Association between treatment with apixaban, dabigatran, rivaroxaban, or warfarin and the risk of osteoporotic fractures among patients with atrial fibrillation: A population-based cohort study

Running title: Osteoporotic Fractures and Oral Anticoagulants

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Abstract

Background: It is unclear whether anticoagulant type is associated with the risk of osteoporotic fracture, a deleterious complication of anticoagulants among patients with atrial fibrillation (AF).

Objective: To compare the risk of osteoporotic fracture between anticoagulants.

Design: Population-based cohort study.

Setting: Territory-wide electronic healthcare record database of the Hong Kong Hospital Authority.

Participants: Patients newly diagnosed with AF between 2010 and 2017 and received a new prescription for warfarin or a direct oral anticoagulant (DOAC: apixaban, dabigatran, rivaroxaban). Follow-up ended on 31 December 2018.

Measurements: Osteoporotic hip and vertebral fractures in anticoagulant users were compared using propensity score-weighted cumulative incidence difference (CID).

Results: There were 23,515 patients identified: apixaban n=3,241; dabigatran n=6,867; rivaroxaban n=3,866; warfarin n=9,541. The overall mean age was 74.4 years (standard deviation=10.8), ranging from 73.1 (warfarin) to 77.9 (apixaban). Over a median follow-up of 423 days, 401 fracture events were identified (crude event number [weighted rate per 100 patient-years]: apixaban: n=53 [0.82]; dabigatran: n=95 [0.76]; rivaroxaban: n=57 [0.67]; warfarin: 196 [1.11]). After 24 months' follow-up, DOACs use was associated with a lower risk of fracture compared to warfarin (apixaban CID:-0.88%, 95% confidence interval [CI]:-1.66% to -0.21%; dabigatran CID:-0.81%, 95%CI:-1.34% to -0.23%; rivaroxaban CID:-1.13%, 95%CI:-1.67% to -0.53%). No differences were observed in all head-to-head comparisons between DOACs at 24-months (apixaban-vs-dabigatran CID:-0.06%, 95%CI:-

0.69% to 0.49%; rivaroxaban-vs-dabigatran CID:-0.32%, 95%CI:-0.84% to 0.18%; rivaroxaban-vs-apixaban CID:-0.25%, 95%CI:-0.86% to 0.40%).

Limitation: Residual confounding is possible.

Conclusions: Among patients with AF, DOACs use may result in a lower risk of osteoporotic fracture compared to warfarin. Fracture risk does not seem to be altered by the choice of DOAC. These findings may help inform the benefit-risk assessment when choosing between anticoagulants.

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Introduction

Osteoporotic fracture is a frequent cause of mortality and disability in the older population.(1) Warfarin, a vitamin K antagonist anticoagulant used for stroke prevention in atrial fibrillation (AF), has long been speculated to increase the risk of osteoporotic fracture.(2-5) Preclinical studies showed that several vitamin K-dependent proteins, such as matrix Gla protein and osteopontin, play a role in bone metabolism,(5) and this has led to concerns that warfarin may give rise to osteoporotic fracture. However, most of the previous studies that investigated the link between warfarin and fracture were conducted in the past decades, and they have yielded inconsistent findings.(2-9)

In recent years, direct oral anticoagulants (DOACs), which include a thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), have been introduced for use as an alternative to warfarin. A recent meta-analysis pooled the adverse events reported in randomized controlled trials of DOACs and found fewer reports of fracture events in DOAC users than in warfarin.(10) However, previous trials of DOACs 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 of osteoporotic fracture for different oral anticoagulants. In mice, rivaroxaban and dabigatran have been shown to influence different pathways in bone formation, resorption, and remodelling.(11, 12) The risk of fracture with apixaban has not been investigated *in vitro*.

DOACs are now recommended over warfarin for stroke prevention in AF mainly because they are at least as efficacious as warfarin in preventing stroke, have lower bleeding risks, and require less monitoring.(13, 14) DOACs are also associated with a lower potential risk of drug-drug interactions when compared to warfarin.(15) However, data on osteoporotic fracture risks with DOACs are limited,(16, 17) and it remains unclear which anticoagulant

should be recommended as the first choice for a patient who is also at risk of osteoporotic fracture. As oral anticoagulants are often prescribed to older adults who have multiple risk factors for osteoporotic fractures,(18) further clarity on their role in fracture risk is needed. This is particularly relevant to individuals with AF, who were reported to have a higher incidence of hip fractures compared to individuals without AF.(19)

We therefore conducted a territory-wide cohort study to investigate whether the use of apixaban, dabigatran, and rivaroxaban is associated with a lower risk of osteoporotic fracture compared to warfarin among patients with AF. We also compared the fracture risks between the DOACs.

Methods

Data Source

We used the anonymised electronic health records of the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority, a statutory body that manages all public hospitals and their ambulatory (general and specialist) clinics in Hong Kong.(20) It serves a population of over 7.4 million and covers approximately 80% of all hospital admissions in Hong Kong.(21) Information including demographics, date of registered deaths, date of hospital admissions and discharges, date of consultations, pharmacy dispensing records, diagnoses, procedures, and laboratory test results are prospectively recorded as part of the clinical care of patients and centralised in CDARS for record-keeping and research purposes. Data validation in CDARS has demonstrated a high coding accuracy for the diagnoses of fractures of the hip (positive predictive value [PPV]=100%) and vertebrae (PPV=86%).(22) CDARS has been extensively used for conducting large-scale drug surveillance studies.(23-30) A more detailed description of CDARS has been reported previously and is also provided in Appendix 1.(28, 31)

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (reference number: UW13-468). Informed patient consent was not required as the data used in this study were anonymised.

