Incidence and Risk of Venous Thromboembolism Among Taiwan Osteoporotic Fracture Population under Osteoporosis Pharmacological Treatments

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Context: There was no clear evidence for the association between oral bisphosphonates or raloxifene and venous thromboembolism (VTE). There might also be ethnic differences in VTE risk.

Objective: The purpose of this study was to compare the incidence and risk of VTEs for different classes of osteoporosis drugs in the Taiwanese osteoporotic fracture population.

Design: This was a retrospective cohort study from 2003 to 2007, with up to 6 years follow-up.

Setting: Enrollees were participants in Taiwan National Health Insurance.

Patients: Patients older than 50 years who had vertebral or hip fractures and were new to osteoporosis therapy were recruited.

Intervention: Patients were classified into the alendronate, calcitonin, or raloxifene group according to exposure after follow-up.

Main Outcome Measure: The primary outcome of our study was all incident VTEs, including deep vein thrombosis and pulmonary embolism. Cox proportional hazard models were used to compare the relative VTE risk among alendronate, raloxifene, and calcitonin groups under an on-treatment scenario.

Results: There were 25 443, 9642, and 31 900 patients in the alendronate, raloxifene, and calcitonin groups, and the mean age was 74.5 years (SD, 9.6). The incidence of VTE in the alendronate, raloxifene, and calcitonin groups was 11.2, 8.5, and 18.8 per 10 000 person-years. Results from Cox analyses showed that alendronate or raloxifene recipients did not have a higher risk for VTE than calcitonin recipients (adjusted hazard ratio for alendronate, 0.84; 95% confidence interval, 0.47–1.51; adjusted hazard ratio for raloxifene, 0.64; 95% confidence interval, 0.33–1.28).

Conclusion: This retrospective analysis found that the incidence of VTE in Taiwanese patients with osteoporosis was low, and the risk of VTE was similar across alendronate, raloxifene, and calcitonin recipients in patients with osteoporotic fractures who were new to osteoporosis therapy. **(*J Clin Endocrinol Metab* 99: 1599–1607, 2014)**

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Abbreviations: CI, confidence interval; DDD, defined daily dose; DVT, deep venous thromboembolism; HR, hazard ratio; HRT, hormone replacement therapy; ICD-9, International Classification of Diseases, 9th ed.; IRR, incidence rate ratio; NHIRD, National Health Insurance Research Database; PE, pulmonary embolism; VTE, venous thromboembolism.

Osteoporosis is a silent disease characterized by decreased bone mass, deterioration of bone tissue and disruption of bone architecture, compromised bone strength, and increased fracture risk (1). Moreover, patients with osteoporosis may be more susceptible to venous thromboembolisms (VTEs) due to aging. Furthermore addition, fractures, immobilization, hospitalization, and surgery, all of which are known risk factors for VTE, are prevalent during aging (2–5). Results from a large British cohort also showed that women with osteoporosis may have a 75% higher VTE risk than women without osteoporosis (6).

Besides osteoporosis itself, the literature addresses adverse cardiovascular events associated with bisphosphonates and raloxifene, which are the mainstays of pharmacological therapy for osteoporosis in the United States and Europe (7, 8). Significantly higher rates of serious atrial fibrillation events have been found in once-yearly zoledronate recipients than om recipients (9), but no clear associations were found in recent observational studies using a health insurance database (10–13). Nevertheless, it was reported that use of bisphosphonates was associated with an increased risk of superficial phlebitis (14, 15). As for raloxifene, results from a clinical trial found that it was associated with an increased risk of deep venous thromboembolism (DVT) and pulmonary embolism (PE) in postmenopausal women (16) and that finding has been further confirmed by a recent meta-analysis (17). However, no clinically significant adverse cardiovascular effects were reported for calcitonin (7).

The association between the use of oral bisphosphonates or raloxifene and VTEs has been examined in real-life settings. Results from Danish population-based studies showed that alendronate and raloxifene recipients had a higher risk for VTE than the general population, but the risk increased before the start of treatment, suggesting that the association might be related to osteoporosis itself (18, 19). In addition, a recent British study found that alendronate recipients did not have a higher risk for VTE than women with untreated osteoporosis (6). Therefore, there was no obvious evidence for the association between oral bisphosphonates or raloxifene and VTE in Western countries. However, it is not clear whether the baseline VTE risk in different races or ethnicities might have affected the relationships between osteoporosis treatments and VTE risk. In our previous work, we showed that the incidence of VTEs among the general population of Taiwan was only one seventh of that among Caucasians (20). Whether the risk of VTE among the Taiwanese osteoporotic population undergoing alendronate or raloxifene treatment differs from that of people taking other osteoporosis drugs is an important issue that warrants further investigation. Since 2002, the reimbursement scheme in Taiwan's Bureau of National Health Insurance has restricted the use of osteoporosis drugs (alendronate, raloxifene, and calcitonin nasal spray) to patients who have already experienced osteoporotic vertebral or hip fractures, thus enabling us to assess the incidence and risk of VTE in the Taiwanese osteoporotic fracture population, who are known to have more risk factors for VTE. Our study objectives were, first, to provide general information on the incidence of VTE in patients with treated and untreated osteoporotic fractures and then to compare the incidence and risk of VTE of different classes of osteoporosis drugs. Calcitonin, which is known not to be associated with VTE, was selected as the control drug.

