Fracture risks among patients with atrial fibrillation receiving different oral anticoagulants: a real-world nationwide cohort study

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Aims	To evaluate the fracture risk among patients with atrial fibrillation (AF) treated with non-vitamin K antagonist oral anticoagulants (NOACs) or warfarin.
Methods and results	We conducted a real-world nationwide retrospective cohort study using Taiwan's National Health Insurance Research Database. All adult patients in Taiwan newly diagnosed with AF between 2012 and 2016 who received NOACs or warfarin were enrolled and followed up until 2017. Patients treated with NOACs were sub-grouped according to the NOAC used (dabigatran, rivaroxaban, and apixaban). Propensity score matching was performed for each head-to-head comparison. Cox regression analysis, with a shared frailty model, was used to calculate the adjusted hazard ratios (aHRs) for hip, vertebral, and humerus/forearm/wrist fractures. After matching, 19 414 patients were included (9707 in each NOAC and warfarin groups). The median follow-up time was 2.4 years. Compared with warfarin, NOACs were associated with a reduced fracture risk [aHR = 0.84, 95% confidence interval (CI) = 0.77–0.93; $P < 0.001$]. Sub-analyses revealed that each NOAC, namely dabigatran (aHR = 0.88, 95% CI = 0.78–0.99; $P = 0.027$), rivaroxaban (aHR = 0.81, 95% CI = 0.72–0.90; $P < 0.001$), and apixaban (aHR = 0.67, 95% CI = 0.52–0.87; $P = 0.003$), had a reduced fracture risk. Analyses including all eligible patients, without propensity score matching, generated similar results.
Conclusion	Compared with warfarin, NOAC was associated with a reduced fracture risk among AF patients. Therefore, if oral anticoagulants are indicated, NOACs rather than warfarin should be considered to lower the risk of fractures. However, further studies are needed to investigate the underlying mechanisms and elucidate causality.
Keywords	Atrial fibrillation • NOAC • Warfarin • Anticoagulant • Fracture • Hip fracture

Introduction

Atrial fibrillation (AF) is common among older people, and its prevalence and incidence are increasing as populations age worldwide. Stroke prevention is a pivotal component of the management of AF, with oral anticoagulants (OACs) being prescribed to achieve this goal.[1] Warfarin, a vitamin K antagonist, has been a cornerstone OAC treatment for stroke prevention in AF patients for decades. More recently, the approval of non-vitamin K antagonist OACs (NOACs) for stroke prevention has provided another OAC option, and their efficacy, safety, and convenience are comparable to warfarin.[2–4]

Osteoporotic fractures, which are major health threats among older people, cause significant morbidity, mortality, and considerable socioeconomic burdens.[5–7] An association between warfarin use and an increased risk for osteoporotic fractures has been suggested in AF patients,[8–10] but the evidence remains controversial.[11] Before NOACs became available, warfarin was the inevitable choice for AF patients and, despite concerns about increased fracture risks, alternative treatments were not available.[12] Since NOACs became available, numerous studies have compared the efficacy and safety of NOACs and warfarin. However, few studies have compared NOACs and warfarin in relation to fracture risks.[12,13] As OACs are usually prescribed to older patients who are vulnerable to both AF and osteoporotic fractures, clinical concerns about the possible effects of warfarin and NOACs on fracture risks are critically important.

To date, comparisons of fracture risks among AF patients administered NOACs or warfarin are limited. Hence, we compared the fracture risks associated with NOACs and warfarin among AF patients.

Methods

Data sources and ethical approval

We conducted a nationwide cohort study by retrieving the claims-based data from Taiwan's National Health Insurance Research Database (NHIRD). Taiwan's National Health Insurance (NHI) programme is administered by the government, is mandatory, and includes >99% of Taiwan's population.[14] The NHIRD represents Taiwan's entire population and comprises detailed health care data from about 23.6 million enrolees. The Health and Welfare Data Science Center at the Ministry of Health and Welfare in Taiwan maintains the data within the NHIRD and ensures they are available for research purposes. Before 2016, the diagnostic and procedure codes were derived from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), and from 2016, they were derived from the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). Hualien Tzu Chi Hospital's Research Ethics Committee approved this study (REC No: IRB107-152-C).

Study population and exposure

All adult patients aged ≥20 years with AF newly diagnosed between 2012 and 2016 were identified within the NHIRD. Atrial fibrillation diagnosis was defined as a discharge diagnosis or a diagnosis confirmed at least twice in an outpatient department using the ICD-9-CM code 427.31. The accuracy of this definition of AF in the NHIRD has been validated.[15] Those patients who were diagnosed with AF before 2012 were excluded to ensure that newly diagnosed AF was identified.

