International Journal of Arrhythmia

RESEARCH

Open Access

Risk for osteoporotic fractures in patients with atrial fibrillation using different oral anticoagulants

Daehoon Kim[1†], Pil-Sung Yang[2†], Jung-Hoon Sung[2], Eunsun Jang[1], Hee Tae Yu[1], Tae-Hoon Kim[1], Jae-Sun Uhm[1], Jong-Youn Kim[1], Hui-Nam Pak[1], Moon-Hyoung Lee[1], Gregory Y. H. Lip[3*†] and Boyoung Joung[1*†]

Abstract

Background: We aimed to investigate the comparative risk of fracture among patients with atrial fibrillation (AF) treated with warfarin or non-vitamin K antagonist oral anticoagulants (NOACs).

Methods: Using the Korean National Health Insurance Service database, patients with AF who received a prescription for apixaban, dabigatran, rivaroxaban, or warfarin between 2013 and 2016 were included. Risk of major fractures (osteoporotic hip, vertebral, or pelvic fractures) were compared using inverse probability of treatment weighting.

Results: There were 70,481 patients identified (41.3% women; mean [SD] age 70.5 [11.3] years); 16,992 apixaban, 22,514 dabigatran, 27,998 rivaroxaban, and 29,390 warfarin users. During a median follow-up of 390 days, 2412 major fractures occurred with weighted incidences per 100 patient-years of 2.56 for apixaban, 2.39 for dabigatran, 2.78 for rivaroxaban, and 3.43 for warfarin. NOAC use was associated with a lower risk for fracture than warfarin use: HR 0.70 (95% confidence interval [CI] 0.57–0.86) for apixaban, HR 0.69 (95% CI 0.60–0.78) for dabigatran, and HR 0.79 (95% CI 0.70–0.90) for rivaroxaban. In head-to-head comparisons between NOACs, there was no significant difference between apixaban and dabigatran. Rivaroxaban was associated with a higher risk for fracture than dabigatran (HR 1.15, 95% CI 1.02–1.31).

Conclusion: In patients with AF, NOAC use may result in a lower risk for osteoporotic fracture compared with warfarin use. Fracture risk does not seem to be altered by the choice of NOAC type, except for rivaroxaban. These associations may help inform benefit–risk assessments when choosing between the different anticoagulant types.

Keywords: Atrial fibrillation, Osteoporosis, Fracture, Oral anticoagulant

Introduction

Osteoporotic fractures are associated with high mortality and reduced quality of life in an elderly population [1]. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general population, being more prevalent in the elderly, and associated with an increased risk of mortality and morbidity from stroke and dementia [2–5].

The vitamin K antagonist (VKA, eg. warfarin) has been used for stroke prevention in persons with AF and has been associated with an increased risk for osteoporotic

*Correspondence: gregory.lip@liverpool.ac.uk; cby6908@yuhs.ac
†Daehoon Kim and Pil-Sung Yang contributed equally to this work
†GregoryY.H. Lip and Boyoung Joung: Joint senior authors
[1] Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 50-1 Yonseiro, Seodaemun-gu, Seoul 03722, Republic of Korea
[3] Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, UK
Full list of author information is available at the end of the article

fracture [6–9]. By regulating vitamin K, warfarin inhibits the g-carboxylation of several proteins, including coagulation factors II, VII, IX, and X [10]. Preclinical studies have shown that several vitamin K–dependent proteins, such as matrix Gla protein and osteopontin, play a role in bone metabolism [9], and this has led to concerns that warfarin may increase the risk for osteoporotic fracture. These results correlate with clinical findings that propose a connection between warfarin and an increased risk of osteoporotic fractures [8–11, 14–17]. Furthermore, patients who are treated with VKAs are subjected to several dietary restrictions that may contribute to a low bone mineral density.

More recently, the non-vitamin K antagonist oral anticoagulants (NOACs) including dabigatran, rivaroxaban, apixaban, and edoxaban have been introduced for use as alternatives to warfarin. Indeed, the NOACs are now recommended over warfarin for stroke prevention in persons with AF mainly because they are at least as efficacious as warfarin in preventing stroke, have lower bleeding risks, and require less monitoring [11, 12]. The NOACs are also associated with a lower potential risk for drug–drug interactions than warfarin [13]. However, data on osteoporotic fracture risks with NOAC use are more limited [14–17], and it remains unclear which anticoagulant type or NOAC agent should be recommended as the first choice for a patient who is also at risk for osteoporotic fracture.

Given that oral anticoagulants are often prescribed to older adults who have multiple risk factors for osteoporotic fractures [18], further clarity on their associations with fracture risk is needed. This is particularly relevant to persons with AF, who were reported to have a higher risk of osteoporotic fracture and subsequent death after fracture than those without AF [19].

In this nationwide cohort study, we aimed to investigate the fracture risk among patients with AF treated with warfarin or NOACs, and second, to compare the fracture risks between the different NOAC agents.

Materials and methods

All data and materials have been made publicly available at the National Health Insurance Service (NHIS) of Korea. The data can be accessed on the National Health Insurance Data Sharing Service homepage of the NHIS (http://nhiss.nhis.or.kr). Applications to use the NHIS data will be reviewed by the inquiry committee of research support and, once approved, raw data will be provided to the authorized researcher with a fee at several permitted sites.

This study was a retrospective cohort analysis using the national health claims database (NHIS-2016–4-009) established by the NHIS of Korea. The NHIS is the single insurer managed by the Korean government. The majority (97.1%) of Korean citizens are mandatory subscribers to the NHIS, and the remaining 3% of the population are under the Medical Aid program. As the NHIS database contains the information of Medical Aid users, it is based on the entire Korean population [2–4, 20–23].

