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Vitamin D and bisphosphonates therapies for osteoporosis are associated with different risks of atrial fibrillation in women

A nationwide population-based analysis

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Abstract

Osteoporosis and atrial fibrillation (AF) are common in post-menopausal women. Vitamin D and bisphosphonates are widely used to treat osteoporosis, and these may have different effects on the risk of AF.

The goal of this study was to evaluate whether different agents for treating osteoporosis modulate the risk of AF in a population-based database.

We identified 20,788 female patients suffering from osteoporosis who were or were not treated with vitamin D or bisphosphonates using the Taiwan National Health Insurance nationwide database from 2000 to 2008 and followed them up for 5 consecutive years to determine if they had a new diagnosis of AF after the diagnosis of osteoporosis.

There were 14 (2.67%) new AF diagnoses in osteoporosis patients treated with bisphosphonates, one (0.28%) new AF diagnosis in patients treated with vitamin D, and 279 (1.40%) new AF diagnoses in patients who were not treated with vitamin D or bisphosphonates (neither group). Osteoporosis patients who received bisphosphonates showed a higher incidence of AF occurrence than those that were not treated with bisphosphonates ($P = .015$). In contrast, 1 patient who received vitamin D had a new diagnosis of AF during the study period; thus, the incidence was significantly lower than that in the patients treated with bisphosphonates ($P = .007$). In addition, the patients who were treated with vitamin D had a lower incidence of AF than did those who were not treated with either vitamin D or bisphosphonates ($P = .074$). Kaplan–Meier analysis also showed a significant difference in AF occurrence in different groups during the 5-year follow-up ($P = .010$).

Different treatment for osteoporosis may carry diverse risks of AF occurrence. Vitamin D may have potential beneficial effects of reducing AF occurrence in osteoporosis patients.

Abbreviations: AF = atrial fibrillation, HDL-C = high-density lipoprotein-cholesterol, NHI = National Health Insurance, OR = odds ratio.

Keywords: atrial fibrillation, bisphosphonates, osteoporosis, vitamin D

1. Introduction

Osteoporosis, a common disease in postmenopausal women, can increase morbidity and mortality with increased disability, hospitalization, and death.[1,2] There was a higher risk of hip fracture in women with AF.[3] Vitamin D is widely used to treat patients with osteoporosis.[4,5] Vitamin D deficiency is a major risk factor for osteoporosis and contributes to the development of cardiovascular disorders including atherosclerosis and heart failure.[6–9] Vitamin D has several biological effects including anti-inflammatory, antioxidative stress, and renin–angiotensin regulatory effects, which play vital roles in the pathophysiology of cardiovascular diseases.[10,11] Aging increases the risk of osteoporosis and also plays a critical role in the pathogenesis of atrial fibrillation (AF). However, it is not clear whether the use of vitamin D can reduce the occurrence of AF via its anti-AF potential.

In contrast, bisphosphonates, which are also commonly used to treat osteoporosis, have potential adverse cardiac effects.[12–15] Although the results are controversial, bisphosphonates were shown to increase the occurrence of AF. Acute administration of bisphosphonates can increase atrial ectopic beats with dysregulation of the autonomic nervous system.[16,17] Moreover, bisphosphonates may induce the release of pro-inflammatory cytokines, which also may cause atrial remodeling and fibrosis

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with an increased risk of AF.[18] However, patient characteristics that predispose an individual to an increased risk of AF have not yet been established. The National Health Insurance (NHI) program provides a database of medical care and is commonly used to analyze real-world practices in Taiwan.[19–21] The NHI database provides useful information to study different risks for AF. Therefore, the purpose of this study was to evaluate whether different agents for treating osteoporosis modulate the risk of AF.

2. Methods

2.1. Study population

This study used NHI nationwide data from 1997 to 2008, which included 480685 females in the data bank. The nationwide data were anonymized before access, thus ethical approval was not necessary. We surveyed 31571 females with osteoporosis from year 2000 to 2003. Patients with a diagnosis of osteoporosis was identified from ICD-9 code of 733.0, 733.01, 733.02, 733.03, and 733.09, and AF or atrial flutter was identified from ICD-9 codes of 427.3, 427.31, and 427.32 as described previously.[19] So We excluded patients with osteoporosis or AF diagnosis before 2000, patients who had ever received bisphosphonates (etidronate, clodronate, pamidronate, alendronate, risedronate), vitamin D, or patients receiving both bisphosphonates and vitamin D (in combination or sequentially) before 2000, patients got AF before osteoporosis onset and patients who taking bisphosphonates or vitamin D over 1 year after osteoporosis onset. There were 20,788 new onset osteoporosis female patients involved in the study. We compared a new diagnosis of AF at the end of 5 years follow-up in bisphosphonates, vitamin D, and neither group.

