# Comparison of Direct Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation and Bioprosthetic Heart Valves

Lewei Duan, MS[a], Jason N Doctor, PhD[b], John L Adams, PhD[c], John A Romley, PhD[b], Leigh-Anh Nguyen, PharmD[d], Jaejin An, PhD[a], and Ming-Sum Lee, MD PhD[e,*]

**There are limited data regarding direct oral anticoagulants (DOACs) for stroke prevention in patients with bioprosthetic heart valves (BHVs) and atrial fibrillation (AF). The objectives of this study were to evaluate the ambulatory utilization of DOACs and to compare the effectiveness and safety of DOACs versus warfarin in patients with AF and BHVs. We conducted a retrospective cohort study at a large integrated health care delivery system in California. Patients with BHVs and AF treated with warfarin, dabigatran, rivaroxaban, or apixaban between September 12, 2011 and June 18, 2020 were identified. Inverse probability of treatment-weighted comparative effectiveness and safety of DOACs compared with warfarin were determined. Use of DOACs gradually increased since 2011, with a significant upward in trend after a stay-at-home order related to COVID-19. Among 2,672 adults with BHVs and AF who met the inclusion criteria, 439 were exposed to a DOAC and 2233 were exposed to warfarin. For the primary effectiveness outcome of ischemic stroke, systemic embolism and transient ischemic attack, no significant association was observed between use of DOACs compared with warfarin (HR 1.19, 95% CI 0.96 to 1.48, p = 0.11). Use of DOACs was associated with lower risk of the primary safety outcome of intracranial hemorrhage, gastrointestinal bleeding, and other bleed (HR 0.69, 95% CI 0.56 to 0.85, p < 0.001). Results were consistent across multiple subgroups in the sensitivity analyses. These findings support the use of DOACs for AF in patients with BHVs.**  **(Am J Cardiol 2021;146:22−28)**

Atrial fibrillation (AF) increases the risk of thromboembolic ischemic stroke and systolic embolism.[1] The use of oral anticoagulation therapy substantially reduces ischemic stroke risk.[2] Compared to warfarin, direct oral anticoagulants (DOACs) are associated with similar or better ischemic stroke prevention and lower risk of serious bleeding complications.[3−5] The ease of dosing with DOACs have led to a steady increase in their use.[6,7] The coronavirus disease 2019 (COVID-19) pandemic has brought additional consideration to the care of patients receiving warfarin therapy.[8] For patients receiving warfarin therapy, frequent blood draws for International Normalized Raio (INR) monitoring may be difficult because of lockdowns. Switching patients from warfarin to DOACs is a potential strategy to minimize patients' need to leave their homes. DOACs were approved for use in nonvalvular AF. The efficacy and safety of DOACs achieved in clinical trials for nonvalvular AF may not apply to patients with valvular heart disease. For example, dabigatran used in patients who had undergone mechanical valve replacement led to excess thromboembolic and bleeding events.[9] One recent study suggests DOAC may be a reasonable alternative to warfarin in patients with BHVs.[10] Using a large population-based cohort from an integrated health care delivery system in California, we evaluated the ambulatory utilization pattern of DOACs in patients with AF and BHVs, and compared the effectiveness and safety of DOACs versus warfarin in this population.

## Methods

This is a retrospective cohort study using data from the Kaiser Permanente Southern California (KPSC) Health System.[11] The study protocol was approved by the KPSC Institutional Review Board. A waiver of informed consent was obtained because of the observational nature of the study.

Adult patients (age ≥18 years) with AF and BHVs between September 12, 2011 and June 18, 2020 were initially identified using *International Classification of Diseases (ICD) 9/10 codes* (Supplementary Table 1). Presence of BHVs was confirmed by manual review of diagnoses, problem lists and anticoagulation clinic notes. In this cohort, 1,724 had bioprosthetic aortic valves (332 in the DOAC group and 1,392 in the warfarin group) and 943 had bioprosthetic mitral valves (104 in the DOAC group and 839 in the warfarin group). The type of bioprosthetic valve could not be determined in 5 cases due to incomplete documentation. The index date was defined as the first

[a]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California; [b]Price School of Public Policy, University of Southern California, Los Angeles, California; [c]Kaiser Permanente Center for Effectiveness & Safety Research and Bernard J. Tyson School of Medicine, Pasadena, California; [d]Clinical Pharmacy Services, Kaiser Permanente Southern California, West Los Angeles, California; and [e]Department of Cardiology, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California. Manuscript received November 12, 2020; revised manuscript received and accepted January 8, 2021.

See page 27 for disclosure information.