Subjects and Methods

Data source

Datasets were obtained from Taiwan's National Health Insurance Research Database (NHIRD). Taiwan launched a single-payer National Health Insurance program in 1995, and by 2007, 99% of the population was enrolled. The NHIRD comprises demographic data of enrollees, information on health care professionals and medical facilities, and service records and expenditure claims from inpatient, ambulatory care, and contracted pharmacies for reimbursement purposes (21). Large computerized databases are provided to scientists in Taiwan for research purposes.

Study design and population

This study is a retrospective cohort analysis that included treatment-naive patients aged older than 50 years who had new osteoporotic vertebral or hip fractures (International Classification of Diseases, 9th ed. [ICD-9], CM codes 733.13, 733.14, 805, and 820) and who were new to osteoporosis drug therapy between 2003 and 2007. Patients were considered as new users if they did not have any osteoporosis drug prescription (alendronate, raloxifene, or calcitonin nasal spray) during the baseline period. The index date was defined as the first date on which patients received a treatment after the new osteoporotic fractures. The baseline period was defined as the 1 year before the index date. Patients were excluded if they had any prior vertebral/hip fractures during the baseline period. Further, we excluded patients with conditions that may be associated with osteoporosis severity: patients whose index osteoporotic fracture was associated with a car accident or high impact trauma (ICD-9 codes E810–E819, E881–E883, and E8841) or those with a diagnosis of Paget disease (ICD-9 code 731.0) or malignant neoplasm (ICD-9 codes 140–208) during the baseline period. Finally, we excluded patients with a history of DVT (ICD 9 codes 4511, 4512, 4519, 4532, 4534, 4538, 4539, and 45181) or PE (ICD 9 code 4151).

Incidence of VTE in the treated and untreated cohorts

Patients who ever received any osteoporosis drug were regarded as the treated group. We further assembled a cohort of

patients aged older than 50 years who experienced a osteoporotic vertebral/hip fracture and had no prior VTE, but who did not receive the study drugs (untreated osteoporotic cohort). We adopted an intent-to-treat scenario when comparing the VTE incidence between treated and untreated groups; ie, all patients were followed from the time a fracture occurred or treatment was initiated until VTE, death, or the end of follow-up.

Exposure to osteoporosis drugs

During the study period, drugs reimbursed for Taiwanese patients with osteoporosis were alendronate, calcitonin, and raloxifene. In addition, during the study period, alendronate was the only oral bisphosphonate reimbursed for patients with osteoporosis. Total supply in days and quantity of drugs were estimated from pharmacy claims originating from the inpatient and outpatient settings and contracted pharmacies of the NHIRD. In the primary analysis for VTE risk, we adopted the on-treatment scenario; ie, patients were censored if they switched to other treatment groups after treatment initiation or were not compliant in taking their drug (last date covered by drug plus 30 days, allowing for a 30-day gap between prescriptions). Patients were classified into the alendronate group, raloxifene, or calcitonin nasal spray group according to the first exposure after their osteoporotic fractures. Calcitonin was selected as the reference drug.

