Annals of Internal Medicine ORIGINAL RESEARCH

Association Between Treatment With Apixaban, Dabigatran, Rivaroxaban, or Warfarin and Risk for Osteoporotic Fractures Among Patients With Atrial Fibrillation

A Population-Based Cohort Study

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

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

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

Design: Population-based cohort study.

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

Participants: Patients newly diagnosed with AF between 2010 and 2017 who received a new prescription for warfarin or a direct oral anticoagulant (DOAC) (apixaban, dabigatran, or 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 differences (CIDs).

Results: There were 23 515 patients identified (3241 apixaban users, 6867 dabigatran users, 3866 rivaroxaban users, and 9541 warfarin users). Overall mean age was 74.4 years (SD, 10.8), ranging from 73.1 years (warfarin) to 77.9 years (apixaban). Over a median follow-up of 423 days, 401 fractures were identified (crude event number [weighted rate per 100 patient-years]: apixaban, 53 [0.82]; dabigatran, 95 [0.76]; rivaroxaban, 57 [0.67]; and warfarin, 196 [1.11]). After 24-month follow-up, DOAC use was associated with a lower risk for fracture than warfarin use (apixaban CID, −0.88% [95% CI, −1.66% to −0.21%]; dabigatran CID, −0.81% [CI, −1.34% to −0.23%]; and rivaroxaban CID, −1.13% [CI, −1.67% to −0.53%]). No differences were seen in all head-to-head comparisons between DOACs at 24 months (apixaban vs. dabigatran CID, −0.06% [CI, −0.69% to 0.49%]; rivaroxaban vs. dabigatran CID, −0.32% [CI, −0.84% to 0.18%]; and rivaroxaban vs. apixaban CID, −0.25% [CI, −0.86% to 0.40%]).

Limitation: Residual confounding is possible.

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

Primary Funding Source: The University of Hong Kong and University College London Strategic Partnership Fund.

Ann Intern Med. 2020;173:1-9. doi:10.7326/M19-3671 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 19 May 2020.

Osteoporotic fracture is a frequent cause of death and disability in the older population (1). Warfarin, a vitamin K antagonist used for stroke prevention in persons with atrial fibrillation (AF), has long been speculated to increase the risk for 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 increase the risk for osteoporotic fracture. However, most of the previous studies that investigated the link between warfarin and fracture were done in previous decades and have yielded inconsistent findings (2–9).

Recently, 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 fractures in DOAC users than in warfarin users (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 for osteoporotic fracture for different oral anticoagulants. In mice, rivaroxaban and dabigatran have been shown to influence different pathways in bone formation, resorption, and remodeling (11, 12). The risk for fracture with apixaban has not been investigated in vitro.

Direct oral anticoagulants are now recommended over warfarin for stroke prevention in persons with AF mainly because they are at least as efficacious as warfarin in preventing stroke, have lower bleeding risks, and require less monitoring (13, 14). They are also associated with a lower potential risk for drug–drug interactions than warfarin (15). However, data on osteoporotic fracture risks with DOAC use 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 for osteoporotic fracture. Given that oral anticoagulants are often prescribed to older adults who have multiple risk factors for osteoporotic fractures (18), further clarity on their role in fracture risk is needed. This is particularly relevant to persons with AF,

who were reported to have a higher incidence of hip fractures than those without AF (19).

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

METHODS

Data Source

We used the anonymized 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 more than 7.4 million and covers approximately 80% of all hospital admissions in Hong Kong (21). Demographic characteristics, dates of registered deaths, dates of hospital admissions and discharges, dates of consultations, pharmacy dispensing records, diagnoses, procedures, and laboratory test results are prospectively recorded as part of the clinical care of patients and are centralized in CDARS for recordkeeping and research purposes. Data validation in CDARS has demonstrated a high coding accuracy for the diagnoses of fractures of the hip (positive predictive value, 100%) and vertebrae (positive predictive value, 86%) (22). The system has been extensively used in large-scale drug surveillance studies (23–30). A more detailed description of CDARS has been reported previously and is also provided in Appendix 1 (available at Annals.org) (28, 31).

The study protocol was approved by the institutional review board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster (reference number: UW13-468). Informed patient consent was not required because the data used in this study were anonymized.

Study Cohort

The study population included adults aged 18 years or older who were newly diagnosed with AF and subsequently received a new prescription for 1 of the anticoagulants of interest. A new diagnosis of AF was defined as the first recorded diagnosis of AF (International Classification of Diseases, 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 (Appendix Table 1, available at Annals.org) were excluded. Patients with transient AF (that is, those who had cardiac surgery or were diagnosed with myocarditis, pericarditis, or pulmonary embolism within 90 days before their first AF occurrence) (Appendix Table 1), those missing information on date of birth or sex, those younger than 18 years, and those 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 before the index date. Patients who had a record of bone tumors, epilepsy, or seizure before the index date or baseline use of hormone replacement therapy (on or within 90 days before the index date) were excluded to reduce their potential residual effects on fractures (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, fractures that were recorded with a traumatic event (ICD-9-CM codes E800 to 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, a switch 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 potential bias due to nonrandomized 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 treatment with anticoagulants but were similar with respect to other measured characteristics (33). The IPTW approach is suitable when comparing several treatment groups (34). Propensity score weights were estimated using generalized 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, available at Annals.org) (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 following potential confounders (3, 32): age, sex, index year (that is, year of treatment commencement), congestive heart failure, ischemic stroke or transient ischemic attack, diabetes mellitus (identified by a record of diabetes mellitus or use of insulin or antidiabetic drugs on or within 90 days 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 (Appendix Table 1). Other covariates included recent use (on or within 90 days before the index date) of angiotensin-converting enzyme inhibitors or angiotensin II–receptor blockers, β-blockers, proton-pump inhibitors, antidepressants (selective serotonin reuptake inhibitors or tricyclic antidepressants), systemic glucocorticoids, and bisphosphonates.

Standardized differences were used to assess the differences in patient characteristics between treatment groups. Proposed cutoffs for acceptable standardized differences range from 0.1 to 0.25 (24). Characteristics with a standardized difference greater than 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, available at Annals.org) (35).

Statistical Analysis

Baseline characteristics were expressed as means and SDs for continuous variables and frequencies and percentages for categorical variables. The cumulative incidence difference (CID) in osteoporotic fractures at 6, 12, 18, and 24 months after treatment commencement was 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, available at Annals.org) (36). The 95% CIs of the CID were estimated using bootstrap methods (500 replications) (Appendix 4) (37).

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

Given that men and women may have a different risk for osteoporotic fracture (38) and differential oral anticoagulant treatment effects (27), subgroup analyses were done by stratifying the study population by sex. Propensity scores and weights were recalculated 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 (Appendix Table 1) were not included as an outcome and were treated as a censoring event. We did additional sensitivity analyses in which patients were not censored if they discontinued the index treatment or switched to another anticoagulant. We also did 2 post hoc sensitivity analyses that included other osteoporotic treatments (denosumab, salcatonin, teriparatide, strontium ranelate, and raloxifene) and dispensing institutions (hospitals or clinics) in the propensity score model.

To further assess the potential effect of any unmeasured confounding on our study, we computed the E-value for our HRs (39). The E-value is defined as the minimum strength of association that an unmeasured confounder would need to have with both treatment and outcome, conditional on the measured covariates, to explain away an observed association (39).

In all statistical analyses, a 2-sided *P* value less than 0.05 was considered statistically significant. For each subgroup analysis, a *P* value for interaction was calculated and a value less than 0.05 denoted a statistically significant difference between subgroups. Statistical analyses were done using SAS, version 9.4 (SAS Institute), and R, version 3.6.1 (The R Project for Statistical Computing).