This study was approved by the institutional review board of the Yonsei University Health System (4-2016-0179), and the requirement for informed consent was waived.

Study population

From the Korean NHIS database covering a population 51.5 million inhabitants, we identified adults (aged 18 years or older) with AF who initiated oral anticoagulant (OAC) treatment (apixaban, dabigatran, rivaroxaban, edoxaban, or warfarin) between January 1, 2013, and December 31, 2016. We defined the date of the OAC prescription as the index date. AF was diagnosed using the International Classification of Disease 10th revision code I48. To ensure diagnostic accuracy, AF was defined as present only when it was a discharge diagnosis or confirmed at least twice in the outpatient department. The AF diagnosis has previously been validated in the NHIS database with a positive predictive value (PPV) of 94.1% [2–4, 20–23].

We excluded patients with valvular heart disease, OAC use prior to AF diagnosis, OAC prescription less than 30 days, catheter ablation for AF, or end-stage renal disease, and those who took unapproved NOAC dosage forms for prevention of AF-related stroke; dabigatran 75 mg; rivaroxaban 2.5 mg and 10 mg. We excluded patients who were exposed to any OACs within the previous year in order to establish an OAC-naive cohort. Patients taking edoxaban were excluded from this study due to their shorter follow-up times (the median follow-up of 5.6 months). Patients who had a record of bone tumors, epilepsy, or seizure before the index date or baseline use of hormone replacement therapy (on or within 90 days before the index date) were excluded to reduce their potential residual effects on fractures (Fig. 1) [24].

Outcomes

The primary outcome was major fracture requiring hospitalization including hip fractures, vertebral fractures, and fractures of the pelvis and acetabulum, which was defined from any discharge diagnoses (details in Additional file 1: Table S1). The diagnosis of major fracture has been validated previously in the NHIS database with PPV of 98% [19]. Patients were followed-up until the occurrence of the study outcome, switching to other OACs, death, emigration, or end of study (December 31, 2016), whichever came earliest.

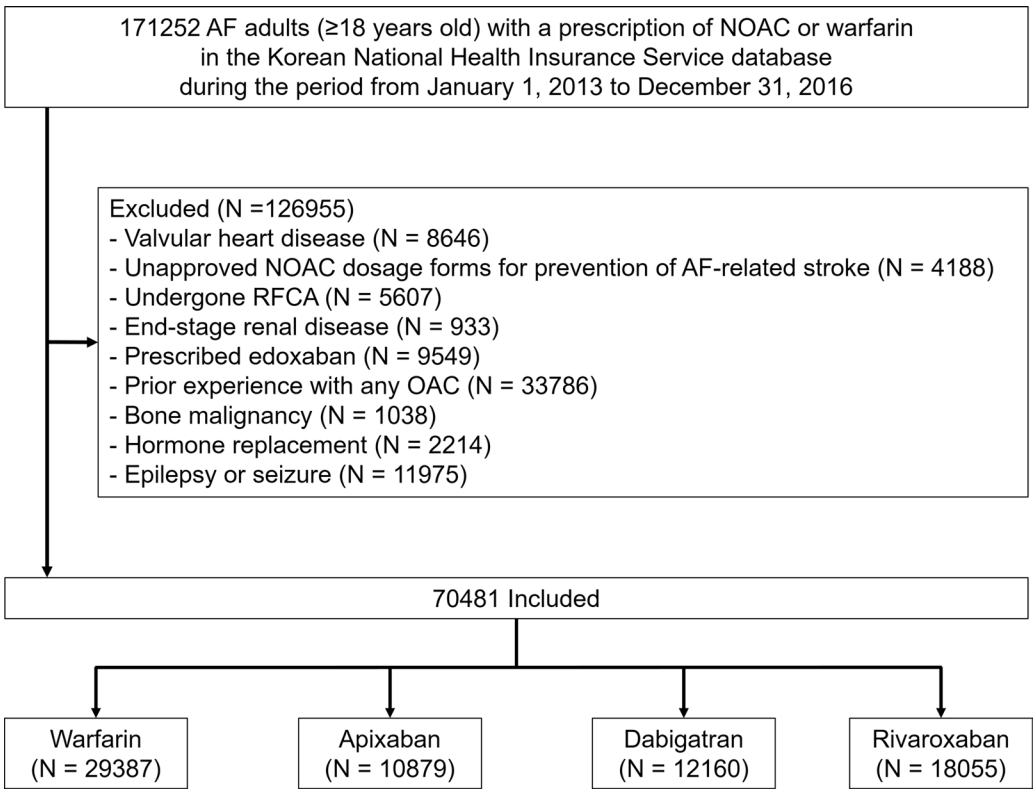

Fig. 1 Flowchart of the enrollment and analysis of the study population. *AF* atrial fibrillation, *NOAC* non-vitamin K antagonist oral anticoagulants, *OAC* oral anticoagulant; RFCA, radiofrequency catheter ablation

Inverse probability of treatment weighting for multiple treatment options

To address potential bias due to nonrandomized treatment allocation, inverse probability of treatment weighting (IPTW) for multiple treatment options based on propensity scores was used to construct a weighted cohort of patients who differed with respect to oral anticoagulants but were balanced with respect to other measured characteristics [25]. The weights were derived to obtain estimates representing population average treatment effects with optimal balance between the treatment populations by using generalized boosted models based on 10,000 regression trees. The predictor variables in the propensity score model are presented in Table 1. The patients were considered to have comorbidities when the condition was a discharge diagnosis or was confirmed at least twice in an outpatient setting, similar to previous studies using NHIS data (Additional file 1: Table S1) [2–4, 20–23]. Balance between treatment populations was evaluated by standardized differences of all covariates, using a threshold of 0.1 to indicate imbalance. Characteristics with a standardized difference greater than 0.1 after IPTW were included as covariates in the subsequent regression model.