2.2. Statistical analysis

Continuous variables were expressed as the mean and standard deviation (SD). Propensity score matching (1:1:5) was conducted in bisphosphonates, vitamin D, and neither group. Categorical variables were reported as frequencies and were compared using a Pearson χ^2 analysis. Kaplan–Meier curves were constructed, and outcomes of different patient groups were compared using the log-rank test. A 2-tailed probability $P < .05$ was considered statistically significant. All statistical analyses were performed with SAS 9.4 (Cary), SPSS 18 (Chicago), Medcalc 11 (Ostend, Belgium), Statistica 8 (Tulsa), and Comprehensive Meta Analysis 2.2 (Englewood) software.

3. Results

In this study, 20,788 female patients were included, among which 525 received bisphosphonates, 354 received vitamin D, and 19,909 received neither bisphosphonates nor vitamin D (Fig. 1). During the 5-year follow-up, there were 14 (2.67%), 1 (0.28%), and 279 (1.40%) new cases of AF diagnoses in osteoporosis patients treated with bisphosphonates, osteoporosis patients treated with vitamin D, and osteoporosis patients without either treatment (neither group), respectively. Osteoporosis patients who received bisphosphonates had a higher incidence of AF occurrence than that in those who were not treated with bisphosphonates ($P = .015$). One patient who received vitamin D had a new diagnosis of AF at the end of the 5-year follow-up period; thus, the incidence of new AF was significantly lower than that in the patients treated with bisphosphonates ($P = .007$). Furthermore, the tendency for the incidence of new AF was lower than that among the patients who were not treated with either vitamin D or bisphosphonates ($P = .074$). Moreover, Kaplan–Meier analysis also showed a trend of different incidences of AF during the 5-year follow-up among the female patients who were treated with bisphosphonates, vitamin D, and neither treatment nor a significant difference in AF occurrence in 5-year follow-up (Fig. 2A). Through propensity score matching (Table 1), the Kaplan-Meier analysis also showed different occurrences of AF among different group in 5 year follow-up (Fig. 2B).

In patients with a new diagnosis of AF, times to a new AF diagnosis were similar for patients who received bisphosphonates (849±457 days) and the neither group (958 ± 523 days). Table 1 shows the age, co-morbidities, and medications used in the 3 groups. Compared to the neither group, the vitamin D group was associated with greater prevalence of hypertension, heart failure, occlusion of cerebral arteries, myocardial infarction, and fractures, whereas the bisphosphonates group was associated

