Association between Dabigatran versus Warfarin and Risk of Osteoporotic Fractures among Patients with Nonvalvular Atrial Fibrillation

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Key Points

Question: What is the risk of osteoporotic fracture associated with the use of dabigatran compared to warfarin among patients with nonvalvular atrial fibrillation?

Findings: In this population-based cohort study of 8152 patients, use of dabigatran was associated with a significantly lower risk of osteoporotic fracture compared to warfarin (incidence 0.7 vs. 1.1 per 100 person-years) during a mean follow-up of approximately 500 days.

Meaning: Among adults with nonvalvular atrial fibrillation receiving anticoagulation, the use of dabigatran compared to warfarin was associated with a lower risk of osteoporotic fracture; further studies may be warranted to assess this further.

Abstract

Importance: The risk of osteoporotic fracture with dabigatran use in patients with nonvalvular atrial fibrillation (NVAF) is unknown.

Objective: To investigate the risk of osteoporotic fracture with dabigatran use and compare it with warfarin in patients with NVAF.

Design, Setting, and Participants: Retrospective cohort study using a population-wide database managed by the Hong Kong Hospital Authority. Patients newly diagnosed with NVAF from 2010 through 2014 and prescribed dabigatran or warfarin were matched by propensity score at 1:2 ratio and followed until July 31, 2016.

Exposures: Dabigatran or warfarin use during the study period.

Main Outcome and Measure: Risk of osteoporotic fracture at hip and vertebrae was compared between dabigatran and warfarin users using Poisson regression. The corresponding incidence rate ratio (IRR) and absolute risk difference (ARD) with 95% confidence interval (CI) were calculated.

Results: Among 51 496 patients newly diagnosed with NVAF, 8152 new users of dabigatran and warfarin were matched by propensity score (50% female; mean [SD] age, 74 [11] years). Osteoporotic fracture was developed in 104 (1.3%) patients during follow-up. This included 32 dabigatran users (1.0%) and 72 warfarin users (1.5%). Results of Poisson regression analysis showed that dabigatran use was significantly associated with a lower risk of osteoporotic fracture compared to warfarin (0.7 vs. 1.1 per 100 person-years [py]; IRR: 0.38 [95%CI: 0.22 to 0.66]; ARD: -0.68 [95%CI: -0.38 to -0.86] per 100 py). The association with lower risk was statistically significant in patients with a history of falls and/or fractures (dabigatran vs. warfarin: 1.6 vs. 3.6 per 100 py; IRR: 0.12 [0.04 to 0.33]; ARD: -3.15 [-2.40

to -3.45] per 100 py), but not in those without a history of falls and fractures (0.6 vs. 0.7 per 100 py; IRR: 0.95 [0.45 to 1.96]; ARD: -0.04 [0.67 to -0.39] per 100 py) (p-value for interaction<0.001).

Conclusions and Relevance: Among adults with NVAF receiving anticoagulation, the use of dabigatran compared with warfarin was associated with a lower risk of osteoporotic fracture. Additional study, perhaps including randomized trials, may be warranted to assess this further.

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Introduction

Warfarin is a traditional oral anticoagulant used for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF). It is a vitamin K antagonist (VKA) that interferes with the γ-carboxylation of glutamic acid (Glu) residues, and consequently inhibits the activation of bone matrix proteins.[1] Several studies have reported the possible link between warfarin use and an increased risk of osteoporotic fracture.[1-4] Particular concern was highlighted by a population-based study of 14 564 Medicare patients in the United States in 2006,[3] which reported an increased risk of osteoporotic fracture (odd ratio 1.25) in patients with AF on long-term (≥1 year) warfarin compared to non-warfarin users. Despite the concerns for fracture risk, warfarin was an inevitable treatment choice for decades as there were no other comparable alternatives available.

Dabigatran is the first non-VKA oral anticoagulant (NOAC) approved for use in patients with NVAF. Although most attention has focused on its effect on stroke or bleeding, a recent animal study reported that the use of dabigatran was associated with higher bone volume, smaller trabecular separation, and lower bone turnover rate compared to warfarin in rats, suggesting potential for a lower risk of osteoporotic fracture over warfarin.[5] Osteoporotic fracture is a key clinical concern because oral anticoagulants are usually prescribed to older people for whom fracture is a significant cause of morbidity and mortality.[6] However, the actual risk of osteoporotic fracture with dabigatran in humans is undefined and its comparison with warfarin in routine clinical practice is unknown.

This population-based cohort study was conducted to determine and compare the risk of osteoporotic fracture in patients with NVAF treated with dabigatran and warfarin.