Role of the Funding Source

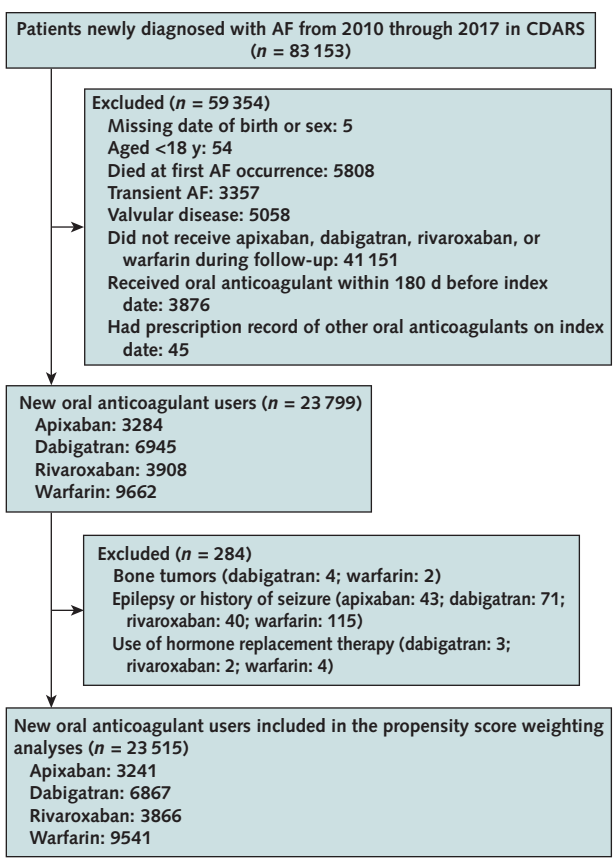
This study was supported by The University of Hong Kong and University College London Strategic Partnership Fund. The funder had no role in the design or conduct of the study; collection, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

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* = 3241], dabigatran [*n* = 6867], rivaroxaban [*n* = 3866], and warfarin [*n* = 9541]) (Figure 1). The mean age of

Figure 1. Selection of cohort.



AF = atrial fibrillation; CDARS = Clinical Data Analysis and Reporting System.

Table 1. Baseline Characteristics

Characteristic	DOACs			Warfarin	Maximum Pairwise Standardized Difference*	
	Apixaban	Dabigatran	Rivaroxaban		Before IPTW	After IPTW
Patients, *n*	3241	6867	3866	9541		
Mean age (SD), *y*	77.9 (10.3)	74.4 (10.0)	75.0 (10.3)	73.1 (11.4)	0.45	0.10
Women, *n* (%)	1678 (51.8)	3376 (49.2)	1913 (49.5)	4313 (45.2)	0.13	0.04
Medical conditions, *n* (%)						
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
Chronic obstructive pulmonary disease	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, *n* (%)						
Angiotensin-converting enzyme inhibitor or angiotensin II–receptor blocker	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 inhibitor	1368 (42.2)	1983 (28.9)	1280 (33.1)	2714 (28.4)	0.30	0.13
Bisphosphonate	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
Antidepressant	116 (3.6)	264 (3.8)	134 (3.5)	311 (3.3)	0.03	0.02

DOACs = direct oral anticoagulants; IPTW = inverse probability of treatment weighting.
* Proposed cutoffs for acceptable standardized differences ranged from 0.1 to 0.25.

the cohort was 74.4 years (SD, 10.8), ranging from 73.1 years (SD, 11.4) (warfarin) to 77.9 years (SD, 10.3) (apixaban) (**Table 1**). Median follow-up was 423 days (interquartile range, 92 to 1001 days), ranging from 384 days (interquartile range, 57 to 1211 days) in warfarin users to 473 days (interquartile range, 116 to 990 days) in rivaroxaban users (**Table 2**). There were 12 548 patients (53.4%) who were censored because they either discontinued the index treatment (n = 8940) or switched to another anticoagulant (n = 3608). After IPTW, all baseline characteristics had standardized differences less than 0.1 except for age, prior ischemic stroke or transient ischemic attack, and proton-pump inhibitor use, which had standardized differences between 0.1 and 0.15 (**Table 1**). The maximum pairwise 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**, available at Annals.org).

Risk for Osteoporotic Fractures

A total of 401 fractures were identified (crude event number [weighted rate per 100 patient-years]: apixaban, 53 [0.82]; dabigatran, 95 [0.76]; rivaroxaban, 57 [0.67]; and warfarin, 196 [1.11]). The crude median time to osteoporotic fracture after the index date ranged from 338 days (apixaban) to 617 days (warfarin) (**Table 2**). Compared with men, women tended to have a higher incidence of osteoporotic fractures, regardless of the type of anticoagulant received (**Table 2**; **Appendix Table 3**, available at Annals.org).

The adjusted cumulative incidences at 6 to 24 months after treatment commencement are shown in **Figure 2**. At 24 months, the adjusted cumulative incidence of osteoporotic fractures was lower with DOAC use than with warfarin use (CIDs, −0.88% [95% CI, −1.66% to −0.21%] for apixaban vs. warfarin −0.81% [CI, −1.34% to −0.23%] for dabigatran vs. warfarin, and −1.13% [CI, −1.67% to −0.53%] for rivaroxaban vs. warfarin). 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 (**Figure 2**).

Cox proportional hazards model analyses over the entire follow-up suggested that DOAC use was associated with a lower risk for osteoporotic fractures than warfarin use (HRs, 0.62 [CI, 0.41 to 0.94] for apixaban vs. warfarin, 0.65 [CI, 0.49 to 0.86] for dabigatran vs. warfarin, and 0.52 [CI, 0.37 to 0.73] for rivaroxaban vs. warfarin) (**Table 3**). The corresponding E-values for the point estimates were 2.61, 2.45, and 3.26 in an HR scale, respectively. Similar results were seen in both men and women (P for interaction > 0.05) (**Table 3**). For all head-to-head comparisons between DOACs, the results were not statistically significant (HRs, 0.96 [CI, 0.63 to 1.47] for apixaban vs. dabigatran, 0.80 [CI, 0.55 to 1.15] for rivaroxaban vs. dabigatran, and 0.83 [CI, 0.52 to 1.33] for rivaroxaban vs. apixaban) (**Table 3**).

The results of the sensitivity analyses that excluded fractures associated with falls from higher than standing height (**Appendix Table 4**, available at Annals.org) or did not censor patients if they discontinued the index treatment or switched to another anticoagulant (**Appendix Table 5**, available at Annals.org) were not materially different from the results of the main analysis. Post hoc analyses that accounted for other osteoporosis treatments (**Appendix Table 6**, available at Annals

.org) and any variation between dispensing institutions in anticoagulant use (**Appendix Figure** and **Appendix Table 7**, available at Annals.org) in the propensity score model also yielded similar results.

Discussion

In this study, DOAC use was associated with a lower risk for osteoporotic fractures than warfarin use. No evidence of a differential fracture risk was found between DOACs. 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 for 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 by Lutsey and colleagues that used insurance claim data and reported a lower risk for osteoporotic fractures with DOACs versus warfarin and no difference in risk between individual DOACs (17). However, our study had a longer on-treatment follow-up than that study (mean, 7 months [SD, 8]), and we used a different analytic approach. Lutsey and colleagues used binary propensity score methods, which meant that the results could be generalized only to patients who would be eligible for a specific pair of anticoagulants (40). On the other hand, 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 4 anticoagulants, which may better reflect current clinical practice. In addition, the mean age of the patients in their study (range, 67 years [dabigatran] to 69 years [apixaban]) is less than the mean age of our study cohort (range, 74.4 years [dabigatran] to 77.9 years [apixaban]). Despite the differences in cohort characteristics, health care systems, and methods between the studies, both yielded consistent results and support the finding that DOAC use may be associated with a lower risk for osteoporotic fractures than warfarin use.