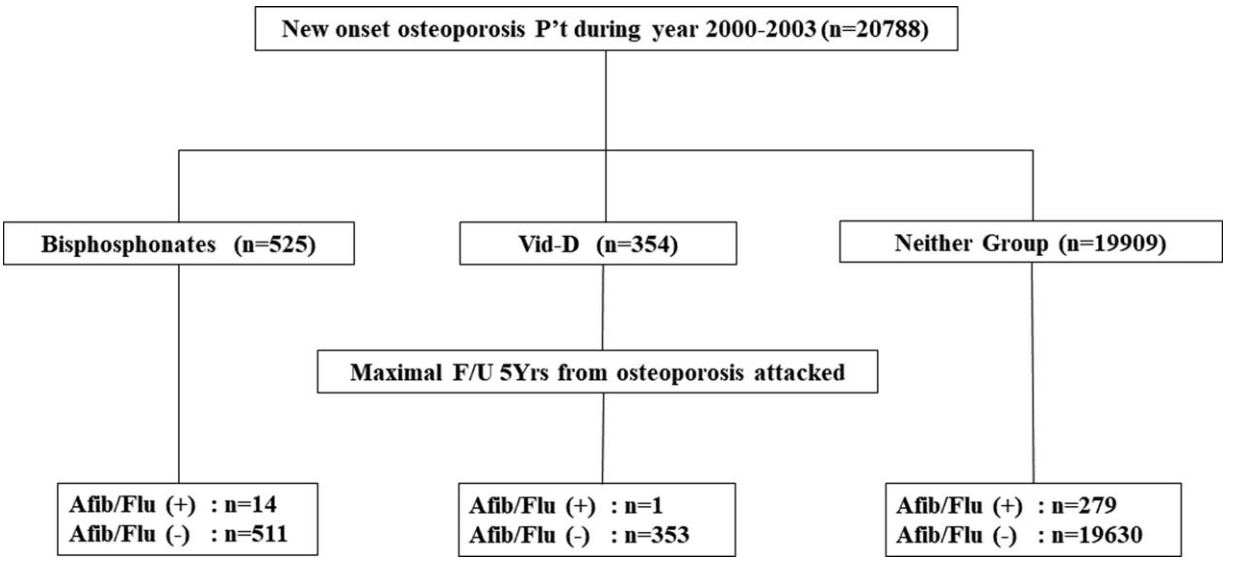


Figure 1. Description of the study patients from the National Health Insurance database.

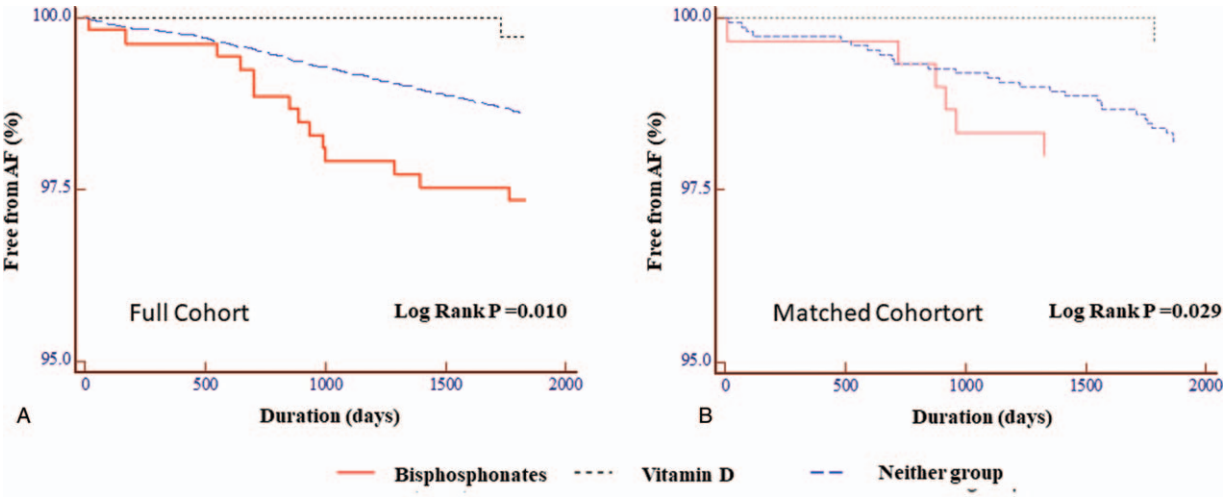


Figure 2. Kaplan-Meier analysis on the occurrence of atrial fibrillation (AF) after a diagnosis of osteoporosis with and without treatment of vitamin D or bisphosphonates from full cohort (panel A) or propensity score matched cohort (panel B).

with greater prevalence of diabetes, hypertension, cerebrovascular disease, occlusion of cerebral arteries, transient cerebral ischemia, and fractures. In addition, comparisons between vitamin D and bisphosphonates groups showed that vitamin D group had a higher prevalence of thyroid gland disorders, but a lower prevalence of factures than the bisphosphonates group. In addition, in the neither group, patients with a new AF diagnosis had more hypertension, ischemic heart disease, acute myocardial infarction, heart failure, peripheral arterial disease, and fractures than those without AF (Table 2). Similarly, in the bisphosphonates group, patient with a new AF diagnosis had more thyroid dysfunction, hypertension, heart failure, transient cerebral ischemia, peripheral arterial disease, and chronic kidney disease (Table 3). However, bisphosphonate-treated patients with and without AF had similar prevalence of fractures. Moreover, the subgroup analysis showed that patients with hypertension had a significant higher risk (odds ratio [OR]=3.305) of AF, and patients with chronic lung diseases also had a tendency for an increased risk (OR=7.148) of AF (Fig. 3).

