ORIGINAL RESEARCH

Risk of Osteoporosis in Patients With Atrial Fibrillation Using Non–Vitamin K Antagonist Oral Anticoagulants or Warfarin

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***Background*—**Warfarin, a vitamin K antagonist, has been shown to affect bone mineral density and cause osteoporosis. However, studies investigating the relationship between non–vitamin K antagonist oral anticoagulants (NOACs) and osteoporosis are limited. We thus compared the risk of osteoporosis in patients with atrial fibrillation treated with either NOACs or warfarin.

***Methods and Results*—**This nationwide, retrospective cohort study used Taiwan's National Health Insurance Research Database. All adult patients in Taiwan who were newly diagnosed with atrial fibrillation and treated with NOACs or warfarin between January 2012 and December 2015 were included and classified into their respective cohorts. Patients who received NOACs were subcategorized into the rivaroxaban, dabigatran, and apixaban subgroups. Propensity score matching was performed for each head-to-head comparison. Adjusted hazard ratios (aHRs) for the risk of osteoporosis were calculated using Cox proportional hazards regression models, with adjustment for confounders. Overall, 17 008 patients were included, with 8504 in each cohort. NOACs were associated with a lower osteoporosis risk than warfarin (aHR=0.82; 95% CI=0.68–0.97). A subgroup effect of treatment duration was identified (namely, the lower osteoporosis risk with NOAC compared with warfarin became stronger in those with longer treatment duration [*P* for interaction <0.001]). Furthermore, significantly lower risks of osteoporosis were observed in the rivaroxaban (aHR=0.68; 95% CI=0.55–0.83) and apixaban (aHR=0.38; 95% CI=0.22–0.66) subgroups, but not in the dabigatran subgroup (aHR=1.04; 95% CI=0.85–1.27).

***Conclusions*—**Compared with warfarin, rivaroxaban and apixaban were associated with a significantly lower risk of osteoporosis in patients with atrial fibrillation. **(*J Am Heart Assoc*. 2020;9:e013845. DOI: 10.1161/JAHA.119.013845.)**

Key Words: atrial fibrillation • oral anticoagulants • osteoporosis • rivaroxaban • warfarin

Osteoporosis, a systemic skeletal disease characterized by impairments in bone density, strength, and microarchitecture, can increase the risk of fragility fractures and cause significant morbidity and mortality. With the aging of the population globally, osteoporosis has become a major issue with considerable medical and socioeconomic burdens.[1] The incidence and prevalence of atrial fibrillation (AF), another major common disease in elderly individuals, continue to increase globally. In the management of AF, stroke prevention is the most pivotal requirement, with oral anticoagulants (OACs) being the most important therapeutic treatment.[2]

Warfarin, a vitamin K antagonist, is a traditional OAC that has been the cornerstone of stroke prevention in patients with AF for decades. Previous studies have indicated that vitamin K deficiency is associated with osteoporosis.[3,4] However, whether warfarin use increases the risks of osteoporosis and consequent fractures has been debated for decades, and to date, the evidence remains conflicting and controversial.[3] Some studies indicate that warfarin is

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Clinical Perspective

What Is New?

- This real-world, nationwide, propensity score–matched cohort study demonstrates that non–vitamin K antagonist oral anticoagulants are associated with a significantly lower risk of osteoporosis when compared with warfarin in Taiwanese patients with atrial fibrillation treated with oral anticoagulants.
- The significantly lower risk of osteoporosis was identified only in patients treated with rivaroxaban and apixaban but not in those treated with dabigatran.

What Are the Clinical Implications?

- If oral anticoagulants are indicated in patients with atrial fibrillation, rivaroxaban and apixaban may be better therapeutic choices than warfarin in terms of decreasing osteoporosis risks.
- However, future studies are needed to confirm causality and to weigh a potential benefit with respect to osteoporosis with the other risks/benefits of the different oral anticoagulant treatments.

associated with reduced bone density and increased risks of osteoporosis or osteoporotic fracture compared with controls[5–7]; other studies, however, have not found a significant association.[4,8,9] Recently, non–vitamin K antagonist OACs (NOACs) have been approved for stroke prevention and demonstrated to be equal or superior to warfarin in terms of efficacy and safety.[10,11] NOACs are thrombin or factor Xa inhibitors that function independently of the mechanism of vitamin K antagonists. Although numerous studies have discussed and compared the efficacy and safety of NOACs with those of warfarin, evidence comparing the risks of osteoporosis between NOACs and warfarin is limited.[3,12]

As OACs are commonly prescribed in older patients who are vulnerable to both AF and osteoporosis, the possible risks of osteoporosis related to NOACs and warfarin constitute a vital clinical issue. Therefore, we conducted a real-world, nationwide cohort study to evaluate the risk of osteoporosis in patients with AF treated with NOACs or warfarin.

Methods

The data set used in this study is managed by the Taiwan Ministry of Health and Welfare and, thus, cannot be made available publicly. Researchers interested in accessing this data set can submit a formal application to the Ministry of Health and Welfare to request access (Taiwan Ministry of Health and Welfare, No. 488, Section 6, Zhongxiao E Rd, Nangang District, Taipei City 115, Taiwan; website: https://dep.mohw.gov.tw/DOS/cp-2516-3591-113.html). All relevant data are cited within the article.

Data Sources

We conducted a nationwide, propensity score–matched retrospective cohort study using the data from Taiwan's National Health Insurance Research Database (NHIRD). The National Health Insurance (NHI) program in Taiwan is a single-payer mandatory health insurance system initiated by the government in March 1995 that covers >99% of Taiwan's population. The NHI program comprehensively reimburses medical fees for almost all outpatient, inpatient, and emergency services. The NHIRD consists of the healthcare data of ≈23.6 million enrollees, representing the vast majority of Taiwan's population. It includes patient demographics and medical claims for all inpatient, outpatient, and emergency services. The diagnostic and procedure codes used in the database are derived using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), codes before 2016 and the *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*), codes since 2016. Previous studies have demonstrated that high-quality information is provided in the NHIRD for diagnoses and prescription use.[13,14] For research purposes, the NHIRD is maintained by and available from the Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan. To protect patient privacy and data security, all personal identifiers in the NHIRD are encrypted before providing access to researchers. The Research Ethics Committee of Hualien Tzu Chi Hospital approved this study (Research Ethics Committee No. IRB107-152-C), and the requirement for informed consent was waived because of anonymized data.