Method

Data source

This study used the anonymized electronic medical records of the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority (HA), a statutory body that manages all public hospitals and their ambulatory clinics in Hong Kong.[7] HA is serving a population of over 7 million through 41 hospitals and institutions, 47 specialist outpatient clinics, and 73 general outpatient clinics.[7] CDARS covers approximately 80% of all hospital admissions in Hong Kong.[8] Electronic patient records in HA, including demographics, date of registered death, date of hospital admission and discharge, date of consultation, drug dispensing records, diagnoses, procedures, and laboratory tests are all centralized in CDARS for research and audit purpose. Patient records are anonymized to protect patient identity. CDARS had been extensively used for conducting high quality large population-based studies.[9-16] Data validation has demonstrated the high coding accuracy in CDARS.[9,10,12] Original clinical records of patients, including radiology reports, results from computed tomography or magnetic resonance imaging scans, surgery records, and documentation in medical charts were reviewed by two independent physicians to confirm the fracture events. A high coding accuracy was found in the diagnosis for fractures at hip (positive predictive value [PPV]=100%; 104/104 cases), vertebrae (PPV=86%; 87/101 cases), wrist and forearm (PPV=100%; 94/94 cases), and humerus (PPV=100%; 83/83 cases). Detailed descriptions of CDARS were reported previously.[10,14,16]

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 anonymized.

Study design and selection of patients

This was a retrospective cohort study. We identified new patients who had a first recorded AF (International Classification of Diseases codes, Ninth-Revision, Clinical Modification [ICD-9]: 427.3) between January 1, 2010 and December 31, 2014 in CDARS. To select patients with NVAF only, patients diagnosed with valvular AF, valvular heart disease or hyperthyroidism, or those who had undergone valve replacement (ICD-9-CM; eTable 1) at or prior to their first AF occurrence were excluded. Any possible cases of transient AF, cardiac surgery, myocarditis, pericarditis, or pulmonary embolism within 3 months before their first AF occurrence were excluded, as were patients with missing date of birth or sex, aged<18 years, or died during their first AF episode (Figure 1).

Index date was defined as the date of the first recorded prescription of dabigatran or warfarin following AF diagnosis. The follow-up for each patient commenced from the index date until the occurrence of fracture, death, switch to other oral anticoagulants (apixaban, dabigatran, rivaroxaban, and warfarin), discontinuation of treatment (defined as >5 days of gap between consecutive prescription refill), or end of study period (July 31, 2016), whichever came first. To select new users of dabigatran and warfarin, patients were excluded if they received either drug within 180 days prior to index date (Figure 1). Patients with bone tumors, epilepsy or history of seizure recorded any time before index date, or baseline use (≤90 days prior to index date) of hormone replacement therapy were excluded to reduce potential residual confounding effects.[17]

Outcome

The outcome of interest was a composite of hip fracture (ICD-9-CM: 820.x) and vertebral fracture (ICD-9-CM: 805.x). To exclude fractures due to trauma, fractures that accompanied a record of motor vehicle accident (ICD-9-CM: E800 – E848) on the same date were not

included as outcome events. Patient follow-up was censored at the date of any fracture associated with motor vehicle accident.

Propensity score matching

Propensity score (PS) was used to reduce potential bias due to treatment allocation.[18] It was estimated by logistic regression, in which the dependent variable was the treatment of interest (dabigatran) and the covariates were the observed patient characteristics including age, sex, index year, and other risk factors for osteoporotic fractures,[3,17] including medical history (recorded any time on or before the index date) of congestive heart failure, ischemic stroke or transient ischemic attack, chronic obstructive pulmonary disease (COPD), diabetes mellitus (detected by a diagnosis for diabetes mellitus or a recent use of insulin or antidiabetic drugs within 90 days on or before index date), liver disease, osteoporosis, rheumatoid arthritis and other inflammatory polyarthropathies, chronic kidney disease, history of falls, and history of fractures (ICD-9-CM; eTable 1); recent use (≤90 days on or before index date) of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers, bisphosphonates, antidepressants (selective serotonin reuptake inhibitors and tricyclic antidepressants), and systemic glucocorticoid. Dabigatran and warfarin patients were matched at 1:2 ratio by PS using greedy matching algorithm, which has been demonstrated to perform well in both actual and simulation studies.[19] Standardized difference was used to assess the difference between treatment groups, of which a value of <0.2 was considered negligible.[18] At present, there is no clear consensus on the criterion for negligible standardized difference.[18] Proposed cut-offs for acceptable standardized differences have ranged from 0.1 to 0.25.[18,20]