*Corresponding author: Tel: (323) 783-4585; fax: (323) 783-5509.
*E-mail address:* mingsum.lee@kp.org (M.-S. Lee).

0002-9149/
https://doi.org/10.1016/j.amjcard.2021.01.016

medication dispensed date (DOAC or warfarin) during the study period. Patients who were not KPSC members, did not have continuous one-year membership prior to the index date (allowing at 30-day gap), or did not have continuous one-year pharmacy-benefit coverage were excluded. For the primary analysis, we included qualified patients from September 12, 2011 to March 18, 2020 with at least 6 months of follow-up to allow adequate follow-up data.

Covariates were identified in the following categories: baseline demographics, medical comorbidities, cardiac risk factors, and use of cardiac medications. Medical comorbidities and cardiac risk factors were collected using ICD codes from the year prior to the index date. Baseline concomitant medications was identified using outpatient pharmacy records. Patients were followed until they reached a study end point, death, disenrolled from the health plan, or the end of the study (June 18, 2020). Patients were then classified into DOAC-exposed or not exposed groups based on their receipt of dispensed DOAC prescriptions from a KPSC pharmacy during the study period. The following DOACs were evaluated: dabigatran, rivaroxaban and apixaban. Patients were considered exposed to a DOAC if they had at least two dispensed prescriptions of a DOAC. Patients were considered exposed to warfarin and not exposed to a DOAC if they were never dispensed a prescription of DOAC, but received at least two prescriptions of warfarin during the study period. The DOAC group included a subset of patients who had previous warfarin exposures, while the warfarin cohort did not include any patients exposed to a DOAC.

The primary effectiveness outcome was a composite of ischemic stroke, transient ischemic attack (TIA) or systemic embolism. The primary safety outcome was a composite of major bleeding including gastrointestinal bleeding, intracranial hemorrhage, and bleeding from other sites. The secondary outcomes were all-cause mortality, and the individual ischemic or bleeding outcomes. Outcomes were identified using ICD-9 and ICD-10 codes (in the Supplementary Table 1) in the primary discharge diagnosis position for inpatient hospitalizations.

Mortality data was extracted from a mortality data mart with integrated death information derived from multiple sources including California state death master files, Social Security Administrative death master files, hospital deaths and insurance enrollment records.

Descriptive statistics on covariates included counts and percentages, as well as means and standard deviations. Time-series plots of utilization were used to depict DOAC versus warfarin usage during the study period. Plots of the 30-day average proportion of DOAC dispensed at KPSC outpatient pharmacy indicate dynamic dispensing.[12] Inverse probability of treatment weighting (IPTW) operated to balance baseline characteristics between the groups.[13–15] Specifically, generalized boosted models estimated the propensity score, and corresponding weights were applied to estimate the average treatment effect (ATE) of switching the population from Warfarin to DOAC. The underlying propensity score model included 29 baseline covariates such as age, sex, race, comorbidities and baseline medication use, with up to 3-way interactions among these covariates. Monte Carlo methods were used to establish the reference distribution for Kolmogorov-Smirnov (KS) statistics for each covariate.[14] Maximum of KS statistics across variables were used as stopping criteria. Absolute standardized bias was used to quantify the balance between the variables in two comparison groups resulting from inverse probability of treatment weighting. This value is also referred to as standardized effect size, calculated as the difference in means or proportions of a variable divided by a pooled estimate of the standard deviation of the variable.[16] A difference of 0.10 or less was considered as adequate balance between the two groups.[17]

Reports of both crude and weighted event rates employed a denominator of 1,000 person-years. Weighted rates were based on the IPTW population and expressed as population average treatment rate per 1,000 person-years. A combination of propensity score weighting and covariate adjustment for unbalanced covariates was applied in a Cox proportional hazard regression model to ensure a "doubly robust" treatment effect estimator.[18,19] Incident Rate Difference (IRD) per 1,000 person-year, hazard ratios (HRs) and 95% confidence intervals (CIs) depicted group differences.

Stratified analyses using IPTW Cox proportional hazards models evaluated heterogeneity of the ATE by potential effect modifiers, including age (18 to 64, 65 to 74, ≥75 years), sex, race (white, black, hispanic, asian, other), body mass index (BMI) (<30 vs ≥ 30), chronic kidney disease (CKD) class, Charlson comorbidity index,[20] CHA2DS2-VASc score,[21] and HAS-BLED score[22] (in the Supplementary Table 2). ATEs on 9 endpoints: all-cause mortality, composite stroke, ischemic stroke, systemic embolism, transient ischemic attack (TIA), composite bleed, gastrointestinal (GI) bleeding, Intracranial Hemorrhage, and other bleed, were assessed. p value <0.05 was the nominal level of significance.