To compare fracture risk in patients treated with NOACs or warfarin, we divided the AF population into two cohorts, the NOAC and the warfarin cohort. Each cohort included only patients who had been continuously treated with either NOACs or warfarin for a period of at least 90 days since initiating treatment after AF diagnosis. The NOAC cohort was further subdivided into three subgroups according to the NOAC type used (dabigatran, rivaroxaban, and apixaban). Edoxaban was not evaluated because it was not available in Taiwan's NHI programme until 2016. The study cohorts were classified according to the treatment status within 90 days of initiating OAC treatment. The index date were defined as the 91st day after initiating OAC treatment, and the follow-up started subsequently. This approached minimized the risk of possible immortal time and survival bias.

Changes in bone health are expected to take place slowly. Hence, the long-term use of two or more OAC types may impact on the capacity to attribute the effect on bone health to a specific OAC. To obtain clear comparisons of the effects of each OAC on fracture risk, we excluded patients who received both a NOAC for ≥90 days and warfarin for ≥90 days, or received more than one NOAC for ≥90 days. We also excluded patients who did not take any OACs or did not continuously take OAC for 90 days after treatment initiation, as well as patients who were diagnosed with the primary outcome before the index date.

Outcome measures

The primary outcome was the development of any new fracture of the hip (ICD-9-CM codes: 820 and 733.14; ICD-10-CM codes: S72.0–S72.2, M80.05, and M80.85), vertebrae (ICD-9-CM codes: 805–806 and 733.13; ICD-10-CM codes: S12.0–S12.6, S22.0, S32.0–S32.2, M80.08, and M80.88), or humerus, forearm, or wrist (ICD-9-CM codes: 812–814, 733.11, and 733.12; ICD-10-CM codes: S42.2–S42.4, S52.x, S62.0–S62.1, M80.02–M80.03, and M80.82–M80.83); these fractures were selected because they are the most common and quintessential osteoporotic fractures. All individuals were followed from the index date until 31 December 2017, or until they developed any of the fractures comprising the primary outcome or died.

We also analysed hip, vertebral, and humerus/forearm/wrist fracture events individually. Patients were followed up until occurrence of any one of these fracture types; if another fracture type occurred earlier, the patient was censored. Furthermore, each NOAC (dabigatran, rivaroxaban, and apixaban) was compared with warfarin in a sub-analysis. Age- and sex-stratified sub-analyses were performed.

Covariates

We obtained patients' baseline and clinical characteristics from the reimbursement claims associated with outpatient, inpatient, and emergency services. A pre-existing comorbidity was defined as a discharge diagnosis or a diagnosis that was confirmed at least twice in an outpatient department within the year before the index date, based on the ICD-9-CM (before 2016), ICD-10-CM (since 2016), and the procedure codes. Baseline medication use was defined as a drug prescribed for ≥30 days within the year before the index date. The baseline comorbidities and medications used, which were considered potential confounders, were selected based on previous studies.[16,17] The Charlson comorbidity index was calculated based on pre-existing comorbidities recorded in each patient file.[18] The CHA_2DS_2-VASc score, which has been used to predict the risk of ischaemic stroke and thromboembolic events, was calculated in our study to determine the indication for OAC prescription.[19,20] Monthly income levels were assessed based on income-related NHI premiums and were stratified into four levels (≥45 000, 30 000–44 999, and 15 840–29 999 New Taiwan dollars, and financially dependent). The time from the first AF diagnosis to start of OAC treatment was retrieved. In addition, information for the hospital and physician specialty regarding the initial OAC prescription was obtained, including the hospital level by accreditation (medical centre, regional hospital, or district hospital and clinics), hospital region (North, Central, or South and Eastern of Taiwan), and physician specialty (cardiologist, neurologist, or other specialties).

Statistical analyses and propensity score matching

For continuous baseline characteristics, independent *t*-test and Wilcoxon rank-sum test were used to compare means and medians, respectively. The χ^2 test was used to compare categorical variables. The cumulative incidence function was used to estimate the fracture incidence, with death as a competing event, with Gray's test used to compare the cumulative

incidence curves. In the sub-analysis for a specific fracture, the development of the other fracture type was considered as a competing event.