Statistical analysis

Baseline characteristics were expressed as mean ± standard deviation for continuous variables and frequencies (percentages) for categorical variables, respectively. The risk of osteoporotic fracture between dabigatran and warfarin users was compared using Poisson regression stratified on PS-matched groups. The result estimates were expressed in terms of incidence rate ratio (IRR) with 95% confidence interval (CI). Absolute risk difference (ARD) was estimated by I x (IRR – 1), where I was the incidence of osteoporotic fracture among warfarin users.[21]

We conducted subgroup analyses to investigate the risk of osteoporotic fractures in dabigatran and warfarin users with different treatment durations. A previous study suggested that only long-term exposure to warfarin (≥1 year), and not short-term exposure (<1 year), was associated with an increased risk of osteoporotic fracture.[3] Therefore, we conducted two subgroup analyses among patients exposed to dabigatran and warfarin for ≥1 year and <1 year, respectively. As patients with a history of falls or fractures are a concerning high-risk group for anticoagulant use due to potentials of fall-related injuries and subsequent risk of excessive bleeding,[22] we stratified patients by history of falls and/or fractures to explore the effect of dabigatran against warfarin. Sensitivity analyses were conducted by excluding fractures that were recorded with falls from higher than standing height (ICD-9-CM, eTable 1). We included fractures at humerus (ICD-9-CM: 812.x), forearm and wrist (813.x-814.x) as a composite outcome of osteoporotic fractures in separate analyses. In addition, we repeated our analyses with 5% trimming of PS to investigate any bias from unmeasured residual confounding.[23] Post-hoc analysis was conducted to compare the risk of osteoporotic fracture between dabigatran and non-treated patients.

Statistical analyses were independently conducted by WCYL and KKCM and cross-checked for quality assurance. SAS (version 9.3; SAS Institute, Inc, Cary, NC) was used for all statistical analyses. A two-sided p-value <0.05 was considered as statistically significant.

Results

Baseline characteristics

There were 51 946 patients newly diagnosed with AF identified in CDARS from January 1, 2010 through December 31, 2014. Following patient exclusion, 10 279 new users of dabigatran and warfarin were eligible for PS-matching, of which 8152 patients were successfully matched (Figure 1). All baseline characteristics had standardized differences <0.2 after PS-matching (Table 1; eFigure 1). When applying 5% trimming of PS in our sensitivity analysis, all baseline characteristics had standardized differences <0.1 (eTable 2). The mean age of the cohort was 74 ± 11 years and 4052 patients (50%) were female. The mean follow-up was 510 ± 507 days for dabigatran group and 496 ± 535 days for warfarin group. The mean follow-up of the overall cohort was 501 ± 524 days.

Risk of osteoporotic fracture

A total of 104 out of 8152 PS-matched patients (1.3%) developed osteoporotic fracture during follow-up. This included 32 dabigatran users (1.0%) and 72 warfarin users (1.5%) respectively. The median time to osteoporotic fracture after the first prescription was 222 days (interquartile range [IQR]: 57-450 days) for dabigatran and 267 days (IQR: 81-638 days) for warfarin.

The results for Poisson regression analysis showed that dabigatran use was significantly associated with a lower risk for osteoporotic fracture compared to warfarin (0.7 vs. 1.1 per 100 person-years [py]; IRR: 0.38, 95%CI: 0.22 to 0.66; ARD: -0.68, 95%CI: -0.38 to -0.86

per 100 py) (Table 2-3). The association with lower risk was statistically significant for both patients with short-term (1.1 vs. 1.4 per 100 py; IRR: 0.41; 95%CI: 0.21 to 0.79; ARD: -0.83, 95%CI: -0.30 to -1.11 per 100 py) and long-term (0.4 vs. 0.9 per 100 py; IRR: 0.27, 95%CI: 0.10 to 0.66; ARD: -0.65, 95%CI: -0.31 to -0.81 per 100 py) exposure of dabigatran versus warfarin. The test for subgroup difference indicated that there was no significant difference between the associations in short-term and long-term exposure groups (p-value for interaction=0.45).