4. Discussions

Both osteoporosis and AF are aging diseases because of the multiple etiologies involved. Osteoporosis significantly increases

Table 1

Co-morbidity in osteoporosis patients with and without treatment of vitamin D or bisphosphonates from full cohort or propensity score matched cohort.

	Full cohort				Matched cohort			
	Neither (n=19909)	Bisphosphonates (n=525)	Vitamin D (n=354)	*P*	Neither (n=1415)	Bisphosphonates (n=283)	Vitamin D (n=283)	*P*
Age, y	61.86±12.38	73.52±10.98*	66.62±11.56*,†	<.001	68.43±11.85	68.06±11.51	70.94±11.73*,†	<.001
Co-morbidity, no. (%)								
Disorders of thyroid gland (240–246)	231 (1.16)	2 (0.38)	8 (2.26)†	.038	23 (1.63)	2 (0.71)	5 (1.77)	.478
Diabetes mellitus (250)	605 (3.04)	25 (4.76)*	16 (4.52)	.024	52 (3.67)	14 (4.95)	12 (4.24)	.580
Disorders of lipoid metabolism (272)	465 (2.34)	12 (2.29)	10 (2.82)	.831	39 (2.76)	6 (2.12)	9 (3.18)	.735
Hypertensive disease (401–405)	1153 (5.79)	58 (11.05)*	35 (9.89)*	<.001	137 (9.68)	32 (11.31)	29 (10.25)	.699
Ischemic heart disease (410–414)	232 (1.17)	8 (1.52)	8 (2.26)	.133	22 (1.55)	4 (1.41)	5 (1.77)	.943
Acute myocardial infarction (410)	3 (0.02)	0 (0)	0 (0)	.936	0 (0)	0 (0)	0 (0)	–
Heart failure (428)	22 (0.11)	1 (0.19)	2 (0.56)*	.045	4 (0.28)	1 (0.35)	1 (0.35)	.967
Cerebrovascular disease (430–438)	141 (0.71)	15 (2.86)*	5 (1.41)	<.001	15 (1.06)	5 (1.77)	4 (1.41)	.578
Occlusion and stenosis of precerebral arteries (433)	6 (0.03)	0 (0)	0 (0)	.876	0 (0)	0 (0)	0 (0)	–
Occlusion of cerebral arteries (434)	46 (0.23)	8 (1.52)*	4 (1.13)*	<.001	9 (0.64)	4 (1.41)	3 (1.06)	.360
Transient cerebral ischemia (435)	12 (0.06)	2 (0.38)*	0 (0)	.018	0 (0)	0 (0)	0 (0)	–
peripheral arterial disease (443, 444)	67 (0.34)	2 (0.38)	3 (0.85)	.266	1 (0.07)	2 (0.71)	1 (0.35)	.078
chronic lung disease (490–496,500–508)	196 (0.98)	10 (1.90)	4 (1.13)	.112	17 (1.2)	2 (0.71)	4 (1.41)	.710
Neoplasms (140–239)	726 (3.65)	9 (1.71)	14 (3.95)	.060	23 (1.63)	8 (2.83)	8 (2.83)	.221
Chronic kidney disease (585)	33 (0.17)	1 (0.19)	2 (0.56)	.200	4 (0.28)	1 (0.35)	1 (0.35)	.967
Fractures (800–829)	1793 (9.01)	257 (48.95)*	51 (14.41)*,†	<.001	242 (17.1)	58 (20.49)	51 (18.02)	.390
Rheumatoid arthritis (714.0)	196 (0.98)	8 (1.52)	2 (0.56)	.336	8 (0.57)	1 (0.35)	2 (0.71)	.848

* $P<.05$ versus neither group.
† $P<.05$ versus bisphosphonate.

Table 2

Co-morbidity in neither group osteoporosis patients with and without AF occurrence.

