bone formation.[20] Recent studies have highlighted their potential advantages, particularly in patients with severe osteoporosis or at a high risk of fractures, emphasizing their importance as first-line options in certain scenarios.[21] However, despite this growing interest, BPs, SERMs, calcium supplements, and vitamin D supplements continue to be the most commonly prescribed treatments in many medical institutions, largely owing to their established efficacy, cost-effectiveness, and widespread accessibility.[22,23]

The observation that patients who received calcium or vitamin D supplements had a higher probability of undergoing a reprocedure for re-fractures than those treated with BPs or SERMs may initially seem counterintuitive. Calcium and vitamin D supplements are generally regarded as supplementary treatments for enhancing bone health, particularly when co-administered with other osteoporosis medications.[24] However, their standalone effects on reprocedure prevention are limited, as supported by the findings of previous studies showing modest reduction in fracture risk when these supplements are used without additional pharmacological agents. One possible explanation for this finding is that calcium or vitamin D supplements alone may have been prescribed to patients with relatively mild osteoporosis or patients ineligible for BP or SERM therapy because of contraindications or comorbidities.[25] Although these patients had relatively milder disease, their continued risk of reprocedures may be attributed to inadequate osteoporosis medication management, consistent with previous studies demonstrating the insufficiency of calcium or vitamin D monotherapy in preventing osteoporotic complications. Conversely, the absence of a significant difference in reprocedure rates between the BP and SERM groups in our multivariate analysis may suggest that the therapeutic efficacy of these agents is limited in patients with advanced osteoporosis, where structural bone integrity is already severely compromised. This finding underscores the need for future research focusing on anabolic agents to evaluate their potential benefits in this high-risk population.[26,27]

Evaluating the relationship between anabolic agent use and reprocedure rates is also of significant importance in this study. However, among patients who received teriparatide, the reprocedure rate was 16.7% (6 patients), with 4 patients (11.1%) undergoing reprocedures within 6 months. The average treatment duration was only 0.1 month. This short duration likely reflects poor medication adherence, which may have resulted from the economic burden of out-of-pocket costs and the inconvenience associated with daily subcutaneous injections, despite physicians prescribing anabolic agents for patients with more severe osteoporosis.[28] Consequently, the combination of severe osteoporosis and insufficient treatment adherence may have contributed to the higher early reprocedure rates observed in this group.

In conclusion, this study provides important clinical insights into the relationship between osteoporosis medication use and reprocedure rates following VA. Unlike previous studies that primarily focused on the incidence of subsequent fractures, our study examined not only the types of medications used but also prescription duration and inferred patient adherence, with specific focus on reprocedure rates as the primary outcome measure. These findings offer valuable real-world evidence to guide postoperative patient management and inform future pharmacologic treatment strategies following VA.

This study has certain limitations. First, the use of NHIS data makes it difficult to collect detailed information regarding several variables. Therefore, if precise BMD values, spinal levels where VA was performed or fractures occurred, and additional information regarding other variables could be identified, it would be possible to more accurately determine the severity of osteoporosis and the occurrence of re-fractures in adjacent areas, thereby de-

riving more precise results. Second, as the NHIS started reimbursing anabolic agents in 2018,[29] it was difficult to verify the results of using anabolic agents as only data from before 2017 were included in this study. Also, our study was initiated in 2021, only data up to 2017 could be requested and obtained, and it was unavoidably limited to that timeframe. For this reason, we are also planning future studies using updated NHIS data involving anabolic agents, which will likely be more helpful in setting treatment directions by comparing anabolic agents with anti-resorptive agents. Third, the inability to reflect current treatment trends with newer osteoporosis medications is a key limitation of this study. As mentioned before, denosumab and romosozumab were not in use during the study period covered by the NHIS data, and even teriparatide, which was available at the time, was subject to strict national insurance criteria. Consequently, most prescriptions were likely made on an out-of-pocket basis, making it difficult to accurately capture the actual usage patterns of these agents within the NHIS data.

Despite these limitations, we consider that our cohort study, which included a 5-year survival analysis of patients who underwent VA in 2012, provides valuable clinical and epidemiological insights. While evaluating the efficacy of newer osteoporosis treatments is undoubtedly important for establishing current therapeutic strategies, it is equally critical to demonstrate the real-world effectiveness of conventional osteoporosis medications that remain widely used in clinical practice. To reduce potential confounding and enhance the validity of our findings, we applied a stringent washout period, covering half of the total data extraction timeframe, prior to defining the final study cohort. By restricting the study period to before 2017, we minimized bias related to the introduction of anabolic agents, which began gaining widespread reimbursement and clinical adoption after 2018 in South Korea. This restriction ensured that our findings primarily reflected the effects of traditional osteoporosis treatments without the confounding influence of newer therapies.

In patients who underwent VA for vertebral fractures, the incidence of reprocedures for re-fractures varied according to the use of osteoporosis medications. Additionally, when classified according to the duration of osteoporosis medication prescriptions, patients who required longer periods of medication prescriptions had a higher incidence of reprocedures for refractures. However, maintaining proper medication usage can reduce the incidence of reprocedures.

CONFLICT OF INTEREST

Kyung-Soo Suk is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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