Outcomes and covariates

The primary outcome of our study was all incident symptomatic VTEs, including DVTs and PEs, in 3 treatment groups. DVTs and PEs were also evaluated separately as the secondary outcomes. The VTE events were identified from the inpatient and outpatient claims and to avoid misdiagnoses, we only selected events that met all of the following criteria: (1) the discharge diagnosis was DVT or PE; (2) the patient received a course of sc or iv anticoagulation therapy with unfractionated heparin or surgical thrombectomy during hospitalization and continued oral warfarin therapy after discharge; and (3) a length of stay of at least 3 days, unless the patient died. We also identified patients with the outcome events through outpatient claims: (1) the principal diagnosis was DVT or thrombophlebitis and (2) the patient received a course of sc anticoagulation therapy with low-molecular-weight heparin and continued oral warfarin therapy. The same criteria were used in previous studies that investigated VTE risk in Taiwan (20, 22). Patient demographic information was identified at treatment initiation, and other covariates were determined by medical and pharmacy claims within 1 year before the index date. The following covariates were included in the assessment of the study outcomes: demographic characteristics (age and sex), income level (using insurance fee as the surrogate), osteoporosis-related factors (osteoporosis and kyphosis), fracture history (all nonvertebral fractures except radius/ulna and hip fracture), major orthopedic operations (close and open reduction of fracture with internal fixation, joint replacement of the lower extremity and other procedures on the spine), comorbid conditions that may increase fracture risk (Alzheimer disease, asthma, diabetes, ischemic stroke, history of falls, and rheumatic arthritis), comorbid conditions that could increase VTE risk (ischemic heart disease, chronic lung disease, ischemic stroke and intracerebral hemorrhage, degenerative and paralytic neurologic disease, and varicose veins of the lower extremities) and comedications that were associated with fracture risk (antiepileptics, β-blockers, benzodiazepines, glucocorticoids, nonsteroidal anti-inflammatory disease/cyclooxygenase 2 agents, hormone replacement therapy (HRT), selective serotonin reuptake inhibitors, thyroid drugs, and sleep/hypnotic agents).

Statistical analysis

Differences between alendronate vs calcitonin and raloxifene vs calcitonin in patient demographic information and other covariates were determined either by ANOVA or Pearson χ^2 test. Then, we used the multivariate Cox proportional hazards model to compare the relative VTE risk among different treatment groups. In the second analysis, the propensity score for each comparison group (alendronate vs calcitonin and raloxifene vs calcitonin) was computed, respectively, using multivariate logistic regression analysis that included all baseline covariates. Using the Greedy $5 \rightarrow 1$ digit technique, the comparison groups were then matched by the propensity score in a 1:1 ratio (23). Further, the Kaplan-Meier method was used to present event rates and time-to-event curves.

We performed a series of sensitivity and subgroup analyses to test the robustness of our findings from the main analyses. First, we extended the duration that patients received therapy to the last date covered by the drug plus 90 days. Second, to further observe sufficient effects from medications, we excluded short-term users if they did not have at least 3 prescriptions of the study drugs. Third, we further estimated the cumulative doses that patients received during the follow-up period in each treatment group according to the World Health Organization defined daily dose (DDD), and cumulative doses were classified into 6 months (180 DDDs), 6 months to 1 year (180−365 DDDs), and more than 1 year (>365 DDDs) equivalents. Fourth, to account for healthy user bias, we examined our results in an intent-to-treat scenario, by assuming patients' exposure to the treatment continued to death or end of follow-up (December 31, 2009). Fifth, we examined the results in series subgroups, which were known to have different VTE risks (female subjects only, patients with a diagnosis of osteoporosis, and different age and fracture risk subgroups), whereas patients with varicose veins, those who had HRT, and those who ever received aspirin or ticlopidine were excluded. Finally, we examined our results using inpatient outcomes only.

Results

Baseline characteristics of osteoporosis drug users

From 2003 to 2007, we identified 80 993 patients with new vertebral/hip fractures who had been exposed to osteoporosis drugs after a fracture occurred. After exclusion of 6234 patients who had cancer or Paget disease, 590 patients who had previous VTE events, 5482 patients who had used osteoporosis drugs during the baseline period, and 349 patients without complete insurance coverage or data, 66 985 patients remained in our study cohort. In our primary analysis, there were 25 443, 9642, and 31 900 patients in the alendronate, raloxifene, and calcitonin groups, respectively (Figure 1).