Two main analytic methods (with and without propensity score matching) were performed to obtain the adjusted hazard ratios (aHRs) of fracture events. When analysing all eligible population without propensity score matching, multivariable Cox proportional hazard regressions were performed to calculate the aHRs and corresponding 95% confidence intervals (CIs), adjusting for covariates listed in *Table 1*. In the analyses applying propensity score matching to balance baseline differences, the aHRs were calculated using Cox regressions with shared frailty model that account for the matching. Each head-to-head comparison (NOACs vs. warfarin, and each NOAC vs. warfarin) was conducted after performing 1:1 propensity score matching for each comparison set. The propensity scores, which estimated the probability of a patient receiving each OAC, were calculated using logistic regressions adjusted for covariates listed in *Table 1*. The propensity score matching was conducted using nearest-neighbour matching algorithms without replacements, with a calliper width equal to 0.2 of the standard deviation of the logit of the propensity score. Standardized difference was used to assess the difference between treatment groups after propensity score matching[21]; a value of <0.1 was considered negligible.

All Cox regressions were performed after determining that the proportional hazard assumptions were met using statistical tests based on the Schoenfeld residuals. A two-sided probability value <0.05 was considered statistically significant. The statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA) and Stata, version 14 (Stata Corporation LLC, College Station, TX, USA).

Sensitivity analyses

The first sensitivity analysis A was performed after excluding AF patients who had rheumatic heart disease, congenital heart disease, or had undergone valve replacement surgery, because these patient populations tend to be prescribed warfarin rather than NOACs, according to the current guidelines,[22] which would bias our results. The second sensitivity analysis B was conducted by following the patients from the index date until the fracture event, death, or use of another type of OAC (censored at the start of the second OAC type). The third sensitivity analysis C was conducted by using the propensity score weighting method and Cox regressions to calculate the aHRs.

Results

Patient characteristics

Our study population included 28 776 AF patients, with 16 110 patients in the NOAC cohort and 12 666 patients in the warfarin cohort. Within the NOAC cohort, 5833, 8474, and 1803 patients were assigned to the dabigatran, rivaroxaban, and apixaban subgroups, respectively. Patients' baseline characteristics, without propensity score matching, are summarized in Supplementary material online, *Table S2*. After propensity score matching, 19 414 patients were included, with 9707 in each NOAC and warfarin cohort. The baseline characteristics were balanced after matching (*Table 1*), with all standardized differences in covariates between the groups in each comparison being <0.1, confirming a negligible between-group difference in covariates after propensity score matching. The between-group balance of the NOAC and warfarin cohorts in the propensity score models is shown in Supplementary material online, *Table S5*. The baseline characteristics of each NOAC subgroup (dabigatran, rivaroxaban, and apixaban) vs. the warfarin group, after propensity score matching, for

each comparison set are summarized in Supplementary material online, *Table S3*. The overall median follow-up time was 2.4 years.

Risk of fracture

After propensity score matching, 737 patients in the NOAC cohort and 1009 patients in the warfarin cohort developed a new hip, vertebrae, or humerus/forearm/wrist fracture. The NOAC cohort had a lower cumulative incidence of fracture development than the warfarin cohort (Gray's test: *P* = 0.038) (*Take home figure A*). The Cox regression models revealed that, compared with warfarin, NOAC was associated with a lower fracture risk (aHR = 0.84, 95% CI = 0.77–0.93; *P* < 0.001) (*Table 2*). Sub-analyses for each NOAC revealed that dabigatran (aHR = 0.88, 95% CI = 0.78–0.99; *P* = 0.027), rivaroxaban (aHR = 0.81, 95% CI = 0.72–0.90; *P* < 0.001), and apixaban (aHR = 0.67, 95% CI = 0.52–0.87; *P* = 0.003) were all associated with a reduced fracture risk compared with warfarin (*Table 3*). The cumulative incidence curves for each NOAC vs. warfarin are shown in *Take home figure B–D*. The analyses including eligible patients without matching revealed similar results (*Tables 2* and *3*). The proportional hazard assumption was not violated in any of the head-to-head comparisons performed.

Risks of hip, vertebral, and humerus/forearm/wrist fracture

Compared with warfarin, NOAC was significantly associated with a lower risk of vertebral fracture (aHR = 0.75, 95% CI = 0.65–0.86; *P* < 0.001). The sub-analyses also revealed that all NOACs (dabigatran, rivaroxaban, and apixaban) were associated with a lower risk of vertebral fracture (*Table 4*). However, the analyses for hip fracture revealed that only apixaban was significantly associated with a lower hip fracture risk (aHR = 0.53, 95% CI = 0.30–0.94; *P* = 0.029). With regard to humerus/forearm/wrist fractures, only rivaroxaban was significantly associated with lower risk of these fractures (aHR: 0.78, 95% CI = 0.62–0.98; *P* = 0.030). The detailed statistical results of these analyses are summarized in *Table 4*.

