Association Between Dabigatran vs Warfarin and Risk of Osteoporotic Fractures Among Patients With Nonvalvular Atrial Fibrillation

Wallis C. Y. Lau, BSc; Esther W. Chan, PhD; Ching-Lung Cheung, PhD; Chor Wing Sing, BSc; Kenneth K. C. Man, MPH; Gregory Y. H. Lip, MD; Chung-Wah Siu, MD; Joanne K. Y. Lam, FHKAM; Alan C. H. Lee, FHKAM; Ian C. K. Wong, PhD

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 vs 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 a 1:2 ratio with follow-up until July 31, 2016.

EXPOSURES Dabigatran or warfarin use during the study period.

MAIN OUTCOMES AND MEASURES Risk of osteoporotic hip fracture and vertebral fracture was compared between dabigatran and warfarin users using Poisson regression. The corresponding incidence rate ratio (IRR) and absolute risk difference (ARD) with 95% CIs were calculated.

RESULTS Among 51 496 patients newly diagnosed with NVAF, 8152 new users of dabigatran (n = 3268) and warfarin (n = 4884) were matched by propensity score (50% women; mean [SD] age, 74 [11] years). Osteoporotic fracture developed in 104 (1.3%) patients during follow-up (32 dabigatran users [1.0%]; 72 warfarin users [1.5%]). Results of Poisson regression analysis showed that dabigatran use was associated with a significantly lower risk of osteoporotic fracture compared with warfarin (0.7 vs 1.1 per 100 person-years; ARD per 100 person-years, −0.68 [95% CI, −0.38 to −0.86]; IRR, 0.38 [95% CI, 0.22 to 0.66]). The association with lower risk was statistically significant in patients with a history of falls, fractures, or both (dabigatran vs warfarin, 1.6 vs 3.6 per 100 person-years; ARD per 100 person-years, −3.15 [95% CI, −2.40 to −3.45]; IRR, 0.12 [95% CI, 0.04 to 0.33]), but not in those without a history (0.6 vs 0.7 per 100 person-years; ARD per 100 person-years, −0.04 [95% CI, 0.67 to −0.39]; IRR, 0.95 [95% CI, 0.45 to 1.96]) (*P* value for interaction, <.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 clinical trials, may be warranted to further understand the relationship between use of dabigatran vs warfarin and risk of fracture.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Ian C. K. Wong, PhD, Room 305, UCL School of Pharmacy, 29-39 Brunswick Square, London, WC1N 1AX, United Kingdom (i.wong@ucl.ac.uk).

W arfarin is a traditional oral anticoagulant used for stroke prevention in patients with nonvalvular atrial fibrillation (NVAF). It is a vitamin K antagonist that interferes with the γ-carboxylation of glutamic acid residues, and it 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 (odds ratio, 1.25) in patients with atrial fibrillation (AF) and long-term (≥1 year) warfarin use compared with patients who were not using warfarin. Despite the concerns for fracture risk, warfarin was an inevitable treatment choice for decades because no other comparable alternatives were available.

Dabigatran is the first non–vitamin K antagonist oral anticoagulant 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 with 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 or 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, a statutory body that manages all public hospitals and their ambulatory clinics in Hong Kong.[7] The Hong Kong Hospital Authority serves a population of more than 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 the Hong Kong Hospital Authority, 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 purposes. 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 high coding accuracy in CDARS.[9,10,12] Original clinical records of patients, including radiology reports, results from computed tomography or magnetic resonance imaging

Key Points

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

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

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

scans, surgery records, and documentation in medical charts were reviewed by 2 independent physicians to confirm the fracture events. A high coding accuracy was found in the diagnosis for fractures at the 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. New patients were identified as those who had a first recorded AF (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code 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, hyperthyroidism, or those who had undergone valve replacement (eTable 1 in the Supplement) 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 patients' first AF occurrence were excluded, as were patients with a missing date of birth or sex, age younger than 18 years, or who died during their first AF episode (**Figure**).