Another recent study in Denmark using registry data reported that DOACs as a group were associated with a lower risk for osteoporotic fracture than warfarin (16). However, the study did not examine the fracture risk for each DOAC (16). A recent meta-analysis of 4 observational studies reported no increase in fracture risk with warfarin versus DOACs as a group (41), but the validity of the findings is doubtful because of potential computational 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 versus women with AF because the lower rates of bleeding with DOACs versus warfarin were not observed in men (27). However, data on sex difference in osteoporotic fracture risk with anticoagulant use are limited. We found that DOACs versus warfarin were associated with a lower risk for osteoporotic fractures in both men and women, and we also identified a higher risk for osteoporotic fractures in women than 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 for fracture.

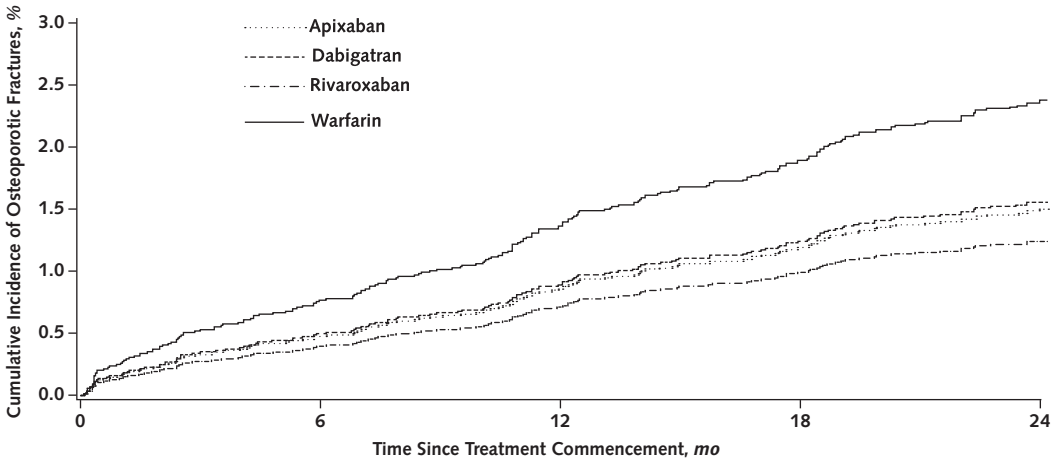
This study has limitations. Given its observational nature, the possibility of unmeasured confounders cannot be ruled out. For instance, we did not have infor-

Table 2. Overall Osteoporotic Fracture Rates in the Study Cohort

Treatment	Total Patients, *n*	Median Follow-up (IQR), *d*	Fractures, *n*	Median Time to Fracture Since Treatment Commencement (IQR), *d*	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	23 515	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	12 235	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	11 280	428 (91–1014)	262	497 (133–1081)	1.29	1.15

IQR = interquartile range.
* After inverse probability of treatment weighting.

Figure 2. Adjusted cumulative incidence curves.



People at risk, *n*				
(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)**

* The 95% CIs were estimated using bootstrap methods.

mation 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 may differ between groups (24). Similarly, alcohol consumption and smoking status are not routinely recorded in the database. However, this 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 with warfarin could only be explained away by an unmeasured confounder that was associated with both DOAC treatment and osteoporotic fractures by an HR ranging from 2.45-fold to 3.26-fold each. This is much greater than well-known, strong risk factors for osteoporotic fractures, such as age, sex, and history of falls (3, 32); therefore, it is unlikely that an additional unmeasured confounder of such large magnitude would exist. Given that body mass index, bone mineral density, smoking status, and alcohol consumption are not a common set

Table 3. Osteoporotic Fractures After IPTW

Treatment	All Patients		Men		Women		*P* Value for Interaction*
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	
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

DOAC = direct oral anticoagulant; IPTW = inverse probability of treatment weighting.
* *P* value for interaction between treatment effect and sex.

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 were undetected. This would tend to bias any result toward the null, assuming the underdetection was nondifferential between treatment groups (24). Although warfarin users may have had more clinical visits than DOAC users because of coagulation testing, screening for asymptomatic fractures is not recommended in the public health care setting of Hong Kong because of 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.

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 for 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 for 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 for osteoporotic fractures should be considered at the point of prescribing an oral anticoagulant to minimize fracture risk (48).

In conclusion, this study found that among patients with AF, use of DOACs was associated with a lower risk for osteoporotic fracture than use of 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 for osteoporotic fractures between individual DOACs. However, any differences in absolute risk were small and likely of minor clinical significance. The treatment effects of DOACs versus warfarin were consistent in men and women. These findings may help inform the benefit–risk assessment when choosing between anticoagulants.

From UCL School of Pharmacy, London, United Kingdom, and Centre for Safe Medication and Practice Research, The University of Hong Kong, Hong Kong, China (W.C.L., K.K.M.); Centre for Safe Medication and Practice Research, The University of Hong Kong, Hong Kong, China (C.C., E.W.C., C.W.S.); Liverpool Centre for Cardiovascular Science, University of Liverpool, and Liverpool Heart and Chest Hospital, Liverpool, United Kingdom, and Aalborg Thrombosis Research Unit, Aalborg University, Aalborg, Denmark (G.Y.L.); Queen Mary Hospital, The University of Hong Kong, Hong Kong, China (C.S.); Osteoporosis Centre, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China (J.K.L., A.C.L.); and UCL School of Pharmacy, London, United Kingdom, Centre for Safe Medication and Practice Research, The University of Hong Kong, Hong Kong, and The University of Hong Kong Shenzhen Hospital, Shenzhen, Guangdong, China (I.C.W.).

Acknowledgment: The authors thank Dr. Elizabeth Jamieson, PhD, UCL School of Pharmacy, for proofreading the manuscript and Mr. John Tazare, MSc, London School of Hygiene and Tropical Medicine, for his advice on adjusted cumulative incidence curves.

Financial Support: By The University of Hong Kong and University College London Strategic Partnership Fund.

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-3671.

Reproducible Research Statement: *Study protocol and data set:* Not available. *Statistical code:* Available from Dr. Lau (e-mail, wallis.lau@ucl.ac.uk).

Corresponding Author: Ian C.K. Wong, PhD, The University of Hong Kong, L2-57, Laboratory Block, Li Ka Shing Faculty of Medicine, 21 Sassoon Road, Pokfulam, Hong Kong; e-mail, wongick@hku.hk.

Current author addresses and author contributions are available at Annals.org.