Analyses stratified by age and sex

Overall, the risk of fracture was significantly lower in both male and female patients, among those treated using NOACs compared with warfarin (*Table 5*). Patients aged 65–79 years or ≥80 years who were treated using NOACs had significantly lower fracture risks compared with patients of the same age who used warfarin. The significant association between NOAC use and lower fracture risks was not found among patients ≤64 years of age (*Table 5*).

Results of sensitivity analyses

Results of our sensitivity analysis A, which was performed after excluding patients who had rheumatic heart disease or congenital heart disease, and those who had undergone valve replacement surgery, were consistent with those of our primary analyses (Supplementary material online, *Table S1*). The patient baseline characteristics in sensitivity analysis A are shown in Supplementary material online, *Table S4*. The sensitivity analysis B, in which the follow-up was censored when a patient started another type of OAC, also revealed similar results (Supplementary material online, *Table S1*). The sensitivity analysis C, in which we applied the propensity score

Table 1 Baseline characteristics of patients with atrial fibrillation who received non-vitamin K antagonist oral anti-coagulant and warfarin after propensity score matching

	NOAC (*n* = 9707)	Warfarin (*n* = 9707)	Standardized difference
Age (years)[a]	72.4 (10.7)	71.3 (11.5)	0.0957
Sex			
Male	5749 (59.2)	5714 (58.9)	0.0132
Female	3958 (40.8)	3993 (41.1)	0.0132
Income level (NTD)			
Financially dependent	2734 (28.2)	2641 (27.2)	0.0215
15 840–29 999	4460 (46.0)	4415 (45.5)	0.0066
30 000–44 999	1405 (14.5)	1481 (15.3)	0.0202
≥45 000	1108 (11.4)	1170 (12.1)	0.0228
Time from AF diagnosis to OAC prescription (days)[b]	16.0 (108.0)	16.0 (69.0)	0.0769
Hospital level			
Medical centre	3960 (40.8)	3748 (38.6)	0.0366
Regional hospital	4083 (42.1)	4227 (43.6)	0.0212
District hospital or clinics	1664 (17.1)	1732 (17.8)	0.0184
Hospital region			
North	4503 (46.4)	4419 (45.5)	0.0176
Central	2145 (22.1)	2205 (22.7)	0.0156
South and Eastern	3059 (31.5)	3083 (31.8)	0.0054
Physician specialty			
Cardiologist	6728 (69.3)	6845 (70.5)	0.0184
Neurologist	1646 (17.0)	1397 (14.4)	0.0651
Others	1333 (13.7)	1465 (15.1)	0.0387
CHA$_2$DS$_2$-VASc score[a]	2.8 (1.6)	2.7 (1.8)	0.0557
Charlson comorbidity index[a]	1.6 (1.7)	1.6 (1.7)	0.0237
Comorbidities			
Hypertension	5443 (56.1)	5386 (55.5)	0.0160
Diabetes mellitus	2485 (25.6)	2513 (25.9)	0.0064
Coronary artery disease	2508 (25.8)	2553 (26.3)	0.0121
Congestive heart failure	2551 (26.3)	2758 (28.4)	0.0496
COPD	801 (8.3)	787 (8.1)	0.0004
Chronic kidney disease	652 (6.7)	762 (7.9)	0.0436
Liver cirrhosis	271 (2.8)	286 (3.0)	0.0068
Hyperthyroidism	231 (2.4)	233 (2.4)	0.0021
Hypothyroidism	108 (1.1)	111 (1.1)	0.0000
Dementia	281 (2.9)	269 (2.8)	0.0062
Depression	190 (2.0)	181 (1.9)	0.0053
Parkinsonism	138 (1.4)	136 (1.4)	0.0053
Epilepsy	92 (1.0)	89 (0.9)	0.0011
Stroke	2662 (27.4)	2509 (25.9)	0.0336
Rheumatoid arthritis	40 (0.4)	40 (0.4)	0.0016
Malignancy	561 (5.8)	538 (5.5)	0.0099
Cataract	345 (3.6)	322 (3.3)	0.0130
Osteoporosis	50 (0.5)	65 (0.7)	0.0154
Medication use			
Corticosteroids	568 (5.9)	584 (6.0)	0.0113
Diuretics	4107 (42.3)	4346 (44.8)	0.0524
NSAID	2536 (26.1)	2488 (25.6)	0.0073
Statins	3266 (33.7)	3045 (31.4)	0.0464
PPI	1029 (10.6)	1029 (10.6)	0.0050
Antiepileptics	868 (8.9)	871 (9.0)	0.0011
Antiparkinsonian	311 (3.2)	310 (3.2)	0.0029

