Comparative safety and effectiveness of warfarin or rivaroxaban versus apixaban in patients with advanced CKD and atrial fibrillation: nationwide US cohort study

Fu, E.L.; Desai, R.J.; Paik, J.M.; Kim, D.H.; Zhang, Y.C.; Mastrorilli, J.M.; ... ; Lin, K.J.

Comparative Safety and Effectiveness of Warfarin or Rivaroxaban Versus Apixaban in Patients With Advanced CKD and Atrial Fibrillation: Nationwide US Cohort Study

Edouard L. Fu, Rishi J. Desai, Julie M. Paik, Dae Hyun Kim, Yichi Zhang, Julianna M. Mastrorilli, Alexander Cervone, and Kueiyu Joshua Lin

Rationale & Objective: Head-to-head data comparing the effectiveness and safety of oral anticoagulants in patients with atrial fibrillation (AF) and advanced chronic kidney disease (CKD) are lacking. We compared the safety and effectiveness of warfarin or rivaroxaban versus apixaban in patients with AF and non–dialysis-dependent CKD stage 4/5.

Study Design: Propensity score–matched cohort study.

Setting & Participants: 2 nationwide US claims databases, Medicare and Optum's deidentified Clinformatics Data Mart Database, were searched for the interval from January 1, 2013, through March 31, 2022, for patients with nonvalvular AF and CKD stage 4/5 who initiated warfarin versus apixaban (matched cohort, n = 12,488) and rivaroxaban versus apixaban (matched cohort, n = 5,720).

Exposures: Warfarin, rivaroxaban, or apixaban.

Outcomes: Primary outcomes included major bleeding and ischemic stroke. Secondary outcomes included all-cause mortality, major gastrointestinal bleeding, and intracranial bleeding.

Analytical Approach: Cox regression was used to estimate HRs, and 1:1 propensity-score matching was used to adjust for 80 potential confounders.

Results: Compared with apixaban, warfarin initiation was associated with a higher rate of major bleeding (HR, 1.85; 95% CI, 1.59-2.15), including major gastrointestinal bleeding (1.86; 1.53-2.25) and intracranial bleeding (2.15; 1.42-3.25). Compared with apixaban, rivaroxaban was also associated with a higher rate of major bleeding (1.69; 1.33-2.15). All-cause mortality was similar for warfarin (1.08; 0.98-1.18) and rivaroxaban (0.94; 0.81-1.10) versus apixaban. Furthermore, no statistically significant differences for ischemic stroke were observed for warfarin (1.14; 0.83-1.57) or rivaroxaban (0.71; 0.40-1.24) versus apixaban, but the CIs were wide. Similar results were observed for warfarin versus apixaban in the positive control cohort of patients with CKD stage 3, consistent with randomized trial findings.

Limitations: Few ischemic stroke events, potential residual confounding.

Conclusions: In patients with AF and advanced CKD, rivaroxaban and warfarin were associated with higher rates of major bleeding compared with apixaban, suggesting a superior safety profile for apixaban in this high-risk population.

Visual Abstract online

Complete author and article information provided before references.

Correspondence to K.J. Lin (jklin@bwh.harvard.edu)

Am J Kidney Dis. 83(3):293-305. Published online October 13, 2023.

doi: 10.1053/j.ajkd.2023.08.017

Atrial fibrillation (AF) is highly prevalent in patients with advanced chronic kidney disease (CKD). It is estimated that 16%-21% of patients with CKD[1,2] have AF. In addition, patients with CKD have a higher risk of thromboembolic complications while simultaneously experiencing a high risk of bleeding.[3-5] For instance, CKD is associated with a 1.5-fold greater risk of thromboembolism.[6-8] Furthermore, the risk of gastrointestinal bleeding was 7 times greater among those with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 than in persons with normal kidney function.[9]

Editorial, p. 288

There is little evidence to guide anticoagulant treatment in patients with advanced stages of CKD,[10] despite the high risks of stroke and bleeding in this population. A small subgroup analysis of the ARISTOTLE trial (Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation) among 269 patients with a creatinine clearance of 25-30 mL/min found that patients randomized to receive warfarin had a higher rate of major bleeding than those randomized to receive apixaban.[11] However, none of the landmark randomized trials that compared direct oral anticoagulants versus warfarin included patients with creatinine clearances <25 mL/min.[12-16] Furthermore, no randomized trials have performed head-to-head comparisons between different direct oral anticoagulants.