Statistical analysis

Baseline characteristics were expressed as means with standard deviations (SDs) for continuous variables and frequencies (percentages) for categorical variables. Incidence rates of dementia were calculated by dividing the number of events by person-time at risk. We compared the incidences of outcomes using the weighted log-rank test and plotted weighted failure curves. Competing risk regression by Fine and Gray using IPTW as a probability weight was performed to estimate the hazard ratio (HR) of the risk for osteoporotic fractures considering all-cause death as a competing event. The proportional hazards assumption was tested on the basis of Schoenfeld residuals. We performed subgroup analyses according to sex. Propensity scores and weights were separately re-calculated for the patients within the subgroups. To assess whether the observed differences in the risk of the primary outcome could be fully explained by an unmeasured confounder, we calculated the E-value for our HRs [26]. The E-value is defined as the minimum strength of association that an unmeasured confounder would need to have with both treatment and outcome, conditional on the measured covariates, to explain away an observed association [26]. A two-sided P-value of < 0.05

Table 1 Baseline characteristics before inverse probability of treatment weighting

Characteristics	Before IPTW				
	Warfarin (*N*=29,387)	Apixaban (*N*=10,879)	Dabigatran (*N*=12,160)	Rivaroxaban (*N*=18,055)	Maximum pairwise ASD
Age	68.5 ± 12.4	73.0 ± 10.0	71.2 ± 10.4	71.8 ± 10.1	0.216
< 65 years	9964 (33.9)	1930 (17.7)	2740 (22.5)	3638 (20.1)	0.197
65–74 years	8884 (30.2)	3574 (32.9)	4434 (36.5)	6539 (36.2)	0.078
≥ 75 years	10,539 (35.9)	5375 (49.4)	4986 (41.0)	7878 (43.6)	0.147
Women	11,373 (38.7)	5504 (50.5)	7174 (59.0)	7818 (43.3)	0.100
AF duration, months	24.3 ± 40.4	34.7 ± 48.2	35.2 ± 46.7	39.4 ± 48.7	0.169
High tertile of income	12,271 (41.8)	5164 (47.5)	5494 (45.2)	8395 (46.5)	0.062
Risk scores					
CHA_2DS_2-VASc	4.0 ± 2.2	4.7 ± 1.9	4.4 ± 1.9	4.5 ± 1.9	0.171
HAS-BLED	5.0 ± 3.2	5.6 ± 3.1	5.3 ± 3.1	5.4 ± 3.1	0.090
Charlson comorbidity index	5.4 ± 6.4	5.9 ± 6.9	5.4 ± 6.5	5.6 ± 6.8	0.041
Medical conditions					
Heart failure	16,249 (55.3)	6443 (59.2)	7045 (57.9)	11,117 (61.6)	0.068
Hypertension	22,518 (76.6)	9273 (85.2)	10,148 (83.5)	15,526 (86.0)	0.129
Diabetes mellitus	9006 (30.6)	3531 (32.5)	3772 (31.0)	5518 (30.6)	0.022
Dyslipidemia	24,523 (83.4)	9773 (89.8)	10,889 (89.5)	16,084 (89.1)	0.097
Ischemic stroke	9210 (31.3)	3980 (36.6)	4611 (37.9)	5642 (31.2)	0.089
Transient ischemic attack	2749 (9.4)	1282 (11.8)	1421 (11.7)	2102 (11.6)	0.040
Intracranial hemorrhage	449 (1.5)	217 (2.0)	218 (1.8)	309 (1.7)	0.019
Previous MI	3521 (12.0)	1414 (13.0)	1395 (11.5)	2171 (12.0)	0.024
Peripheral artery disease	5259 (17.9)	2186 (20.1)	2474 (20.3)	3629 (20.1)	0.031
Chronic kidney disease	2828 (9.6)	1063 (9.8)	785 (6.5)	1425 (7.9)	0.071
Proteinuria	2652 (9.0)	986 (9.1)	1076 (8.8)	1534 (8.5)	0.011
Osteoporosis	9860 (33.6)	4728 (43.5)	4644 (38.2)	7343 (40.7)	0.111
COPD	5997 (20.4)	2622 (24.1)	2781 (22.9)	4413 (24.4)	0.053
Chronic liver disease	13,222 (45.0)	5158 (47.4)	5793 (47.6)	8786 (48.7)	0.038
Malignant neoplasm	7614 (25.9)	3445 (31.7)	3540 (29.1)	5839 (32.3)	0.080
Hyperthyroidism	3720 (12.7)	1501 (13.8)	1518 (12.5)	2540 (14.1)	0.029
Hypothyroidism	3701 (12.6)	1685 (15.5)	1709 (14.1)	2760 (15.3)	0.048
History of fall	131 (0.4)	76 (0.7)	72 (0.6)	103 (0.6)	0.017
History of any fracture	5446 (18.5)	2252 (20.7)	2441 (20.1)	3837 (21.3)	0.037
History of major fracture	2454 (8.4)	1086 (10.0)	1056 (8.7)	1816 (10.1)	0.037
Rheumatoid arthritis	597 (2.0)	259 (2.4)	269 (2.2)	437 (2.4)	0.015
Recent medication use					
Antiplatelet agents	5723 (19.5)	1477 (13.6)	1782 (14.7)	2360 (13.1)	0.092
Statin	11,021 (37.5)	5514 (50.7)	5952 (48.9)	8927 (49.4)	0.135
β-blocker	13,794 (46.9)	6148 (56.5)	6564 (54.0)	10,347 (57.3)	0.113
ACEi/ARB	15,748 (53.6)	6863 (63.1)	7318 (60.2)	11,432 (63.3)	0.109
DHP CCB	13,386 (45.6)	5813 (53.4)	6058 (49.8)	9207 (51.0)	0.083
Non-DHP CCB	2832 (9.6)	1465 (13.5)	1623 (13.3)	2436 (13.5)	0.061
Loop/thiazide diuretics	15,645 (53.2)	6504 (59.8)	6963 (57.3)	10,979 (60.8)	0.085
K^+ sparing diuretics	3926 (13.4)	1653 (15.2)	1780 (14.6)	2854 (15.8)	0.037
Digoxin	4338 (14.8)	1760 (16.2)	2291 (18.8)	3533 (19.6)	0.076
AAD class Ic	1358 (4.6)	1045 (9.6)	1129 (9.3)	1393 (7.7)	0.107
AAD class III	1127 (3.8)	712 (6.5)	784 (6.4)	1168 (6.5)	0.061
Alpha blocker	2744 (9.3)	1166 (10.7)	1284 (10.6)	1886 (10.4)	0.024
Systemic glucocorticoid	6086 (20.7)	2891 (26.6)	2935 (24.1)	4794 (26.6)	0.078
Antidepressant	4257 (14.5)	2063 (19.0)	2159 (17.8)	3483 (19.3)	0.069
Bisphosphonate	3862 (13.1)	2029 (18.7)	1932 (15.9)	3205 (17.8)	0.084
Proton-pump inhibitor	6853 (23.3)	3559 (32.7)	3779 (31.1)	5927 (32.8)	0.112