Study Population and Exposure

Using Taiwan's entire populace as the study population, we identified all patients in NHIRD aged ≥20 years who were diagnosed with new-onset AF between 2012 and 2015. In Taiwan, the use of NOACs for stroke prevention in patients with AF was approved in 2012. Thus, to avoid selection bias, we included only those patients who began NOAC or warfarin treatment after NOAC approval, as this ensured that individuals had the opportunity to receive either NOACs or warfarin. AF was identified when patients were diagnosed at least once in inpatient services, or twice in outpatient services, with *ICD-9-CM* code 427.31. The high accuracy of AF diagnosis in the NHIRD has been previously reported.[15] To increase the likelihood of identifying only newly diagnosed AF, patients who were diagnosed with AF before 2012 were excluded.

The population with AF was divided into NOAC and warfarin cohorts. The NOAC and warfarin cohorts included

patients who received NOACs (rivaroxaban, dabigatran, or apixaban) and warfarin, respectively, for at least 90 days after AF diagnosis during the follow-up period. To analyze the effect of each NOAC, the NOAC cohort was further categorized into 3 subgroups (rivaroxaban, dabigatran, and apixaban), with patients in these subgroups having received the NOAC for at least 90 days. Edoxaban was not evaluated in this study because it was unavailable until 2016 in the NHI program. The index date was defined as the date of the first prescription of NOAC or warfarin. To clearly compare the effects of each OAC on the risk of osteoporosis, we excluded patients who received both NOAC and warfarin for ≥90 days and those who received >1 NOAC for ≥90 days to avoid contamination of the data by mixed-drug use. Patients who did not receive any OACs, received OACs for <90 days, or had initiated treatment with NOAC or warfarin before the index date were also excluded. To accurately identify the incidence of osteoporosis, patients diagnosed with osteoporosis before the index date were additionally excluded.

Outcome Measures

The primary outcome was defined as a new diagnosis of osteoporosis (*ICD-9-CM* codes 733.0 and 733.1; *ICD-10-CM* codes M80 and M81). In Taiwan, osteoporosis is diagnosed according to the T-score derived from bone mineral density (normal, T-score ≥−1; low bone mass, T-score between −1 and −2.5; and osteoporosis, T-score ≤−2.5) or according to low-impact fractures diagnosed via clinical history, which conforms to the Taiwanese osteoporosis practice guidelines developed by the Taiwanese Osteoporosis Association.[16] All individuals were followed up from the index date until the occurrence of the primary outcome, death, or December 31, 2016 (the final date in our data set), whichever was earliest. In addition to the comparison between all NOACs and warfarin, each NOAC was also individually compared with warfarin and with the other NOACs in subanalyses. Furthermore, the duration of treatment in the subanalyses was stratified (90–180, 181–365, and >365 days) to investigate whether a cumulative treatment effect existed. Age- and sex-stratified subanalyses were also performed.

Covariates and Confounders

We retrieved baseline characteristics and clinical details from both the outpatient and inpatient data that were considered potential confounders, according to *ICD-9-CM* codes and prescription codes. A preexisting comorbidity was defined as a disease diagnosed in at least 1 inpatient or 2 outpatient services before the index date. Charlson comorbidity index scores were calculated on the basis of preexisting comorbidities.[17] We also calculated the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74, female) score, commonly used to determine whether OACs should be prescribed, because of this score's ability to predict the risk of ischemic stroke and thromboembolic events.[18,19] Baseline medication was defined as a drug prescribed for at least 30 days within the year preceding the index date. Baseline comorbidities and medications that were considered potential confounders were selected on the basis of previous studies.[20,21] The monthly income level was estimated according to the income-related NHI premiums and was classified into 4 levels (new Taiwan dollars: ≥45 000, 30 000−44 999, 15 840−29 999, and financially dependent). To eliminate a possible confounding effect caused by healthcare use, we calculated the average number of outpatient visits, emergency department visits, and hospitalizations per year for each patient during the follow-up period.

Propensity Score Matching

Propensity score matching is widely used in observational studies that estimate the effects of treatments compared with controls on outcomes. The propensity score method allows one to design and analyze an observational (nonrandomized) study so that it mimics some of the particular characteristics of a randomized controlled trial.[22] To balance baseline differences and minimize the selection bias between the NOAC and warfarin cohorts, propensity score matching was implemented before performing the analyses. The propensity score associated with the reception of each OAC was calculated for each patient using logistic regression models based on all the covariates listed in Table 1. Propensity score matching was performed using the nearest-neighbor matching algorithm without replacement, with a caliper width equal to 0.2 of the SD of the logit of the propensity score.[23,24] In all head-to-head comparisons (ie, NOACs versus warfarin and each NOAC versus warfarin), 1:1 propensity score matching was performed. Standardized difference was used to assess the difference in baseline characteristics between groups, and a value of <0.1 was considered negligible.

Statistical Analysis

Continuous variables were compared using an independent *t* test, and categorical variables were compared using χ^2 tests. The cumulative incidences of osteoporosis were estimated using Nelson-Aalen methods, and the differences between the cumulative incidence curves were determined by log-rank tests. The proportional hazard assumption was tested using Schoenfeld residuals test to ensure the validity of conducting a Cox regression analysis. The hazard ratios (HRs) and 95% CIs for incident osteoporosis were calculated

Table 1. Baseline Characteristics of Patients With AF Treated With NOAC and Warfarin