Study Cohort

The study population included adults 18 years and older with a new diagnosis of AF who subsequently received a new prescription for one of the anticoagulants of interest. A new diagnosis of AF was defined as the first-ever recorded AF (*International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9-CM]* code 427.3) in either a hospital or an outpatient setting between 1 January 2010 and 31 December 2017 in CDARS. Patients with a recorded diagnosis of valvular heart disease or hyperthyroidism, or who had a valve replacement (ICD-9-CM; Appendix Table 1) were excluded. Patients with transient AF i.e. who had undergone cardiac surgery, or who were diagnosed with myocarditis, pericarditis, or pulmonary embolism within 90 days prior to their first AF occurrence (ICD-9-CM; Appendix Table 1), and patients with a missing date of birth or sex information, aged<18 years, or who died during their first AF occurrence were excluded.

We identified patients who received a new prescription for apixaban, dabigatran, rivaroxaban, or warfarin after the AF diagnosis. The date of the first prescription was defined as the index date. To identify new users of anticoagulants, we excluded patients who were exposed to any oral anticoagulants (apixaban, dabigatran, rivaroxaban, or warfarin) within 180 days prior to the index date. Patients who had a record of bone tumors, epilepsy or seizure prior to the index date, or who had baseline use of hormone replacement therapy (within 90 days on or before the index date) were excluded to reduce their potential residual effects on fractures.(32)

Outcome

The primary outcome was defined as a composite of hip and vertebral fractures, which were identified using ICD-9 CM codes (Appendix Table 1). To exclude possible cases of traumatic fractures, fracture events that were recorded with a traumatic event (ICD-9-CM: E800 – E848) were regarded as censoring events and were not included as outcome events. Patients were followed until the occurrence of the study outcome, treatment discontinuation, switching from the index medication to another oral anticoagulant (apixaban, dabigatran, rivaroxaban, warfarin, or edoxaban), or the end of the study period (31 December 2018), whichever came first.

Inverse Probability of Treatment Weighting

To address any potential bias due to non-randomised treatment allocation, inverse probability of treatment weighting (IPTW) based on propensity scores was used to construct a weighted cohort of patients who differed with respect to anticoagulation treatment but were similar with respect to other measured characteristics.(33) The IPTW approach is suitable for use when comparing multiple treatment groups.(34) Propensity score weights were estimated using generalised boosted models, based on a search limit of 10,000 regression trees for optimal balance between the treatment populations (details are provided in Appendix 2).(34) These weights were derived to obtain estimates representing the average treatment effects in the population. The predictor variables in the propensity score model included the potential confounders(3, 32): age, sex, index year (i.e. year of treatment commencement), congestive heart failure, ischemic stroke or transient ischemic attack, diabetes mellitus (identified by a record of diabetes mellitus or recent use of insulin or antidiabetic drugs within 90 days on or before the index date), chronic obstructive pulmonary disease, liver disease, chronic kidney disease, osteoporosis, history of fractures, rheumatoid arthritis and other inflammatory

polyarthropathies, and history of falls (ICD-9-CM, Appendix Table 1). Other covariates included recent use of medications (within 90 days on or before the index date): angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers, beta blockers, proton pump inhibitors, antidepressants (selective serotonin reuptake inhibitors and/or tricyclic antidepressants), systemic glucocorticoids, and bisphosphonates.

Standardised differences were used to assess the differences in patient characteristics between treatment groups. Proposed cut-offs for acceptable standardized differences range from 0.1 to 0.25.(24) Characteristics with standardized difference >0.1 after IPTW were included as covariates in the subsequent regression model. We also calculated variance ratios for the continuous variable (age) and raw differences in proportion for the categorical variables (all covariates other than age) to evaluate covariate balance in terms of distributions (Appendix 3).(35)

Statistical Analysis

Baseline characteristics were expressed as mean ± standard deviation for continuous variables and frequencies (percentages) for categorical variables, respectively. The cumulative incidence difference (CID) in osteoporotic fractures at 6, 12, 18, and 24 months after treatment commencement were compared between the anticoagulants, with adjustment for IPTW and the covariates that were not completely balanced after IPTW (details of the adjustment methods are described in Appendix 4) (36). The 95% confidence intervals of the CID were estimated using bootstrap methods (500 replications) (Appendix 4).(37)

In additional analyses, Cox proportional hazard regression using IPTW as a probability weight was applied to estimate the hazard ratio (HR) of the risk of osteoporotic fractures between different oral anticoagulants over the entire follow-up period. The proportional hazard assumption of the Cox model was assessed by including time-dependent covariates in

the model and conducting the proportionality test. The results indicated that the assumption was met.

As men and women may have a different risk of osteoporotic fracture(38) and differential oral anticoagulant treatment effects,(27) subgroup analyses were conducted by stratifying the study population by sex. Propensity scores and weights were re-calculated for the patients within the subgroups and covariate balances were confirmed using standardized differences as in the main analyses. In sensitivity analyses, fractures that accompanied a record of falls from higher than standing height (ICD-9-CM; Appendix Table 1) were not included as an outcome and were treated as a censoring event. We conducted additional sensitivity analyses in which patients were not censored if they discontinued the index medication or switched to another anticoagulant. We further conducted two post hoc sensitivity analyses that included other osteoporotic treatments (denosumab, salcatonin, teriparatide, strontium ranelate, and raloxifene) and dispensing institutions (hospitals/clinics) in the propensity score model, respectively.