Table 1 (continued)

Values are presented as mean ± standard deviation or *n* (%)

AAD anti-arrhythmic drug, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *ASD* absolute standardized difference, *COPD* chronic obstructive pulmonary disease, *DHP* dihydropyridine, *IPTW* inverse probability of treatment weighting

was considered significant. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA) and R version 3.5.3 (The R Foundation, www.R-project.org).

Results

Patient characteristics

A total of 70,481 new anticoagulant users met the inclusion criteria: apixaban ($n=10,879$), dabigatran ($n=12,160$), rivaroxaban ($n=18,055$), and warfarin ($n=29,387$) (Fig. 1). The mean age of the cohort was 70.5 years (SD 11.3), ranging from 68.5 years (warfarin) to 73.0 (apixaban) and 41.3% were female (Table 1). Median follow-up was 390 days (interquartile range 187–704 days). After IPTW, all baseline characteristics had standardized differences less than 0.1 (Table 2).

Risk for osteoporotic fractures

A total of 2412 fractures were identified (crude event number [weighted rate per 100 patient-years]: apixaban, 263 [2.56]; dabigatran, 273 [2.39]; rivaroxaban, 535 [2.78]; and warfarin, 1341 [3.43]). The crude median time to fracture (interquartile range) was 374 (172–672) days in overall anticoagulant users, ranging from 234 (106–386) days in apixaban users to 705 (337–1047) days in warfarin users (Fig. 2). Compared with men, women tended to have a higher incidence of osteoporotic fractures, regardless of the type of anticoagulant received (Fig. 2).

The adjusted cumulative incidences at 6 to 24 months after treatment initiation are shown in Fig. 3. At 24 months, the weighted cumulative incidence of osteoporotic fractures was lower with NOAC use than with warfarin use (3.9% for apixaban, 4.2% for dabigatran, 4.8% for rivaroxaban and 5.4% for warfarin). In men, the weighted cumulative incidence was consistently higher in patients with warfarin use, whereas rivaroxaban and warfarin users had similarly higher incidences of 9.1% and 8.8% in women.

Competing risk regression over the entire follow-up suggested that NOAC use was associated with a lower risk for osteoporotic fractures than warfarin use; HR 0.70 (95% confidence interval [CI] 0.57–0.86) for apixaban vs. warfarin, HR 0.69 (95% CI 0.60–0.78) for dabigatran vs. warfarin, and HR 0.79 (95% CI 0.70–0.90) for rivaroxaban vs. warfarin (Fig. 2). However, there were no differences observed between rivaroxaban and warfarin in women (HR 0.87, 95% CI 0.75–1.02) (P for interaction = 0.019). In head-to-head comparisons between NOACs, rivaroxaban use was associated with a higher risk for fractures than dabigatran use (HR 1.15, 95% CI 1.02–1.31) (Table 3). This observation was prominent for women with a HR of 1.22 (95% CI 1.05–1.42). No differences were observed in other head-to-head comparisons between NOACs.

The corresponding E-values for the point estimates of apixaban, dabigatran, rivaroxaban in comparisons with warfarin were 2.21, 2.27, and 1.85, respectively, which suggests that an unmeasured confounder would be needed to explain away the observed effect estimates only if the confounder was associated with both the treatment and the outcome by a risk ratio of approximately two-fold each, but weaker confounding could not do so.

Discussion

The principal finding of this study was that NOAC use was associated with a lower risk of osteoporotic fractures compared with warfarin use. Second, in head-to-head comparisons between NOACs, rivaroxaban use was associated with a higher risk for fracture than dabigatran, whereas there was no difference between dabigatran and apixaban. To our knowledge, this is the first study that shows significant differences in fracture risk according to individual NOACs, suggesting that rivaroxaban might be associated with a higher risk for fractures than other NOACs.

Accumulating evidence suggests that AF itself is an independent risk factor for osteoporotic fractures [19]. Especially in patients with AF, warfarin use has been suggested to have deleterious effects on bone density and be associated with a higher risk of subsequent fractures [7, 27], but the evidence remains controversial across the literature [28, 29]. The NOACs, which are emerging alternative anticoagulants, have no influence on the synthesis of osteocalcin and patients taking NOACs are not subjected to any dietary restrictions regarding several vegetables which could contribute to a low bone marrow density. A recent meta-analysis pooled the adverse events reported in randomized controlled trials of NOACs and found fewer reports of fractures in NOAC users than in warfarin users [30]. However, previous trials of NOACs were not designed to provide reliable estimates of fracture risks in clinical practice, and a range of population-based studies are needed to inform the risk for osteoporotic fracture for different oral anticoagulants.