Sensitivity analyses were performed to assess the robustness of the findings based on primary analyses. Definition of the cohort inclusion and the length of follow-up time were adjusted for the sensitivity analyses. The effects of DOAC use versus warfarin use on clinical outcomes were assessed for DOAC patients without previous warfarin exposure, and DOAC patients using dabigatran only. Measurement of effects were repeated at 3- and 12- month follow-up. All statistical analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, NC) and R version 3.60.[23]

## Results

The temporal utilization pattern of anticoagulation therapy is shown in Figure 1 and in the Supplementary Figure 1. At the start of the study period, the majority of patients were treated with warfarin. There was a gradual increase in the use of DOAC over time. The trend of the proportion of patients who treated with DOAC increased after March 19, 2020, when the State of California issued a stay-at-home order due to the COVID-19 pandemic.

To compare the effectiveness and safety of direct oral anticoagulants versus warfarin, we identified patients with AF and BHVs treated with anticoagulant therapy. Between 2011 and 2020, there were 3,351 adults with BHVs and concomitant AF who were treated with anticoagulation (Figure 2). After excluding 197 patients without continuous 1-year


Figure 1. Temporal trends in DOAC prescriptions for patients with bioprosthetic valves between March 19, 2019 and June 18, 2020. March 19, 2020 was the date when the state of California issued a "stay-at-home" order.

membership information and 491 patients without adequate follow-up time, the final study cohort included 2,672 patients. Of these patients, 439 patients received DOAC, and 2,233 patients took warfarin alone. Among the DOAC users, 362 took dabigatran, 60 apixaban, and 17 rivaroxaban.

Table 1 shows the baseline characteristics of the study population. Demographic factors including age, sex, and race/ethnicity were similar between the DOACs and the warfarin group. A higher proportion of patients in the warfarin group had heart failure, coronary artery disease and end-stage renal failure. A higher proportion of patients in the DOACs group had a history of ischemic stroke. After propensity score weighting, the groups were well-balanced, with most covariates having absolute standardized differences below 0.10 except for age and chronic kidney disease stages.

During follow-up (mean = 2.9, SD = 2.2) years, there were 180 ischemic strokes, 11 systemic embolisms, and 82 TIAs. The primary effectiveness outcome was a composite of ischemic stroke, TIA, and systemic embolism. After applying propensity score weighting, no statistically significant association was observed between use of DOACs versus warfarin and composite stroke events (HR 1.19, 95% CI 0.96 to 1.48, p = 0.106) (Table 2).

A total of 371 composite bleeding events were observed. Patients on DOACs had fewer bleeding events relative to warfarin (HR 0.69, 95% CI 0.56 to 0.85, $p < 0.001$). The rate of intracranial hemorrhage was significantly lower in the DOACs group vs warfarin (HR 0.43, 95% CI 0.25 to 0.73, $p < 0.001$).

There were 40.37 and 52.78 total deaths per 1000 person-years among DOACs users and warfarin users (weighted IRD -10.92/1,000 person-years, 95% CI −31.72 to 9.88). No association was observed between exposure to DOACs and all-cause mortality (HR 0.87, 95% CI 0.72 to 1.05, p = 0.16).

Stratified analyses were consistent with the main findings (Supplementary Figures 2, 3, and 4). No significant interaction was observed with age, sex, race, heart failure, history of ischemic stroke, or history of bleeding were not significant.

Several sensitivity analyses yielded consistent results. When comparing DOACs users without previous warfarin exposure to those treated with warfarin, DOAC exposure was associated with comparable ischemic risk and lower risk of bleeding (Supplementary Table 3). When the analyses were performed comparing an individual DOAC (dabigatran) with warfarin, we found that dabigatran was associated with lower risk of composite bleeding and comparable risk of the composite ischemic endpoint (Supplementary Table 4). The analyses were repeated with different follow-up time periods (3 months and 12 months), resulting in similar findings (Supplementary Tables 5 and 6). Similar findings were observed in patients with aortic valves and mitral valves (Supplementary Tables 7 and 8).