Characteristics	NOAC (n=8504)		Warfarin (n=8504)		Standardized Difference
	n	%	n	%	
Age, y					
<65	2882	33.9	2656	31.2	0.057
65–79	3529	41.5	3637	42.8	0.026
≥80	2093	24.6	2211	26.0	0.032
Mean±SD	71.0	±11.4	70.8	±11.9	0.015
Sex					
Men	5002	58.8	5074	59.7	0.017
Women	3502	41.2	3430	40.3	0.017
Income level (NTD)					
Financially dependent	1697	20.0	1748	20.6	0.015
15 840–29 999	3518	41.4	3513	41.3	0.001
30 000–44 999	1682	19.8	1638	19.3	0.013
≥45 000	1607	18.9	1605	18.9	0.001
Healthcare use, mean±SD, No. of times/y					
Outpatient visits	35.0	±21.4	34.7	±19.1	0.012
Emergency department visits	1.2	±2.4	1.1	±1.9	0.009
Hospitalizations	1.0	±1.8	0.9	±1.5	0.025
CHA_2DS_2-VASc score, mean±SD	2.4	±1.7	2.5	±1.7	0.036
Charlson comorbidity index, mean±SD	4.1	±2.8	4.2	±2.9	0.035
Comorbidities					
Hypertension	6465	76.0	6579	77.4	0.032
Diabetes mellitus	2832	33.3	2922	34.4	0.022
Coronary artery disease	3769	44.3	3851	45.3	0.019
Congestive heart failure	3485	41.0	3295	38.8	0.046
COPD	1953	23.0	2014	23.7	0.017
Chronic kidney disease	1581	18.6	1472	17.3	0.033
Cirrhosis	1075	12.6	1120	13.2	0.016
Hyperthyroidism	343	4.0	345	4.1	0.002
Hypothyroidism	168	2.0	166	2.0	0.002
Dementia	515	6.1	548	6.4	0.016
Depression	438	5.2	476	5.6	0.020
Parkinsonism	249	2.9	265	3.1	0.011
Epilepsy	136	1.6	136	1.6	0.000
Stroke	2862	33.7	3030	35.6	0.042
Rheumatoid arthritis	145	1.7	138	1.6	0.007
Malignancy	680	8.0	745	8.8	0.027
Cataract	2216	26.1	2414	28.4	0.052
Fracture	952	11.2	984	11.6	0.012
Use of medication					
Corticosteroids	458	5.4	451	5.3	0.004
Diuretics	2670	31.4	2557	30.1	0.029
NSAIDs	2290	26.9	2315	27.2	0.007
Statins	1699	20.0	1865	21.9	0.048
PPIs	681	8.0	671	7.9	0.004
Antiepileptics	584	6.9	587	6.9	0.001
Antiparkinsonian agents	196	2.3	217	2.6	0.016
Antipsychotics	338	4.0	335	3.9	0.002
Anxiolytics	1886	22.2	1978	23.3	0.026
Hypnotics and sedatives	1056	12.4	1069	12.6	0.005
Antidepressants	592	7.0	619	7.3	0.012
Thyroxine	158	1.9	163	1.9	0.004
Antithyroid drugs	170	2.0	165	1.9	0.004

Continuous variables are expressed as means±SDs; categorical variables are expressed as numbers and percentages. AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; NOAC, non–vitamin K antagonist oral anticoagulant; NTD, new Taiwan dollar; PPI, proton pump inhibitor; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65–74, female.

using univariable and multivariable Cox proportional hazards regression models. All the covariates listed in Table 1 were used to adjust the multivariable Cox proportional hazards regression models. Stratified analyses were performed for age, sex, and duration of anticoagulant use; tests for interaction were used to determine whether a subgroup effect on osteoporosis risk existed. Results with a 2-sided $P<0.05$ were considered statistically significant. Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, NC) and Stata 15 (Stata Corporation, College Station, TX).

Sensitivity Analyses

Three sensitivity analyses were performed. Although propensity score matching can help balance baseline characteristics, a portion of the study population that could not be matched to

a case or control was excluded, and this exclusion may be a source of selection bias. Thus, we conducted a sensitivity analysis that included all eligible patients without performing propensity score matching before the analyses (sensitivity analysis A). In addition, to determine whether the method of propensity score matching with and without replacement influenced the study results, we performed analyses using the propensity score matching with replacement (nearest-neighbor matching with replacement; sensitivity analysis B). Furthermore, we performed the analysis after excluding patients with AF with a history of rheumatic heart disease or congenital heart disease or who had undergone valve replacement surgery, for whom there is a tendency to prescribe warfarin rather than NOACs, according to the current clinical guidelines.[25] Therefore, we determined whether this possible indication bias existed and could affect our results (sensitivity analysis C).

Results

Patient Characteristics

A total of 25 355 patients with new-onset AF and treated with OACs were identified before propensity score matching; 15 006 and 10 349 patients were treated with NOACs and warfarin, respectively. After propensity score matching, 17 008 patients were included, with 8504 patients each in the NOAC and warfarin cohorts. Many baseline characteristics varied between the NOAC and warfarin cohorts before matching (Table S1). However, after propensity score matching, all baseline characteristics were well balanced, with all standardized differences <0.1 (Table 1). The baseline characteristics for each individual NOAC and warfarin comparison set after propensity score matching are summarized in Table S2. The overall median follow-up time was 2.1 years.

Risk of Osteoporosis

During the follow-up period, 210 patients in the NOAC cohort and 328 patients in the warfarin cohort developed osteoporosis (Table 2). The cumulative incidence curves revealed that the NOAC cohort had a lower cumulative incidence of osteoporosis compared with the warfarin cohort (log-rank test, *P*=0.061; Figure). The Schoenfeld residuals test confirmed that the proportional hazard assumption was not violated for head-to-head comparison conducted. Overall, NOAC treatment was associated with a lower risk of osteoporosis than warfarin treatment in patients with AF, as determined by a multivariable Cox proportional hazards regression model (adjusted HR [aHR]=0.82; 95% CI=0.68–0.97; *P*=0.024; Table 2).

Table 2. Risk of Osteoporosis in Patients With AF Treated With NOAC Versus Warfarin

Variables	NOAC (n=8504)	Warfarin (n=8504)
Event No.	210	328
Person-years	14 466	20 378
Incidence rate*	14.5	16.1
Univariable model		
Crude HR (95% CI)	0.85 (0.71–1.01)	1 (Reference)
P value	0.062	
Multivariable model†		
Adjusted HR (95% CI)	0.82 (0.68–0.97)	1 (Reference)
P value	0.024	

AF indicates atrial fibrillation; HR, hazard ratio; NOAC, non–vitamin K antagonist oral anticoagulant.
*Per 1000 person-years.
†Multivariable Cox proportional hazard regression model with adjustments for all baseline characteristics listed in Table 1.