The association with lower risk was statistically significant only for patients with a history of falls and/or fractures (1.6 vs. 3.6 per 100 py; IRR: 0.12, 95%CI: 0.04 to 0.33; ARD: -3.15, 95%CI: -2.40 to -3.45 per 100 py) but not for patients without a history of falls and fractures (0.6 vs. 0.7 per 100 py; IRR: 0.95, 95%CI: 0.45 to 1.96; ARD: -0.04, 95%CI: 0.67 to -0.39 per 100 py) (Table 3), p-value for interaction <0.001. When fractures associated with falls from higher than standing height were excluded using a sensitivity analysis, the findings remained similar (0.7 vs. 1.1 per 100 py; IRR: 0.39, 95%CI: 0.22 to 0.67; ARD: -0.67, 95%CI: -0.36 to -0.85 per 100 py). Consistently, a lower risk of osteoporotic fracture with dabigatran was observed when fractures at humerus, forearm and wrist were included as a composite outcome of osteoporotic fractures (1.2 vs. 1.6 per 100 py; IRR: 0.56, 95%CI: 0.36 to 0.85; ARD: -0.71, 95%CI: -0.24 to -1.02 per 100 py). Further analysis with 5% propensity-score trimming to reduce bias from unmeasured residual confounding also yielded similar results (0.6 vs. 1.0 per 100 py; IRR: 0.37, 95%CI: 0.19 to 0.70; ARD: -0.63, 95%CI: -0.30 to -0.81 per 100 py) (Table 3). Post-hoc analysis showed that dabigatran was associated with a lower incidence of osteoporotic fracture when compared to non-treated patients (IRR: 0.52, 95%CI: 0.33 to 0.81; ARD: -0.62, 95%CI: -0.25 to -0.87) (eTable 3-4; eFigure 2-3)

Discussion

In this population-based study, patients on dabigatran were associated with a lower risk of osteoporotic fracture compared to those on warfarin (IRR, 0.38), with an ARD of -0.68 per 100 py. The results suggested that the association with lower risk applied to both short-term (<1 year) and long-term (≥1 year) treatment of dabigatran versus warfarin. High-risk patients with a history of falls and/or fractures were found to have a greater ARD (-3.15 per 100 py). The results were robust to all sensitivity analyses which accounted for possible falls from height, different sites of osteoporotic fracture, and effects on unmeasured residual confounding.

Possible mechanism for study findings

Several factors might explain why dabigatran was associated with a lower risk of osteoporotic fracture compared to warfarin. Firstly, the mechanism for any deleterious effect of dabigatran on bone has not been identified.[24] However, the mechanism of warfarin is related to a reduction in bone formation.[1] Warfarin antagonizes vitamin K-dependent processes including the γ-carbonxylation of osteocalcin and other bone matrix proteins, which are required in bone mineralization.[1] Previous studies have demonstrated an increased level of under-carboxylated osteocalcin in warfarin users[3] and its association with reduced bone mineral density and increased fracture risk.[25] In contrast, the mechanism of dabigatran is independent of vitamin K and theoretically does not interfere with bone metabolism.[24] Therefore, it is biologically plausible that dabigatran may be associated with a lower risk for osteoporotic fracture compared to warfarin. Patients with a history of falls and/or fractures might reflect weaker baseline bone strength and therefore might be more susceptible to any further deleterious effect of warfarin on bone.[26] This is in line with the findings that the effect estimate in patients with a history of falls and/or fractures was stronger than that in patients

without such history, and that both effect estimates went towards a lower risk in dabigatran users than warfarin users.

Secondly, patients on warfarin are advised to limit dietary intake of vitamin K in order to achieve an optimal anticoagulation effect.[27] Vitamin K is involved in multiple stages of bone metabolism and a deficiency of it has been linked to an increased risk of bone loss and fracture.[28] As the use of dabigatran requires no dietary restrictions, it is less likely to be associated with osteoporotic fracture due to vitamin K deficiency. As the decrease in bone mass is a gradual process, the observed higher risk of osteoporotic fracture with <1 year use of warfarin versus dabigatran warrants further investigation. This could mean that there was an alternative mechanism by which dabigatran reduced the likelihood of osteoporotic fracture. Recently, results from an in vivo study indicated that dabigatran use was associated with higher bone volume, reduced trabecular separation, and lower bone turnover rate compared to warfarin in rats.[5] However, no similar studies have been conducted in humans. Post-hoc sensitivity analysis also showed that dabigatran was associated with a lower incidence of osteoporotic fracture than non-treated patients. Such finding may be due to unmeasured residual confounding effects; however, the biological effects of dabigatran on bone cannot be excluded. Additional epidemiological and mechanistic studies are warranted to further investigate effects of dabigatran on bone.