Continued

Table 1 *Continued*

	NOAC (*n = 9707*)	Warfarin (*n = 9707*)	Standardized difference
Antipsychotics	556 (5.7)	537 (5.5)	0.0041
Anxiolytics	2684 (27.7)	2717 (28.0)	0.0037
Hypnotics and sedatives	1464 (15.1)	1508 (15.5)	0.0043
Antidepressants	886 (9.1)	859 (8.9)	0.0087
Thyroxine	266 (2.7)	268 (2.8)	0.0038
Antithyroid drugs	275 (2.8)	295 (3.0)	0.0106
Antiosteoporotic drugs	86 (0.9)	95 (1.0)	0.0122

Data are expressed as *n* (%) unless otherwise indicated.

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

[a]Values are expressed as mean (SD).

[b]Values are expressed as median (IQR).
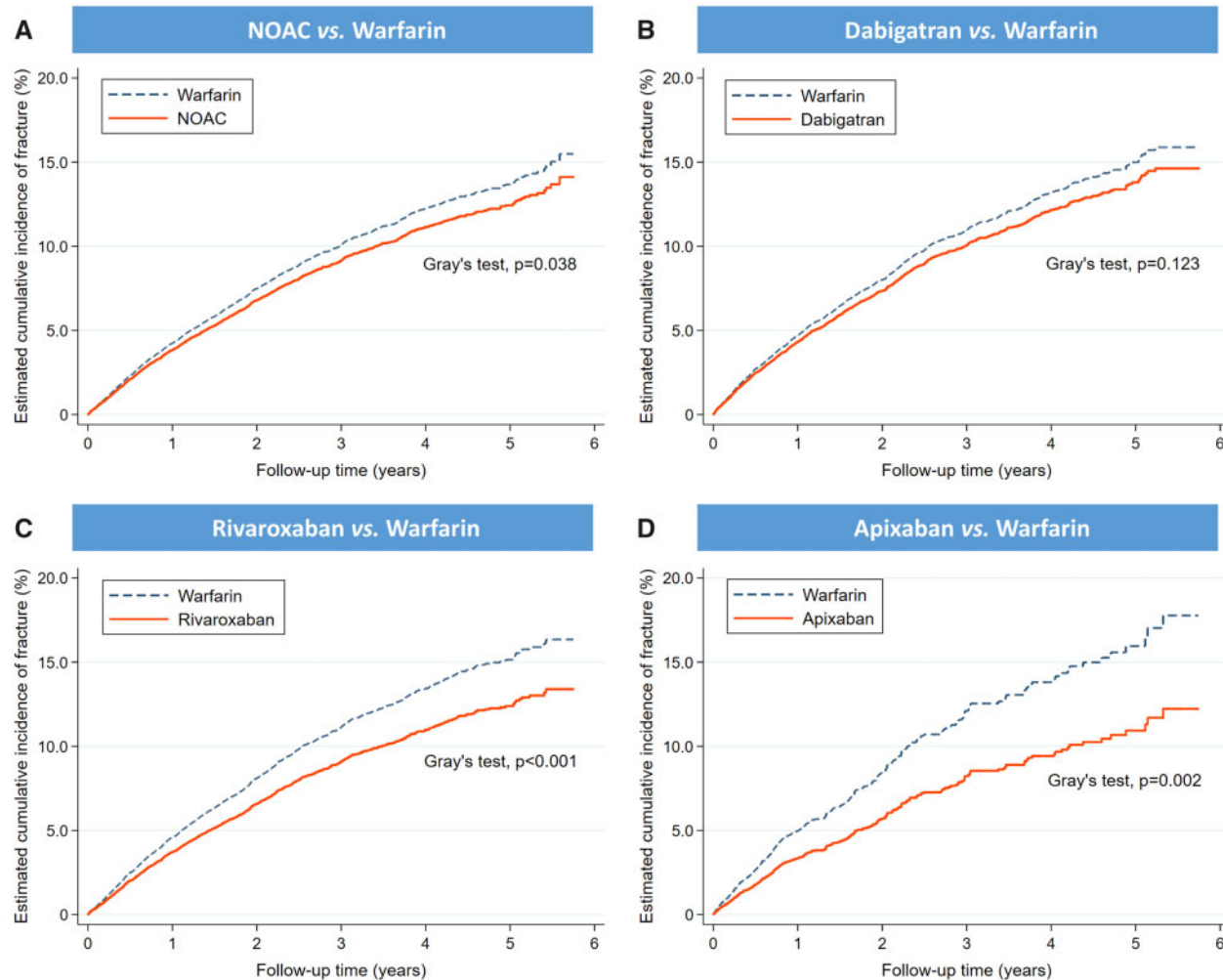
Take home figure Compared with warfarin, non-vitamin K antagonist oral anticoagulants were associated with a significant decrease in fracture risk among patients with atrial fibrillation. This figure illustrates the estimated cumulative incidences of fractures for (A) non-vitamin K antagonist oral anticoagulant overall vs. warfarin, (B) dabigatran vs. warfarin, (C) rivaroxaban vs. warfarin, and (D) apixaban vs. warfarin among patients with atrial fibrillation.