Stratified Analyses and Interaction Tests for Sex, Age, and OAC Treatment Duration

After stratification by sex, a significantly lower risk of osteoporosis with NOAC compared with warfarin treatment was observed only in female patients (aHR=0.79; 95% CI=0.64–0.98; *P*=0.029), but not in male patients (aHR=0.88; 95% CI=0.63–1.23; *P*=0.462). As well, a significantly lower risk of osteoporosis between NOAC and warfarin groups was identified only in patients aged ≥65 years (aHR=0.81; 95% CI=0.67–0.98; *P*=0.029), but not in patients aged <65 years (aHR=0.85; 95% CI=0.47–1.52; *P*=0.577; Table 3). However, the interaction tests did not reveal a significant subgroup effect of age and

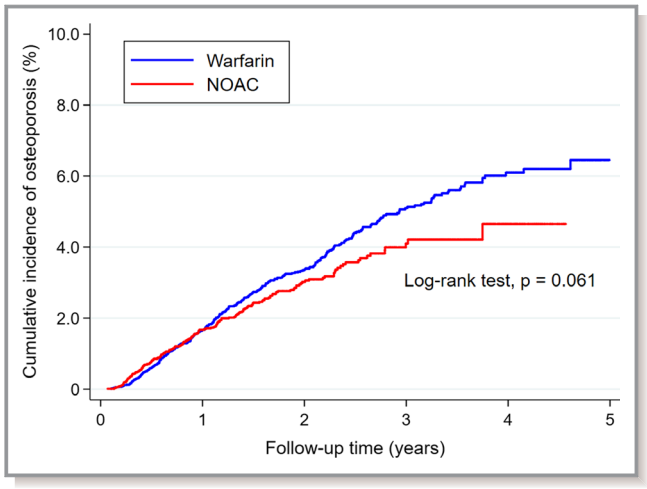

Figure. The cumulative incidence curves of osteoporosis in patients with atrial fibrillation treated with non–vitamin K antagonist oral anticoagulants (NOACs) or warfarin.

Table 3. Risk of Osteoporosis in Patients With AF Treated With NOAC Versus Warfarin After Stratification

Variables	Univariable Model		Multivariable Model*		
	Crude HR (95% CI)†	*P* Value	Adjusted HR (95% CI)†	*P* Value	*P* Value for Interaction
Sex‡					
Men	0.90 (0.65–1.24)	0.510	0.88 (0.63–1.23)	0.462	0.618
Women	0.82 (0.66–1.01)	0.056	0.79 (0.64–0.98)	0.029	
Age, y§					
<65	0.91 (0.52–1.58)	0.726	0.85 (0.47–1.52)	0.577	0.589
≥65	0.86 (0.72–1.04)	0.112	0.81 (0.67–0.98)	0.029	
Duration of anticoagulant use, d‖					
90–180	1.42 (1.03–1.97)	0.034	1.35 (0.95–1.90)	0.093	<0.001
181–365	0.69 (0.50–0.96)	0.026	0.69 (0.50–0.97)	0.031	
>365	0.71 (0.54–0.94)	0.016	0.72 (0.54–0.96)	0.024	

AF indicates atrial fibrillation; HR, hazard ratio; NOAC, non–vitamin K antagonist oral anticoagulant.
*Multivariable Cox proportional hazards regression model with adjustments for all baseline characteristics shown in Table 1.
†The HRs were calculated using patients treated with warfarin as the reference group in the Cox proportional hazards regression model.
‡In the male stratum, there were 5002 and 5074 patients in the NOAC and warfarin groups, respectively; in the female stratum, there were 3502 and 3430 patients in the NOAC and warfarin groups, respectively.
§In the stratum of age <65 years, there were 2882 and 2656 patients in the NOAC and warfarin groups, respectively; in the stratum of age ≥65 years, there were 5622 and 5848 patients in the NOAC and warfarin groups, respectively.
‖In the stratum of duration of 90 to 180 days, there were 1388 and 1442 patients in the NOAC and warfarin groups, respectively; in the stratum of duration of 181 to 365 days, there were 1928 and 1617 patients in the NOAC and warfarin groups, respectively; in the stratum of duration of >365 days, there were 5188 and 5445 patients in the NOAC and warfarin groups, respectively.

sex on osteoporosis risk (sex: *P* for interaction=0.618; age: *P* for interaction=0.589).

In the analyses stratified by OAC treatment duration, a cumulative treatment effect was observed. The association between NOAC use and a lower incidence of osteoporosis seemed to be stronger in those with longer treatment duration (90–180 days: aHR=1.35, 95% CI=0.95–1.90, *P*=0.093; 181–365 days: aHR=0.69, 95% CI=0.50–0.97, *P*=0.031; >365 days: aHR=0.72, 95% CI=0.54–0.96, *P*=0.024). The interaction test also revealed that a subgroup effect of treatment duration on osteoporosis risk existed (*P* for interaction <0.001) (Table 3).

Subanalyses for Each NOAC (Rivaroxaban, Dabigatran, and Apixaban) Versus Warfarin

In the subanalyses evaluating individual NOACs versus warfarin, we found that rivaroxaban and apixaban were associated with lower risks of osteoporosis compared with warfarin, with aHRs of 0.68 (95% CI=0.55–0.83; *P*<0.001) and 0.38 (95% CI=0.22–0.66; *P*<0.001), respectively. However, there was no significant difference in the risk of osteoporosis between patients treated with dabigatran and those treated with warfarin (aHR=1.04; 95% CI=0.85–1.27; *P*=0.698; Table 4).

Subanalyses for Comparison Between Specific NOACs (Rivaroxaban, Dabigatran, and Apixaban)

Because of the differing results for each NOAC versus warfarin, we performed further subanalyses to compare the osteoporosis risk between the different NOACs. Compared with dabigatran, both rivaroxaban (aHR=0.63; 95% CI=0.50–0.80; *P*<0.001) and apixaban (aHR=0.39; 95% CI=0.22–0.67; *P*<0.001) were associated with a lower risk of osteoporosis. There was no significant difference in osteoporosis risk when comparing apixaban and rivaroxaban (aHR=0.72; 95% CI=0.38–1.34; *P*=0.298; Table S3).

Results of Sensitivity Analyses

All of the sensitivity analyses, including analysis A (which included all the eligible patients for analyses without propensity score matching), analysis B (in which propensity score matching using nearest-neighbor matching with replacement was performed), and analysis C (which excluded patients who had rheumatic heart disease, had congenital heart disease, or had undergone valve replacement surgery), revealed similar results and led to the same conclusions as our primary analyses. The detailed statistical values for each of these analyses are shown in Table 5.