Comparisons with other studies

Although the risk of osteoporotic fracture with dabigatran has not been described in the literature, the possible link between warfarin use and osteoporotic fracture has been demonstrated previously.[2-4] However, some studies reported no increased risk of osteoporotic fracture associated with warfarin.[29-33] Studies that found no increased risk of fracture with warfarin were noted to involve smaller sample sizes,[30,32,33] shorter treatment duration[29], and

self-reported data[31,32] compared to those that found an increased risk.[3,4] However, as most studies compared patients prescribed warfarin against no treatment, the underlying characteristics between comparison groups were likely to be different with respect to stroke risk and comorbidities,[27] which themselves are also risk factors for osteoporotic fracture.[34] It is possible that non-treated patients were healthier and anticoagulation was not indicated, or in contrast, more severe patients where anticoagulation was deemed inappropriate.[27] Therefore, residual confounding was possible and the results could have been biased towards either direction. For similar reasons, the previous observation that patients on <1 year of warfarin was not associated with an increased risk of fracture compared to non-treated patients does not necessarily contradict our findings. Dabigatran has the same indication as warfarin.[27] Further, the current study used PS matching where patients with a high tendency of receiving dabigatran or warfarin were excluded from the comparison. Therefore, the results were less likely than previous studies to be confounded by indication.

Clinical implications

The finding that dabigatran was associated with a lower risk of osteoporotic fracture compared to warfarin is of particular clinical relevance given that osteoporotic fracture is a major cause of morbidity and mortality in older populations.[6] Many risk factors for osteoporotic fracture, such as older age, history of stroke, and diabetes mellitus, are also risk factors for stroke amongst NVAF patients requiring anticoagulation.[17] While surgery is usually required to treat a fracture, perioperative management of anticoagulation can be challenging given the need to balance the reduction in thromboembolism against excessive bleeding. The ARD observed in the overall cohort was moderate but much more pronounced in patients with a history of falls and/or fractures, it is potentially clinical significant as our results suggest that dabigatran might serve as a safer alternative to warfarin for reducing the risk of osteoporotic fracture in patients with NVAF. Randomized clinical trials and

population-based studies are warranted as, if this association is confirmed, screening of patients with NVAF for the risk for osteoporotic fracture could be considered to inform the choice of oral anticoagulant prescribed in clinical practice.

Strengths and limitations

To our knowledge, this is the first population-based study that determined the risk of osteoporotic fracture with dabigatran versus warfarin in patients with NVAF. This study utilized the territory-wide healthcare database in Hong Kong, which has been recognized to provide high-quality data for large drug surveillance studies.[9-16]

This study has several limitations. As inherent in epidemiological studies, the possibility of unmeasured residual confounding effects cannot be excluded. Similar to other healthcare databases, information such as bone mineral density and body mass index are not routinely recorded in CDARS. However, these factors are not typically considered to differentiate eligible users of dabigatran and warfarin[27] and therefore are unlikely to introduce confounding by indication. Similarly, tobacco and alcohol consumptions are not routinely recorded in CDARS. However, other important confounding factors which may partially account for these risk factors were included (e.g. COPD and liver disease)[35,36] and several sensitivity analyses were conducted, which showed that the results were consistent. Since the potential risk of osteoporotic fracture with warfarin use has long been noted,[2-4] patients with concerned risk of osteoporotic fracture might tend to receive dabigatran over warfarin. This might mask any association with lower risk with dabigatran use compared to warfarin if patient characteristics were not perfectly controlled by PS. However, this did not apply to our findings.

Similar to other healthcare databases research, the fractures identified in this study could not be classified into symptomatic or asymptomatic as such information is not available in

CDARS. Vertebral compression fracture is often asymptomatic and may not be diagnosed, which might lead to an underestimation of any risk with dabigatran and warfarin. However, more severe cases would draw clinical attention and be recorded. Although warfarin users may have had more frequent visits than dabigatran users due to coagulation testing, it is unusual to perform routine screening for asymptomatic vertebral fractures.[37] The decision to obtain spine x-rays is generally a response to conditions that warrant medical attention (e.g. chronic lower back pain), and if such conditions had been presented in patients taking dabigatran it would generally have been reported during their routine clinical visits, where a fracture would also be detected if present. Therefore, it is unlikely that the potential underestimation would occur differentially for dabigatran and warfarin users, consequently, this would not affect the conclusion of our results.

Conclusion

Among adults with NVAF receiving anticoagulation, the use of dabigatran compared with warfarin was associated with a lower risk of osteoporotic fracture. Additional study, perhaps including randomized trials, may be warranted to assess this further.

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Study concept and design: Lau, Wong.