The absence of trial evidence in patients with advanced CKD highlights the urgent need for a comprehensive assessment of different oral anticoagulants in this population at high risk for adverse outcomes. The aim of this study was to compare the safety and effectiveness of warfarin or rivaroxaban versus apixaban among patients with non–dialysis-dependent CKD stage 4/5 and nonvalvular AF or flutter in routine clinical practice.

Methods

Data Source

We used data from 2 large US health insurance databases, Optum's deidentified Clinformatics Data Mart (CDM)

PLAIN-LANGUAGE SUMMARY

Different anticoagulants have been shown to reduce the risk of stroke in patients with atrial fibrillation, such as warfarin and direct oral anticoagulants like apixaban and rivaroxaban. Unfortunately, the large-scale randomized trials that compared direct anticoagulants versus warfarin excluded patients with advanced chronic kidney disease. Therefore, the comparative safety and effectiveness of warfarin, apixaban, and rivaroxaban are uncertain in this population. In this study, we used administrative claims data from the United States to answer this question. We found that warfarin and rivaroxaban were associated with increased risks of major bleeding compared with apixaban. There were few stroke events, with no major differences among the 3 drugs in the risk of stroke. In conclusion, this study suggests that apixaban has a better safety profile than warfarin and rivaroxaban.

database and Medicare fee-for-service Parts A (inpatient), B (outpatient), and D (pharmacy claims). The CDM includes a national commercially insured US population. Medicare is a federal health insurance program that provides health care coverage for US residents aged at least 65 years and those younger than 65 years with disabilities, including patients with end-stage kidney disease. The databases contain deidentified, longitudinal, individual-level data on health care use, inpatient and outpatient diagnoses, diagnostic tests and procedures, outpatient laboratory results (~45% of patients in the CDM database), and pharmacy dispensing of drugs. The study was approved by the Mass General Brigham Institutional Review Board, which granted a waiver of informed consent because only deidentified claims data were used. Signed data license agreements were in place for all data sources.

Study Design and Study Population

We constructed 2 active-comparator, new-user cohorts of patients who newly initiated warfarin versus apixaban (cohort 1) and rivaroxaban versus apixaban (cohort 2) between January 1, 2013, and the end of available data (March 31, 2022, for CDM and December 31, 2020, for Medicare).[17] The longitudinal design overview is shown in Fig S1. Individuals were required to not have used any oral anticoagulant (ie, warfarin, apixaban, rivaroxaban, dabigatran, edoxaban) in the previous 365 days, be at least 18 years old (≥65 years for Medicare), have at least 12 months of continuous enrollment preceding the cohort entry date, and have a diagnosis of AF or flutter. In addition, eligible individuals were required to have 2 diagnosis codes for CKD stage 4/5. In an internal validation study, the positive predictive value of 2 diagnosis codes of CKD stage 4/5 for eGFR <30 mL/min/1.73 m^2 was 76.1%. Details about the validation study are provided in Item S1 and Fig S2. We excluded individuals with joint replacement, pulmonary embolism, deep vein thrombosis, or valvular heart disease in the preceding 1 year or major bleeding in the 30 days before cohort entry date. Individuals with a recent stroke were not excluded from the main analysis but were excluded in a sensitivity analysis.