## Discussion

In this cohort of patients with BHVs and AF, we assessed the effectiveness and safety of DOACs compared with warfarin. The principal findings are as follows: first,

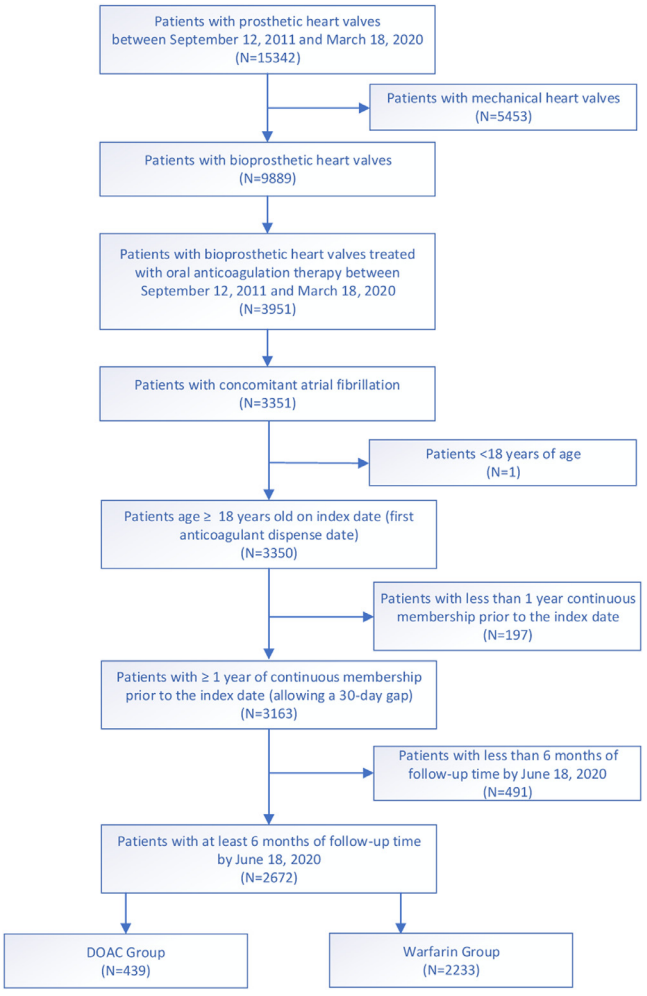


Figure 2. Derivation of the study cohort.

DOACs were as effective as warfarin in preventing ischemic strokes, systemic embolism and transient ischemic attacks; second, patients treated with DOACs had fewer bleeding events, including fewer intracranial hemorrhage, when compared to warfarin; third, there was a gradual increase in DOAC use, with a marked increase after March 19, 2020, when stay-at-home orders were issued in California due to the COVID-19 pandemic.

To our knowledge, this study is one of the largest real-world evaluations comparing DOACs and warfarin in patients with BHVs and AF. In patients with non-valvular AF, DOACs have demonstrated at least equivalent efficacy in comparison to warfarin.[3–5] However, patients with mechanical valves had higher thromboembolic events when treated with dabigatran.[9] DOACs were also found to be associated with increased risk of major adverse cardiovascular events in patients with adult congenital heart disease, a population who frequently had cardiac surgery including valve replacements.[24]

There is limited data on the use of DOACs in the setting of BHVs. A small pilot study involving 27 patients showed low rates of thromboembolic events associated with the use of dabigatran in patients with BHVs and AF.[25] A sub-analysis of 104 patients with BHVs enrolled in the ARISTOTLE trial showed no significant difference in thromboembolic events between apixaban and warfarin.[26] In patients with BHVs and AF, one study found rivaroxaban to be noninferior to warfarin.[27] These early results suggest DOAC use may be reasonable in patients with BHVs. The current study expands on these early findings, showing that use of DOACs in patients with BHVs can achieve comparable outcomes for both effectiveness and safety in comparison to warfarin. The results were consistent regardless of age, sex, and race.

Intracranial bleeding is the most serious bleeding complication since mortality and morbidity associated with intracranial bleed is much higher than other types of bleeding.[28] Our finding that DOACs were associated with lower rates of intracranial hemorrhage is consistent with results from the pivotal clinical trials. In RELY (dabigatran), ROCKET-AF (rivaroxaban), and ARISTOTLE (apixaban), the relative risk for major bleeding and intracranial bleeding with DOACs were significantly lower compared with warfarin.[29] Given the comparable risks of the primary effectiveness endpoint, and lower risk of intracranial bleeding, DOACs may have higher net clinical benefits compared with warfarin in this population.

The use of DOACs has steadily increased because of their ease of use, and favorable efficacy and safety profile.[30] Yet, these drugs have seen even a greater rise in use since the COVID-19 pandemic. Patients treated with warfarin require ongoing Internationalized Normalized Ratio (INR) monitoring, which can be difficult during COVID-19 because of social distancing and quarantine rules. In suitable candidates, switching patients from warfarin to a DOAC is a potential strategy to minimize patients' need to travel. In California, the governor issued a stay-at-home order on March 19, 2020 due to COVID-19. We observed a significant increase in proportion of patient treated with DOAC since March 19. Given similar safety and effectiveness of DOACs in this population, switching from warfarin to DOAC may be advisable during a pandemic.