Acquisition, analysis, or interpretation of data: Lau, Wong, Chan, Cheung, Sing, Man, Lip, Siu, Lam, Lee.

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Critical revision of the manuscript for important intellectual content: Lau, Wong, Chan, Cheung, Sing, Man, Lip, Siu, Lam, Lee.

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Figure 1. Selection of patients

Table 1. Baseline characteristics

	Before propensity-score matching			After propensity-score matching		
	Dabigatran	Warfarin	Standardized difference[a]	Dabigatran	Warfarin	Standardized difference[a]
N	3298	6981		3268	4884	
Age, mean ± SD	74.3 ± 10.1	72.1 ± 11.7	0.20	74.2 ± 10.1	73.3 ± 11.0	0.08
Female	1685 (51.1)	3227 (46.2)	0.10	1657 (50.7)	2395 (49.0)	0.03
Baseline medical conditions						
$CHADS_2$, mean ± SD	2.1 ± 1.5	2.1 ± 1.6	0.02	2.1 ± 1.5	2.1 ± 1.6	0.02
CHA_2DS_2-VASc, mean ± SD	3.4 ± 2.2	3.3 ± 2.2	0.04	3.4 ± 2.2	3.4 ± 2.3	0.02
Congestive heart failure	689 (20.9)	2205 (31.6)	-0.24	689 (21.1)	1271 (26.0)	-0.12
Prior ischemic stroke/transient ischemic attack	1116 (33.8)	2073 (29.7)	0.09	1094 (33.5)	1515 (31.0)	0.05
Chronic Obstructive Pulmonary Disease	274 (8.3)	581 (8.3)	<0.001	270 (8.3)	406 (8.3)	<0.001
Diabetes mellitus	997 (30.2)	1982 (28.4)	0.04	984 (30.1)	1402 (28.7)	0.03
History of falls	518 (15.7)	931 (13.3)	0.07	505 (15.5)	723 (14.8)	0.02
History of fractures	237 (7.2)	446 (6.4)	0.03	234 (7.2)	336 (6.9)	0.01
Liver disease	16 (0.5)	44 (0.6)	-0.02	16 (0.5)	30 (0.6)	-0.02
Osteoporosis	40 (1.2)	69 (1.0)	0.02	38 (1.2)	53 (1.1)	0.01
Rheumatoid arthritis and other inflammatory polyarthropathies	14 (0.4)	45 (0.6)	-0.03	14 (0.4)	23 (0.5)	-0.01
Chronic kidney disease	94 (2.9)	536 (7.7)	-0.22	94 (2.9)	181 (3.7)	-0.05
Baseline medication use						
ACE inhibitor or ARB	1552 (47.1)	3332 (47.7)	-0.01	1533 (46.9)	2313 (47.4)	-0.01
Beta-blocker	2011 (61.0)	4028 (57.7)	0.07	1986 (60.8)	2874 (58.8)	0.04
Bisphonsphonates	43 (1.3)	54 (0.8)	0.05	34 (1.0)	42 (0.9)	0.02
Systemic glucocorticoid	213 (6.5)	583 (8.4)	-0.07	213 (6.5)	364 (7.5)	-0.04
Antidepressants	128 (3.9)	224 (3.2)	0.04	125 (3.8)	170 (3.5)	0.02

Values are expressed as frequency (%) unless otherwise specified. Abbreviations: SD, standard deviation; $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke/transient ischemic attack/systemic embolism (doubled); CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, age 65–74 years, prior stroke/transient ischemic attack/systemic embolism (doubled), vascular disease, and sex category (female); CHA_2DS_2-VASc score ranges from 0-9, where a higher score indicates a higher risk for stroke; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. [a]Standardized difference is the difference in mean or proportion of covariates in dabigatran group versus warfarin group divided by the pooled standard deviation; standardized difference <0.2 indicates a negligible difference in covariates between treatment groups.