Drug Exposure and Follow-up

The study exposure was initiation of warfarin, rivaroxaban, or apixaban. We used apixaban as the reference group because it is currently the preferred anticoagulant in the United States.[18] We did not investigate dabigatran or edoxaban because they are not recommended in patients with low creatinine clearance[19] and because few individuals with advanced CKD used these medications in our study population. Follow-up began the day after cohort entry and continued with an as-treated approach until treatment discontinuation or a switch to a drug in the comparator class, outcome occurrence, death, end of continuous health plan enrollment, or end of available data, whichever occurred first. Discontinuation was defined by an absence of prescription refills for the index exposure in the 30 days after the most recent prescription had ended.

Study Outcomes

The primary safety outcome was time to first hospitalization with major bleeding (including gastrointestinal, intracranial, and extracranial bleeding), and the primary effectiveness outcome was time to first ischemic stroke. Secondary outcomes included all-cause mortality, time to first major gastrointestinal bleeding event, and time to first intracranial bleeding event. Outcomes were defined using previously validated algorithms, with positive predictive values of 85%-90% for ischemic stroke[20,21] and 86%-96% for bleeding[22] (definitions provided in Supplementary File 2). Death as a clinical end point was only assessed in the Medicare population because death ascertainment in the CDM database is based only on discharge status and therefore considered incomplete.

Baseline Covariates

We assessed a total of 80 baseline characteristics using information during the 365 days before or on the cohort entry date. These included demographic data, comorbid conditions, medication use, measures of health care use, geographic region, calendar year, and the following risk scores: CHA_2DS_2-VASc (Congestive heart failure [or left ventricular systolic dysfunction], Hypertension [blood pressure consistently >140/90 mm Hg or treated with medication], Age [≥75 y], Diabetes mellitus, Prior Stroke or transient ischemic attack or thromboembolism, Vascular disease [eg, peripheral artery disease, myocardial infarction, aortic plaque], Age 65-74 y, Sex category [ie, female sex])[23,24] for ischemic stroke risk and modified HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke,

Bleeding history or predisposition, Labile international normalized ratio, Elderly [>65 y], Drugs/alcohol concomitantly)[25] for bleeding risk. The burden of comorbidity was quantified using a combined comorbidity score.[26] Frailty was measured using a claims-based frailty index that has been validated against clinical measures of frailty.[27-29] We also adjusted for a prediction score for anticoagulation control quality (predicted time in therapeutic range).[30] Definitions of each covariate and the variables included in the risk scores are provided in Supplementary File 2.

Statistical Analysis

We used 1:1 propensity score (PS) matching using the nearest-neighbor method with a caliper of 0.01 of the PS to adjust for confounding.[31] We estimated the probability of receiving warfarin versus apixaban (cohort 1) or rivaroxaban versus apixaban (cohort 2) as a function of 80 baseline covariates using multivariable logistic regression. Eligible patients initiating apixaban could be included in both cohorts. All covariates listed in Table S1 were included in the PS model. PS model development and PS matching were performed separately for each database. We assessed covariate balance before and after matching using standardized mean differences. For all outcomes, we calculated PS-matched numbers of events, incidence rates (IRs), adjusted IR differences (IRDs), and adjusted hazard ratios (HRs). The IRDs and HRs with their 95% confidence intervals (CIs) were estimated separately within each database. We pooled database-specific IRs and IRDs based on pooled event number and person-years and used the standard error formulas to calculate their 95% CIs. The database-specific HRs were pooled using random-effects meta-analysis. HRs were estimated using Cox proportional hazards regression for all-cause mortality and cause-specific hazard models for other outcomes in the presence of competing events, and IRDs were estimated using generalized linear regression with identity link function and normal error distribution. Furthermore, we estimated absolute risks for ischemic stroke and major bleeding using cumulative incidence functions, which do not overestimate absolute risks in the presence of the competing risk of death. All analyses were performed using the Aetion Evidence Platform (https://www.aetion.com) and R version 4.1.3 (R Foundation for Statistical Computing).