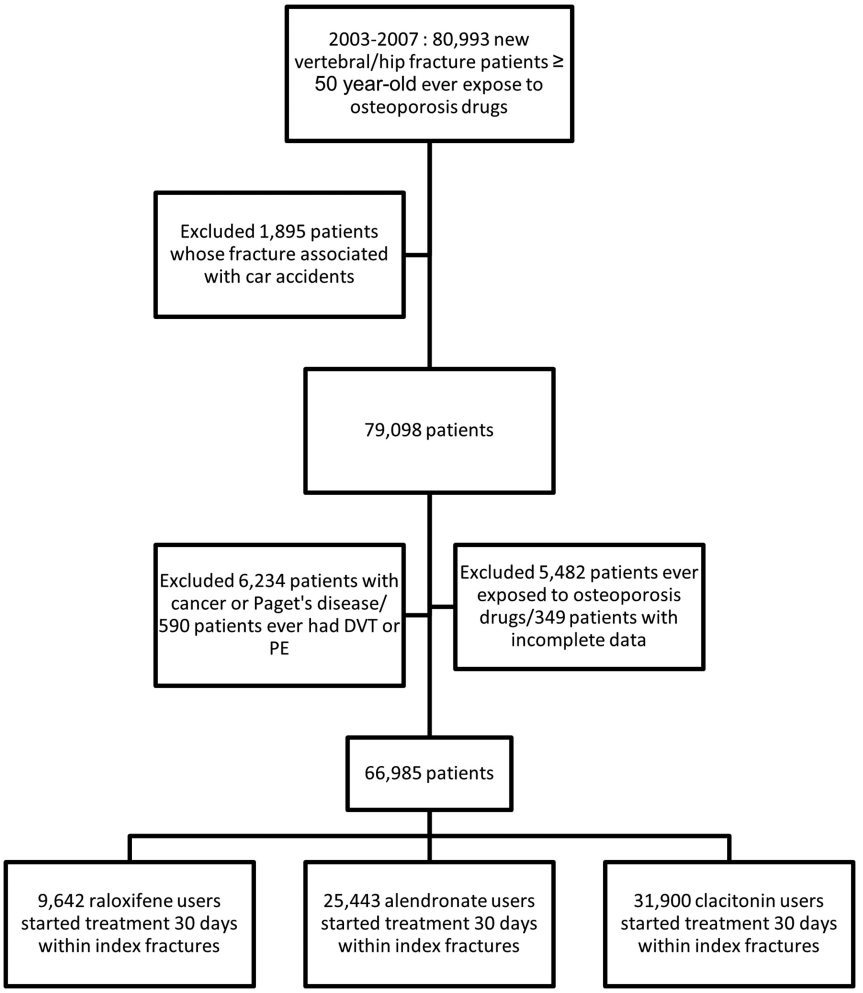

Figure 1. Study inclusion flowchart.

In general, the distribution of baseline characteristics was not even across the 3 treatment groups (Table 1). Calcitonin users tended to be older, had predominantly vertebral fracture, and were less likely to have a history of other nonvertebral fractures but more likely to have used benzodiazepines, steroids, thiazides, and thyroid drugs. Alendronate and raloxifene users were more similar in age, comorbid conditions, and comedication exposure (Table 1). To account for the differences between groups in baseline characteristics, we further matched 20 489 patients in the alendronate and calcitonin groups and 8034 patients in the raloxifene and calcitonin groups by the propensity score. After matching by propensity score, the distribution of baseline characteristics was even in the alendronate vs calcitonin and raloxifene vs calcitonin comparisons.

Incidence of VTE in the treated and untreated cohorts

The incidence of VTE is presented in Table 2. Overall, the incidence of VTE in the treated groups, including the alendronate, raloxifene, and calcitonin groups, was slightly higher than that in the untreated group. Nevertheless, the VTE incidence increased with age in the treated and untreated groups, and the incidence was highest in patients older than 80 years. Further, male patients had slightly higher VTE incidence than women in the alendronate group (12.3 vs.9.7 per 10 000 person-years). However, the incidence of VTE in women in the calcitonin and untreated groups was comparable.

Risk of VTE for alendronate or raloxifene compared with that for calcitonin

In the primary analysis, we did not find a significantly higher VTE risk among alendronate or raloxifene recipients than among calcitonin recipients (adjusted hazard ratio [HR] for alendronate, 0.84; 95% confidence interval [CI], 0.47–1.51; adjusted HR for raloxifene, 0.64; 95% CI, 0.33–1.28). Similar results were found when we changed the outcome to DVT or PE only (Table 3). In addition, the differences in risk for VTE, DVT, or PE were not significant after matching comparison groups by propensity scores. In the multivariate Cox model, we found that age and varicose veins were the only 2 factors that were significantly associated with elevated VTE risk (adjusted HR for age, 1.02; 95% CI, 1.00–1.03; adjusted HR for varicose veins, 5.35; 95% CI, 1.29–22.11).

The incidence of VTE in the alendronate, raloxifene, and calcitonin groups was 11.2, 8.5, and 18.8 per 10 000 person-years when the on-treatment scenario was adopted (Table 3). When outcomes were analyzed with time-to-event methods, the Kaplan-Meier analysis did not find a significant difference between the groups in VTE rate during the 6-year follow-up period ($P = .3180$, log rank test) (Figure 2). There was no significant difference between the 3 groups in DVT- or PE-only outcome ($P = .1711$, DVT log rank test; $P = .8930$, PE log rank test). Results of sensitivity and subgroup analyses are summarized in Table 4. The risk for VTE was similar in alendronate vs calcitonin and raloxifene vs calcitonin comparisons in the primary analysis when we extended the follow-up by 90 days and excluded short-term users. Similar patterns of results