Table 2. Crude estimates before propensity score matching

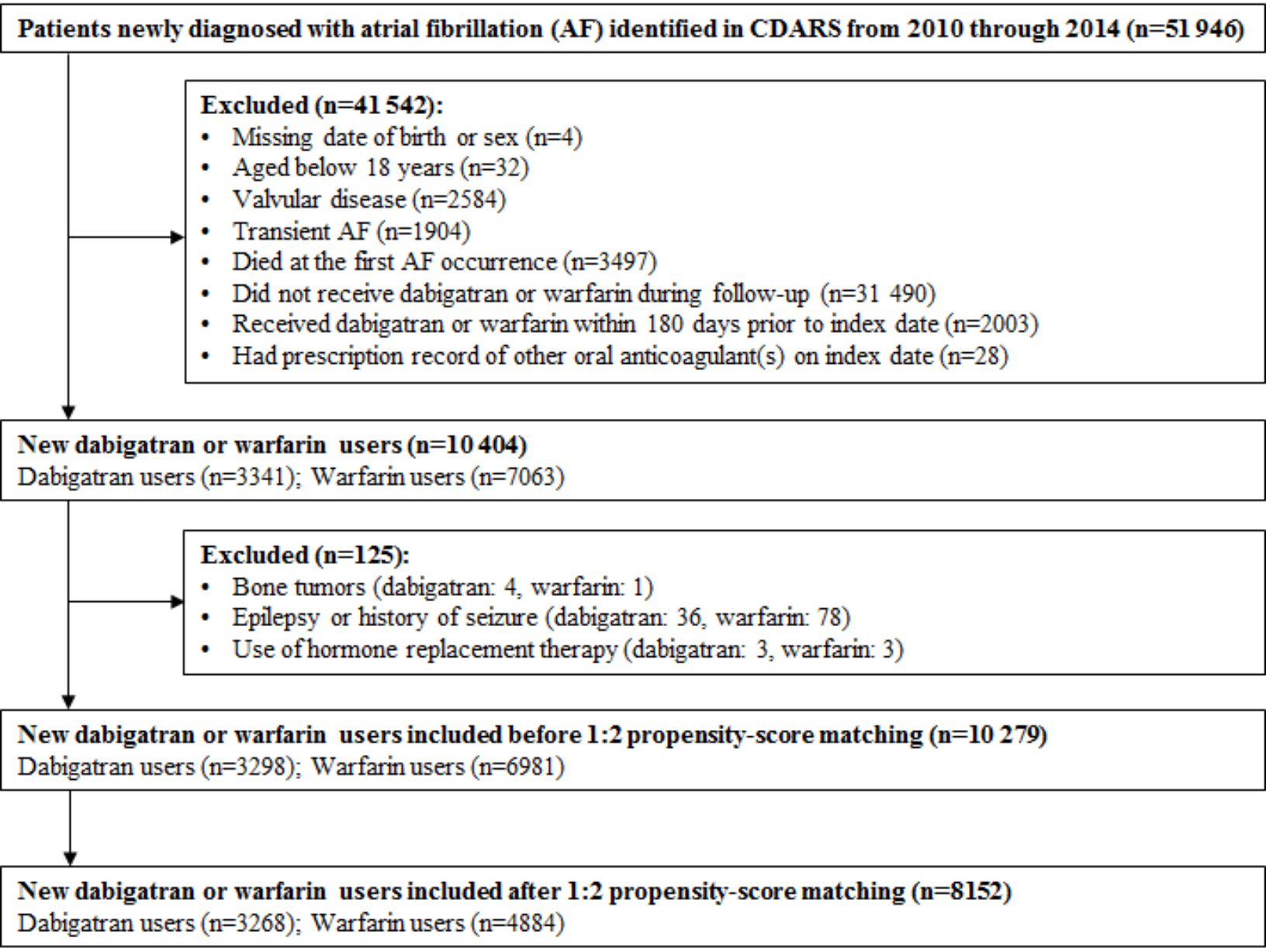
	Dabigatran			Warfarin			Dabigatran vs. Warfarin		
	N	No. of cases/py	incidence per 100 py	N	No. of cases/py	incidence per 100 py	ARD (95% CI)	IRR (95% CI)	p
Overall	3298	34/4594	0.7	6981	95/10 746	0.9	-0.15 (0.21 to -0.39)	0.84 (0.57 to 1.24)	.37
Stratified by treatment duration									
Short-term use (< 1 year)	3298	24/2093	1.1	6981	51/4210	1.2	-0.06 (0.64 to -0.50)	0.95 (0.58 to 1.54)	.82
Long-term use (≥1 year)	1537	10/2501	0.4	3247	44/6537	0.7	-0.28 (0.13 to -0.49)	0.59 (0.30 to 1.18)	.14
Stratified by history of falls/fractures									
With history of falls or fractures	528	11/665	1.7	952	37/1129	3.3	-1.64 (-0.04 to -2.45)	0.50 (0.26 to 0.99)	.04
Without history of falls and fractures	2770	23/3929	0.6	6029	58/9618	0.6	-0.02 (0.34 to -0.24)	0.97 (0.60 to 1.57)	.90
Sensitivity analysis (fracture sites: hip, vertebral, wrist, forearm, humerus)	3298	56/4563	1.2	6981	142/10 680	1.3	-0.10 (0.34 to -0.42)	0.92 (0.68 to 1.26)	.61
Excluding fractures with falls from higher than standing height	3298	34/4594	0.7	6981	94/10 746	0.9	-0.14 (0.23 to -0.39)	0.85 (0.57 to 1.25)	.40
PS trimming at 5%[a]	3298	34/4594	0.7	6981	95/10 746	0.9	-0.15 (0.21 to -0.39)	0.84 (0.57 to 1.24)	.37