To further assess the potential impact of any unmeasured confounding on our study, we computed the E-value of our HR results.(39) 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.(39)

A two-sided p-value <0.05 was considered as statistically significant. For each subgroup analyses, a p-value for interaction for the results was calculated and a value of <0.05 denoted a statistically significant difference between subgroups. Statistical Analysis System® v9.4 (SAS Institute Inc., Cary, North Carolina) and R 3.6.1 were used for conducting statistical analyses.

Role of Funding Source

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Results

Patient Characteristics

There were 83,153 patients newly diagnosed with AF identified from CDARS between 1 January 2010, and 31 December 2017. Of these, 23,515 new anticoagulant users met the inclusion criteria (apixaban n=3,241, dabigatran n=6,867, rivaroxaban n=3,866, warfarin n=9,541) (Figure 1). The mean age of the cohort was 74.4 ± 10.8 years, ranging from 73.1 ± 11.4 (warfarin) to 77.9 ± 10.3 years (apixaban) (Table 1). The median follow-up time was 423 days (interquartile range [IQR]=92 to 1001), ranging from 384 days (IQR=57 to 1211) in warfarin users to 473 days (IQR=116 to 990) in rivaroxaban users (Table 2). There were 12,548 patients (53.4%) who were censored either because they discontinued the index anticoagulant medication (n=8,940) or switched to another anticoagulant (n=3,608). After IPTW, all baseline characteristics had standardised differences <0.1 except for age, prior ischemic stroke/transient ischemic attack, and proton pump inhibitors use which fell between 0.1 and 0.15 (Table 1). The maximum pair-wise variance ratio of age was 1.14, which is close to 1 and indicative of group balance.(35) The raw differences in proportion for all categorical variables were small (<0.10) (Appendix Table 2).

Risk of Osteoporotic Fractures

A total of 401 fracture events were identified (apixaban: n=53, 0.82 per 100 patient-years; dabigatran n=95, 0.76 per 100 patient-years; rivaroxaban n=57, 0.67 per 100 patient-years; warfarin n=196, 1.11 per 100 patient-years). The crude median time to osteoporotic fracture after the index date ranged from 338 days (apixaban) to 617 days (warfarin) (Table 2). Women tended to have a higher incidence of osteoporotic fractures compared to men, regardless of the type of anticoagulant received (Table 2 & Appendix Table 3).

The adjusted cumulative incidences at 6 months to 24 months after treatment commencement are shown in Figure 2. At 24-months, the adjusted cumulative incidence of osteoporotic fractures was lower with DOACs use than with warfarin use (apixaban-vs-warfarin CID: -0.88% (95%CI: -1.66% to -0.21%); dabigatran-vs-warfarin CID: -0.81% (95%CI: -1.34% to -0.23%); rivaroxaban-vs-warfarin CID: -1.13% (95%CI: -1.67% to -0.53%). The CIDs in osteoporotic fractures between DOACs were small and not statistically significant across all time points, ranging from 0.06% to 0.32% at 24 months of follow-up (Figure 2).

Cox model analyses over the entire follow-up period suggested that DOACs use was associated with a lower risk of osteoporotic fractures when compared to warfarin (HR=0.62, 95%CI=0.41-0.94 for apixaban vs warfarin; HR=0.65 (95%CI=0.49-0.86) for dabigatran vs warfarin; and HR=0.52 (95%CI=0.37-0.73) for rivaroxaban vs warfarin) (Table 3). The corresponding E-values for the result point estimates were 2.61, 2.45, 3.26 in a HR scale, respectively. Similar results were observed in both men and women ($p_{interaction}>0.05$, Table 3). For all head-to-head comparisons between DOACs, the results were not statistically significant (apixaban-vs-dabigatran HR=0.96, 95%CI=0.63-1.47; rivaroxaban-vs-dabigatran HR=0.80, 95%CI=0.55-1.15; rivaroxaban-vs-apixaban HR=0.83, 95%CI=0.52-1.33) (Table 3).

The results of the sensitivity analyses that excluded fractures associated with falls from higher than standing height (Appendix Table 4) or did not censor patients if they discontinued the index medication or switched to another anticoagulant (Appendix Table 5) were not materially different from the results from the main analysis. Post hoc analyses that accounted for other osteoporosis treatments (Appendix Table 6) and any variation between dispensing institutions in anticoagulant use (Appendix Figure 1 and Appendix Table 7) in the propensity score model also yielded similar results.

Discussion

This study found that DOACs use was associated with a lower risk of osteoporotic fractures when compared to warfarin. No evidence of a differential fracture risk between DOACs was found. Given its limited power to compare between DOACs, this study can only rule out more than a 2-fold higher or a 50% lower relative risk of osteoporotic fractures between individual DOACs. However, any absolute risk differences were small and would likely be of minor clinical significance. These results were consistent in men and women.