Table 1. Baseline Characteristics of New Osteoporosis Drug Users

	Alendronate (n = 25 443)	Raloxifene (n = 9642)	Calcitonin (n = 31 900)	*P* Value
Mean age (SD), y	74.2 (9.6)	73.8 (9.7)	74.9 (9.5)	<.0001
Female sex, %	78.0	98.8	79.7	<.0001
Index osteoporotic fracture, %				<.0001
Hip	28.7	32.1	9.0	
Vertebral	71.3	67.9	91.0	
Comorbid conditions, %				
Osteoporosis	78.9	79.8	78.5	.0193
Other nonvertebral fracture	19.9	18.5	15.8	<.0001
Major orthopedic surgery	55.9	23.2	20.9	<.0001
Alzheimer disease	7.5	7.3	6.9	.0576
Diabetes mellitus	24.6	27.3	24.9	<.0001
Parkinsonism	5.7	5.3	5.9	.0458
Renal insufficiency	6.7	8.6	9.2	<.0001
Hyperlipidemia	18.1	18.4	16.4	<.0001
Systemic lupus erythematosus	1.7	1.9	1.6	.1556
Rheumatoid arthritis	3.5	3.9	3.2	.0033
Hypertension	57.1	58.6	57.5	.0455
Heart failure	8.4	9.1	10.3	<.0001
Ischemic heart disease	23.6	22.4	25.0	<.0001
Chronic lung disease	23.6	20.1	24.7	<.0001
Ischemic stroke and intracerebral hemorrhage	10.3	9.5	10.2	.0597
Degenerative and paralytic neurologic disease	18.0	17.3	18.0	.2074
Varicose veins of lower extremities	0.6	0.5	0.6	.9710
Comedications, %				
Antiepileptic drugs	8.8	8.5	8.8	.5969
β-Blockers	27.1	28.7	28.5	.0002
BZDs	51.8	52.0	53.7	<.0001
Glucocorticoids	27.5	25.3	29.5	<.0001
HRT	3.5	3.9	3.2	.0020
COX2	24.7	22.8	22.1	<.0001
SSRIs	3.5	3.5	3.4	.9450
Thiazides	7.5	8.3	8.3	.0005
Thyroid drugs	7.5	5.6	15.3	<.0001
BMD	5.9	4.4	5.0	<.0001
Income, %				<.0001
Low	40.8	41.0	40.8	
Middle	24.1	17.9	25.4	
High	35.1	41.2	33.8	

Abbreviations: BMD, bone mineral density; BZD, benzodiazepine; COX2, cyclooxygenase 2; DM, diabetes mellitus; SSRI, selective serotonin reuptake inhibitors.

were found among comparison groups with different cumulative dose ranges, but with wider confidence intervals around the point estimates due to the smaller sample size of the subgroups. Moreover, no event was found in raloxifene recipients who received a 180 to 365 DDD cumulative dose. Consistent results were also found in the intent-to-treat analysis and in the subgroup analyses, including patients with a diagnosis of osteoporosis, patients with

Table 2. Incidence of VTE/10 000 Person-Years in Patients With Treated and Untreated Osteoporotic Fractures

	Treated (n = 66 985)	Untreated (n = 35 433)	Alendronate (n = 25 443)	Raloxifene (n = 9642)	Calcitonin (n = 31 900)
VTE event, n	264	131	106	39	119
Overall	9.2	7.3	10.3	9.9	8.3
Age					
50–65 y	5.0	6.3	5.0	3.1	5.8
65–80 y	9.4	8.9	9.7	9.3	9.2
≥80	11.0	11.9	14.3	15.4	12.1
Sex					
Female	9.3	8.8	9.7	10.0	8.7
Male	8.9	7.2	12.3	—[a]	6.7

[a] —, no event.

Table 3. Incidence and Risk of VTE of Osteoporosis Drugs Compared With Those for Calcitonin

Outcome	Event, n	Incidence Rate/ 10 000 Person-Years	HR (95% CI) Unadjusted	*P* Value	Adjusted M1[a]	*P* Value	PS Matching	*P* Value
VTE								
Alendronate	31	11.2	0.76 (0.431.31)	.3202	0.84 (0.471.51)	.5581	0.64 (0.331.28)	.2079
Raloxifene	6	8.5	0.53 (0.211.29)	.1615	0.57 (0.221.45)	.2358	0.59 (0.172.10)	.4189
Calcitonin	24	18.8	1.00 (reference)		1.00 (reference)		1.00 (reference)	
DVT								
Alendronate	20	7.2	0.62 (0.321.18)	.1339	0.67 (0.341.32)	.2442	0.59 (0.261.34)	.2047
Raloxifene	4	5.7	0.43 (0.151.28)	.1301	0.45 (0.151.39)	.1634	0.47 (0.102.15)	.3247
Calcitonin	20	15.7	1.00 (reference)		1.00 (reference)		1.00 (reference)	
PE								
Alendronate	11	4.0	1.08 (0.363.21)	.1093	1.30 (0.424.08)	.6494	0.79 (0.232.76)	.7146
Raloxifene	2	2.8	0.75 (0.143.90)	.1016	0.87 (0.164.80)	.8755	1.06 (0.1011.85)	.9632
Calcitonin	5	3.9	1.00 (reference)		1.00 (reference)		1.00 (reference)	

Abbreviation: PS, propensity score.