Abbreviations: py: person-years; ARD: absolute risk difference per 100 person-years; IRR, incidence rate ratio; CI, confidence interval; PS, propensity score. [a]Propensity score trimming was performed by excluding patients who had a propensity score below the 5th percentile of that of the dabigatran-treated patients or above the 95th percentile of that of the warfarin-treated patients. This was done to investigate any effect of bias from unmeasured residual confounding on the result.

Table 3. Risk of osteoporotic fracture with dabigatran and warfarin after propensity score matching

	Dabigatran			Warfarin			Dabigatran vs. Warfarin		
	N	No. of cases/py	incidence per 100 py	N	No. of cases/py	incidence per 100 py	ARD (95% CI)	IRR (95% CI)	p
Overall	3268	32/4563	0.7	4884	72/6629	1.1	-0.68 (-0.38 to -0.86)	0.38 (0.22 to 0.66)	<.001
Stratified by treatment duration									
Short-term use (< 1 year)	3268	22/2078	1.1	4884	41/2891	1.4	-0.83 (-0.30 to -1.11)	0.41 (0.21 to 0.79)	.006
Long-term use (≥1 year)	1509	9/2468	0.4	2125	32/3573	0.9	-0.65 (-0.31 to -0.81)	0.27 (0.10 to 0.66)	.002
Stratified by history of falls/fractures									
With history of falls or fractures	513	10/642	1.6	777	32/881	3.6	-3.15 (-2.40 to -3.45)	0.12 (0.04 to 0.33)	<.001
Without history of falls and fractures	2747	23/3909	0.6	4107	40/5747	0.7	-0.04 (0.67 to -0.39)	0.95 (0.45 to 1.96)	1.00
Sensitivity analysis (fracture sites: hip, vertebral, wrist, forearm, humerus)	3268	54/4532	1.2	4884	104/6595	1.6	-0.71 (-0.24 to -1.02)	0.56 (0.36 to 0.85)	.006
Excluding fractures with falls from higher than standing height	3268	32/4563	0.7	4884	71/6629	1.1	-0.67 (-0.36 to -0.85)	0.39 (0.22 to 0.67)	<.001
PS trimming at 5%[a]	2799	24/3992	0.6	4207	55/5696	1.0	-0.63 (-0.30 to -0.81)	0.37 (0.19 to 0.70)	.002

Abbreviations: py: person-years; ARD: absolute risk difference per 100 person-years; IRR, incidence rate ratio; CI, confidence interval; PS, propensity score. [a]Propensity score trimming was performed by excluding patients who had a propensity score below the 5th percentile of that of the dabigatran-treated patients or above the 95th percentile of that of the warfarin-treated patients. This was done to investigate any effect of bias from unmeasured residual confounding on the result.


Patients newly diagnosed with atrial fibrillation (AF) identified in CDARS from 2010 through 2014 (n=51 946)
Excluded (n=41 542):
• Missing date of birth or sex (n=4)
• Aged below 18 years (n=32)
• Valvular disease (n=2584)
• Transient AF (n=1904)
• Died at the first AF occurrence (n=3497)
• Did not receive dabigatran or warfarin during follow-up (n=31 490)
• Received dabigatran or warfarin within 180 days prior to index date (n=2003)
• Had prescription record of other oral anticoagulant(s) on index date (n=28)
New dabigatran or warfarin users (n=10 404)
Dabigatran users (n=3341); Warfarin users (n=7063)
Excluded (n=125):
• Bone tumors (dabigatran: 4, warfarin: 1)
• Epilepsy or history of seizure (dabigatran: 36, warfarin: 78)
• Use of hormone replacement therapy (dabigatran: 3, warfarin: 3)
New dabigatran or warfarin users included before 1:2 propensity-score matching (n=10 279)
Dabigatran users (n=3298); Warfarin users (n=6981)
New dabigatran or warfarin users included after 1:2 propensity-score matching (n=8152)
Dabigatran users (n=3268); Warfarin users (n=4884)