weighting method, also revealed that NOAC use overall and for rivaroxaban and apixaban was associated with a lower fracture risk; this significant association was not found in the subgroup comparison for dabigatran (Supplementary material online, Table S1). Overall, the sensitivity analyses generated comparable results to our primary analyses.

Discussion

This nationwide cohort study used real-world data from routine clinical practice. Compared with warfarin, NOAC use was associated with reduced hip, vertebral, or humerus/forearm/wrist fractures risks

Table 2 Risk of developing fractures in patients with atrial fibrillation treated with non-vitamin K antagonist oral anticoagulant vs. warfarin

	Without propensity score matching		With propensity score matching	
	NOAC	Warfarin	NOAC	Warfarin
Patient number	16 110	12 666	9707	9707
Event number	1259	1209	737	1009
Person-years	33 108	34 417	20 094	25 790
Incidence rate[a]	38.0	35.1	36.7	39.1
aHR[b]	0.81	1.00	0.84	1.00
95% CI	0.74–0.88	Ref.	0.77–0.93	Ref.
P value	<0.001		<0.001	

aHR, adjusted hazard ratio; CI, confidence interval; NOAC, non-vitamin K antagonist oral anticoagulant; Ref., reference.

[a]Per 1000 person-years.

[b]Without propensity score matching, the aHR was calculated using multivariable Cox regression model with adjustments for all baseline characteristics shown in Table 1, whereas with 1:1 propensity score matching, the aHR was calculated using Cox regressions with shared frailty model that account for the matching.

in AF patients. In the sub-analyses for different types of NOAC, associations between the use of dabigatran, rivaroxaban, and apixaban and reduced fractures risks were identified. To date, few studies have compared NOACs and warfarin in relation to fracture risk; this study uses a large-scale nationwide cohort to address this knowledge gap.

Although the precise mechanism was not elucidated, some factors might explain the lower risk of fractures associated with NOACs. Previous studies' findings indicate that warfarin interferes with the processes that contribute to bone formation.[10] Warfarin antagonizes vitamin K-dependent processes and further impairs the γ-carboxylation of osteocalcin and other bone matrix proteins, which play important roles in bone mineralization [10,11]. Conversely, NOACs act independently of mechanisms associated with vitamin K antagonists and theoretically do not interfere with bone metabolism. One study's findings showed a higher bone volume, reduced trabecular separation, and lower bone turnover rate in dabigatran-treated rats than in warfarin-treated rats.[13] Another study's findings demonstrated that rivaroxaban had positive effects on fracture healing in rats with fractured femurs, with larger calluses and marginal increases in the bone tissue mineral density in the fracture zones compared with those in control rats.[23] Although such studies have not been conducted on humans, these results indicate possible positive effects of NOACs on bone biology. Our study, which found a 12% and 19% decrease in the fracture risk associated with dabigatran and rivaroxaban treatment, respectively, compared with warfarin treatment, demonstrated comparable results to those generated from previous animal studies. Additionally, the potential effects of NOACs themselves on bone health and in relation to the prevention of falls that are unrelated to warfarin or vitamin K have been described recently.[24] Future studies that evaluate the mechanisms underlying the effects of NOACs on bone health and fracture risks are warranted.