	With AF (n = 279)	Without AF (n = 19630)	*P*
Age, y	73.62 ± 11.43	61.69 ± 12.31	.043
Co-morbidity, no. (%)			
Disorders of thyroid gland (240–246)	5 (1.79)	226 (1.15)	.224
Diabetes mellitus (250)	8 (2.87)	597 (3.04)	.659
Disorders of lipoid metabolism (272)	3 (1.08)	462 (2.35)	.453
Hypertensive disease (401–405)	32 (11.47)	1121 (5.71)	<.001
Ischemic heart disease (410–414)	10 (3.58)	222 (1.13)	<.001
Acute myocardial infarction (410)	1 (0.36)	2 (0.01)	.010
Heart failure (428)	4 (1.43)	18 (0.09)	<.001
Cerebrovascular disease (430–438)	4 (1.43)	137 (0.70)	.120
Occlusion and stenosis of precerebral arteries (433)	0 (0)	6 (0.03)	.092
Occlusion of cerebral arteries (434)	1 (0.36)	45 (0.23)	.986
Transient cerebral ischemia (435)	1 (0.36)	11 (0.06)	.313
peripheral arterial disease (443, 444)	3 (1.08)	64 (0.33)	.041
chronic lung disease (490–496,500–508)	3 (1.36)	193 (1.01)	.828
Neoplasms (140–239)	8 (2.87)	718 (3.66)	.880
Chronic kidney disease (585)	0 (0)	33 (0.17)	.826
Fractures (800–829)	45 (16.13)	1748 (8.90)	<.001
Rheumatoid arthritis (714.0)	2 (0.72)	194 (0.99)	.828

AF = atrial fibrillation.

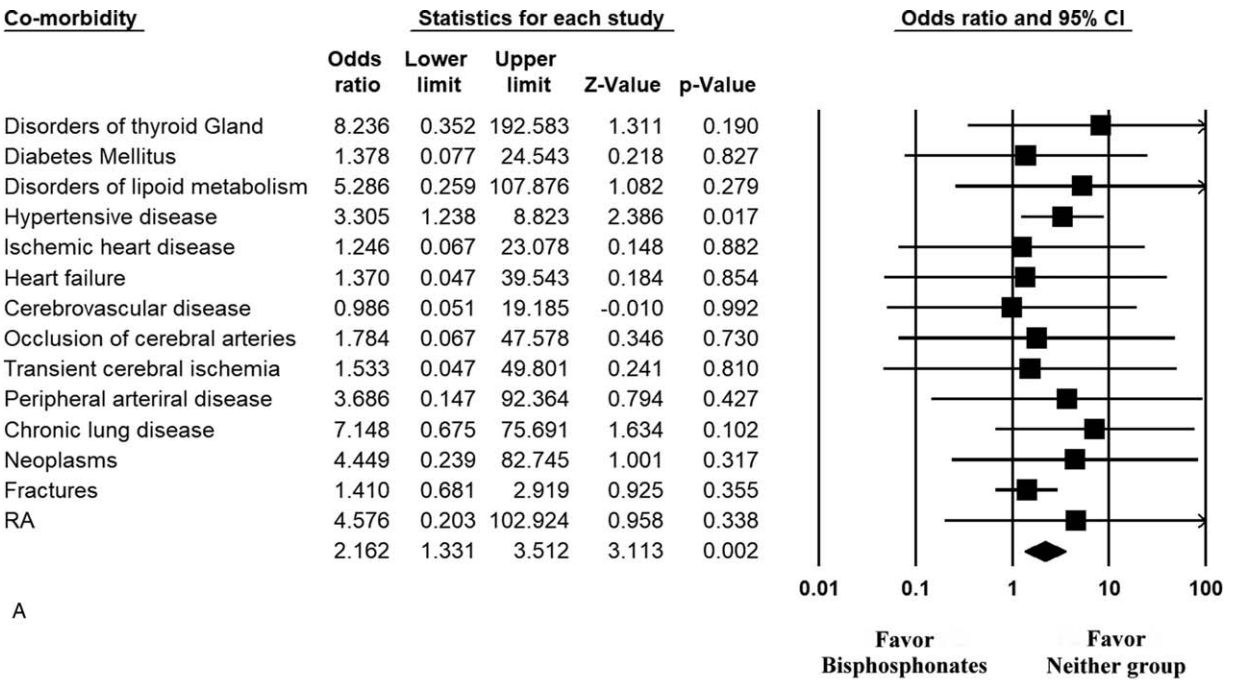
the social burden because of increased medical expenses due to the high degree of co-morbidity and hospitalization associated with it.[1,2] However, the current treatment for osteoporosis is not satisfactory due to inadequate responses or potential adverse effects. Vitamin D deficiency is a common cause of osteoporosis and induces several cardiovascular morbidities,[6–9] which are expected to increase the risk of AF. Several clinical studies have also highlighted the relationship between vitamin D deficiency and a risk of AF. There are also some clinical studies showing cardiac autonomic functions are impaired in patients with vitamin D deficiency.[22] In addition, the relationship between vitamin D status and the extent of left atrial fibrosis would have potential clinical implication.[23,24] However, the role of vitamin D supplement in AF control has not yet been well established. In this study, through a nationwide population-based analysis, we found that vitamin D treatment may be associated with a lower AF occurrence and this effect was significantly demonstrated during the 5-year follow-up period. These results suggest that vitamin D may have anti-AF activity during the treatment of osteoporosis in the relatively intermediate period of follow-up. Although this study did not evaluate the potential mechanisms of action of vitamin D on AF, it was found that vitamin D can reduce atrial fibrosis, cardiac hypertrophy, and antioxidative stress and modulate renin-angiotensin activity,[10,11,25] which have been proposed to have an anti-AF potential through the strategy of upstream therapy. A clinical study indicated that adequate serum levels of vitamin D are significantly associated with a decrease in elevated blood pressure, elevated triglyceride, and reduced