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, change of prescription to another oral anticoagulant (apixaban, dabigatran, rivaroxaban, or warfarin), discontinuation of treatment (>5-day time frame between consecutive prescription refill), or end of study period (July 31, 2016), whichever came first. Patients were excluded if they received dabigatran or warfarin within 180 days prior to index date, or if they had a prescription record of other oral anticoagulant use on the index date (Figure). 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 therapy were excluded to reduce potential residual confounding effects.[17]

Outcome

The outcome of interest was a composite of hip fracture (*ICD-9-CM* code 820.x) and vertebral fracture (*ICD-9-CM* code 805.x). To exclude fractures due to trauma, fractures that accompanied a record of motor vehicle accident (*ICD-9-CM* codes 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 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), 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 the index date], liver disease, osteoporosis, rheumatoid arthritis and other inflammatory polyarthropathies, chronic kidney disease, history of falls, and history of fractures (eTable 1 in the Supplement), and recent use (≤90 days on or before the index date) of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β-blockers, bisphosphonates, antidepressants (selective serotonin reuptake inhibitors and tricyclic antidepressants), and systemic glucocorticoids. Patients using dabigatran and warfarin were matched at a 1:2 ratio by propensity score using a 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 less than 0.2 was considered negligible.[18] At the time of this study, there was no clear consensus on the criterion for negligible standardized difference.[18] Proposed cutoffs for acceptable standardized differences have ranged from 0.1 to 0.25.[18,20]

Statistical Analysis

Baseline characteristics were expressed as mean (standard deviation [SD]) for continuous variables and as frequencies (percentages) for categorical variables. The risk of osteoporotic fracture between dabigatran and warfarin users was compared using Poisson regression stratified on propensity score–matched groups. The result estimates were expressed using incidence rate ratios (IRRs) with 95% CIs. Absolute risk difference (ARD) was estimated by I × (IRR−1) (I indicates the incidence of osteoporotic fracture among warfarin users).[21]

In the present study, subgroup analyses were conducted 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] There-

Figure. Selection of Nonvalvular Atrial Fibrillation Patients for Analysis of Osteoporotic Fracture Risk With Dabigatran or Warfarin Use
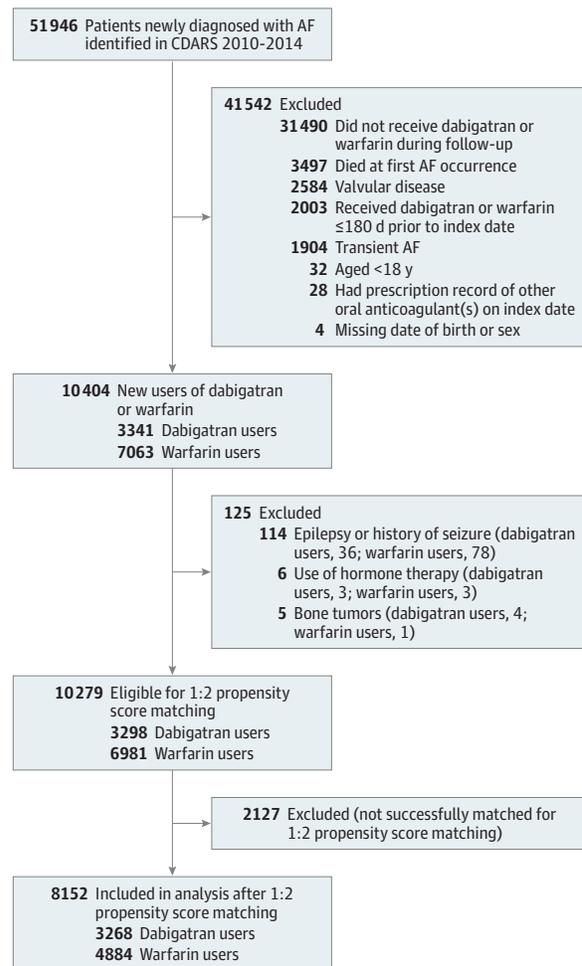
CDARS indicates the Clinical Data Analysis and Reporting System (of the Hong Kong Hospital Authority); AF, atrial fibrillation.