Our results are consistent with a recent study using insurance claim data by Lutsey et al. that reported a lower risk of osteoporotic fractures with DOACs vs warfarin and no difference in risk between individual DOACs.(17) However, our study has a longer on-treatment follow-up period than Lutsey et al. (mean ± standard deviation: 7 ± 8 months) and we used a different analysis approach: Lutsey et al. used binary propensity scores methods which meant that the results could only be generalizable to patients who would be eligible for a specific pair of anticoagulants;(40) whereas we accounted for all anticoagulants simultaneously in the propensity score models and aimed to generalize our results to the entire population who would be eligible to receive any of the four anticoagulants, which might better reflect current clinical practice. In addition, the mean age of the patients in Lutsey et al. (which ranged from

67 years [dabigatran] to 69 years [apixaban]) is younger than our study cohort (which ranged from 74.4 years [dabigatran] to 77.9 years [apixaban]). Despite the differences in cohort characteristics, healthcare systems and methodology, both Lutsey et al. and our study have yielded consistent results and support the finding that DOACs use may be associated with a lower risk of osteoporotic fractures compared to warfarin.

Another recent study in Denmark using registry data reported that DOACs as a group was associated with a lower risk of osteoporotic fracture compared to warfarin.(16) However, the study did not examine the fracture risk for each DOAC.(16) A recent meta-analysis of four observational studies reported no increase in fracture risk with warfarin vs DOACs as a group,(41) but the validity of the findings is doubtful due to potential computation errors in the results.(42)

It has been reported that the advantage of DOACs over warfarin may not be as great in men with AF compared to women because the lower rates of bleeding with DOACs vs warfarin was not observed in men.(27) However, data regarding sex difference in osteoporotic fracture risk with the use of anticoagulants is limited. We found that DOACs vs warfarin was associated with a lower risk of osteoporotic fractures in both men and women and we also identified a higher risk of osteoporotic fractures in women compared to men who received oral anticoagulants. These results imply that lowering fracture risk may be an additional advantage of DOACs over warfarin in both men and women, and that women requiring oral anticoagulation may particularly benefit from DOACs given their higher risk of fracture.

The present study has limitations. Due to the observational nature of the study, the possibility of unmeasured confounders cannot be ruled out. For instance, we did not have information on body mass index and bone mineral density. However, these factors do not typically determine whether a patient is eligible to receive an oral anticoagulant, and so are not anticipated to

cause confounding by indication, although they still might be different between groups.(24) Similarly, alcohol consumption and smoking status are not routinely recorded in the database. However, the present study included liver disease and chronic obstructive pulmonary disease, which partially accounted for these unmeasured factors.(43) Importantly, the E-value suggested that our observed association of the lower risk with DOACs compared to warfarin could only be explained away by an unmeasured confounder that was associated with both DOAC treatment and osteoporotic fractures by a hazard ratio ranging from 2.45-fold to 3.26-fold each. Given that this is much greater than those well-known strong risk factors for osteoporotic fractures such as age, sex, and history of falls,(3, 32) it is unlikely that an additional unmeasured confounder of such large magnitude would exist. As body mass index, bone mineral density, smoking status, and alcohol consumption are not a common set of factors to inform the choice of oral anticoagulants,(13, 14) it is unlikely that the joint effect of these unmeasured confounders could have accounted for an association of this strength.

It is possible that asymptomatic fractures might have been undetected. This would tend to bias any result towards the null, assuming the under-detection was non-differential between treatment groups.(24) Although warfarin users may have had more clinical visits than DOAC users due to coagulation testing, screening for asymptomatic fractures is not recommended in the public healthcare setting of Hong Kong due to cost containment and avoidance of exposing patients to unnecessary radiation.(44) If DOAC users were symptomatic, it would generally have been reported during their regular follow-up visits, meaning a fracture would still have been detected. Therefore, this would not have a material effect on the study results. Finally, because edoxaban is a recently approved DOAC, its use is still limited in Hong Kong (27); thus, this treatment was not examined in this study.

Our study has important clinical implications. Osteoporotic fracture and AF share common risk factors such as older age, hypertension, and diabetes; but in practice, the risk of

osteoporotic fractures is often neglected when choosing an oral anticoagulant for patients with AF. Surgery is often required to treat a fracture, making perioperative management of anticoagulation difficult because a balance between the risk of stroke and excessive bleeding must be achieved. Therefore, prevention of fracture is an important aspect of anticoagulant management in patients with AF.(45) Given the supportive evidence from experimental settings,(46, 47) findings from our study using clinical data, and the indirect evidence provided by the previous meta-analysis of randomized controlled trials,(10) there exists a compelling case for evaluating whether the risk of osteoporotic fractures should be considered at the point of prescribing an oral anticoagulant in order to minimize fracture risk.(48)

Conclusions

This study found that among patients with AF, apixaban, rivaroxaban, and dabigatran use was associated with a lower risk of osteoporotic fracture compared to warfarin. No evidence on a differential fracture risk between DOACs was found. Given its limited power to compare between DOACs, this study can only rule out more than a 2-fold higher or a 50% lower relative risk of osteoporotic fractures between individual DOACs. However, any differences in absolute risk were small and likely of minor clinical significance. The treatment effects of DOACs vs warfarin were consistent in men and women. These findings may help inform the benefit-risk assessment when choosing between anticoagulants.

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Contributors: Study concept and design: WCYL, ICKW; Acquisition, analysis, or interpretation of data: WCYL, ICKW, CLC, KKCM, EWC, CWS, GYHL, CWS, JKYL, ACHL; Drafting of the manuscript: WCYL; Critical revision of the manuscript for important intellectual content: WCYL, ICKW, CLC, KKCM, EWC, CWS, GYHL, CWS, JKYL, ACHL; Statistical analysis: WCYL, KKCM; Study supervision: ICKW.