Discussion

In this real-world, nationwide, propensity score–matched cohort study, we demonstrated that NOACs are associated with a lower risk of osteoporosis when compared with warfarin in patients with AF who received OACs. More important, a

Table 4. Risk of Osteoporosis in Patients With AF Treated With Each NOAC (Rivaroxaban, Dabigatran, and Apixaban) Versus Warfarin

Variables	Event No.	Incidence Rate*	Univariable Model		Multivariable Model†	
			Crude HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Rivaroxaban vs warfarin						
Rivaroxaban (n=6579)	154	14.3	0.73 (0.60–0.89)	0.002	0.68 (0.55–0.83)	<0.001
Warfarin (n=6579)	287	18.3	1.00 (Reference)		1.00 (Reference)	
Dabigatran vs warfarin						
Dabigatran (n=5276)	199	18.5	1.09 (0.89–1.32)	0.407	1.04 (0.85–1.27)	0.698
Warfarin (n=5276)	211	16.2	1.00 (Reference)		1.00 (Reference)	
Apixaban vs warfarin						
Apixaban (n=1382)	18	11.8	0.46 (0.27–0.78)	0.004	0.38 (0.22–0.66)	<0.001
Warfarin (n=1382)	76	23.7	1.00 (Reference)		1.00 (Reference)	

AF indicates atrial fibrillation; HR, hazard ratio; NOAC, non–vitamin K antagonist oral anticoagulant.
*Per 1000 person-years.
†Multivariable Cox proportional hazards regression model with adjustments for all baseline characteristics shown in Table 1.

subgroup effect of treatment duration was identified (namely, the association between a lower osteoporosis risk with NOAC use compared with warfarin use tended to be stronger in those with longer treatment duration). Subanalyses further revealed that significantly lower risks of osteoporosis were found in patients treated with rivaroxaban and apixaban, but not in those treated with dabigatran. To the best of our knowledge, the present study is the first to evaluate the risk of osteoporosis in patients with AF treated with NOACs or warfarin using nationwide, large-scale data.

A previous retrospective cohort study, published in 2017, demonstrated that dabigatran, compared with warfarin, was associated with a lower risk of osteoporotic fractures (combined hip or vertebral fractures as a single outcome).[26] However, because that study used claims-based data, it could not determine the exact fracture mechanism and thus could

Table 5. Comparison for the Risk of Osteoporosis in Patients Treated With NOACs Versus Warfarin in the Sensitivity Analyses

	Sensitivity Analysis A*		Sensitivity Analysis B†		Sensitivity Analysis C‡	
	Adjusted HR (95% CI)§	*P* Value	Adjusted HR (95% CI)§	*P* Value	Adjusted HR (95% CI)§	*P* Value
NOAC vs warfarin						
NOAC overall	0.85 (0.73–0.99)	0.031	0.84 (0.74–0.95)	0.007	0.83 (0.68–1.01)	0.066
Warfarin	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Rivaroxaban vs warfarin						
Rivaroxaban	0.71 (0.59–0.85)	<0.001	0.65 (0.54–0.78)	<0.001	0.64 (0.51–0.81)	<0.001
Warfarin	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Dabigatran vs warfarin						
Dabigatran	1.07 (0.90–1.27)	0.461	1.05 (0.87–1.27)	0.601	1.06 (0.86–1.31)	0.588
Warfarin	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Apixaban vs warfarin						
Apixaban	0.55 (0.34–0.90)	0.016	0.40 (0.22–0.71)	0.002	0.41 (0.20–0.84)	0.015
Warfarin	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	

HR indicates hazard ratio; NOAC, non–vitamin K antagonist oral anticoagulant.
*Sensitivity analysis A was conducted by including all the eligible patients for analyses without performing propensity score matching.
†Sensitivity analysis B was conducted by performing propensity score matching with replacement (nearest-neighbor matching with replacement) before analyses.
‡Sensitivity analysis C was conducted by excluding patients who had rheumatic heart disease, who had congenital heart disease, or who had undergone valve replacement surgery before analyses.
§The HRs were calculated using multivariable Cox proportional hazard regression models adjusted for all baseline characteristics shown in Table 1.

not definitively state that the fractures originated from osteoporosis. In addition, there was debate about whether the observed decreased fracture risk in dabigatran users in that study originated from other mechanisms, such as prevention of falls or improvement of bone volume.[26–28] Furthermore, the previous study evaluated only one type of NOAC (dabigatran, a direct thrombin inhibitor), without comparison to other NOAC types (factor Xa inhibitors, such as rivaroxaban and apixaban). Another recent study, the only study we found that evaluated the risk of osteoporosis associated with NOACs versus warfarin in humans, also had some major limitations.[12] Specifically, the study evaluated a small sample size, with a total of 334 patients, and included only 3 cases treated with warfarin. In that study, only 11 osteoporosis events were eventually identified, and the odds ratio of osteoporosis could not be calculated appropriately because of the insufficient number of events.[12] Moreover, the observational cross-sectional study design did not allow for longitudinal follow-up.[12]

In our study, we used a large-scale cohort study design with a long-term follow-up duration and comprehensive analyses. Our study not only performed comparisons of osteoporosis risk between all NOACs and warfarin but also compared specific NOACs (dabigatran, rivaroxaban, and apixaban) with warfarin and with each other. Our findings provide stronger and more comprehensive evidence for the association between osteoporosis and the different OACs. Of note, in our subanalysis for each specific NOAC, the significant lower osteoporosis risk was observed only in the rivaroxaban and apixaban subgroups, but not in the dabigatran subgroup, when compared with that in warfarin users. This finding appears to be incompatible with that of a previous study that found dabigatran, compared with warfarin, to be associated with lower fracture risks.[26] Because of the undetermined fracture mechanism in that study (as mentioned above), as well as the retrospective cohort study design used in both that study and ours, we suggest that further prospective studies, including randomized controlled trials and in which detailed bone mineral density data and fracture mechanisms are included, should be conducted in the future.

Although the exact mechanisms underlying the association between a lower osteoporosis risk and NOAC use compared with warfarin are not well understood, there are some possible explanations. Previous studies have indicated that warfarin may interfere with processes that contribute to bone formation because of its antagonistic actions against vitamin K.[29] By opposing vitamin K–dependent processes, warfarin impairs γ-carboxylation of osteocalcin and other bone matrix proteins, which may result in impaired bone mineralization and bone formation, and further promote osteoporosis.[3,26,29] In contrast, NOACs act independently of vitamin K antagonism and therefore theoretically do not interfere with bone metabolism.[3] Some animal studies have found that NOACs are associated with increased bone volume, decreased trabecular separation, lower bone turnover rate, and better fracture healing when compared with warfarin or placebo.[30,31] Recently, a possible positive effect of NOACs on bone health that is unrelated to warfarin or vitamin K has also been proposed.[27] Furthermore, our subanalyses revealed that only factor Xa inhibitors (rivaroxaban and apixaban), rather than thrombin inhibitors (dabigatran), were associated with decreased osteoporosis risks. This finding implies that each NOAC may have its own effect on bone health rather than simply avoiding the negative effects of vitamin K antagonism. Further studies are necessary to investigate the possible underlying mechanisms of the effects of each NOAC on bone health.