There are several limitations to this study. First, there may be exposure misclassification related to non-compliance. Nevertheless, using pharmacy dispense information allows us to avoid any recall bias. Second, residual confounding may persist despite careful adjustment with the use of IPTW, and firm conclusions cannot be drawn about causality. Third, use of over-the-counter medications such as aspirin and non-steroidal anti-inflammatory agents that may increase bleeding risk could not be accurately assessed in this study. Fourth, the majority of patients in the DOAC group were treated with dabigatran. Clinicians wrote only a small number of prescriptions to patients for rivaroxaban and apixaban. Additional studies that specifically evaluate apixaban and rivaroxaban may be warranted. Fifth, information on prosthetic valve function was not available. Finally, the study population has insurance. As such, the results do not generalize to patients without insurance.

In conclusion, in this large contemporary study of patients with AF and BHVs, DOACs were as effective as warfarin in preventing ischemic events, while associated with less intracranial bleeds. These findings support the use of DOACs for AF in patients with BHVs.

Table 1
Baseline demographics before and after IPTW weighting

| Variable | Crude | | | | IPTW Weighted* | | | |
|---|---|---|---|---|---|---|---|---|
| | Warfarin (N=2233) | DOAC (N=439) | Standardized Bias | p value | Warfarin (N=2233) | DOAC (N=439) | Standardized Bias | p value |
| Age (years) | | | | | | | | |
| 18-64 | 13.6% | 12.1% | 0.045 | 0.682 | 13.2% | 9.8% | 0.101 | 0.15 |
| 65-74 | 30.2% | 31.0% | 0.017 | | 30.2% | 33.9% | 0.08 | |
| >=75 | 56.2% | 56.9% | 0.015 | | 56.5% | 56.3% | 0.005 | |
| Sex | | | | | | | | |
| Women | 39.0% | 41.2% | 0.046 | 0.374 | 39.2% | 39.9% | 0.014 | 0.82 |
| Men | 61.0% | 58.8% | 0.046 | | 60.8% | 60.1% | 0.014 | |
| Race / Ethnicity | | | | | | | | |
| Asian or Pacific Islander | 6.8% | 5.9% | 0.034 | 0.601 | 6.5% | 4.9% | 0.067 | 0.453 |
| Hispanic | 18.0% | 17.5% | 0.013 | | 17.8% | 17.9% | 0.003 | |
| Non-Hispanic Black | 7.3% | 5.5% | 0.07 | | 7.1% | 5.1% | 0.079 | |
| Non-Hispanic White | 67.4% | 70.4% | 0.064 | | 68.0% | 71.4% | 0.073 | |
| Others | 0.5% | 0.7% | 0.02 | | 0.5% | 0.7% | 0.023 | |
| BMI (Kg/$m^2$) | | | | | | | | |
| <18.5 | 1.9% | 1.6% | 0.024 | 0.038 | 1.9% | 1.8% | 0.005 | 0.712 |
| 18.5 - 25 | 30.3% | 24.6% | 0.126 | | 29.6% | 27.8% | 0.039 | |
| 25 - 30 | 35.8% | 35.8% | 0.001 | | 35.7% | 34.1% | 0.034 | |
| > 30 | 31.9% | 38.0% | 0.13 | | 32.8% | 36.3% | 0.074 | |
| Insurance | | | | | | | | |
| Commercial | 12.2% | 10.5% | 0.054 | 0.238 | 11.9% | 9.4% | 0.079 | 0.375 |
| Medicaid | 0.7% | 1.4% | 0.072 | | 0.7% | 0.9% | 0.025 | |
| Medicare | 87.1% | 88.2% | 0.033 | | 87.4% | 89.7% | 0.07 | |
| Comorbidities | | | | | | | | |
| Hypertension | 54.3% | 56.9% | 0.053 | 0.312 | 54.2% | 52.4% | 0.037 | 0.566 |
| Congestive Heart Failure | 76.0% | 70.2% | 0.136 | 0.009 | 75.3% | 74.3% | 0.022 | 0.701 |
| Myocardial Infarction | 22.1% | 19.8% | 0.056 | 0.285 | 22.0% | 19.1% | 0.071 | 0.252 |
| Peripheral Vascular Disease | 11.9% | 10.7% | 0.037 | 0.459 | 12.0% | 10.3% | 0.054 | 0.329 |
| Alcoholism | 10.3% | 11.4% | 0.036 | 0.496 | 10.4% | 9.9% | 0.016 | 0.788 |
| Dementia | 13.6% | 14.4% | 0.023 | 0.663 | 13.5% | 12.4% | 0.031 | 0.585 |