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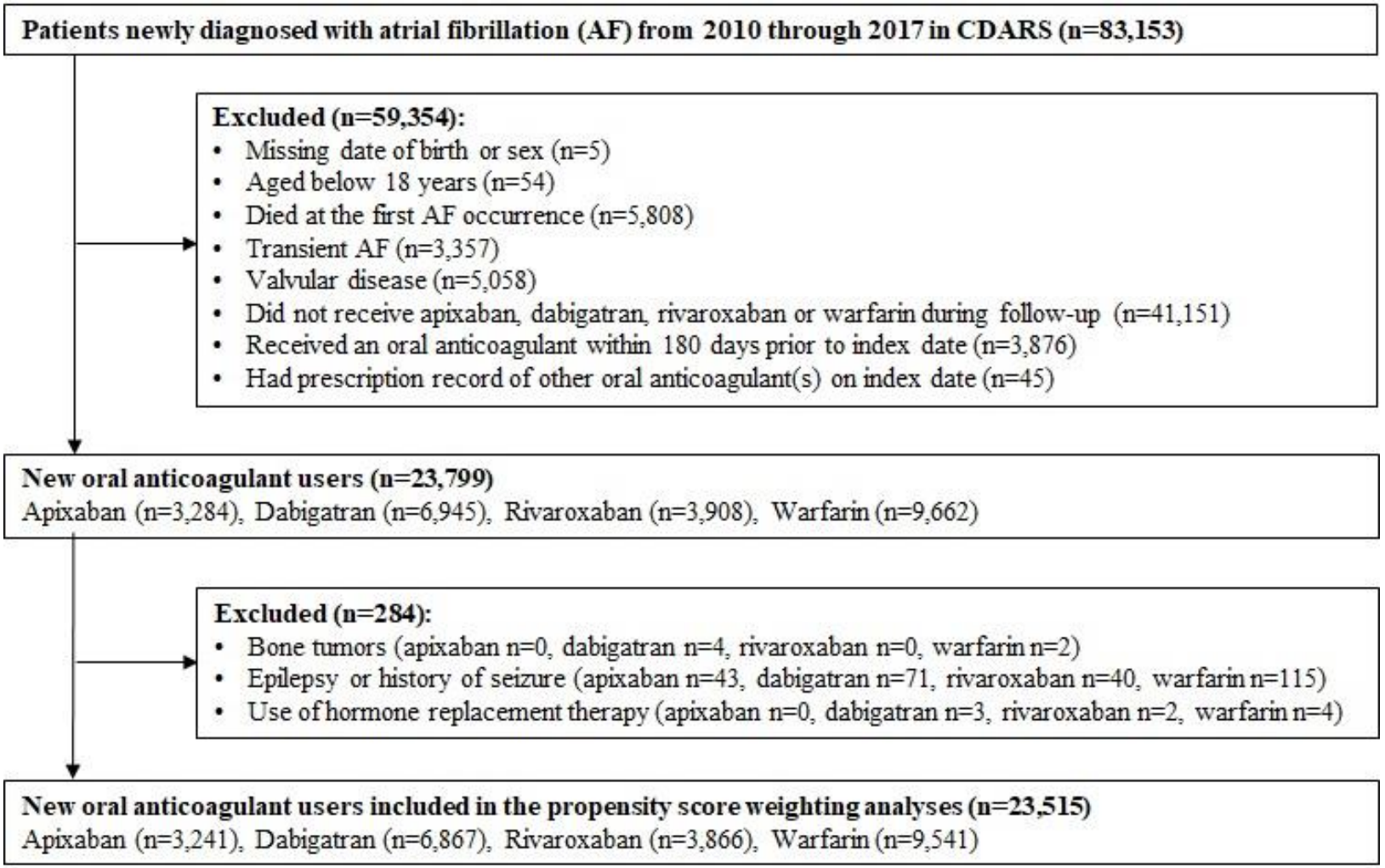
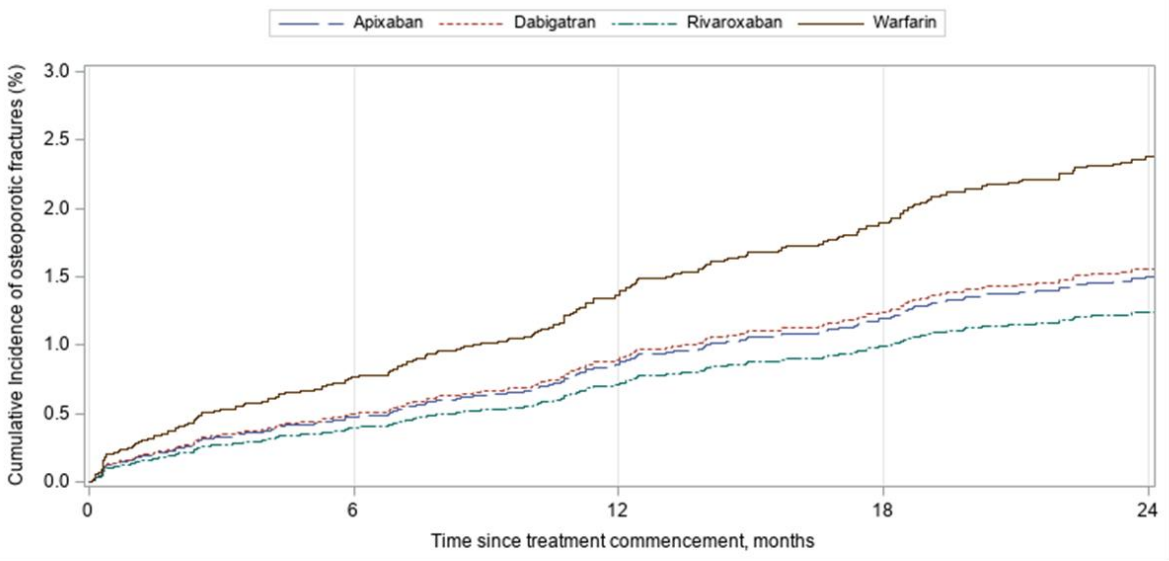