Our finding that NOAC use is associated with a lower risk of osteoporotic fractures is consistent with several

Table 2 Baseline characteristics after inverse probability of treatment weighting

Characteristics	After IPTW				
	Warfarin (*N* = 69,168)	Apixaban (*N* = 67,947)	Dabigatran (*N* = 68,716)	Rivaroxaban (*N* = 68,882)	Maximum pairwise ASD
Age	70.4 ± 11.3	70.7 ± 11.1	70.5 ± 11.2	70.6 ± 11.1	0.011
< 65 years	26.2%	25.2%	25.5%	25.6%	0.012
65–74 years	33.1%	33.6%	33.8%	33.4%	0.008
≥ 75 years	40.7%	41.2%	40.7%	41.0%	0.006
Women	41.4%	41.7%	41.2%	41.4%	0.011
AF duration, months	30.9 ± 44.9	31.3 ± 45.1	31.3 ± 45.1	31.4 ± 45.2	0.006
High tertile of income	44.1%	44.9%	44.4%	44.7%	0.008
Risk scores					
CHA_2DS_2-VASc	4.3 ± 2.1	4.3 ± 2.0	4.3 ± 2.0	4.3 ± 2.0	0.006
HAS-BLED	5.3 ± 3.2	5.3 ± 3.1	5.3 ± 3.1	5.3 ± 3.2	0.004
Charlson comorbidity index	5.5 ± 6.5	5.4 ± 6.4	5.4 ± 6.5	5.4 ± 6.5	0.005
Medical conditions					
Congestive heart failure	57.9%	57.9%	57.9%	58.2%	0.004
Hypertension	81.5%	81.3%	81.4%	81.6%	0.004
Diabetes mellitus	31.1%	30.9%	30.7%	30.7%	0.005
Dyslipidemia	86.7%	87.2%	87.1%	87.1%	0.006
Ischemic stroke	33.3%	33.5%	33.5%	33.1%	0.005
Transient ischemic attack	10.5%	10.7%	10.9%	10.7%	0.005
Intracranial hemorrhage	1.6%	1.7%	1.7%	1.7%	0.004
Previous MI	12.1%	11.8%	11.8%	11.8%	0.005
Peripheral artery disease	19.0%	18.8%	19.1%	18.9%	0.005
Chronic kidney disease	8.6%	8.6%	8.3%	8.4%	0.008
Proteinuria	9.0%	9.0%	8.8%	8.6%	0.008
Osteoporosis	37.5%	37.9%	37.7%	37.5%	0.005
COPD	22.5%	22.2%	22.2%	22.4%	0.004
Chronic liver disease	46.7%	46.9%	46.6%	46.7%	0.002
Malignant neoplasm	28.7%	29.2%	28.6%	29.0%	0.008
Hyperthyroidism	13.1%	13.1%	12.9%	13.1%	0.003
Hypothyroidism	13.8%	14.0%	13.9%	14.0%	0.003
History of fall	0.5%	0.5%	0.5%	0.5%	0.004
History of any fracture	19.6%	19.6%	20.0%	19.9%	0.006
History of major fracture	9.1%	8.9%	8.9%	9.1%	0.006
Rheumatoid arthritis	2.2%	2.1%	2.2%	2.2%	0.002
Recent medication use					
Antiplatelet agents	16.2%	15.5%	16.1%	15.8%	0.011
Statin	44.3%	44.9%	44.9%	44.8%	0.006
β-blocker	52.0%	52.8%	52.2%	52.4%	0.008
ACEi/ARB	58.3%	59.0%	58.4%	58.8%	0.008
DHP CCB	48.7%	49.4%	49.0%	48.9%	0.008
Non-DHP CCB	11.6%	11.9%	11.9%	11.8%	0.005
Loop/thiazide diuretics	56.8%	56.5%	56.4%	56.7%	0.006
K^+ sparing diuretics	14.3%	14.3%	14.2%	14.3%	0.001
Digoxin	16.8%	16.5%	16.9%	16.7%	0.006
AAD class Ic	6.7%	7.0%	7.1%	6.9%	0.009
AAD class III	5.3%	5.5%	5.4%	5.4%	0.005
Alpha blocker	10.1%	9.8%	9.8%	9.8%	0.005
Systemic glucocorticoid	23.5%	24.1%	23.5%	23.8%	0.009

Table 2 (continued)

Characteristics	After IPTW				
	Warfarin (*N* = 69,168)	Apixaban (*N* = 67,947)	Dabigatran (*N* = 68,716)	Rivaroxaban (*N* = 68,882)	Maximum pairwise ASD
Antidepressant	16.7%	16.9%	17.0%	17.1%	0.005
Bisphosphonate	15.6%	15.7%	15.7%	15.8%	0.002
Proton-pump inhibitor	28.2%	28.8%	28.8%	28.6%	0.007

Values are presented as mean ± standard deviation or %

Numbers of patients are weighted

AAD anti-arrhythmic drug, *ACEi* angiotensin-converting enzyme inhibitor, *ARB* angiotensin II receptor blocker, *ASD* absolute standardized difference, *CCB* calcium channel blocker, *COPD* chronic obstructive pulmonary disease, *DHP* dihydropyridine, *IPTW* inverse probability of treatment weighting