| COPD | 28.8% | 24.6% | 0.092 | 0.077 | 28.4% | 25.8% | 0.058 | 0.345 |
| Dialysis | 3.8% | 1.4% | 0.133 | 0.011 | 3.5% | 1.8% | 0.095 | 0.173 |
| Chronic Kidney Disease stage | | | | | | | | |
| 1 | 21.6% | 23.9% | 0.055 | 0.017 | 21.8% | 22.1% | 0.008 | 0.097 |
| 2 | 33.7% | 37.8% | 0.086 | | 34.2% | 35.1% | 0.019 | |
| 3 | 37.8% | 35.1% | 0.057 | | 37.7% | 39.8% | 0.044 | |
| 4 | 4.7% | 2.7% | 0.096 | | 4.4% | 2.6% | 0.088 | |
| 5 | 2.1% | 0.5% | 0.123 | | 1.9% | 0.3% | 0.116 | |
| Prior Events of Clinical Outcome | | | | | | | | |
| Prior Ischemic Stroke | 12.2% | 16.9% | 0.139 | 0.008 | 12.6% | 14.2% | 0.046 | 0.464 |
| Prior Systemic Embolism | 1.1% | 1.4% | 0.023 | 0.659 | 1.1% | 0.9% | 0.026 | 0.613 |
| Prior TIA | 9.6% | 10.7% | 0.038 | 0.469 | 9.7% | 10.9% | 0.039 | 0.556 |
| Prior GI Bleeding | 12.9% | 13.9% | 0.028 | 0.589 | 12.9% | 13.8% | 0.028 | 0.66 |
| Prior IC Bleeding | 2.7% | 3.9% | 0.071 | 0.175 | 2.7% | 2.6% | 0.009 | 0.856 |
| Prior Other Bleeding | 6.8% | 6.8% | 0.003 | 0.957 | 6.7% | 4.9% | 0.071 | 0.17 |
| Baseline Medications | | | | | | | | |
| Anti-hypertensive medications | 94.5% | 94.5% | 0 | 0.998 | 94.5% | 94.9% | 0.021 | 0.72 |
| Diabetes medications | 27.5% | 22.1% | 0.122 | 0.019 | 26.8% | 23.8% | 0.069 | 0.295 |
| Antiplatelet | 29.3% | 39.4% | 0.218 | <0.001 | 30.5% | 33.3% | 0.062 | 0.326 |
| Statin | 83.3% | 85.9% | 0.069 | 0.188 | 83.4% | 84.4% | 0.027 | 0.695 |
| Antiarrhythmic | 21.9% | 22.8% | 0.022 | 0.669 | 21.7% | 20.9% | 0.019 | 0.76 |
| Charlson Comorbidity Index (CCI) | | | | | | | | |
| 0-1 | 5.8% | 4.3% | 0.063 | 0.4 | 5.6% | 4.0% | 0.069 | 0.352 |
| 2-3 | 23.5% | 22.6% | 0.023 | | 23.8% | 26.5% | 0.063 | |
| >=4 | 70.7% | 73.1% | 0.053 | | 70.6% | 69.5% | 0.024 | |
| CHA2DS2−VASc Score | | | | | | | | |
| 0-1 | 4.9% | 3.4% | 0.073 | 0.254 | 4.8% | 4.0% | 0.036 | 0.824 |
| 2-3 | 25.2% | 27.6% | 0.055 | | 25.3% | 26.0% | 0.018 | |
| >=4 | 69.9% | 69.0% | 0.018 | | 70.0% | 70.0% | 0 | |

(*continued*)

Table 1 (***Continued***)

| Variable | Crude | | | | IPTW Weighted* | | | |
|---|---|---|---|---|---|---|---|---|
| | Warfarin (N=2233) | DOAC (N=439) | Standardized Bias | p value | Warfarin (N=2233) | DOAC (N=439) | Standardized Bias | p value |
| Has-Bled Score | | | | | | | | |
| 0-2 | 48.7% | 42.4% | 0.126 | 0.016 | 47.8% | 47.7% | 0.003 | 0.962 |
| >=3 | 51.3% | 57.6% | 0.126 | | 52.2% | 52.3% | 0.003 | |

COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack; GI = gastro intestinal; IC = intracranial.

* Baseline covariates used for IPTW: age, sex, race, body mass index, insurance type, dialysis status, Charlson Comorbidity Index, CHA2DS2-VASc Score, HAS-BLED score, history of congestive heart failure, history of myocardial infarction, history of peripheral vascular disease, history of uncontrolled hypertension, history of alcoholism, history of dementia, history of chronic obstructive pulmonary disease, history of gastrointestinal bleed, history of intracranial hemorrhage, history of other bleed, history of ischemic stroke, history of systemic embolism, history of transient ischemic attack, indication for warfarin usage prior to index date, baseline antiarrhythmic medication, baseline antiplatelets, baseline heparin, baseline statin, baseline diabetes drugs, baseline antihypertensive drug.