Table 3

Co-morbidity in bisphosphonates-treated osteoporosis patients with and without AF occurrence.

	With AF (n = 14)	Without AF (n = 511)	*P*
Age, y	77.93 ± 5.27	73.40 ± 11.07	.028
Co-morbidity, no. (%)			
Disorders of thyroid Gland (240–246)	0 (0)	2 (0.39)	.050
Diabetes Mellitus (250)	0 (0)	25 (4.89)	.832
Disorders of lipoid metabolism (272)	0 (0)	12 (2.35)	.744
Hypertensive disease (401–405)	5 (35.71)	53 (10.37)	.011
Ischemic heart disease (410–414)	0 (0)	8 (1.57)	.526
Acute myocardial infarction (410)	0 (0)	0 (0)	
Heart failure (428)	0 (0)	1 (0.2)	.003
Cerebrovascular disease (430–438)	0 (0)	15 (2.94)	.871
Occlusion and stenosis of precerebral arteries (433)	0 (0)	0 (0)	
Occlusion of cerebral arteries (434)	0 (0)	8 (1.57)	.526
Transient cerebral ischemia (435)	0 (0)	2 (0.39)	.050
peripheral arterial disease (443, 444)	0 (0)	2 (0.39)	.050
chronic lung disease (490–496,500–508)	1 (7.14)	9 (1.76)	.645
Neoplasms (140–239)	0 (0)	9 (1.76)	.587
Chronic kidney disease (585)	0 (0)	1 (0.2)	.003
Fractures (800–829)	9 (64.29)	248 (48.53)	.372
Rheumatoid arthritis (714.0)	0 (0)	8 (1.57)	.526

AF = atrial fibrillation.