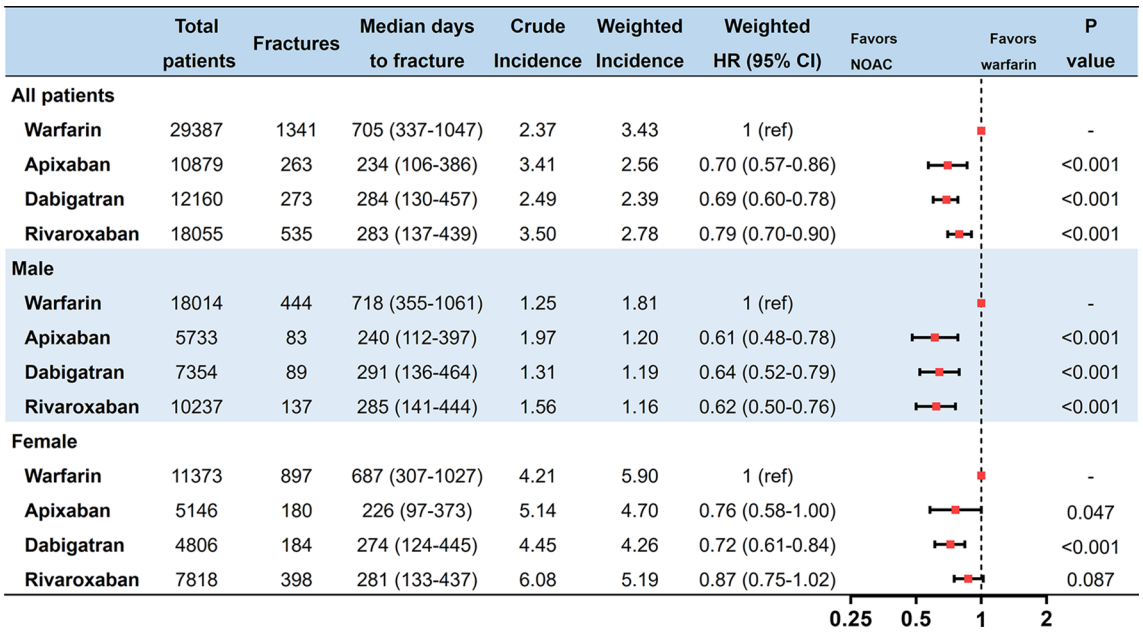

Fig. 2 Risk of major fracture after inverse probability of treatment weighting. Incidence rates are per 100 person-years. *CI* confidence interval, *HR* hazard ratio, *NOAC* non-vitamin K antagonist oral anticoagulant

recent studies [14–17]. In the present study, we extended prior observations by enrolling a larger number of participants and allowing a longer follow-up. And we used propensity score-weighting for multiple treatment options, accounting for the differences in baseline characteristics of all the four anticoagulants (warfarin and 3 NOACs) simultaneously. This approach makes it possible to generalize the results to the entire population who would be eligible to receive any of the four anticoagulants, which may better reflect real-world clinical practice [17].

Prior studies have reported that warfarin therapy might interfere the process of bone formation. Warfarin not only antagonizes vitamin-K-dependent coagulation cascade but also impairs the γ-carboxylation of osteocalcin and other proteins which contributes to bone mineralization [9, 31]. Binding et al. suggested that the dietary restrictions regarding some vegetables recommended in warfarin users, which were associated with a low intake of folic acid and subsequent hyperhomocysteinemia, could explain the warfarin's deleterious effects on bone health [14]. Hyperhomocysteinemia is associated with an increase in osteoclast activity and a decreased in osteoblast activity [32]. Furthermore, it is associated with an increase in matrix metalloproteinases that degrade extracellular bone matrix [33]. NOACs act independently of the vitamin-K associated mechanism, and there are no specific dietary restrictions in users of any of the NOACs. Gage et al. reported that long-term (≥ 1 year) warfarin

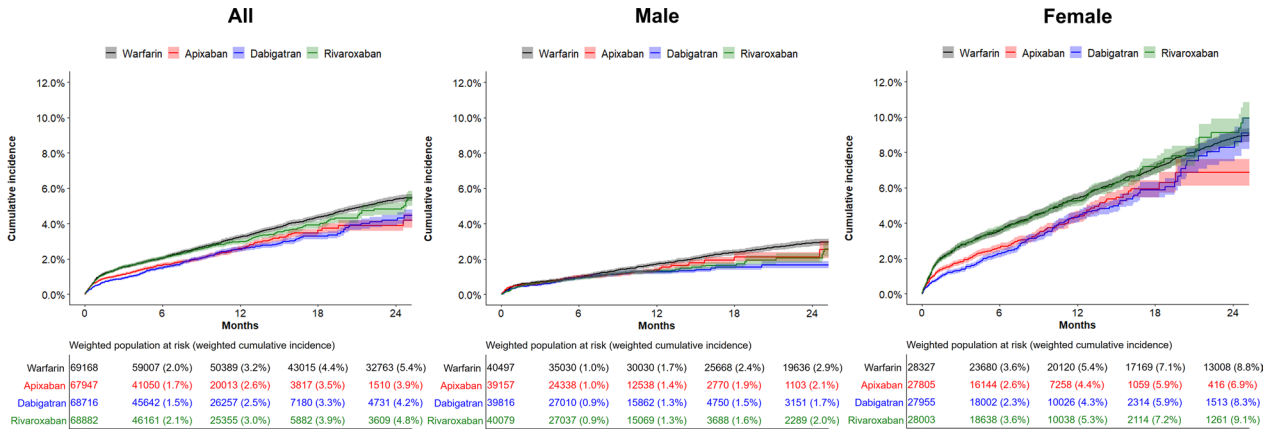

Fig. 3 Weighted cumulative incidence curves of osteoporotic fracture

Table 3 Risk of major fracture comparing inverse probability of treatment weighted users of NOACs