References

1. **Dyer SM, Crotty M, Fairhall N, et al; Fragility Fracture Network (FFN) Rehabilitation Research Special Interest Group.** A critical review of the long-term disability outcomes following hip fracture. BMC Geriatr. 2016;16:158. [PMID: 27590604] doi:10.1186/s12877-016-0332-0
2. **Caraballo PJ, Heit JA, Atkinson EJ, et al.** Long-term use of oral anticoagulants and the risk of fracture. Arch Intern Med. 1999;159:1750-6. [PMID: 10448778]
3. **Gage BF, Birman-Deych E, Radford MJ, et al.** Risk of osteoporotic fracture in elderly patients taking warfarin: results from the National Registry of Atrial Fibrillation 2. Arch Intern Med. 2006;166:241-6. [PMID: 16432096]
4. **Rejnmark L, Vestergaard P, Mosekilde L.** Fracture risk in users of oral anticoagulants: a nationwide case-control study. Int J Cardiol. 2007;118:338-44. [PMID: 17055083]
5. **Sugiyama T, Kugimiya F, Kono S, et al.** Warfarin use and fracture risk: an evidence-based mechanistic insight [Letter]. Osteoporos Int. 2015;26:1231-2. [PMID: 25300528] doi:10.1007/s00198-014-2912-1
6. **Misra D, Zhang Y, Peloquin C, et al.** Incident long-term warfarin use and risk of osteoporotic fractures: propensity-score matched cohort of elders with new onset atrial fibrillation. Osteoporos Int. 2014;25:1677-84. [PMID: 24833176] doi:10.1007/s00198-014-2662-0
7. **Pilon D, Castilloux AM, Dorais M, et al.** Oral anticoagulants and the risk of osteoporotic fractures among elderly. Pharmacoepidemiol Drug Saf. 2004;13:289-94. [PMID: 15133779]
8. **Mamdani M, Upshur RE, Anderson G, et al.** Warfarin therapy and risk of hip fracture among elderly patients. Pharmacotherapy. 2003;23:1-4. [PMID: 12523455]
9. **Jamal SA, Browner WS, Bauer DC, et al.** Warfarin use and risk for osteoporosis in elderly women. Study of Osteoporotic Fractures Research Group. Ann Intern Med. 1998;128:829-32. [PMID: 9599195]

10. **Gu ZC, Zhou LY, Shen L, et al.** Non-vitamin K antagonist oral anticoagulants vs. warfarin at risk of fractures: a systematic review and meta-analysis of randomized controlled trials. Front Pharmacol. 2018;9:348. [PMID: 29692734] doi:10.3389/fphar.2018.00348
11. **Sparkenbaugh EM, Chantrathammachart P, Mickelson J, et al.** Differential contribution of FXa and thrombin to vascular inflammation in a mouse model of sickle cell disease. Blood. 2014;123:1747-56. [PMID: 24449213] doi:10.1182/blood-2013-08-523936
12. **Loi F, Córdova LA, Pajarinen J, et al.** Inflammation, fracture and bone repair. Bone. 2016;86:119-30. [PMID: 26946132] doi:10.1016/j.bone.2016.02.020
13. **January CT, Wann LS, Calkins H, et al.** 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019;74:104-132. [PMID: 30703431] doi:10.1016/j.jacc.2019.01.011
14. **Kirchhof P, Benussi S, Kotecha D, et al; ESC Scientific Document Group.** 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37:2893-2962. [PMID: 27567408] doi:10.1093/eurheartj/ehw210
15. **Steffel J, Verhamme P, Potpara TS, et al; ESC Scientific Document Group.** The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018;39:1330-1393. [PMID: 29562325] doi:10.1093/eurheartj/ehy136
16. **Binding C, Bjerring Olesen J, Abrahamsen B, et al.** Osteoporotic fractures in patients with atrial fibrillation treated with conventional versus direct anticoagulants. J Am Coll Cardiol. 2019;74:2150-2158. [PMID: 31648707] doi:10.1016/j.jacc.2019.08.1025
17. **Lutsey PL, Norby FL, Ensrud KE, et al.** Association of anticoagulant therapy with risk of fracture among patients with atrial fibrillation. JAMA Intern Med. 2019. [PMID: 31764956] doi:10.1001/jamainternmed.2019.5679
18. **Gadsbøll K, Staerk L, Fosbøl EL, et al.** Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. Eur Heart J. 2017;38:899-906. [PMID: 28110293] doi:10.1093/eurheartj/ehw658
19. **Wong CX, Gan SW, Lee SW, et al.** Atrial fibrillation and risk of hip fracture: a population-based analysis of 113,600 individuals. Int J Cardiol. 2017;243:229-232. [PMID: 28528985] doi:10.1016/j.ijcard.2017.05.012
20. **Hospital Authority.** Introduction: caring for our community's health. Accessed at www.ha.org.hk/visitor/ha_visitor_index.asp?Content_ID=10008&Lang=ENG&Dimension=100&Parent_ID=10004 on 8 August 2019.
21. **Hospital Authority.** Hospital Authority Statistical Report 2016-2017. Accessed at www.ha.org.hk/haho/ho/stat/HASR16_17_2.pdf on 8 August 2019.
22. **Sing CW, Woo YC, Lee ACH, et al.** Validity of major osteoporotic fracture diagnosis codes in the Clinical Data Analysis and Reporting System in Hong Kong. Pharmacoepidemiol Drug Saf. 2017;26:973-976. [PMID: 28371079] doi:10.1002/pds.4208
23. **Chiu SS, Lau YL, Chan KH, et al.** Influenza-related hospitalizations among children in Hong Kong. N Engl J Med. 2002;347:2097-103. [PMID: 12501221]
24. **Lau WC, Chan EW, Cheung CL, et al.** Association between dabigatran vs warfarin and risk of osteoporotic fractures among patients with nonvalvular atrial fibrillation. JAMA. 2017;317:1151-1158. [PMID: 28324091] doi:10.1001/jama.2017.1363
25. **Man KKC, Chan EW, Ip P, et al.** Prenatal antidepressant use and risk of attention-deficit/hyperactivity disorder in offspring: population based cohort study. BMJ. 2017;357:j2350. [PMID: 28566274] doi:10.1136/bmj.j2350
26. **Wong AY, Root A, Douglas IJ, et al.** Cardiovascular outcomes associated with use of clarithromycin: population based study. BMJ. 2016;352:h6926. [PMID: 26768836] doi:10.1136/bmj.h6926
27. **Law SWY, Lau WCY, Wong ICK, et al.** Sex-based differences in outcomes of oral anticoagulation in patients with atrial fibrillation. J Am Coll Cardiol. 2018;72:271-282. [PMID: 30012320] doi:10.1016/j.jacc.2018.04.066
28. **Chan EW, Lau WC, Leung WK, et al.** Prevention of dabigatran-related gastrointestinal bleeding with gastroprotective agents: a population-based study. Gastroenterology. 2015;149:586-95.e3. [PMID: 25960019] doi:10.1053/j.gastro.2015.05.002
29. **Lau WCY, Li X, Wong ICK, et al.** Bleeding-related hospital admissions and 30-day readmissions in patients with non-valvular atrial fibrillation treated with dabigatran versus warfarin. J Thromb Haemost. 2017;15:1923-1933. [PMID: 28748652] doi:10.1111/jth.13780
30. **Chan EW, Lau WC, Siu CW, et al.** Effect of suboptimal anticoagulation treatment with antiplatelet therapy and warfarin on clinical outcomes in patients with nonvalvular atrial fibrillation: a population-wide cohort study. Heart Rhythm. 2016;13:1581-8. [PMID: 27033342] doi:10.1016/j.hrthm.2016.03.049
31. **Man KKC, Ip P, Hsia Y, et al.** ADHD drug prescribing trend is increasing among children and adolescents in Hong Kong. J Atten Disord. 2017;21:1161-1168. [PMID: 24994875] doi:10.1177/1087054714536047
32. **Hippisley-Cox J, Coupland C.** Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. BMJ. 2009;339:b4229. [PMID: 19926696] doi:10.1136/bmj.b4229
33. **Austin PC.** An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res. 2011;46:399-424. [PMID: 21818162]
34. **McCaffrey DF, Griffin BA, Almirall D, et al.** A tutorial on propensity score estimation for multiple treatments using generalized boosted models. Stat Med. 2013;32:3388-414. [PMID: 23508673] doi:10.1002/sim.5753
35. **Austin PC.** Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28:3083-107. [PMID: 19757444] doi:10.1002/sim.3697
36. **Zhang X, Loberiza FR, Klein JP, et al.** A SAS macro for estimation of direct adjusted survival curves based on a stratified Cox regression model. Comput Methods Programs Biomed. 2007;88:95-101. [PMID: 17850917]
37. **Efron B, Tibshirani RJ.** An Introduction to the Bootstrap. Chapman & Hall; 1993.
38. **Cawthon PM.** Gender differences in osteoporosis and fractures. Clin Orthop Relat Res. 2011;469:1900-5. [PMID: 21264553] doi:10.1007/s11999-011-1780-7
39. **VanderWeele TJ, Ding P.** Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med. 2017;167:268-274. [PMID: 28693043] doi:10.7326/M16-2607
40. **Lopez MJ, Gutman R.** Estimation of causal effects with multiple treatments: a review and new ideas. Stat Sci. 2017;32:432-54. doi:10.1214/17-STS612
41. **Fiordellisi W, White K, Schweizer M.** A systematic review and meta-analysis of the association between vitamin K antagonist use and fracture. J Gen Intern Med. 2019;34:304-311. [PMID: 30511289] doi:10.1007/s11606-018-4758-2
42. **Lau WCY, Man KKC, Wong ICK.** Vitamin K antagonist use and fracture [Letter]. J Gen Intern Med. 2020;35:396-397. [PMID: 31342326] doi:10.1007/s11606-019-05185-2
43. **Henau K, Van Eycken E, Silversmit G, et al.** Regional variation in incidence for smoking and alcohol related cancers in Belgium. Cancer Epidemiol. 2015;39:55-65. [PMID: 25466934] doi:10.1016/j.canep.2014.10.009
44. **Ip TP, Cheung SK, Cheung TC, et al; OSHK Task Group for Formulation of 2013 OSHK Guideline for Clinical Management of Postmenopausal Osteoporosis in Hong Kong.** The Osteoporosis Society of Hong Kong (OSHK): 2013 OSHK guideline for clinical management of postmenopausal osteoporosis in Hong Kong. Hong Kong Med J. 2013;19 Suppl 2:1-40. [PMID: 23535738]
45. **Douketis JD.** Perioperative management of patients who are receiving warfarin therapy: an evidence-based and practical approach. Blood. 2011;117:5044-9. [PMID: 21415266] doi:10.1182/blood-2011-02-329979