The main strength of the present study is its large-scale, nationwide study design using real-world data. However, some limitations need to be addressed. First, the study design was retrospective, and the outcome assessment relied on administrative diagnosis codes. We could not confirm the diagnostic accuracy of osteoporosis by directly evaluating patients but only on the basis of the diagnostic codes to define the osteoporosis outcome. Therefore, misclassifications could lead to false associations. Second, we lacked granular data on clinical characteristics, such as smoking history, bone mineral density, and serum calcium and vitamin D levels. It would be unrealistic to gather such data for a national population. Although we carefully designed the current study by including propensity score matching to balance the baseline differences between the groups and incorporating multivariable Cox proportional hazards regression models to eliminate residual confounding effects, biases related to unmeasured confounders remain a potential issue, given the nature of this study. Third, although NOAC and warfarin have similar clinical indications for stroke prevention in patients with AF, we could not obtain the actual and detailed information or reasons as to why physicians choose to prescribe warfarin or NOAC, on the basis of the administrative database, and, thus, we were unable to add these potential factors into propensity score models or to adjust for these factors in our regression models. Fourth, previous studies have indicated that patients undergoing oral anticoagulant treatment are also, because of their age, often those at higher risk for falls,[32,33] which may present as a potential confounder. However, using the claims-based data set, we could not identify fall events. We also could not determine the exact reasons for diagnosing osteoporosis in this claims-based study. Further studies resolving these issues are required. In addition, although the follow-up period in the present study allowed us to identify a significant difference in osteoporosis risk between NOACs and warfarin, change in bone density is a long-term process, and further studies with longer follow-up periods are necessary to confirm our

findings. Finally, the present study was performed in the Taiwanese population; thus, generalization of the study findings to populations of other countries or races is undetermined. Further studies are necessary to examine the external generalizability.

Conclusions

In this real-world, nationwide, propensity score–matched cohort study, NOAC use was associated with a significantly lower risk of osteoporosis when compared with warfarin in patients with AF treated with OACs. More important, a subgroup effect of treatment duration was found; the association of lower osteoporosis risk with NOAC compared with warfarin seems to be stronger in those with longer treatment duration. In addition, the significantly lower risk of osteoporosis was found only in patients treated with rivaroxaban and apixaban, but not in those treated with dabigatran. Future studies are needed to understand the mechanisms that underlie the observed association between a decrease in the cumulative risk of osteoporosis in patients with AF and NOACs, compared with warfarin, and to determine the causal relationship.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics of patients with atrial fibrillation treated with oral anticoagulants before propensity score matching.

	NOAC				Warfarin (n = 10,349)
	Overall (n = 15,006)	Rivaroxaban (n = 7,977)	Dabigatran (n = 5,644)	Apixaban (n = 1,385)	
	n (%)	n (%)	n (%)	n (%)	n (%)
Age, years					
< 65	2,971 (19.8)	1,502 (18.8)	1,219 (21.6)	250 (18.1)	4,354 (42.1)
65–79	7,249 (48.3)	3,769 (47.3)	2,805 (49.7)	675 (48.7)	3,730 (36.0)
≥ 80	4,786 (31.9)	2,706 (33.9)	1,620 (28.7)	460 (33.2)	2,265 (21.9)
Mean (SD)	73.9 (10.3)	74.3 (10.4)	73.2 (10.3)	74.4 (10.0)	68.4 (12.6)
Sex					
Male	9,025 (60.1)	4,634 (58.1)	3,596 (63.7)	795 (57.4)	6,132 (59.3)
Female	5,981 (39.9)	3,343 (41.9)	2,048 (36.3)	590 (42.6)	4,217 (40.8)
Income level (NTD)					
Financially dependent	3,408 (22.7)	1,774 (22.2)	1,314 (23.3)	320 (23.1)	1,998 (19.3)
15,840–29,999	6,277 (41.8)	3,388 (42.5)	2,330 (41.3)	559 (40.4)	4,148 (40.1)
30,000–44,999	2,537 (16.9)	1,329 (16.7)	975 (17.3)	233 (16.8)	2,196 (21.2)
≥ 45,000	2,784 (18.6)	1,486 (18.6)	1,025 (18.2)	273 (19.7)	2,007 (19.4)
Healthcare utilization (No. of times/year), mean (SD)					
Outpatient visits	33.9 (20.1)	34.0 (20.0)	33.2 (20.0)	35.7 (20.8)	34.2 (19.3)
Emergency department visits	1.1 (2.1)	1.1 (2.1)	0.9 (1.9)	1.2 (2.8)	1.1 (2.0)
Hospitalizations	0.8 (1.5)	0.8 (1.5)	0.7 (1.3)	0.8 (1.7)	1.0 (1.6)
CHA2DS2-VASc score, mean (SD)	2.8 (1.6)	2.8 (1.6)	2.6 (1.5)	3.0 (1.7)	2.3 (1.7)