NOAC vs. NOAC	All patients		Male		Female		*P* value for interaction[a]
	Weighted HR (95% CI)	*P* value	Weighted HR (95% CI)	*P* value	Weighted HR (95% CI)	*P* value	
Apixaban versus Dabigatran	1.02 (0.84–1.25)	0.847	0.95 (0.74–1.23)	0.689	1.06 (0.82–1.37)	0.665	0.646
Rivaroxaban versus dabigatran	1.15 (1.02–1.31)	0.023	0.96 (0.77–1.20)	0.716	1.22 (1.05–1.42)	0.010	0.088
Rivaroxaban versus apixaban	1.13 (0.93–1.38)	0.227	1.01 (0.78–1.31)	0.935	1.15 (0.89–1.50)	0.294	0.544

CI confidence interval, *HR* hazard ratio, *NOAC* non-vitamin K antagonist oral anticoagulant

[a] P value for interaction between treatment effect and sex

use was associated with osteoporotic fractures in men with AF whereas prescribed warfarin for less than a year did not increase the risk of fracture [7]. Consistently, the median time to fracture after initiating anticoagulation was over a year (374 days) in this study, suggesting that the protective associations of NOACs with lower fracture risk over warfarin could be observed with the proviso that anticoagulants were prescribed for a sufficiently long time.

Evidence is scarce regarding possible differences in the fracture risk by individual NOACs [15, 17]. Prior studies analyzing administrative claim data of Hong Kong and Taiwan reported there were no significant differences in fracture risk in head-to-head comparisons between NOACs, although the strongest beneficial effect estimates were observed for apixaban when comparing individual NOACs with warfarin [15, 17].

To our knowledge, this is the first study to demonstrate significant differences in fracture risk according to individual NOACs, suggesting that rivaroxaban might be associated with a higher risk for fractures than other NOACs. Although the finding might be due to uncontrolled confounding such as NOAC dosing and treatment adherence, it might help to establish NOAC prescription strategies for minimizing the risk of fractures among patients with AF and high fracture risk. Randomized controlled trials investigating comparing the risk of fractures between NOACs are warranted.

Study limitations

The present study has several limitations. First, studies using administrative databases might be susceptible to errors arising from coding inaccuracies. To minimize this problem, we applied the definition that has been previously validated in previous studies using the Korean NHIS sample cohort [2–4, 20–22]. Second, given its observational nature, causal relationships could not be assessed and the possibility of unmeasured confounders cannot be ruled out. The E-value in this study suggested that a rare unmeasured confounder could explain our observed associations of NOAC use with lower fracture risk compared with warfarin only. Third, we did not have access to information on time in therapeutic range among warfarin users. Thus, our comparisons between

NOAC and warfarin users should still be interpreted carefully. Lastly, the study enrolled only Asian patients, and it is therefore unknown whether the results in this study apply to other populations.

Conclusion

In patients with AF, NOAC use may result in a lower risk for osteoporotic fracture compared with warfarin use. Fracture risk does not seem to be altered by the choice of NOAC type, except for rivaroxaban. These associations may help inform benefit–risk assessments when choosing between the different anticoagulant types.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42444-021-00032-0.

Additional file 1: Table S1. Definitions and ICD-10 codes used for defining the medical conditions, risk scores, and clinical outcomes.

Abbreviations

AF: Atrial fibrillation; CI: Confidence interval; HR: Hazard ratio; IPTW: Inverse probability of treatment weighting.; NHIS: National Health Insurance Service; NOAC: Non-vitamin K antagonist oral anticoagulant; OAC: Oral anticoagulant; SD: Standard deviation; PPV: Positive predictive value; VKA: Vitamin K antagonists.

Acknowledgements

The database analyzed in this study was provided by the NHIS of Korea. The authors would like to thank the NHIS for cooperation.

Authors' contributions

BJ and GYHL contributed to the conception and design of the work and critical revision of the manuscript. DK contributed to the conception and design of the work, interpretation of data for the work, and drafting of the manuscript. P-SY and EJ contributed to the acquisition and analysis of data for the work. J-HS, HTY, T-HK, J-SU, J-YK, H-NP, and M-HL contributed to the conception and design of the work and revising the manuscript. All authors approved the final version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

Funding

This work was supported by research grants from the Korean Heart Rhythm Society and Korean Healthcare Technology R&D project funded by the Ministry of Health & Welfare (HI15C1200, HC19C0130).

Availability of data and materials

The data underlying this article are available in the NHIS of Korea at https://nhiss.nhis.or.kr. Applications to use the data will be reviewed by the inquiry committee of research support and, once approved, raw data will be provided to the authorized researcher with a fee at several permitted sites.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Yonsei University Health System (4-2016-0179). The requirement for informed consent was waived because personal identification information was removed after cohort generation, in accordance with the strict confidentiality guidelines.

Consent for publication

All authors have permitted the publication.

Competing interests

Dr. Gregory Y.H. Lip has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo and as a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. Dr. Boyoung Joung has served as a speaker for Bayer, BMS/Pfizer, Medtronic, and Daiichi-Sankyo and received research funds from Medtronic and Abbott. Neither author has received any fees directly. The other authors have nothing to declare.

Author details

[1] Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 50-1 Yonseiro, Seodaemun-gu, Seoul 03722, Republic of Korea. [2] Department of Cardiology, CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea. [3] Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, UK.