Additional and Sensitivity Analyses

We performed the following analyses to test the robustness of our findings. First, to assess potential residual confounding, we replicated our analyses in a positive control cohort of patients with CKD stage 3, among whom we would expect a higher risk of major bleeding with warfarin versus apixaban, consistent with previous findings from the ARISTOTLE trial.[32] Furthermore, no differences were observed for ischemic stroke or all-cause mortality in that trial among participants with an eGFR ≤50 mL/min.[32] Second, to account for potential residual confounding, we adjusted for a larger confounder set by applying a high-dimensional PS (HDPS).[33] The HDPS algorithm evaluates thousands of diagnoses, procedures, and medication claims codes and prioritizes each variable based on its potential for bias according to the Bross formula by assessing the variable's prevalence and univariate association with the treatment and outcome. The automatically selected variables based on the HDPS algorithm were then added to the 80 prespecified confounders in a PS model. We then performed 1:1 PS matching again. Third, we defined discontinuation using gaps of 15 and 45 days between prescription refills rather than the 30 days used in our main analysis.[34] Fourth, to assess potential informative censoring, we performed a 183-day intention-to-treat follow-up, whereby patients were analyzed according to their initial exposure group regardless of treatment discontinuation or switch. Fifth, we investigated the influence of dose and compared warfarin versus apixaban 5 mg and warfarin versus apixaban 2.5 mg.[35] Sixth, we excluded individuals who had experienced a stroke in the 60 days before drug initiation to avoid misclassification of prior stroke as an incident event during follow-up. Finally, we excluded individuals who were admitted for short-term skilled nursing facility care to avoid misclassification of direct oral anticoagulant exposure because Medicare Part D does not cover medications during short-term skilled nursing facility stays.

Results

Baseline Characteristics

We constructed 2 new-user 1:1 PS-matched cohorts of persons with CKD stage 4/5 and AF who initiated warfarin versus apixaban (n = 12,488) and rivaroxaban versus apixaban (n = 5,720; Fig S3). Before matching, most baseline characteristics were comparable for warfarin versus apixaban initiators. For instance, they had similar mean ages (78.8 vs 78.7 years), CHA_2DS_2-VASc scores (5.4 vs 5.4), HAS-BLED scores (2.9 vs 2.9), and comorbidity scores (7.1 vs 7.1; Table S1). In general, rivaroxaban initiators also had similar characteristics as apixaban initiators before matching, with similar mean ages (78.5 vs 78.4 years), CHA_2DS_2-VASc scores (5.3 vs 5.3), HAS-BLED scores (2.9 vs 2.9), and comorbidity scores (6.9 vs 6.9; Table S2). All baseline characteristics were well balanced in both cohorts after 1:1 PS matching, with all standardized mean differences lower than 0.10 (Table 1; Tables S1 and S2). PS distributions before and after matching are shown in Fig S4. After matching, 67% of apixaban initiators used a dose of 2.5 mg in the warfarin versus apixaban cohort. In addition, 81% used rivaroxaban doses ≤15 mg and 65% used apixaban 2.5 mg in the rivaroxaban versus apixaban cohort (Table S3).

Table 1. Selected Baseline Characteristics of Patients With Atrial Fibrillation and Nondialysis CKD Stage 4/5 Initiating Warfarin Versus Apixaban or Rivaroxaban Versus Apixaban After 1:1 Propensity-Score Matching