Figure 1. Selection of cohort. AF=atrial fibrillation; CDARS=Clinical Data Analysis and Reporting System.



Number of people at risk
(adjusted cumulative incidence, %)

Apixaban (N=3241)	2267 (0.48)	1800 (0.86)	1245 (1.19)	792 (1.50)
Dabigatran (N=6867)	4553 (0.50)	3830 (0.90)	3016 (1.24)	2388 (1.56)
Rivaroxaban (N=3866)	2678 (0.40)	2244 (0.71)	1784 (0.99)	1427 (1.25)
Warfarin (N=9541)	5816 (0.77)	4873 (1.37)	4176 (1.89)	3607 (2.38)

Absolute differences in
adjusted cumulative incidence (95% CI)*, %

Apixaban vs warfarin	-0.29 (-0.54 to -0.06)	-0.51 (-0.89 to -0.13)	-0.70 (-1.21 to -0.14)	-0.88 (-1.66 to -0.21)
Dabigatran vs warfarin	-0.27 (-0.45 to -0.08)	-0.47 (-0.77 to -0.15)	-0.65 (-1.07 to -0.21)	-0.81 (-1.34 to -0.23)
Rivaroxaban vs warfarin	-0.37 (-0.56 to -0.18)	-0.66 (-1.01 to -0.29)	-0.90 (-1.28 to -0.42)	-1.13 (-1.67 to -0.53)
Apixaban vs dabigatran	-0.02 (-0.23 to 0.20)	-0.04 (-0.42 to 0.35)	-0.05 (-0.55 to 0.53)	-0.06 (-0.69 to 0.49)
Rivaroxaban vs dabigatran	-0.10 (-0.25 to 0.08)	-0.18 (-0.47 to 0.13)	-0.25 (-0.66 to 0.21)	-0.32 (-0.84 to 0.18)
Rivaroxaban vs apixaban	-0.08 (-0.30 to 0.15)	-0.15 (-0.54 to 0.23)	-0.20 (-0.75 to 0.32)	-0.25 (-0.86 to 0.40)

Figure 2. Adjusted cumulative incidence curves. CI=confidence interval. *The 95% confidence intervals were estimated using bootstrap methods.

Table 1. Baseline characteristics.

	DOACs				Maximum pair-wise standardized difference*	
Characteristics	**Apixaban**	**Dabigatran**	**Rivaroxaban**	**Warfarin**	**Before**	**After**
N	3241	6867	3866	9541		
Age, mean (SD), year	77.9 (10.3)	74.4 (10.0)	75.0 (10.3)	73.1 (11.4)	0.45	0.10
Women	1678 (51.8)	3376 (49.2)	1913 (49.5)	4313 (45.2)	0.13	0.04
Medical conditions						
Congestive heart failure	772 (23.8)	1360 (19.8)	771 (19.9)	2921 (30.6)	0.25	0.06
Prior ischemic stroke or transient ischemic attack	968 (29.9)	2007 (29.2)	953 (24.7)	2664 (27.9)	0.12	0.13
COPD	334 (10.3)	575 (8.4)	314 (8.1)	887 (9.3)	0.08	0.04
Diabetes mellitus	918 (28.3)	2009 (29.3)	1059 (27.4)	2926 (30.7)	0.07	0.03
History of falls	645 (19.9)	1080 (15.7)	608 (15.7)	1481 (15.5)	0.12	0.04
History of fractures	296 (9.1)	479 (7.0)	285 (7.4)	684 (7.2)	0.08	0.06
Liver disease	18 (0.6)	41 (0.6)	10 (0.3)	67 (0.7)	0.06	0.06
Osteoporosis	46 (1.4)	85 (1.2)	50 (1.3)	101 (1.1)	0.03	0.02
Rheumatoid arthritis and other inflammatory polyarthropathies	26 (0.8)	42 (0.6)	36 (0.9)	66 (0.7)	0.04	0.02
Chronic kidney disease	139 (4.3)	157 (2.3)	124 (3.2)	835 (8.8)	0.29	0.06
Recent medication use						
ACE inhibitor or ARB	1620 (50)	3116 (45.4)	1881 (48.7)	4619 (48.4)	0.09	0.08
β-blocker	1948 (60.1)	4141 (60.3)	2372 (61.4)	5575 (58.4)	0.06	0.05
Proton pump inhibitors	1368 (42.2)	1983 (28.9)	1280 (33.1)	2714 (28.4)	0.30	0.13
Bisphosphonates	50 (1.5)	76 (1.1)	44 (1.1)	75 (0.8)	0.08	0.01
Systemic glucocorticoid	287 (8.9)	504 (7.3)	317 (8.2)	907 (9.5)	0.08	0.04
Antidepressants	116 (3.6)	264 (3.8)	134 (3.5)	311 (3.3)	0.03	0.02

Values are expressed as frequency (%) unless otherwise specified.