fore, 2 subgroup analyses were conducted among patients exposed to dabigatran and warfarin for at least 1 year and for less than 1 year. Because patients with a history of falls or fractures are a concerning high-risk group for anticoagulant use due to potential of fall-related injuries and subsequent risk of excessive bleeding,[22] participants were stratified by history of falls, fractures, or both 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 (eTable 1 in the Supplement). Fractures at the humerus (*ICD-9-CM*, 812.x) and the forearm and wrist (*ICD-9-CM*, 813.x-814.x) were included as a composite outcome of osteoporotic fractures in separate analyses. In addition, analyses were repeated with 5% trimming of propensity score to investigate any bias from unmeasured residual confounding.[23] Posthoc analysis was conducted to compare the risk of osteoporotic fracture between dabigatran users and nontreated patients.

Statistical analyses were conducted by 2 coauthors (W.C.Y.L. and K.K.C.M.) and crosschecked for quality assurance.

Table 1. Baseline Characteristics[a]

Characteristics	Before Propensity Score Matching			After Propensity Score Matching		
	Dabigatran	Warfarin	Standardized Difference[b]	Dabigatran	Warfarin	Standardized Difference[b]
No.	3298	6981		3268	4884	
Age, mean (SD), y	74.3 (10.1)	72.1 (11.7)	0.20	74.2 (10.1)	73.3 (11.0)	0.08
Women	1685 (51.1)	3227 (46.2)	0.10	1657 (50.7)	2395 (49.0)	0.03
Medical conditions						
CHADS$_2$, mean (SD)[c]	2.1 (1.5)	2.1 (1.6)	0.02	2.1 (1.5)	2.1 (1.6)	0.02
CHA$_2$DS$_2$-VASc, mean (SD)[d]	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 or TIA	1116 (33.8)	2073 (29.7)	0.09	1094 (33.5)	1515 (31.0)	0.05
COPD	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
Medication use						
ACE inhibitor or ARB	1552 (47.1)	3332 (47.7)	−0.01	1533 (46.9)	2313 (47.4)	−0.01
β-blocker	2011 (61.0)	4028 (57.7)	0.07	1986 (60.8)	2874 (58.8)	0.04
Bisphosphonates	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

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack.

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

[b] Standardized difference indicates difference in mean or proportion of covariates in the dabigatran group vs the warfarin group divided by the pooled standard deviation. A standardized difference of less than 0.2 indicates a negligible difference in covariates between treatment groups.

[c] CHADS$_2$ indicates patients with congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, prior stroke or TIA or systemic embolism (doubled). CHADS$_2$ score ranges from 0 to 6 (higher score indicates a higher risk for stroke).

[d] CHA$_2$DS$_2$-VASc indicates patients with congestive heart failure, hypertension, age 75 years or older (doubled), diabetes mellitus, age 65 to 74 years, prior stroke or TIA or systemic embolism (doubled), vascular disease, and sex category (women). CHA$_2$DS$_2$-VASc score ranges from 0 to 9 (higher score indicates a higher risk for stroke).

SAS (version 9.3; SAS Institute, Inc) was used for all statistical analyses. A 2-sided P value of less than .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 exclusion of ineligible participants, 10 279 new users of dabigatran and warfarin were eligible for propensity score matching, of whom 8152 were successfully matched (3268 dabigatran users and 4884 warfarin users; Figure). All baseline characteristics had standardized differences of less than 0.2 after propensity score matching (Table 1; eFigure 1 in the Supplement). When applying 5% trimming of propensity score in the sensitivity analysis, all baseline characteristics had standardized differences of less than 0.1 (eTable 2 in the Supplement). The mean (SD) age of

the cohort was 74 (11) years, and 4052 patients (50%) were women. The mean (SD) follow-up was 510 (507) days for the dabigatran group and 496 (535) days for the warfarin group. The mean follow-up of the overall cohort was 501 (524) days.