46. **Namba S, Yamaoka-Tojo M, Kakizaki R, et al.** Effects on bone metabolism markers and arterial stiffness by switching to rivaroxaban from warfarin in patients with atrial fibrillation. Heart Vessels. 2017; 32:977-982. [PMID: 28233091] doi:10.1007/s00380-017-0950-2
47. **Klüter T, Weuster M, Brüggemann S, et al.** Rivaroxaban does not impair fracture healing in a rat femur fracture model: an experimental study. BMC Musculoskelet Disord. 2015;16:79. [PMID: 25886252] doi:10.1186/s12891-015-0502-9
48. **Tufano A, Coppola A, Contaldi P, et al.** Oral anticoagulant drugs and the risk of osteoporosis: new anticoagulants better than old? Semin Thromb Hemost. 2015;41:382-8. [PMID: 25703521] doi:10.1055/s-0034-1543999

AD LIBITUM

Bored

for Dorothea

She's just bored with it
this disease.
She should have been gone
months ago
did all the last things
but didn't die in her sleep
like the doctor promised

and now there's a ceiling leak
and a workman at the door

and the pain.
No god to pray to
no drug to distract her
when it sings
on its one-string violin

A friend tells her to think of it–
the pain, the dying (she isn't sure)–
as one more adventure
in an adventurous life.

So, at 80, she
pulls herself up
gathers herself
once again opens the door

Veneta Masson, MA, RN
Sage Femme Press
Silver Spring, Maryland

Current Author Address: Veneta Masson, MA, RN, Sage Femme Press, 15901 Woods Center Road, Silver Spring, MD 20906-1167; e-mail, veneta.masson@gmail.com.

Current Author Addresses: Drs. Lau and Man: UCL School of Pharmacy, Mezzanine Floor, Tavistock House, Entrance A, Tavistock Square, London WC1H 9JP, United Kingdom.
Dr. Cheung: Centre for Safe Medication and Practice Research, The University of Hong Kong, L2-52, 2/F, Laboratory Block, Li Ka Shing Faculty of Medicine Building, 21 Sassoon Road, Pokfulam, Hong Kong.
Dr. Chan: Centre for Safe Medication and Practice Research, The University of Hong Kong, L02-08, 2/F, Laboratory Block, Li Ka Shing Faculty of Medicine Building, 21 Sassoon Road, Pokfulam, Hong Kong.
Dr. Sing: Centre for Safe Medication and Practice Research, The University of Hong Kong, 2/F, Laboratory Block, Li Ka Shing Faculty of Medicine Building, 21 Sassoon Road, Pokfulam, Hong Kong.
Dr. Lip: Liverpool Centre for Cardiovascular Science, University of Liverpool, 6 West Derby Street, Liverpool L7 8TX, United Kingdom.
Dr. Siu: Queen Mary Hospital, 1929B, Block K, Pokfulam, Hong Kong.
Dr. Lam: Queen Mary Hospital, Room 22, 4/F, Block K, Pokfulam, Hong Kong.
Dr. Lee: Queen Mary Hospital, A1 Medical Office, Department of Medicine, 102 Pokfulam Road, Hong Kong.
Dr. Wong: The University of Hong Kong, L2-57, Laboratory Block, Li Ka Shing Faculty of Medicine, 21 Sassoon Road, Pokfulam, Hong Kong.

Author Contributions: Conception and design: W.C.Y. Lau, I.C.K. Wong.
Analysis and interpretation of the data: W.C.Y. Lau, C.-L. Cheung, K.K.C. Man, E.W. Chan, C.W. Sing, G.Y.H. Lip, C.-W. Siu, A.C.H. Lee, I.C.K. Wong.
Drafting of the article: W.C.Y. Lau.
Critical revision of the article for important intellectual content: W.C.Y. Lau, C.-L. Cheung, K.K.C. Man, E.W. Chan, C.W. Sing, G.Y.H. Lip, I.C.K. Wong.
Final approval of the article: W.C.Y. Lau, C.-L. Cheung, K.K.C. Man, E.W. Chan, C.W. Sing, G.Y.H. Lip, C.-W. Siu, J.K.Y. Lam, A.C.H. Lee, I.C.K. Wong.
Statistical expertise: W.C.Y. Lau, K.K.C. Man.
Obtaining of funding: I.C.K. Wong.
Collection and assembly of data: W.C.Y. Lau, K.K.C. Man, C.-W. Siu.

Appendix 1: The CDARS Database

This study used the electronic health records of the CDARS of the Hong Kong Hospital Authority (20), which is a statutory body that manages all public hospitals and their ambulatory clinics in Hong Kong. The Hong Kong Hospital Authority uses a computer information system, called the clinical management system (CMS), to generate consultation and discharge summaries in daily practice (31, 49). The records in CMS are linked among all institutions via a unique patient identifier. Electronic health records in CMS, including patient demographic characteristics, dates of registered deaths, dates of hospital admissions and discharges, dates of consultations, drug dispensing records, diagnoses, and procedures are electronically transmitted to CDARS on a daily basis for research and audit purposes. All patient records in CDARS are anonymized to protect patient confidentiality.