Abbreviations: DOACs, direct oral anticoagulants; SD, standard deviation; COPD, chronic obstructive pulmonary disease; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

*The maximum pair-wise standardized difference before and after inverse probability of treatment weighting. Proposed cut-offs for acceptable standardized differences ranged from 0.1 to 0.25.

Table 2. Overall osteoporotic fracture rates in the study cohort.

	Total patients	Follow-up*	Fracture events	Time to fracture since treatment commencement*	Crude incidence per 100 patient-years	Weighted incidence per 100 patient-years†
All patients						
Apixaban	3241	414 (125-711)	53	338 (89-537)	1.24	0.82
Dabigatran	6867	442 (110-1000)	95	372 (122-917)	0.77	0.76
Rivaroxaban	3866	473 (116-990)	57	551 (118-799)	0.88	0.67
Warfarin	9541	384 (57-1211)	196	617 (175-1245)	1.02	1.11
Total	23515	423 (92-1001)	401	468 (144-1016)	0.95	0.84
Men						
Apixaban	1563	413 (126-692)	18	329 (36-523)	0.89	0.58
Dabigatran	3491	439 (112-979)	29	422 (174-891)	0.47	0.45
Rivaroxaban	1953	446 (118-957)	22	554 (250-833)	0.69	0.46
Warfarin	5228	388 (60-1220)	70	437 (219-1240)	0.66	0.71
Total	12235	419 (93-993)	139	434 (174-943)	0.63	0.55
Women						
Apixaban	1678	414 (123-734)	35	358 (203-547)	1.56	1.07
Dabigatran	3376	448 (104-1024)	66	368 (122-917)	1.07	1.09
Rivaroxaban	1913	511 (113-1022)	35	522 (20-799)	1.05	0.88
Warfarin	4313	378 (55-1199)	126	652 (153-1338)	1.47	1.55
Total	11280	428 (91-1014)	262	497 (133-1081)	1.29	1.15

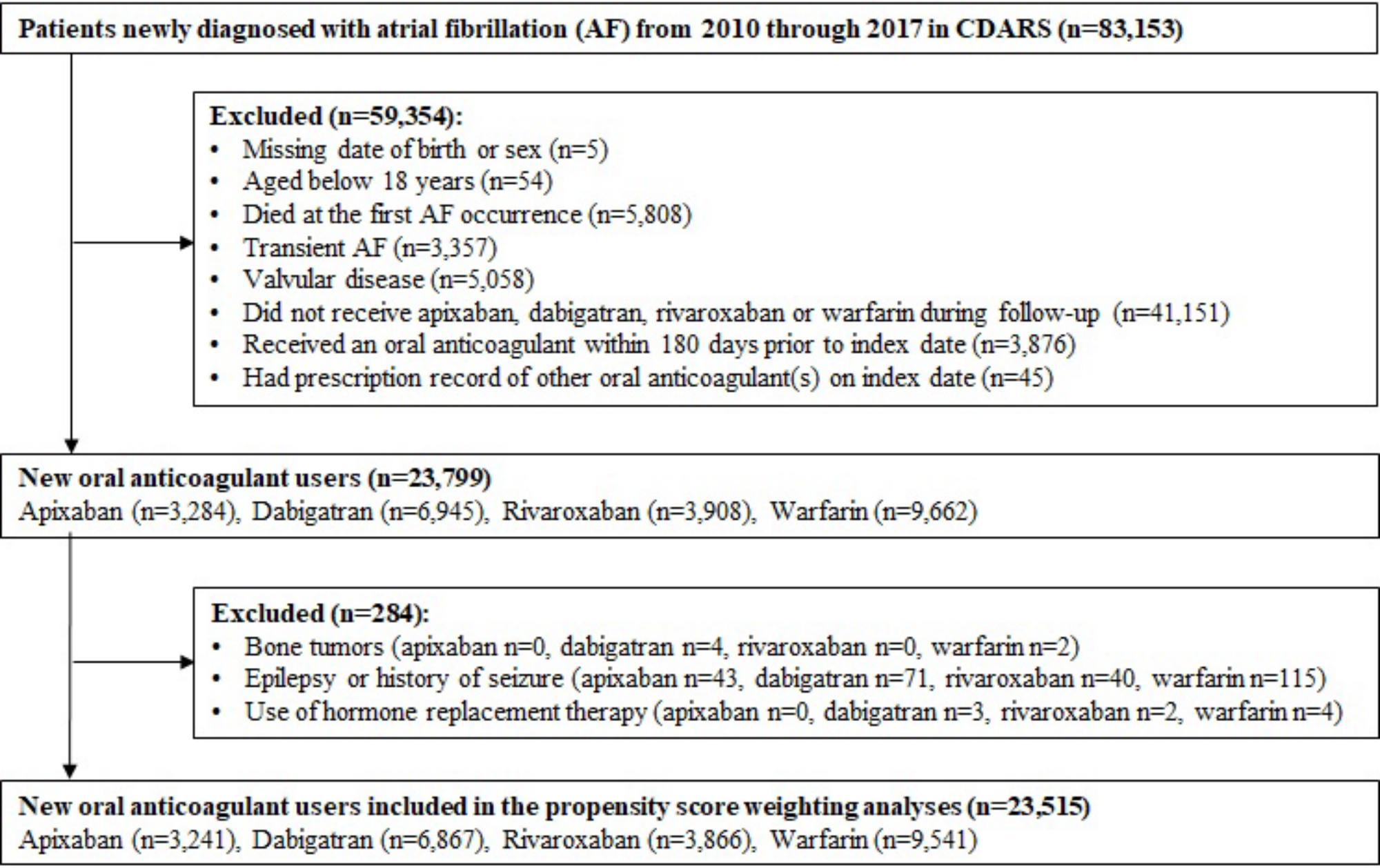
*Values are presented as median (interquartile range).