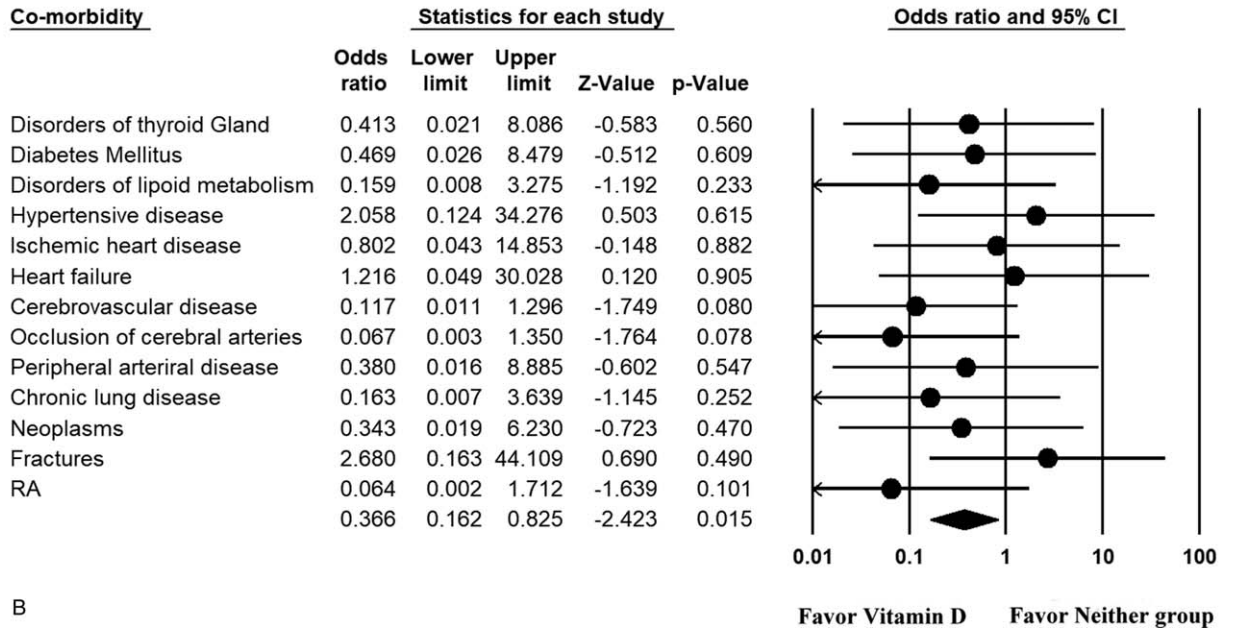


Figure 3. Risk of atrial fibrillation (AF) from the baseline to the end of follow-up in patients with and without treatment of vitamin D or bisphosphonates. A, The risk difference between the patients of neither group and bisphosphonates group. B, The risk difference between the patients of the neither group or vitamin D group.

high-density lipoprotein-cholesterol (HDL-C) levels in postmenopausal women.[26] Since metabolic syndrome contributes to AF occurrence, vitamin D supplementation may reduce AF occurrence at least in part through the improvement of blood pressure and lipid profile. Nevertheless, vitamin D supplementation might partially relieve postmenopause- related complications since vitamin D plays a role in estrogen biosynthesis in part by maintaining extracellular calcium homeostasis.[27] Moreover, vitamin D has direct cardiac electrophysiological effects and reduces the occurrence of rapid atrial pacing-induced AF.[28] AF is also a major social burden due to a high risk of stroke, heart failure, hospitalization, and mortality, this real-world experience suggests that vitamin D may be the drug of choice in the treatment of osteoporosis associated with a high risk of AF. In this study, we found that osteoporosis patients treated with vitamin D had more comorbidities than osteoporosis patients without treatment. Comorbidities are important risk factors for the pathogenesis of AF.[29–32] Similarly, this study also found that the incidences of co-morbidities in osteoporosis patients with AF were higher than those among osteoporosis patients without AF. The incidence of comorbidities was higher in the vitamin D group than in the neither group, which suggests that the beneficial effects of vitamin

D on reducing AF may be rather underestimated. However, stricter clinical trials may be needed to confirm our findings.

Bisphosphonates are a potent treatment for osteoporosis and were shown to reduce fractures in postmenopausal women with osteoporosis.[33,34] Previous studies showed that bisphosphonates may have controversial effects on the risk of AF.[13–15] In this study, we found that more osteoporosis patients treated with bisphosphonates had a new diagnosis of AF than did those in the neither group or the vitamin D group. Since the incidence of co-morbidities was higher in the bisphosphonate and vitamin D groups than in the neither group, the risk of AF occurrence associated with bisphosphonates remains unclear. In contrast, the bisphosphonate group had a lower incidence of co-morbidities than did the vitamin D group. Therefore, patients treated with vitamin D may have a much lower risk of AF than would patients treated with bisphosphonates.

There are some limitations to this study. ICD code system for data set could be limited by unrecorded data. The National Health Research Institutes (NHRI) database provides no biochemical information or heart function, which may have modulated the pathogenesis of AF in study patients. The AF pattern (paroxysmal, persistent or permanent) and the severity of osteoporosis were not clarified in this study. Since vitamin D may be available without a prescription, it is possible that some patients took vitamin D without it being recorded in the NHRI database. Moreover, we cannot exclude the possibility that some co-morbidities related to the risk of AF might not have been completely identified from the ICD codes in the database.

In conclusion, different treatment for osteoporosis is associated with diverse risk of AF occurrence. Vitamin D may have potential beneficial effects of reducing the AF occurrence in osteoporosis patients.

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