[a] Adjusted for all variables in Table 1.

different nonvertebral or hip fracture histories, female patients, patients with a previous diagnosis of varicose veins, or patients who received HRT.

Discussion

This retrospective analysis showed that the incidence of VTE in Taiwanese patients with osteoporosis was low. In addition, the incidence and risk of VTEs were similar in patients with osteoporotic fractures who were new to osteoporosis therapy (alendronate, raloxifene, and calcitonin recipients). Age and comorbid varicose veins were factors that were significantly associated with elevated VTE risk. Consistent results were found in a series of sensitivity and subgroup analyses.

We found that the incidence of VTEs in the Taiwanese treated osteoporotic population was 9.2 per 10 000 person-years, which was much higher than our previous finding in the Taiwanese general population aged older than 50 years (4.5 per 10 000 person-years) (20). However, there were ethnic differences in VTE incidence, in that the

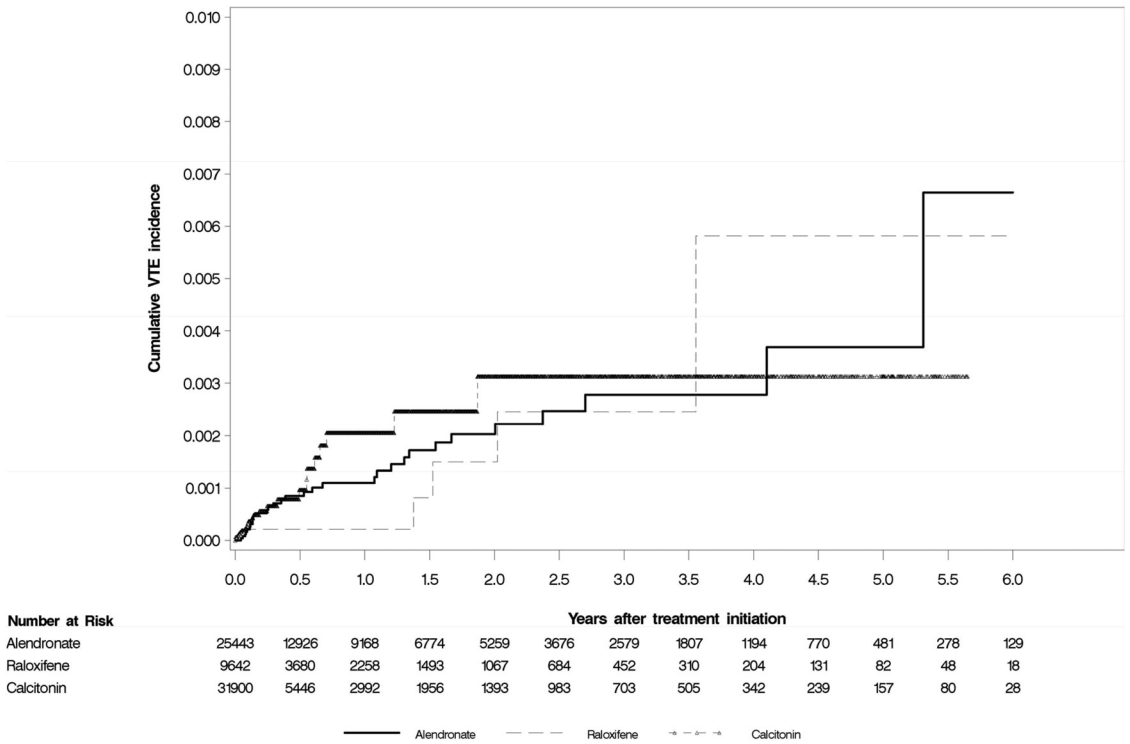

Figure 2. Kaplan-Meier analysis for risk of VTE.