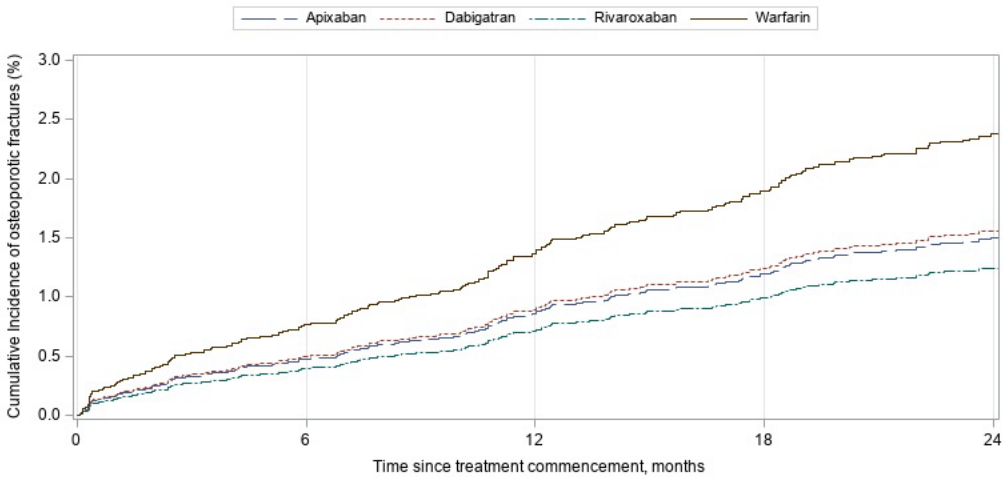
†After inverse probability of treatment weighting.

Table 3. Osteoporotic fractures after inverse probability of treatment weighting.

	All patients		Men		Women		
	Hazard Ratios (95% CI)	p	Hazard Ratios (95% CI)	p	Hazard Ratios (95% CI)	p	p interaction*
DOAC vs warfarin							
Apixaban vs warfarin	0.62 (0.41-0.94)	0.025	0.71 (0.35-1.44)	0.35	0.60 (0.38-0.96)	0.035	0.71
Dabigatran vs warfarin	0.65 (0.49-0.86)	0.003	0.62 (0.39-0.99)	0.046	0.71 (0.50-1.01)	0.058	0.66
Rivaroxaban vs warfarin	0.52 (0.37-0.73)	<0.001	0.57 (0.33-0.96)	0.035	0.51 (0.32-0.80)	0.004	0.76
DOAC vs DOAC							
Apixaban vs dabigatran	0.96 (0.63-1.47)	0.85	1.14 (0.55-2.38)	0.73	0.85 (0.52-1.38)	0.51	0.52
Rivaroxaban vs dabigatran	0.80 (0.55-1.15)	0.23	0.91 (0.50-1.64)	0.75	0.72 (0.45-1.15)	0.166	0.54
Rivaroxaban vs apixaban	0.83 (0.52-1.33)	0.44	0.80 (0.36-1.77)	0.58	0.84 (0.48-1.47)	0.54	0.91

Abbreviations: DOAC, direct oral anticoagulant; CI, confidence interval.
*p-value for interaction between treatment effect and sex.


Patients newly diagnosed with atrial fibrillation (AF) from 2010 through 2017 in CDARS (n=83,153)
Excluded (n=59,354):
• Missing date of birth or sex (n=5)
• Aged below 18 years (n=54)
• Died at the first AF occurrence (n=5,808)
• Transient AF (n=3,357)
• Valvular disease (n=5,058)
• Did not receive apixaban, dabigatran, rivaroxaban or warfarin during follow-up (n=41,151)
• Received an oral anticoagulant within 180 days prior to index date (n=3,876)
• Had prescription record of other oral anticoagulant(s) on index date (n=45)
New oral anticoagulant users (n=23,799)
Apixaban (n=3,284), Dabigatran (n=6,945), Rivaroxaban (n=3,908), Warfarin (n=9,662)
Excluded (n=284):
• Bone tumors (apixaban n=0, dabigatran n=4, rivaroxaban n=0, warfarin n=2)
• Epilepsy or history of seizure (apixaban n=43, dabigatran n=71, rivaroxaban n=40, warfarin n=115)
• Use of hormone replacement therapy (apixaban n=0, dabigatran n=3, rivaroxaban n=2, warfarin n=4)
New oral anticoagulant users included in the propensity score weighting analyses (n=23,515)
Apixaban (n=3,241), Dabigatran (n=6,867), Rivaroxaban (n=3,866), Warfarin (n=9,541)



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