The CMS is also used to record data in relation to direct clinical orders, such as prescriptions and laboratory tests (49). Drug prescriptions are ordered through CMS and electronically transmitted to the pharmacy to reduce transcription errors (50). Prescription details are then verified by registered pharmacists for dispensing. Details of the drug dispensed, including drug name, dosing, quantity, frequency, drug route, and date of dispensing, are stored in the CMS. Therefore, the data in CDARS represent the actual clinical information recorded by the health care professionals as part of their patients' care, and they have been widely used in pharmacoepidemiologic research (24, 25, 51, 52).

Appendix 2: Propensity Score Modeling for Multiple Treatments

We used the generalized boosting model (GBM), a nonparametric machine-learning method (34), to estimate propensity score weights for the 4 anticoagulant treatment groups in the study. Compared with multinomial logistic regression models, GBM is more flexible on model assumptions and is able to model nonlinear relationships between treatment choice and patient characteristics. Previous simulation studies have shown that GBM provides more stable weights and better covariate balance than parametric logistic regression models (53, 54).

We used the SAS twang macros, which call functions from the twang package in R for computing the GBM. The SAS twang macros (55) and the sample codes for using them (56) are publicly available. We used a maximum of 10 000 iterations (or regression trees), with an iteration stopping point that minimizes the absolute standardized mean difference of the effect size (effect size mean). The average treatment effect weights were used to estimate the treatment effects in the entire population. The SAS PROC SURVEYPHREG, which treats average treatment effect weights as probability weights (56), was used for fitting the weighted Cox proportional hazards regression model and calculating the HRs of the outcomes between treatment groups.

Appendix 3: Variance Ratios and Raw Differences in Proportion

To assess the covariate balance in terms of distributions (in addition to means) after propensity score weighting, we calculated the ratios of variances for the continuous covariate (age) and the raw differences in proportion for the categorical covariates between treat-

ment groups (35). The R package COBALT was used for the analyses (57).

The results showed that the maximum pairwise variance ratio of age was 1.14, which is close to 1 (indicative of group balance) (35) and within the acceptable range (0.5 to 2) (58). The raw differences in proportion for all binary variables are small (<0.10). These results suggested that the covariates were reasonably balanced in terms of distributions after propensity score weighting. The detailed figures are reported in Appendix Table 2.

Appendix 4: Adjusted Cumulative Incidence Curves and Bootstrap Methods

We used the direct adjustment method to create the adjusted cumulative incidence curves (Figure 2) that account for the inverse probability of treatment weights and the covariates that were not completely balanced after propensity score weighting. This method computed the predicted survival probability for every patient in the cohort for 4 times—at each time, the values of the treatment variable for all patients were set to 1 of the 4 anticoagulants (apixaban, dabigatran, rivaroxaban, and warfarin). The predicted probabilities were then averaged across the patients within each treatment group to obtain the adjusted survival curves for each treatment group (36). The SAS PROC PHREG with the direct adjustment option (DIRADJ) in the BASELINE statement was used to compute the adjusted survivals (36, 59). The cumulative incidences of fractures were then derived using (1 minus adjusted survivals). The sample SAS codes for creating adjusted survival curves are publicly available (59).

We calculated the differences in adjusted cumulative incidence (CIDs) between the anticoagulant treatment groups at 6, 12, 18, and 24 months of follow-up. Because the estimation of SEs for direct adjusted cumulative incidence is complex (60, 61) and to avoid making inappropriate assumptions about the data, we used bootstrap methods to empirically construct the CIs of the CIDs (37). Bootstrap methods allow for estimation of CIs through repeated sampling of data. We randomly selected 500 bootstrap samples with replacement from the original data set using SAS PROC SURVEYSELECT. Five hundred bootstrap samples has been considered sufficient for the estimation of CIs (37, 62). The CIDs were calculated within each bootstrap sample. The CIs of the CIDs were derived by identifying the 2.5th and 97.5th percentiles of the distributions of CIDs across the bootstrap samples (37).

Appendix Table 1. ICD-9-CM Codes Used in the Study

Atrial fibrillation
- 427.3 Atrial fibrillation and flutter

Valvular heart diseases/replacement or hyperthyroidism
- 242 Thyrotoxicosis with or without goiter
- 394.0 Mitral stenosis

Valvular heart surgery (procedure codes)
- 35.20 Open and other replacement of unspecified heart valve
- 35.22 Open and other replacement of aortic valve
- 35.24 Open and other replacement of mitral valve
- 35.26 Open and other replacement of pulmonary valve
- 35.28 Open and other replacement of tricuspid valve

Transient atrial fibrillation (recorded on or within 90 days before the first diagnosis for atrial fibrillation)

Cardiac surgery (procedure codes)
- 00.5 Other cardiovascular procedures
- 35 Operations on valves and septa of heart
- 36 Operations on vessels of heart
- 37 Other operations on heart and pericardium

Pericarditis
- 391 Rheumatic fever with heart involvement
- 393 Chronic rheumatic pericarditis
- 420 Acute pericarditis
- 423.2 Constrictive pericarditis
- 036.41 Meningococcal pericarditis
- 074.21 Coxsackie pericarditis
- 093.81 Syphilitic pericarditis
- 098.83 Gonococcal pericarditis

Myocarditis
- 130.3 Myocarditis due to toxoplasmosis
- 391.2 Acute rheumatic myocarditis
- 398.0 Rheumatic myocarditis
- 422 Acute myocarditis
- 429.0 Myocarditis, unspecified
- 032.82 Diphtheritic myocarditis
- 036.43 Meningococcal myocarditis
- 074.23 Coxsackie myocarditis
- 093.82 Syphilitic myocarditis

Pulmonary embolism
- 415.1 Pulmonary embolism and infarction

Congestive heart failure
- 398.91 Rheumatic heart failure (congestive)
- 402.01 Malignant hypertensive heart disease with heart failure
- 402.11 Benign hypertensive heart disease with heart failure
- 402.91 Unspecified hypertensive heart disease with heart failure
- 404.01 Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
- 404.03 Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end-stage renal disease
- 404.11 Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
- 404.13 Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end-stage renal disease
- 404.91 Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified
- 404.93 Hypertensive heart and chronic kidney disease, unspecified, with heart failure and chronic kidney disease stage V or end-stage renal disease
- 428 Heart failure

Continued on following page

Appendix Table 1–Continued

Hypertension
401 Essential hypertension
402 Hypertensive heart disease
403 Hypertensive chronic kidney disease
404 Hypertensive heart and chronic kidney disease
405 Secondary hypertension
437.2 Hypertensive encephalopathy

Diabetes
250 Diabetes mellitus

Ischemic stroke
433.01 Occlusion and stenosis of basilar artery with cerebral infarction
433.11 Occlusion and stenosis of carotid artery with cerebral infarction
433.21 Occlusion and stenosis of vertebral artery with cerebral infarction
433.31 Occlusion and stenosis of multiple and bilateral precerebral arteries with cerebral infarction
433.81 Occlusion and stenosis of other specified precerebral artery with cerebral infarction
433.91 Occlusion and stenosis of unspecified precerebral artery with cerebral infarction
434 Occlusion of cerebral arteries
436 Acute, but ill-defined, cerebrovascular disease
437.0 Cerebral atherosclerosis
437.1 Other generalized ischemic cerebrovascular disease

Transient ischemic attack
435 Transient cerebral ischemia

Systemic embolism
444 Arterial embolism and thrombosis
445 Atheroembolism

Vascular disease
410–414 Ischemic heart disease
443.8 Other specified peripheral vascular diseases
443.9 Peripheral vascular disease, unspecified