A retrospective cohort study published in 2017 was the first to compare an NOAC, dabigatran alone, with warfarin, reporting a significantly lower risk of osteoporotic fractures associated with the use of NOACs among AF patients, with an incidence rate ratio of 0.38.[12] This study used a composite of hip and vertebral fractures as the

Table 3 Risk of developing fractures in patients with atrial fibrillation treated with each non-vitamin K antagonist oral anticoagulant (rivaroxaban, dabigatran, and apixaban) vs. warfarin

	Without propensity score matching				With propensity score matching			
	Event number	IR[a]	aHR (95% CI)	P value	Event number	IR[a]	aHR (95% CI)	P value
Dabigatran vs. warfarin								
Dabigatran	539	39.2	0.90 (0.80–0.99)	0.049	535	39.1	0.88 (0.78–0.99)	0.027
Warfarin	1209	35.1	1.00 (ref.)		660	43.4	1.00 (ref.)	
Rivaroxaban vs. warfarin								
Rivaroxaban	629	37.9	0.76 (0.68–0.84)	<0.001	530	36.9	0.81 (0.72–0.90)	<0.001
Warfarin	1209	35.1	1.00 (ref.)		831	43.7	1.00 (ref.)	
Apixaban vs. warfarin								
Apixaban	91	33.2	0.63 (0.50–0.78)	<0.001	89	33.1	0.67 (0.52–0.87)	0.003
Warfarin	1209	35.1	1.00 (ref.)		204	47.1	1.00 (ref.)	

aHR, adjusted hazard ratio; CI, confidence interval; IR, incidence rate; NOAC, non-vitamin K antagonist oral anticoagulant; ref., reference.

[a]Per 1000 person-years.

Table 4 Comparisons for the risk of hip, vertebral, and humerus/forearm/wrist fractures according to the oral anticoagulant received

	Without propensity score matching			With propensity score matching		
	aHR	95% CI	*P* value	aHR	95% CI	*P* value
Hip fracture						
Warfarin	1.00	Ref.		1.00	Ref.	
NOAC overall	0.89	0.75–1.06	0.195	0.85	0.70–1.04	0.123
Dabigatran	1.00	0.81–1.25	0.972	1.00	0.79–1.26	0.995
Rivaroxaban	0.87	0.70–1.08	0.209	0.89	0.71–1.12	0.323
Apixaban	0.57	0.35–0.93	0.025	0.53	0.30–0.94	0.029
Vertebral fracture						
Warfarin	1.00	Ref.		1.00	Ref.	
NOAC overall	0.75	0.67–0.85	<0.001	0.75	0.65–0.86	<0.001
Dabigatran	0.82	0.70–0.96	0.012	0.81	0.68–0.95	0.011
Rivaroxaban	0.73	0.63–0.84	<0.001	0.73	0.62–0.85	<0.001
Apixaban	0.55	0.40–0.77	<0.001	0.60	0.41–0.88	0.009
Humerus/forearm/wrist fractures						
Warfarin	1.00	Ref.		1.00	Ref.	
NOAC overall	0.87	0.73–1.03	0.106	0.88	0.73–1.06	0.190
Dabigatran	0.96	0.78–1.19	0.721	0.96	0.76–1.20	0.694
Rivaroxaban	0.76	0.61–0.95	0.013	0.78	0.62–0.98	0.030
Apixaban	0.86	0.57–1.28	0.452	1.04	0.63–1.74	0.869

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

primary outcome. However, due to an insufficient event number and statistical power, the authors could not investigate hip and vertebral fractures separately. The authors did suggest that hip and vertebral fractures should be analysed separately given the possibility of different fracture mechanisms because unlike hip fractures, most vertebral fractures occur without falls.[24] Furthermore, that study only evaluated dabigatran as a representative NOAC, without analysing other types of NOACs. Although studies evaluating NOACs and warfarin in relation to fracture risks were scarce before 2017,[12] a recently published meta-analysis that included several clinical trials that involved patients with AF, deep vein thrombosis, and pulmonary embolism reported that fracture risk was associated with NOACs and warfarin.[25] Nevertheless, the clinical trials included were not specifically designed to assess fracture risk, and most of the fracture events were reported as one of many adverse events only in the ClinicalTrials.gov database.[26–37] Of note, the reported incidence and number of fractures and other events, including osteoporosis, seemed to be much lower among patients in these trials than in the general population. Furthermore, the only significant difference identified between NOAC and warfarin treatment was in relation to the overall fracture (any fracture) risk, and no difference was reported in association with any individual fracture risk, for example, hip and vertebral fractures, which are the most important and severe osteoporotic fracture events. Additional potential biasing effects included the relatively low fracture rates reported in the trials, insufficient treatment durations, and inadequate follow-up duration to observe fracture events, which was ≤12 months in over half of the trials, and the trials were not specifically designed to identify fractures. Furthermore, although the data in ClinicalTrials.gov describe events

that are specific to each fracture site for each trial, the database does not report the proportions or exact numbers of patients who experienced any fracture (overall fracture) in each trial included in the meta-analysis[25]; thus, the number of patients who experienced any fracture would be overestimated even if that current data already showed a relatively low fracture rate compared with the real-world rate.