Table 2
Association between DOAC use and clinical outcomes after IPTW weighting

| | Crude rate/1000 person-years | | IPTW weighted* | | |
|---|---|---|---|---|---|
| | DOAC user (N=439) | Warfarin user (N=2233) | Incidence rate difference/1000 person-year (95%CI) | Hazard ratio (95%) | p value |
| *All-Cause Mortality* | 40.37 | 52.78 | -10.92 (-31.72 to 9.88) | 0.87 (0.72 to 1.05) | 0.155 |
| *Stroke (Composite)* | 43.72 | 31.54 | 10.26 (-9.89 to 30.4) | 1.19 (0.96 to 1.48) | 0.106 |
| Ischemic Stroke | 28.84 | 23.98 | 4.8 (-12.27 to 21.86) | 1.05 (0.82 to 1.35) | 0.705 |
| Systemic Embolism | 4.18 | 1.15 | 0.32 (-3.47 to 4.1) | 2.1 (0.64 to 6.88) | 0.219 |
| Transient Ischemic Attack (TIA) | 15.55 | 10.44 | 3.89 (-7.85 to 15.63) | 1.36 (0.94 to 1.98) | 0.106 |
| *Bleed (Composite)* | 41.32 | 52.95 | -16.05 (-36.01 to 3.9) | 0.69 (0.56 to 0.85) | <0.001 |
| Gastrointestinal (GI) bleeding | 32.58 | 29.56 | -0.81 (-18 to 16.37) | 0.92 (0.72 to 1.17) | 0.48 |
| Intracranial Hemorrhage | 5.58 | 11.80 | -7.69 (-15.45 to 0.07) | 0.43 (0.25 to 0.73) | 0.002 |
| Other Bleed | 7.00 | 13.97 | -6.54 (-15.5 to 2.41) | 0.5 (0.31 to 0.79) | 0.003 |

COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack; GI = gastro intestinal; IC = intracranial.

* Baseline covariates used for IPTW: age, sex, race, body mass index, insurance type, dialysis status, Charlson Comorbidity Index, CHA2DS2-VASc Score, HAS-BLED score, history of congestive heart failure, history of myocardial infarction, history of peripheral vascular disease, history of uncontrolled hypertension, history of alcoholism, history of dementia, history of chronic obstructive pulmonary disease, history of gastrointestinal bleed, history of intracranial hemorrhage, history of other bleed, history of ischemic stroke, history of systemic embolism, history of transient ischemic attack, indication for warfarin usage prior to index date, baseline antiarrhythmic medication, baseline antiplatelets, baseline heparin, baseline statin, baseline diabetes drugs, baseline antihypertensive drug.

## Authors' Contributions

Lewei Duan: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing – Review & Editing, Visualization. Jason N Doctor: Supervision, Writing - Review & Editing, Methodology. John L Adams: Supervision. John A Romley: Supervision, Writing - Review & Editing, Methodology. Leigh-Anh Nguyen: Supervision, Data Curation. Jaejin An: Supervision, Writing - Review & Editing, Methodology. Ming-Sum Lee: Conceptualization, Methodology, Investigation, Writing - Original Draft, Supervision.

## Funding and Support

LD is supported in part by the Edwards Lifesciences Doctoral Fellowship.

## Acknowledgments

The authors thank Ernest Shen, PhD, for critically reading the manuscript.

## Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.01.016.

1. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM, Yancy CW. 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.
2. van Walraven C, Hart RG, Singer DE, Laupacis A, Connolly S, Petersen P, Koudstaal PJ, Chang Y, Hellemons B. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA* 2002;288:2441–2448.

3. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, Committee R-LS, Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139–1151.
4. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L, Committees A. Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981–992.
5. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, Investigators RA. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883–891.
6. Olesen JB, Sorensen R, Hansen ML, Lamberts M, Weeke P, Mikkelsen AP, Kober L, Gislason GH, Torp-Pedersen C, Fosbol EL. Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naive atrial fibrillation patients: Danish nationwide descriptive data 2011-2013. *Europace* 2015;17:187–193.
7. Vinter N, Linder M, Andersen M, Pedersen AB, Madsen M, Schachterle SE, Ataher Q, Mo J, Johnsen SP, Ehrenstein V. Classification and characteristics of on-label and off-label apixaban use in Denmark and Sweden. *Pharmacoepidemiol Drug Saf* 2019;28:867–878.
8. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, Nigoghossian C, Ageno W, Madjid M, Guo Y, Tang LV, Hu Y, Giri J, Cushman M, Quere I, Dimakakos EP, Gibson CM, Lippi G, Favaloro EJ, Fareed J, Caprini JA, Tafur AJ, Burton JR, Francese DP, Wang EY, Falanga A, McLintock C, Hunt BJ, Spyropoulos AC, Barnes GD, Eikelboom JW, Weinberg I, Schulman S, Carrier M, Piazza G, Beckman JA, Steg PG, Stone GW, Rosenkranz S, Goldhaber SZ, Parikh SA, Monreal M, Krumholz HM, Konstantinides SV, Weitz JI, Lip GYH. Global Covid-19 Thrombosis Collaborative Group EbtINE, the Iua SbtESCWGoPC, Right Ventricular F. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;75:2950–2973.
9. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, Blatchford J, Devenny K, Friedman J, Guiver K, Harper R, Khder Y, Lobmeyer MT, Maas H, Voigt JU, Simoons ML, Van de Werf F, Investigators R-A. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;369:1206–1214.
10. Guimaraes HP, Lopes RD, de Barros ESPGM, Liporace IL, Sampaio RO, Tarasoutchi F, Hoffmann-Filho CR, de Lemos Soares Patriota R, Leiria TLL, Lamprea D, Precoma DB, Atik FA, Silveira FS, Farias FR, Barreto DO, Almeida AP, Zilli AC, de Souza Neto JD, Cavalcante MA, Figueira F, Kojima FCS, Damiani L, Santos RHN, Valeis N, Campos VB, Saraiva JFK, Fonseca FH, Pinto IM, Magalhaes CC, Ferreira JFM, Alexander JH, Pavanello R, Cavalcanti AB, Berwanger O, Investigators RT. Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. *N Engl J Med* 2020;383:2117–2126.
11. Derose SF, Contreras R, Coleman KJ, Koebnick C, Jacobsen SJ. Race and ethnicity data quality and imputation using U.S. Census data in an integrated health system: the Kaiser Permanente Southern California experience. *Med Care Res Rev* 2013;70:330–345.
12. Dancho M VDT. Tidy Quantitative Financial Analysis R package 2020.
13. Robins JM HMaBB. Marginal structural models and causal inference in epidemiology 2000.
14. Ridgeway G MD, Morral A, Burgette L and Griffin BA. RAND Corporation. Toolkit for Weighting and Analysis of Nonequivalent Groups: A tutorial for the twang package 2020.
15. Ridgeway G MD, Morral A, Griffin BA, Burgette L, Burgette ML, Ridgeway M and Burgette M. Package 'twang' 2020.
16. Wooldridge JM. *Econometric Analysis of Cross Section and Panel Data*. Cambridge, Mass: MIT Press; 2002:752..
17. 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;15:234–249.
18. Bang H, Robins JM. Doubly robust estimation in missing data and causal inference models. *Biometrics* 2005;61:962–973.
19. Hullsiek KH, Louis TA. Propensity score modeling strategies for the causal analysis of observational data. *Biostatistics* 2002;3:179–193.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–383.
21. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest* 2010;137:263–272.
22. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138:1093–1100.
23. RC T. *R: A Language and Environment for Statistical Computing*.. R Foundation for Statistical Computing; 2019.
24. Freisinger E, Gerss J, Makowski L, Marschall U, Reinecke H, Baumgartner H, Koeppe J, Diller GP. Current use and safety of novel oral anticoagulants in adults with congenital heart disease: results of a nationwide analysis including more than 44 000 patients. *Eur Heart J* 2020;41:4168–4177.
25. Sun JC, Davidson MJ, Lamy A, Eikelboom JW. Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. *Lancet* 2009;374:565–576.
26. Guimaraes PO, Pokorney SD, Lopes RD, Wojdyla DM, Gersh BJ, Giczewska A, Carnicelli A, Lewis BS, Hanna M, Wallentin L, Vinereanu D, Alexander JH, Granger CB. Efficacy and safety of apixaban vs warfarin in patients with atrial fibrillation and prior bioprosthetic valve replacement or valve repair: Insights from the ARISTOTLE trial. *Clin Cardiol* 2019;42:568–571.
27. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM. Investigators EA-T. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093–2104.
28. Fang MC, Go AS, Chang Y, Hylek EM, Henault LE, Jensvold NG, Singer DE. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am J Med* 2007;120:700–705.
29. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955–962.
30. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. *Am J Med* 2015;128:1300–1305.e1302.