Table 4. Sensitivity and Subgroup Analysis

	Alendronate		Raloxifene	
	Participants, n	HR[a] (95% CI)	Participants, n	HR[a] (95% CI)
Primary analysis	25 443	0.84 (0.47–1.51)	9642	0.57 (0.22–1.45)
Extended the follow-up by 90 days	25 443	1.17 (0.69–1.99)	9642	0.89 (0.40–1.97)
Excluded short-term users	17 737	0.69 (0.37–1.26)	5838	0.47 (0.17–1.29)
Cumulative doses				
≤180 DDDs	15 904	1.54 (0.79–3.00)	7152	0.82 (0.27–2.50)
180–365 DDDs	3618	0.73 (0.08–6.47)	1193	—[b]
>365 DDDs	5921	0.31 (0.05–1.78)	1297	0.31 (0.04–2.85)
Intent-to-treat scenario	25 443	1.23 (0.94–1.62)	9642	1.18 (0.81–1.71)
Index osteoporotic fracture				
Vertebral fracture	18 152	0.76 (0.40–1.45)	6545	0.44 (0.13–1.51)
Hip fracture	7291	1.07 (0.22–5.25)	3097	0.88 (0.14–5.77)
Fracture history				
No fracture history	20 376	0.59 (0.30–1.14)	7856	0.59 (0.22–1.52)
Patients with osteoporosis diagnosis stratified by age groups	20 070	0.71 (0.37–1.36)	7697	0.52 (0.19–1.46)
50–65 y	3337	0.40 (0.02–7.59)	1493	—
65–80 y	14 043	0.49 (0.22–1.09)	5231	0.46 (0.15–1.45)
≥80 y	7732	1.99 (0.70–5.63)	2836	0.94 (0.17–5.11)
Female only	19 832	0.67 (0.36–1.28)	9530	0.50 (0.20–1.28)
Excluded patients				
Varicose veins of lower extremities	25 303	0.83 (0.46–1.50)	9591	0.59 (0.23–1.50)
HRT	24 558	0.91 (0.50–1.66)	9263	0.62 (0.24–1.60)
Ever received aspirin/ticlopidine	21 884	0.93 (0.49–1.79)	8323	0.59 (0.21–1.68)
Inpatients only	25 443	0.68 (0.17–2.78)	9642	0.73 (0.18–2.97)

[a] Adjusted for all variables in Table 1.

[b] —, no VTE events in raloxifene recipients.

incidence of VTE in the Taiwanese general population was much lower than that in the US or UK populations (crude incidence rate ratio [IRR], 0.15) (20, 24). Whether there were also ethnic differences in VTE incidence in the osteoporotic population is worthy of further investigation. In 2010, Breart et al (6) first compared the incidence of VTE between the osteoporotic and nonosteoporotic populations using the UK General Practice Research Database. They reported that the osteoporotic population had a significantly higher VTE rate (56 per 10 000 person-years) than the nonosteoporotic population (32 per 10 000 person-years). In addition, they found that the incidence of VTE among alendronate recipients was 72 per 10 000 person-years. In our study, we included Taiwanese patients with osteoporotic fractures aged older than 50 years and found the incidence of VTE among Taiwanese alendronate recipients was 11.2 per 10 000 person-years, which was only one seventh of that of UK alendronate recipients (crude IRR, 0.14). Therefore, comparing Taiwan with Western countries, we found that the IRR for VTE was similar in the general population and the osteoporotic population receiving treatment (crude IRRs, 0.15 and 0.14, respectively), which confirmed that the incidence of VTE in Taiwan is only one seventh of that of Western countries. In addition to the previous finding in a UK study that there was no significant difference in VTE rates between treated and untreated osteoporotic populations (6), we further found no difference in VTE rates between alendronate, raloxifene, and calcitonin recipients in Taiwan.

To date, three large studies have used the health insurance database to investigate the association between bisphosphonates and VTE (6, 18, 19) but with different study designs and comparison groups. Two Danish register–based studies, using either retrospective cohort (19) or case-control (18) designs, showed that oral bisphosphonates including alendronate did not have increase the risk for VTE compared with that for the age- and sex-matched general population. In addition, they failed to find a dose-response relationship between the use of alendronate and VTE (19). Moreover, results from a cohort study using the General Practice Research Database showed that the risk of VTE in alendronate recipients was similar to that of the untreated osteoporotic population (HR, 0.99; 95% CI, 0.80–1.23) (6). However, there were large differences in the VTE risk factors between the comparison groups in the above studies, and the exposure statuses during follow-up were not clear. In modern pharmacoepidemiology, selecting new users as the study population and using active controls may provide more unbiased and homogeneous comparisons (25). In our study, we first selected new users of alendronate and adopted calcitonin recipients as the

active control because there was no report of risk for VTE associated with calcitonin from preclinical and clinical studies and postmarketing data (7). We examined our results in the on-treatment scenario first, in which the persistence of patients taking their medications during the follow-up was more accurately depicted. We then matched alendronate and calcitonin recipients by propensity score, which minimized the likelihood of confounding by indication and enabled more homogeneous comparisons (26). No significant difference in VTE risk between the alendronate and the control group was found in the original and propensity score–matched cohort and on-treatment and intent-to-treat scenario. Furthermore, we did not observe a dose-response relationship between the use of alendronate and risk of VTE either. Therefore, our study further supports the findings from a previous study (6) that alendronate recipients did not have excess risk among the osteoporotic population, even in a population such as that in Taiwan in which the VTE rate was only one seventh that of Caucasians.