Received: 26 December 2020 Accepted: 17 February 2021
Published online: 17 March 2021

References

1. Dyer SM, Crotty M, Fairhall N, *et al*. A critical review of the long-term disability outcomes following hip fracture. BMC Geriatr. 2016;16:158.
2. Kim D, Yang PS, Jang E, *et al*. 10-year nationwide trends of the incidence, prevalence, and adverse outcomes of non-valvular atrial fibrillation nationwide health insurance data covering the entire Korean population. Am Heart J. 2018;202:20–6.
3. Kim D, Yang PS, Jang E, *et al*. Increasing trends in hospital care burden of atrial fibrillation in Korea, 2006 through 2015. Heart. 2018;104:2010–7.
4. Lee H, Kim TH, Baek YS, *et al*. The trends of atrial fibrillation-related hospital visit and cost, treatment pattern and mortality in Korea: 10-year nationwide sample cohort data. Korean Circ J. 2017;47:56–64.
5. Joung B, Lee JM, Lee KH, *et al*. 2018 Korean guideline of atrial fibrillation management. Korean Circ J. 2018;48:1033–80.
6. Caraballo PJ, Heit JA, Atkinson EJ, *et al*. Long-term use of oral anticoagulants and the risk of fracture. Arch Intern Med. 1999;159:1750–6.
7. Gage BF, Birman-Deych E, Radford MJ, Nilasena DS, Binder EF. Risk of osteoporotic fracture in elderly patients taking warfarin: results from the National Registry of Atrial Fibrillation 2. Arch Intern Med. 2006;166:241–6.
8. Rejnmark L, Vestergaard P, Mosekilde L. Fracture risk in users of oral anticoagulants: a nationwide case–control study. Int J Cardiol. 2007;118:338–44.
9. Sugiyama T, Kugimiya F, Kono S, Kim YT, Oda H. Warfarin use and fracture risk: an evidence-based mechanistic insight. Osteoporos Int. 2015;26:1231–2.
10. Tew BY, Hong TB, Otto-Duessel M, *et al*. Vitamin K epoxide reductase regulation of androgen receptor activity. Oncotarget. 2017;8:13818–31.
11. January CT, Wann LS, Calkins H, *et al*. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019;74:104–32.
12. Hindricks G, Potpara T, Dagres N, *et al*. ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2020;2020:ehaa612.
13. Steffel J, Verhamme P, Potpara TS, *et al*. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39:1330–93.
14. Binding C, Bjerring Olesen J, Abrahamsen B, *et al*. Osteoporotic fractures in patients with atrial fibrillation treated with conventional versus direct anticoagulants. J Am Coll Cardiol. 2019;74:2150–8.
15. Lutsey PL, Norby FL, Ensrud KE, *et al*. Association of anticoagulant therapy with risk of fracture among patients with atrial fibrillation. JAMA Intern Med. 2019;180:245–53.
16. Huang HK, Liu PP, Hsu JY, *et al*. Fracture risks among patients with atrial fibrillation receiving different oral anticoagulants: a real-world nationwide cohort study. Eur Heart J. 2020;41:1100–8.

17. Lau WCY, Cheung CL, Man KKC, *et al*. Association between treatment with Apixaban, Dabigatran, Rivaroxaban, or Warfarin and risk for osteoporotic fractures among patients with atrial fibrillation: a population-based cohort study. Ann Intern Med. 2020;173:1–9.
18. Gadsboll K, Staerk L, Fosbol EL, *et al*. Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. Eur Heart J. 2017;38:899–906.
19. Kim D, Yang PS, Kim TH, *et al*. Effect of atrial fibrillation on the incidence and outcome of osteoporotic fracture—a nationwide population-based study. Circ J. 2018;82:1999–2006.
20. Kim D, Yang PS, Kim TH, *et al*. Ideal blood pressure in patients with atrial fibrillation. J Am Coll Cardiol. 2018;72:1233–45.
21. Kim TH, Yang PS, Yu HT, *et al*. Effect of hypertension duration and blood pressure level on ischaemic stroke risk in atrial fibrillation: nationwide data covering the entire Korean population. Eur Heart J. 2019;40:809–19.
22. Kim D, Yang PS, Yu HT, *et al*. Risk of dementia in stroke-free patients diagnosed with atrial fibrillation: data from a population-based cohort. Eur Heart J. 2019;40:2313–23.
23. Kim D, Yang PS, Sung JH, *et al*. Less dementia after catheter ablation for atrial fibrillation: a nationwide cohort study. Eur Heart J. 2020;41:4483–93.
24. Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. BMJ. 2009;339:b4229.
25. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res. 2011;46:399–424.
26. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med. 2017;167:268–74.
27. Caraballo PJ, Gabriel SE, Castro MR, Atkinson EJ, Melton LJ 3rd. Changes in bone density after exposure to oral anticoagulants: a meta-analysis. Osteoporos Int. 1999;9:441–8.
28. Tufano A, Coppola A, Contaldi P, Franchini M, Minno GD. Oral anticoagulant drugs and the risk of osteoporosis: new anticoagulants better than old? Semin Thromb Hemost. 2015;41:382–8.
29. Jamal SA, Browner WS, Bauer DC, Cummings SR. Warfarin use and risk for osteoporosis in elderly women. Study of Osteoporotic Fractures Research Group. Ann Intern Med. 1998;128:829–32.
30. Gu ZC, Zhou LY, Shen L, *et al*. Non-vitamin K antagonist oral anticoagulants vs. Warfarin at risk of fractures: a systematic review and meta-analysis of randomized controlled trials. Front Pharmacol. 2018;9:348.
31. Namba S, Yamaoka-Tojo M, Hashikata T, *et al*. Long-term warfarin therapy and biomarkers for osteoporosis and atherosclerosis. BBA Clin. 2015;4:76–80.
32. Herrmann M, Umanskaya N, Wildemann B, *et al*. Stimulation of osteoblast activity by homocysteine. J Cell Mol Med. 2008;12:1205–10.
33. Vacek TP, Kalani A, Voor MJ, Tyagi SC, Tyagi N. The role of homocysteine in bone remodeling. Clin Chem Lab Med. 2013;51:579–90.