Although randomized controlled trials (RCTs) are considered the gold standard for evaluating treatment outcomes, the strict entry criteria and controlled conditions under which they are conducted lead to low generalizability.[38] Conversely, studies that use real-world data can capture a treatment's characteristics and its safety issues more effectively, despite the potential effects of confounders.[39] Studies based on real-world evidence reflect the characteristics of actual clinical practice and can complement RCTs.[38,39] Herein, we analysed real-world data from a nationwide large-scale sample that enabled comparisons of each NOAC to warfarin, as well as evaluation of hip and vertebral fracture risk among AF patients. The sensitivity analyses also revealed similar results to the findings of our primary analysis. Our results also showed that the effect size of the reduced fracture risk varied among the different NOACs. Further studies are needed to evaluate possible differences in the reduction of the fracture risk by individual NOACs and the underlying mechanisms.

The finding that NOACs were associated with a lower risk of fracture among AF patients is of clinical importance. Osteoporotic fractures, especially hip and vertebral fractures, are major threats to older people among whom the incidence is high, and cause significant morbidity, mortality, and high socioeconomic burdens.[5–7] Previous studies have identified AF itself as a risk factor for osteoporotic fractures.[40,41] Among AF patients, many risk factors for osteoporotic

Table 5 Risk of developing fractures in patients receiving non-vitamin K antagonist oral anticoagulants vs. warfarin, stratified according to age and sex

	Without propensity score matching			With propensity score matching		
	aHR[a]	95% CI	P value	aHR[a]	95% CI	P value
Sex						
Male	0.82	0.71–0.95	0.007	0.78	0.67–0.92	0.003
Female	0.83	0.74–0.93	0.001	0.82	0.72–0.92	0.001
Age (years)						
≤64	1.04	0.80–1.37	0.752	0.90	0.67–1.20	0.464
65–79	0.80	0.70–0.91	0.001	0.76	0.65–0.88	<0.001
≥80	0.80	0.70–0.91	0.001	0.81	0.70–0.94	0.006

aHR, adjusted hazard ratio; CI, confidence interval.
[a]The aHRs were calculated using patients who received warfarin as the reference group.

fractures, including old age and previous histories of diabetes mellitus and stroke, are also risk factors for stroke that requires anticoagulant treatment.[12,42] Thus, AF patients who take anticoagulants should be considered vulnerable to fractures. Additionally, if fractures occur, surgical intervention is usually required. The concurrent use of anticoagulants usually presents challenges to the perioperative management of anticoagulation, and the risks of thromboembolism and bleeding should be evaluated.[43,44] Therefore, strategies for preventing fractures among AF patients who use anticoagulants are important, and our study findings suggest that NOACs, including rivaroxaban, dabigatran, and apixaban, are safer alternatives to warfarin because of their lower fracture risks among these patients.

A key strength of our study is the large-scale nationwide analysis with longitudinal follow-up. However, the results should be interpreted in the context of the following limitations. First, the study design was retrospective using an administrative database and lacked granular data on clinical characteristics, such as smoking and alcohol history, bone mineral density data, and serum calcium and vitamin D levels. Possible factors related to the decision of OAC prescription were also lacking (e.g. physician's discretion and patient's preference). It would be unrealistic to gather such data for an entire national population. Although we adequately deal with several important confounders by regression models and propensity score method, unknown or unmeasured confounders may still exist and increase the risk of bias, given the observational, retrospective nature of our study. Second, we could not confirm patients' diagnoses by directly evaluating the study population because of the policy of patient anonymity within the NHIRD. However, the diagnostic codes for AF, fractures, and many other diseases, have been validated within Taiwan's NHIRD, and these analyses have revealed high levels of accuracy.[15,45–48] Third, our study only enrolled Taiwanese people, and whether the results can be extrapolated to other countries or populations requires further investigation.

Conclusions

This real-world nationwide cohort study revealed that, compared with warfarin, NOAC use was associated with a lower fracture risk among AF patients. Sub-analyses of the individual NOACs, namely dabigatran, rivaroxaban, and apixaban, demonstrated an association between the use of these NOACs and a lower fracture risk. Therefore, if OAC treatment is indicated, we suggest that NOACs, rather than warfarin, should be considered to lower fracture risk. Further studies are required to investigate the mechanisms underlying the lower fracture risk associated with NOACs and establish causality.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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