Charlson comorbidity index, mean (SD)	4.4 (2.9)	4.5 (2.9)	4.2 (2.7)	4.8 (3.0)	4.0 (2.9)
Comorbidities					
Hypertension	12,131 (80.8)	6,474 (81.2)	4,503 (79.8)	1,154 (83.3)	7,493 (72.4)
Diabetes mellitus	5,246 (35.0)	2,743 (34.4)	1,960 (34.7)	543 (39.2)	3,318 (32.1)
Coronary artery disease	6,943 (46.3)	3,827 (48.0)	2,411 (42.7)	705 (50.9)	4,458 (43.1)
Congestive heart failure	5,120 (34.1)	2,824 (35.4)	1,802 (31.9)	494 (35.7)	4,209 (40.7)
COPD	3,910 (26.1)	2,133 (26.7)	1,388 (24.6)	389 (28.1)	2,258 (21.8)
Chronic kidney disease	2,054 (13.7)	1,132 (14.2)	664 (11.8)	258 (18.6)	1,846 (17.8)
Cirrhosis	2,058 (13.7)	1,129 (14.2)	699 (12.4)	230 (16.6)	1,350 (13.0)
Hyperthyroidism	571 (3.8)	281 (3.5)	222 (3.9)	68 (4.9)	446 (4.3)
Hypothyroidism	321 (2.1)	177 (2.2)	101 (1.8)	43 (3.1)	202 (2.0)
Dementia	1,149 (7.7)	665 (8.3)	383 (6.8)	101 (7.3)	565 (5.5)
Depression	1,001 (6.7)	552 (6.9)	344 (6.1)	105 (7.6)	530 (5.1)
Parkinsonism	515 (3.4)	293 (3.7)	169 (3.0)	53 (3.8)	277 (2.7)
Epilepsy	257 (1.7)	150 (1.9)	76 (1.4)	31 (2.2)	151 (1.5)
Stroke	6,380 (42.5)	3,260 (40.9)	2,580 (45.7)	540 (39.0)	3,237 (31.3)
Rheumatoid arthritis	245 (1.6)	128 (1.6)	84 (1.5)	33 (2.4)	161 (1.6)
Malignancy	1,526 (10.2)	842 (10.6)	531 (9.4)	153 (11.1)	838 (8.1)
Cataract	5,210 (34.7)	2,846 (35.7)	1,832 (32.5)	532 (38.4)	2,565 (24.8)
Fracture	1,944 (13.0)	1,085 (13.6)	663 (11.8)	196 (14.2)	1,112 (10.7)
Use of medication					
Corticosteroids	758 (5.1)	407 (5.1)	287 (5.1)	64 (4.6)	514 (5.0)
Diuretics	4,099 (27.3)	2,182 (27.4)	1,477 (26.2)	440 (31.8)	3,091 (29.9)
NSAIDs	4,163 (27.7)	2,226 (27.9)	1,590 (28.2)	347 (25.1)	2,657 (25.7)
Statins	3,914 (26.1)	2,113 (26.5)	1,372 (24.3)	429 (31.0)	2,015 (19.5)
PPIs	1,086 (7.2)	599 (7.5)	383 (6.8)	104 (7.5)	815 (7.9)
Antiepileptics	936 (6.2)	525 (6.6)	319 (5.7)	92 (6.6)	716 (6.9)
Antiparkinsonian	447 (3.0)	253 (3.2)	158 (2.8)	36 (2.6)	230 (2.2)

Antipsychotics	572 (3.8)	330 (4.1)	184 (3.3)	58 (4.2)	394 (3.8)
Anxiolytics	3,673 (24.5)	1,982 (24.9)	1,336 (23.7)	355 (25.6)	2,276 (22.0)
Hypnotics and sedatives	1,893 (12.6)	992 (12.4)	711 (12.6)	190 (13.7)	1,252 (12.1)
Antidepressants	1,114 (7.4)	589 (7.4)	417 (7.4)	108 (7.8)	704 (6.8)
Thyroxine	316 (2.1)	177 (2.2)	102 (1.8)	37 (2.7)	184 (1.8)
Antithyroid drugs	271 (1.8)	129 (1.6)	108 (1.9)	34 (2.5)	216 (2.1)

Continuous variables are expressed as means (SD); categorical variables are expressed as numbers (%).

COPD = chronic obstructive pulmonary disease; NTD = New Taiwan Dollar; NOAC = non-vitamin K antagonist oral anticoagulant; NSAID = non-steroid anti-inflammatory drug; PPI = proton pump inhibitor; SD = standard deviation.

Table S2. Baseline characteristics of patients with atrial fibrillation treated with each NOAC compared with warfarin after propensity score matching.

	Rivaroxaban (n = 6,579)	Warfarin (n = 6,579)	Dabigatran (n = 5,276)	Warfarin (n = 5,276)	Apixaban (n = 1,382)	Warfarin (n = 1,382)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age, years						
< 65	1,500 (22.8)	1,485 (22.6)	1,219 (23.1)	1,189 (22.5)	250 (18.1)	258 (18.7)
65–79	3,133 (47.6)	3,103 (47.2)	2,575 (48.8)	2,587 (49.0)	672 (48.6)	678 (49.1)
≥ 80	1,946 (29.6)	1,991 (30.3)	1,482 (28.1)	1,500 (28.4)	460 (33.3)	446 (32.3)
Mean (SD)	73.3 (10.7)	72.8 (11.2)	72.9 (10.4)	72.4 (11.1)	74.4 (10.0)	73.7 (10.6)
Sex						
Male	3,788 (57.6)	3,795 (57.7)	3,278 (62.1)	3,306 (62.7)	793 (57.4)	793 (57.4)
Female	2,791 (42.4)	2,784 (42.3)	1,998 (37.9)	1,970 (37.3)	589 (42.6)	589 (42.6)
Income level (NTD)						
Financially dependent	1,397 (21.2)	1,413 (21.5)	1,185 (22.5)	1,180 (22.4)	319 (23.1)	333 (24.1)
15,840–29,999	2,799 (42.5)	2,784 (42.3)	2,198 (41.7)	2,199 (41.7)	559 (40.5)	560 (40.5)
30,000–44,999	1,170 (17.8)	1,141 (17.3)	926 (17.6)	926 (17.6)	232 (16.8)	205 (14.8)
≥ 45,000	1,213 (18.4)	1,241 (18.9)	967 (18.3)	971 (18.4)	272 (19.7)	284 (20.6)
Healthcare utilization (No. of times/year), mean (SD)						
Outpatient visits	34.7 (20.7)	34.6 (18.5)	33.7 (20.2)	33.8 (18.3)	35.6 (20.7)	36.8 (20.0)
Emergency department visits	1.1 (2.1)	1.1 (1.9)	0.9 (1.9)	0.9 (1.6)	1.2 (2.8)	1.3 (2.0)
Hospitalizations	0.9 (1.6)	0.9 (1.4)	0.7 (1.4)	0.8 (1.2)	0.8 (1.8)	0.8 (1.3)
CHA2DS2-VASc score, mean (SD)	2.7 (1.7)	2.7 (1.6)	2.6 (1.6)	2.6 (1.6)	3.0 (1.7)	2.8 (1.6)
Charlson comorbidity index, mean(SD)	4.2 (2.9)	4.3 (2.9)	4.2 (2.7)	4.2 (2.8)	4.8 (3.0)	4.9 (3.2)
Comorbidities						
Hypertension	5,190 (78.9)	5,237 (79.6)	4,161 (78.9)	4,170 (79.0)	1,151 (83.3)	1,149 (83.1)