Chronic obstructive pulmonary disease
490–496 Chronic obstructive pulmonary disease and allied conditions
500 Coal workers' pneumoconiosis
501 Asbestosis
502 Pneumoconiosis due to other silica or silicates
503 Pneumoconiosis due to other inorganic dust
504 Pneumonopathy due to inhalation of other dust
505 Pneumoconiosis, unspecified
506.4 Respiratory conditions due to chemical fumes and vapors

Liver disease
456.0 Esophageal varices with bleeding
456.1 Esophageal varices without bleeding
456.2 Esophageal varices in diseases classified elsewhere
571.2 Alcoholic cirrhosis of liver
571.4 Chronic hepatitis
571.5 Cirrhosis of liver without mention of alcohol
571.6 Biliary cirrhosis
572.2 Hepatic encephalopathy
572.3 Portal hypertension
572.4 Hepatorenal syndrome
572.8 Other sequelae of chronic liver disease

Chronic kidney disease
403 Hypertensive chronic kidney disease
404 Hypertensive heart and chronic kidney disease
582 Chronic glomerulonephritis
585 Chronic kidney disease (CKD)
590.0 Chronic pyelonephritis

Continued

Appendix Table 1–Continued

Rheumatoid arthritis and other inflammatory polyarthropathies
710.0 Systemic lupus erythematosus
710.1 Systemic sclerosis
710.4 Polymyositis
714.0 Rheumatoid arthritis
714.1 Felty's syndrome
714.2 Other rheumatoid arthritis with visceral or systemic involvement
714.81 Rheumatoid lung
725 Polymyalgia rheumatica

Bone tumor
170 Malignant neoplasm of bone and articular cartilage

Epilepsy/seizure
333.2 Myoclonus
345 Epilepsy and recurrent seizures
780.33 Posttraumatic seizures
780.39 Other convulsions

Osteoporosis
733.0 Osteoporosis

Fractures
805 Fracture of vertebral column without mention of spinal cord injury
812 Fracture of humerus
813 Fracture of radius and ulna
814 Fracture of carpal bone(s)
820 Fracture of neck of femur

History of falls
781.2 Abnormality of gait
781.3 Lack of coordination
781.99 Other symptoms involving nervous and musculoskeletal systems
V15.88 History of fall
E880–E888 Accidental falls

Motor vehicle accidents
E800–E807 Railway accidents
E810–E819 Motor vehicle traffic accidents
E820–E825 Motor vehicle nontraffic accidents
E826–E829 Other road vehicle accidents
E830–E831 Water transport accidents
E840–E845 Air and space transport accidents
E846–E848 Vehicle accidents, not elsewhere classifiable

Accidental falls from height
E880 Accidental fall on or from stairs or steps
E881 Accidental fall on or from ladders or scaffolding
E882 Accidental fall from or out of building or other structure
E883 Accidental fall into hole or other opening in surface
E884.0 Accidental fall from playground equipment
E884.1 Accidental fall from cliff

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

Appendix Table 2. Variance Ratios and Raw Differences in Proportion for the Baseline Characteristics Before and After Propensity Score Weighting

Characteristic	Maximum Pairwise Variance Ratios/Raw Difference in Proportion*	
	Before Weighting	After Weighting
Age	1.30	1.14
Women	0.07	0.02
Medical conditions		
Congestive heart failure	0.11	0.03
Prior ischemic stroke or transient ischemic attack	0.05	0.06
Chronic obstructive pulmonary disease	0.02	0.01
Diabetes mellitus	0.03	0.02
History of falls	0.04	0.01
History of fractures	0.02	0.02
Liver disease	<0.01	<0.01
Osteoporosis	<0.01	<0.01
Rheumatoid arthritis and other inflammatory polyarthropathies	<0.01	<0.01
Chronic kidney disease	0.06	0.01
Recent medication use		
Angiotensin-converting enzyme inhibitor or angiotensin II–receptor blocker	0.05	0.04
β-Blocker	0.03	0.02
Proton-pump inhibitor	0.14	0.06
Bisphosphonate	0.01	<0.01
Systemic glucocorticoid	0.02	0.01
Antidepressant	0.01	<0.01

* Variance ratios were obtained by computing the ratios of variances of a continuous variable (age) between 2 treatment groups. A value that is close to 1 and within 0.5 to 2.0 indicates a group balance. Raw differences in proportion were obtained by computing the differences in proportion of a categorical variable (all variables except age) between 2 treatment groups.

Appendix Table 3. Cumulative Rates of Osteoporotic Fracture Before and After Inverse Probability of Treatment Weighting

Time Since Treatment Commencement	Apixaban			Dabigatran			Rivaroxaban			Warfarin		
	Events, *n*	Crude Incidence	Weighted Incidence*	Events, *n*	Crude Incidence	Weighted Incidence*	Events, *n*	Crude Incidence	Weighted Incidence*	Events, *n*	Crude Incidence	Weighted Incidence*
All patients												
6 mo	15	0.53	0.38	28	0.49	0.49	16	0.46	0.41	51	0.72	0.82
12 mo	29	1.24	0.99	46	0.93	0.95	21	0.66	0.57	78	1.22	1.37
18 mo	40	1.98	1.42	59	1.31	1.29	28	1.01	0.84	92	1.53	1.65
24 mo	44	2.38	1.58	66	1.57	1.53	37	1.56	1.32	108	1.94	2.02
Men												
6 mo	8	0.57	0.47	8	0.28	0.33	5	0.30	0.25	15	0.38	0.34
12 mo	10	0.79	0.66	13	0.51	0.55	7	0.46	0.35	30	0.90	0.94
18 mo	14	1.35	1.01	18	0.81	0.82	10	0.79	0.53	36	1.13	1.16
24 mo	15	1.62	1.10	20	0.97	1.01	15	1.41	1.02	42	1.41	1.43
Women												
6 mo	7	0.49	0.35	20	0.72	0.75	11	0.62	0.57	36	1.12	1.31
12 mo	19	1.65	1.12	33	1.36	1.41	14	0.86	0.77	48	1.62	1.80
18 mo	26	2.56	1.69	41	1.83	1.81	18	1.25	1.06	56	2.01	2.16
24 mo	29	3.07	1.89	46	2.18	2.12	22	1.71	1.47	66	2.57	2.67

* After inverse probability of treatment weighting.

Appendix Table 4. Sensitivity Analyses That Excluded Fractures Associated With Falls From Higher Than Standing Height

Treatment	All Patients		Men		Women		*P* Value for Interaction*
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	
DOAC vs. warfarin							
Apixaban vs. warfarin	0.63 (0.42–0.96)	0.030	0.74 (0.36–1.51)	0.41	0.60 (0.38–0.96)	0.035	0.64
Dabigatran vs. warfarin	0.66 (0.50–0.87)	0.003	0.65 (0.41–1.03)	0.068	0.71 (0.50–1.01)	0.058	0.75
Rivaroxaban vs. warfarin	0.52 (0.37–0.74)	<0.001	0.59 (0.35–1.00)	0.050	0.51 (0.32–0.80)	0.004	0.68
DOAC vs. DOAC							
Apixaban vs. dabigatran	0.96 (0.63–1.47)	0.85	1.14 (0.55–2.39)	0.72	0.85 (0.52–1.38)	0.51	0.51
Rivaroxaban vs. dabigatran	0.80 (0.55–1.15)	0.23	0.91 (0.50–1.65)	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	0.42

DOAC = direct oral anticoagulant.
* *P* value for interaction between treatment effect and sex.