Risk of Osteoporotic Fracture

A total of 129 of 10 279 patients (1.3%) developed osteoporotic fracture during follow-up (34 dabigatran users [1.0%] and 95 warfarin users [1.4%]; Table 2). In the propensity score-matched sample, 104 of 8152 patients (1.3%) developed osteoporotic fracture during follow-up (32 dabigatran users [1.0%] and 72 warfarin users [1.5%]). 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 with warfarin (0.7 vs 1.1 per 100 person-years; ARD per 100 person-years, −0.68 [95% CI, −0.38 to −0.86]; IRR, 0.38 [95% CI, 0.22 to 0.66]; Table 3).

Table 2. Crude Estimates of Osteoporotic Fracture Risk Before Propensity Score Matching

	Dabigatran			Warfarin			Dabigatran vs Warfarin		
	No.	No. of Cases/ Person-Years	Incidence per 100 Person-Years	No.	No. of Cases/ Person-Years	Incidence per 100 Person-Years	ARD Per 100 Person-Years (95% CI)	IRR (95% CI)	P Value
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 y)	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 y)	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 or 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 or 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[a]	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
Propensity score trimming at 5%[b]	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: ARD, absolute risk difference; IRR, incidence rate ratio.

[a] Fracture sites: hip, vertebral, wrist, forearm, humerus.

[b] Performed by excluding patients with 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 (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		
	No.	No. of Cases/ Person-Years	Incidence per 100 Person-Years	No.	No. of Cases/ Person-Years	Incidence per 100 Person-Years	Adjusted ARD Per 100 Person-Years (95% CI)[a]	Adjusted IRR (95% CI)	P Value
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 y)	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 y)	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 or 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 or 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)	>.99
Sensitivity analysis[b]	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
Propensity score trimming at 5%[c]	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: ARD, absolute risk difference; IRR, incidence rate ratio.

[a] ARD per 100 person-years is calculated by incidence per 100 person-years for warfarin × (IRR−1).

[b] Fracture sites: hip, vertebral, wrist, forearm, humerus.

[c] Performed by excluding patients with 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 (to investigate any effect of bias from unmeasured residual confounding on the result).

The association with lower risk was statistically significant for patients with short-term exposure (1.1 for dabigatran vs 1.4 for warfarin per 100 person-years; ARD per 100 person-years, −0.83 [95% CI, −0.30 to −1.11]; IRR, 0.41 [95% CI, 0.21 to 0.79]) as well as long-term exposure (0.4 for dabigatran vs 0.9 for warfarin per 100 person-years]; ARD per 100 person-years, −0.65 [95% CI, −0.31 to −0.81]; IRR, 0.27 [95% CI, 0.10 to 0.66]). The test for subgroup difference indicated no sig-

nificant difference between the associations in short-term and long-term exposure groups (P value for interaction, .45).

The association with lower risk was statistically significant only for patients with a history of falls or fractures (1.6 for dabigatran vs 3.6 for warfarin per 100 person-years; ARD per 100 person-years, −3.15 [95% CI, −2.40 to −3.45]; IRR, 0.12 [95% CI, 0.04 to 0.33]) but not for patients without a history of falls and fractures (0.6 for dabigatran vs 0.7 for warfarin per

100 person-years; ARD per 100 person-years, −0.04 [95% CI, 0.67 to −0.39]; IRR, 0.95 [95% CI, 0.45 to 1.96]; Table 3] (P value for interaction, <.001). When fractures associated with falls from higher than standing height were excluded using a sensitivity analysis, the findings remained similar (0.7 for dabigatran vs 1.1 for warfarin per 100 person-years; ARD per 100 person-years, −0.67 [95% CI, −0.36 to −0.85]; IRR, 0.39 [95% CI, 0.22 to 0.67]). Consistently, a lower risk of osteoporotic fracture with dabigatran was observed when fractures at the humerus, forearm, and wrist were included as a composite outcome of osteoporotic fractures (1.2 for dabigatran vs 1.6 for warfarin per 100 person-years; ARD per 100 person-years, −0.71 [95% CI, −0.24 to −1.02]; IRR, 0.56 [95% CI, 0.36 to 0.85]). Further analysis with 5% propensity score trimming to reduce bias from unmeasured residual confounding also yielded similar results (0.6 for dabigatran vs 1.0 for warfarin per 100 person-years; ARD per 100 person-years, −0.63 [95% CI, −0.30 to −0.81]; IRR, 0.37 [95% CI, 0.19 to 0.70]; Table 3). On posthoc analysis, dabigatran was associated with a lower incidence of osteoporotic fracture when compared with nontreated patients (ARD per 100 person-years, −0.62 [95% CI, −0.25 to −0.87]; IRR, 0.52 [95% CI, 0.33 to 0.81]) (eTable 3, eTable 4, eFigure 2, and eFigure 3 in the Supplement).