Diabetes mellitus	2,210 (33.6)	2,272 (34.5)	1,787 (33.9)	1,798 (34.1)	540 (39.1)	551 (39.9)
Coronary artery disease	3,006 (45.7)	3,090 (47.0)	2,276 (43.1)	2,310 (43.8)	703 (50.9)	708 (51.2)
Congestive heart failure	2,520 (38.3)	2,531 (38.5)	1,778 (33.7)	1,800 (34.1)	494 (35.8)	509 (36.8)
COPD	1,612 (24.5)	1,682 (25.6)	1,285 (24.4)	1,269 (24.1)	387 (28.0)	393 (28.4)
Chronic kidney disease	1,081 (16.4)	1,066 (16.2)	663 (12.6)	669 (12.7)	258 (18.7)	252 (18.2)
Cirrhosis	845 (12.8)	907 (13.8)	659 (12.5)	683 (13.0)	227 (16.4)	251 (18.2)
Hyperthyroidism	237 (3.6)	236 (3.6)	213 (4.0)	213 (4.0)	68 (4.9)	67 (4.9)
Hypothyroidism	141 (2.1)	148 (2.3)	97 (1.8)	109 (2.1)	43 (3.1)	35 (2.5)
Dementia	462 (7.0)	466 (7.1)	350 (6.6)	358 (6.8)	101 (7.3)	100 (7.2)
Depression	381 (5.8)	389 (5.9)	301 (5.7)	319 (6.1)	103 (7.5)	116 (8.4)
Parkinsonism	219 (3.3)	229 (3.5)	158 (3.0)	152 (2.9)	53 (3.8)	53 (3.8)
Epilepsy	109 (1.7)	103 (1.6)	70 (1.3)	75 (1.4)	31 (2.2)	33 (2.4)
Stroke	2,418 (36.8)	2,509 (38.1)	2,224 (42.2)	2,277 (43.2)	538 (38.9)	537 (38.9)
Rheumatoid arthritis	105 (1.6)	114 (1.7)	79 (1.5)	70 (1.3)	33 (2.4)	40 (2.9)
Malignancy	592 (9.0)	635 (9.7)	476 (9.0)	462 (8.8)	152 (11.0)	151 (10.9)
Cataract	2,059 (31.3)	2,111 (32.1)	1,656 (31.4)	1,677 (31.8)	529 (38.3)	546 (39.5)
Fracture	785 (11.9)	827 (12.6)	608 (11.5)	600 (11.4)	195 (14.1)	200 (14.5)
Use of medication						
Corticosteroids	351 (5.3)	338 (5.1)	262 (5.0)	278 (5.3)	64 (4.6)	74 (5.4)
Diuretics	1,946 (29.6)	1,942 (29.5)	1,437 (27.2)	1,462 (27.7)	440 (31.8)	435 (31.5)
NSAIDs	1,854 (28.2)	1,820 (27.7)	1,485 (28.2)	1,468 (27.8)	345 (25.0)	356 (25.8)
Statins	1,419 (21.6)	1,560 (23.7)	1,197 (22.7)	1,233 (23.4)	426 (30.8)	416 (30.1)
PPIs	508 (7.7)	521 (7.9)	365 (6.9)	372 (7.1)	104 (7.5)	101 (7.3)
Antiepileptics	450 (6.8)	441 (6.7)	306 (5.8)	294 (5.6)	92 (6.7)	87 (6.3)
Antiparkinsonian	170 (2.6)	185 (2.8)	140 (2.7)	145 (2.8)	36 (2.6)	35 (2.5)
Antipsychotics	270 (4.1)	263 (4.0)	176 (3.3)	197 (3.7)	58 (4.2)	62 (4.5)
Anxiolytics	1,575 (23.9)	1,573 (23.9)	1,235 (23.4)	1,263 (23.9)	354 (25.6)	343 (24.8)
Hypnotics and sedatives	840 (12.8)	811 (12.3)	661 (12.5)	705 (13.4)	189 (13.7)	206 (14.9)
Antidepressants	480 (7.3)	471 (7.2)	371 (7.0)	394 (7.5)	107 (7.7)	120 (8.7)

Thyroxine	130 (2.0)	140 (2.1)	96 (1.8)	105 (2.0)	37 (2.7)	27 (2.0)
Antithyroid drugs	111 (1.7)	117 (1.8)	102 (1.9)	101 (1.9)	34 (2.5)	39 (2.8)

All standardized differences of the covariates between the treatment groups in each comparison are less than 0.1, which indicates a negligible difference in the covariates between the groups after propensity score matching.

Continuous variables are expressed as means (SD); categorical variables are expressed as numbers (%).

COPD = chronic obstructive pulmonary disease; NTD = New Taiwan Dollar; NOAC = non-vitamin K antagonist oral anticoagulant; NSAID = non-steroid anti-inflammatory drug; PPI = proton pump inhibitor; SD = standard deviation.

Table S3. Comparison of the risk of osteoporosis between atrial fibrillation patients treated with different NOACs (rivaroxaban, dabigatran, and apixaban).

	Event no.	Incidence rate*	Univariable model		Multivariable model†	
			crude HR (95% CI)	p-value	adjusted HR (95% CI)	p-value
Rivaroxaban vs. dabigatran						
Rivaroxaban (n = 5,529)	109	11.7	0.60 (0.48–0.76)	<0.001	0.63 (0.50–0.80)	<0.001
Dabigatran (n = 5,529)	214	18.9	1.00 (ref.)		1.00 (ref.)	
Apixaban vs. dabigatran						
Apixaban (n = 1,368)	18	11.9	0.44 (0.25–0.74)	0.002	0.39 (0.22–0.67)	<0.001
Dabigatran (n = 1,368)	66	24.3	1.00 (ref.)		1.00 (ref.)	
Apixaban vs. rivaroxaban						
Apixaban (n = 1,383)	18	11.8	0.87 (0.48–1.57)	0.635	0.72 (0.38–1.34)	0.298
Rivaroxaban (n = 1,383)	31	14.0	1.00 (ref.)		1.00 (ref.)	

*Per 1000 person-years.

†Multivariable Cox proportional hazards regression model with adjustments for all baseline characteristics shown in Table 1.

HR, hazard ratio; CI, confidence interval; NOAC, non-vitamin K antagonist oral anticoagulant; ref., reference.