Appendix Table 5. Sensitivity Analyses in Which Patients Were Not Censored If They Discontinued the Index Treatment or Switched to Another Anticoagulant

Treatment	All Patients		Men		Women		*P* Value for Interaction*
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	
DOAC vs. warfarin							
Apixaban vs. warfarin	0.65 (0.44–0.96)	0.032	0.57 (0.31–1.05)	0.069	0.71 (0.47–1.07)	0.100	0.55
Dabigatran vs. warfarin	0.75 (0.59–0.94)	0.015	0.84 (0.55–1.27)	0.40	0.73 (0.56–0.93)	0.013	0.56
Rivaroxaban vs. warfarin	0.62 (0.46–0.85)	0.003	0.61 (0.39–0.96)	0.031	0.64 (0.43–0.93)	0.021	0.90
DOAC vs. DOAC							
Apixaban vs. dabigatran	0.87 (0.58–1.32)	0.51	0.68 (0.34–1.35)	0.27	0.97 (0.63–1.50)	0.91	0.38
Rivaroxaban vs. dabigatran	0.83 (0.60–1.15)	0.27	0.73 (0.45–1.18)	0.20	0.88 (0.59–1.31)	0.52	0.57
Rivaroxaban vs. apixaban	0.96 (0.61–1.49)	0.84	1.08 (0.53–2.21)	0.83	0.90 (0.55–1.46)	0.67	0.67

DOAC = direct oral anticoagulant.
* *P* value for interaction between treatment effect and sex.

Appendix Table 6. Post Hoc Sensitivity Analyses That Included Bisphosphonates and Other Osteoporosis Treatments in the Propensity Score Model

Treatment	All Patients		Men		Women		*P* Value for Interaction*
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	
DOAC vs. warfarin							
Apixaban vs. warfarin	0.62 (0.41–0.93)	0.022	0.72 (0.36–1.44)	0.36	0.59 (0.37–0.94)	0.027	0.64
Dabigatran vs. warfarin	0.65 (0.49–0.86)	0.003	0.62 (0.39–0.99)	0.046	0.71 (0.50–1.00)	0.050	0.68
Rivaroxaban vs. warfarin	0.51 (0.36–0.72)	<0.001	0.57 (0.34–0.96)	0.036	0.53 (0.34–0.82)	0.004	0.81
DOAC vs. DOAC							
Apixaban vs. dabigatran	0.95 (0.62–1.46)	0.82	1.16 (0.56–2.39)	0.69	0.84 (0.52–1.37)	0.48	0.47
Rivaroxaban vs. dabigatran	0.79 (0.54–1.14)	0.21	0.91 (0.51–1.64)	0.76	0.74 (0.47–1.18)	0.21	0.59
Rivaroxaban vs. apixaban	0.83 (0.51–1.33)	0.43	0.79 (0.36–1.71)	0.54	0.89 (0.51–1.53)	0.66	0.81

DOAC = direct oral anticoagulant.
* *P* value for interaction between treatment effect and sex.

Appendix Figure. Distribution of oral anticoagulant use among hospital clusters in the study cohort.

The Hong Kong Hospital Authority organizes its services into 7 hospital clusters. A cluster is a group of hospitals and ambulatory clinics under the same management structure in a region of Hong Kong. Some bars total more than 100% due to rounding.

Appendix Table 7. Post Hoc Sensitivity Analyses That Included Dispensing Institution as a Covariate in the Propensity Score Model

Treatment	All Patients		Men		Women		*P* Value for Interaction*
	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	Hazard Ratio (95% CI)	*P* Value	
DOAC vs. warfarin							
Apixaban vs. warfarin	0.63 (0.41–0.95)	0.027	0.74 (0.36–1.52)	0.41	0.66 (0.40–1.09)	0.108	0.80
Dabigatran vs. warfarin	0.69 (0.51–0.94)	0.019	0.56 (0.35–0.91)	0.019	0.72 (0.51–1.01)	0.057	0.43
Rivaroxaban vs. warfarin	0.64 (0.45–0.90)	0.011	0.58 (0.33–0.99)	0.046	0.56 (0.36–0.88)	0.012	0.95
DOAC vs. DOAC							
Apixaban vs. dabigatran	0.90 (0.58–1.42)	0.66	1.32 (0.63–2.73)	0.46	0.93 (0.56–1.55)	0.77	0.44
Rivaroxaban vs. dabigatran	0.92 (0.63–1.34)	0.66	1.02 (0.56–1.85)	0.95	0.79 (0.49–1.25)	0.31	0.50
Rivaroxaban vs. apixaban	1.02 (0.63–1.63)	0.95	0.78 (0.35–1.73)	0.54	0.85 (0.48–1.51)	0.58	0.86

DOAC = direct oral anticoagulant.
* *P* value for interaction between treatment effect and sex.

Web-Only References

49. **Cheung NT, Fung KW, Wong KC, et al.** Medical informatics–the state of the art in the Hospital Authority. Int J Med Inform. 2001;62: 113-9. [PMID: 11470614]

50. **Fung KW, Vogel LH.** Will decision support in medications order entry save money? A return on investment analysis of the case of the Hong Kong Hospital Authority. AMIA Annu Symp Proc. 2003:244-8. [PMID: 14728171]

51. **Chai Y, Luo H, Wong GHY, et al.** Risk of self-harm after the diagnosis of psychiatric disorders in Hong Kong, 2000-10: a nested case-control study. Lancet Psychiatry. 2020;7:135-147. [PMID: 31974072] doi:10.1016/S2215-0366(20)30004-3

52. **Man KKC, Coghill D, Chan EW, et al.** Association of risk of suicide attempts with methylphenidate treatment. JAMA Psychiatry. 2017; 74:1048-1055. [PMID: 28746699] doi:10.1001/jamapsychiatry.2017.2183

53. **Lee BK, Lessler J, Stuart EA.** Improving propensity score weighting using machine learning. Stat Med. 2010;29:337-46. [PMID: 19960510] doi:10.1002/sim.3782

54. **Harder VS, Stuart EA, Anthony JC.** Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. Psychol Methods. 2010;15: 234-49. [PMID: 20822250] doi:10.1037/a0019623

55. **Griffin BA, Ridgeway G, Morral AR, et al.** Toolkit for weighting and analysis of nonequivalent groups (TWANG) website. Accessed at www.rand.org/statistics/twang/downloads.html on 25 January 2020.

56. **McCaffrey D, Burgette L, Griffin BA, et al.** Propensity scores for multiple treatments: a tutorial for the mnps macro in the twang SAS macros. Accessed at www.rand.org/content/dam/rand/pubs/tools/TL100/TL169z1/RAND_TL169z1.pdf on 25 January 2020.

57. **Greifer N.** Covariate balance tables and plots. Accessed at https://cran.r-project.org/web/packages/cobalt/cobalt.pdf on 10 January 2020.

58. **Rubin DB.** Using propensity scores to help design observational studies: application to the tobacco litigation. Health Serv Outcomes Res Methodol. 2001;2:169-88. doi:10.1023/A:1020363010465

59. **SAS Institute.** The PHREG procedure: example 89.8 survival curves. Accessed at https://documentation.sas.com/?docsetId=statug&docsetVersion=15.1&docsetTarget=statug_phreg_examples08.htm&locale=en on 15 January 2020.
60. **Therneau TM, Crowson CS, Atkinson EJ.** Adjusted survival curves. Accessed at https://cran.r-project.org/web/packages/survival/vignettes/adjcurve.pdf on 15 January 2020.
61. **Diaz-Ramirez LG, Boscardin JW, Lee AK, et al.** Survival estimates prediction with survey data. Accessed at https://pdfs.semanticscholar.org/8703/3cf769177558d7bc1b001538ffc1b2e0c285.pdf on 12 March 2020.
62. **Austin PC.** Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. Stat Med. 2016;35:5642-5655. [PMID: 27549016] doi:10.1002/sim.7084