Discussion

In this population-based study, patients who used dabigatran had a lower risk of osteoporotic fracture compared with warfarin users (IRR, 0.38), with an ARD of −0.68 per 100 person-years. The results suggest that the association with lower risk applies to both short-term (<1 year) and long-term (≥1 year) treatment with dabigatran vs warfarin. High-risk patients with a history of falls, fractures, or both were found to have a greater ARD (−3.15 per 100 person-years). 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 with warfarin. First, although mechanism for any deleterious effect of dabigatran on bone has not been identified,[24] the mechanism of action of warfarin may interfere with processes that contribute to bone formation.[1] Warfarin antagonizes vitamin K–dependent processes including the γ-carboxylation of osteocalcin and other bone matrix proteins that are required in bone mineralization.[1] Previous studies have demonstrated an increased level of undercarboxylated 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 with warfarin. Patients with a history of falls, fractures, or both 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, fractures, or both was stronger than that in patients without such history, and that both effect estimates went toward a lower risk in dabigatran users than warfarin users.

Second, patients who are warfarin users 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 vitamin K has been linked to an increased risk of bone loss and fracture.[28] Because the use of dabigatran requires no dietary restrictions, and it is less likely to be associated with osteoporotic fracture due to vitamin K deficiency. Because the decrease in bone mass is a gradual process, the observed higher risk of osteoporotic fracture with less than 1-year use of warfarin vs 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 with warfarin in rats.[5] However, no similar studies have been conducted in humans. On posthoc sensitivity analysis, dabigatran was associated with a lower incidence of osteoporotic fracture than in nontreated 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 involved smaller sample sizes,[30,32,33] shorter treatment duration,[29] and self-reported data[31,32] compared with those that found an increased risk.[3,4] However, because most studies compared patients prescribed warfarin against those receiving no treatment, the underlying characteristics between comparison groups were likely to be different with respect to stroke risk and comorbidities,[27] which are also risk factors for osteoporotic fracture.[34] It is possible that nontreated patients were healthier and anticoagulation was not indicated, or in contrast, more severe patients in whom anticoagulation was deemed inappropriate.[27] Therefore, residual confounding was possible, and the results could have been biased toward either direction. For similar reasons, the previous observation that patients using warfarin for less than 1 year was not associated with an increased risk of fracture compared with nontreated patients does not necessarily contradict the findings of the current study. Dabigatran has the same indication as warfarin.[27] Further, the current study used propensity score matching—excluding patients with a high tendency of receiving dabigatran or warfarin from the compari-

son. 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 with 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 among NVAF patients requiring anticoagulation.[17] Although 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, fractures, or both; it has potential clinical significance because the current 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 because, 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 vs warfarin in patients with NVAF. This study used the territory-wide health care 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 health care 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 consumption are not routinely re-

corded in CDARS. However, other important confounding factors, which may partially account for these risk factors, were included (eg, COPD and liver disease),[35,36] and several sensitivity analyses were conducted, which showed that the results were consistent. Because 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 with warfarin if patient characteristics were not perfectly controlled by propensity score. However, this did not apply to the findings of the current study.

Similar to research accessing other health care databases, the fractures identified in this study could not be classified into symptomatic or asymptomatic because 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 (eg, 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 when 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.

Conclusions

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 clinical trials, may be warranted to further understand the relationship between use of dabigatran vs warfarin and risk of fracture.

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