It is well known that the use of raloxifene may increase VTE risk in postmenopausal women (7, 16, 17). Results from clinical trials and meta-analyses showed that raloxifene users may have a 2 times higher risk of VTE (16, 17, 27) and 91% higher risk of PE than placebo users in Western countries. However, related reports in Asian populations were limited. In a short-term randomized controlled trial, no VTE event was observed in an Asian postmenopausal population during 6 months of daily treatment with raloxifene (28). Consistent with the results of a previous Asian study (28), we found that the incidence of VTE among Taiwanese raloxifene recipients was extremely low (8.5/10 000 person-years), and no event occurred after 3.5 years of consistent exposure to raloxifene. Further, we did not find an excessive risk of VTE among raloxifene recipients compared with calcitonin recipients. The incidence of VTE in calcitonin recipients was indeed slightly higher than that in the untreated group; however; this result might be attributable to the selection bias. Therefore, it is likely that calcitonin did not have an increased baseline risk of VTE in the Taiwanese osteoporosis population, and our results also suggested that VTE risk may not be a concern with use of raloxifene in Taiwan.

Although we adjusted the results extensively with multivariate and propensity score matching models and performed a series of sensitivity and subgroup analyses, there were several limitations and unmeasured confounders in our study. First, because we focused only on symptomatic VTEs, the incidence of VTE in the Taiwanese osteoporosis population may have been underestimated. Patients with asymptomatic VTEs or those who died before VTE could be diagnosed or treatment could be initiated were not captured in our study. Nevertheless, using symptomatic VTEs as the outcome may reduce the potential for misclassification bias. The definition of an incident VTE event in our study was a diagnosis of VTE in a patient who had previously received anticoagulant therapies, which may have provided more valid risk estimation. Second, there might exist some unmeasured confounders in the NHIRD, and there is no information on the severity of osteoporosis of patients in our cohort. However, all patients included in our cohort had experienced vertebral or hip fractures, consistent with the definition of severe or established osteoporosis by the National Osteoporosis Foundation criteria (1). In addition, data on socioeconomic factors were lacking: although we used the insurance premium paid as a surrogate for income level, the validity thereof is unknown. Furthermore, information about use of self-paid medications (Vitamin D or calcium) and patients' lifestyles and behavior, such as body mass index, smoking status, and travel histories, which could modify VTE risk, were not available in our claims database. Finally, further investigations are needed to explore the potential association between osteoporosis drugs and VTEs in higher cumulative doses or long-term users in real-world settings because suboptimal patient compliance with osteoporosis drug treatment may influence outcomes. Published studies and our previous work showed that fewer than 50% of patients remain compliant to their drugs within the first year after treatment initiation (29), elevating the difficulty of selecting patients receiving higher cumulative doses and making subject selection impractical in real-world practice. Nevertheless, when interpreting our results, one should notice that the number of long-term users was limited in this study. Despite several limitations in our study, there were several strengths as well. First, our study was the first large-scale study in Asia to assess the incidence and risk for VTE among the osteoporotic fracture population, which is known to have higher VTE risk. Second, the database we used (NHIRD) comprised >99% of the Taiwanese population; thus, the osteoporotic cohort in our study has good generalizability. Third, we reported our findings with extended length of follow-up (maximum 6 years). Finally, we included potential confounders in our database for adjustment and further matched patients by propensity score based on these confounders, which minimized the potential bias from these factors.

Our study shows that regardless of whether patients in the Taiwanese osteoporotic fracture population received alendronate, raloxifene, or calcitonin treatment, the incidence and risk for VTE among these patients were similar. In addition, we found that there were ethnicity-based differences in VTE incidence between Taiwan and Western countries; specifically, the VTE incidence was much lower

in Taiwan than in Western countries, both in general (20) and in the osteoporosis populations in our study. The results indicate that there was no significant difference in risk of VTE among Asian osteoporotic fracture patients receiving alendronate, raloxifene, or calcitonin. Osteoporotic fractures have a significant impact on mortality and future fracture risks, but they can be prevented with proper pharmacological treatments (1). Efforts should be made to ensure that fracture patients receive secondary prevention measures and remain compliant with their therapies.

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