Characteristic	Warfarin vs Apixaban Cohort		Rivaroxaban vs Apixaban Cohort	
	Apixaban (n = 6,244)	Warfarin (n = 6,244)	Rivaroxaban (n = 2,860)	Apixaban (n = 2,860)
Sociodemographic				
Age, y	78.8 ± 7.7	78.7 ± 7.5	78.4 ± 7.7	78.5 ± 7.6
Sex				
Male	3,148 (50.4%)	3,176 (50.9%)	1,366 (47.8%)	1,371 (47.9%)
Female	3,096 (49.6%)	3,068 (49.1%)	1,494 (52.2%)	1,489 (52.1%)
Race				
White	5,209 (83.4%)	5,199 (83.3%)	2,343 (81.9%)	2,337 (81.7%)
Black	577 (9.2%)	592 (9.5%)	270 (9.4%)	288 (10.1%)
Other/missing/unknown	365 (5.9%)	369 (5.9%)	231 (8.1%)	225 (7.9%)
Risk scores				
CHA_2DS_2-VASc score	5.38 ± 1.50	5.38 ± 1.50	5.29 ± 1.55	5.32 ± 1.51
HAS-BLED score	2.91 ± 0.68	2.91 ± 0.65	2.85 ± 0.67	2.85 ± 0.67
CCI score	7.13 ± 2.66	7.18 ± 2.62	7.01 ± 2.67	7.05 ± 2.78
CFI score	0.26 ± 0.08	0.26 ± 0.08	0.26 ± 0.08	0.26 ± 0.08
Predicted anticoagulation control quality	0.51 ± 0.08	0.51 ± 0.08	0.50 ± 0.08	0.51 ± 0.09
Cardiovascular conditions				
Acute myocardial infarction	887 (14.2%)	891 (14.3%)	279 (9.8%)	290 (10.1%)
Cardiac ablation	44 (0.7%)	45 (0.7%)	12 (0.4%)	15 (0.5%)
Cardioversion	311 (5.0%)	322 (5.2%)	179 (6.3%)	170 (5.9%)
Cerebrovascular disease	2,176 (34.8%)	2,204 (35.3%)	960 (33.6%)	1,004 (35.1%)
Congestive heart failure (inpatient)	3,125 (50.0%)	3,161 (50.6%)	1,231 (43.0%)	1,234 (43.1%)
Congestive heart failure (outpatient)	3,943 (63.1%)	3,991 (63.9%)	1,707 (59.7%)	1,717 (60.0%)
Coronary revascularization	328 (5.3%)	349 (5.6%)	112 (3.9%)	113 (4.0%)
Hypertension	6,114 (97.9%)	6,115 (97.9%)	2,802 (98.0%)	2,801 (97.9%)
Ischemic heart disease	4,137 (66.3%)	4,138 (66.3%)	1,769 (61.9%)	1,802 (63.0%)
PVD or PVD surgery	1,702 (27.3%)	1,689 (27.0%)	770 (26.9%)	771 (27.0%)
Stroke (inpatient)	778 (12.5%)	782 (12.5%)	278 (9.7%)	285 (10.0%)
Stroke (outpatient)	995 (15.9%)	991 (15.9%)	444 (15.5%)	484 (16.9%)
Syncope	867 (13.9%)	828 (13.3%)	410 (14.3%)	394 (13.8%)
Noncardiovascular conditions				
Acute kidney injury	3,762 (60.2%)	3,851 (61.7%)	1,572 (55.0%)	1,598 (55.9%)
Alcohol abuse or dependence	124 (2.0%)	119 (1.9%)	47 (1.6%)	51 (1.8%)
Anemia	3,963 (63.5%)	4,034 (64.6%)	1,755 (61.4%)	1,741 (60.9%)
CKD stage 3	2,396 (38.4%)	2,365 (37.9%)	1,175 (41.1%)	1,201 (42.0%)
COPD	2,159 (34.6%)	2,179 (34.9%)	1,053 (36.8%)	1,059 (37.0%)
Dementia	669 (10.7%)	679 (10.9%)	351 (12.3%)	368 (12.9%)
Diabetes	4,053 (64.9%)	4,062 (65.1%)	1,787 (62.5%)	1,795 (62.8%)
Endoscopy	322 (5.2%)	305 (4.9%)	134 (4.7%)	125 (4.4%)
Falls	613 (9.8%)	605 (9.7%)	309 (10.8%)	305 (10.7%)
Fractures	714 (11.4%)	697 (11.2%)	322 (11.3%)	347 (12.1%)
GI bleeding (inpatient)	672 (10.8%)	700 (11.2%)	289 (10.1%)	293 (10.2%)
GI bleeding (outpatient)	1,036 (16.6%)	992 (15.9%)	489 (17.1%)	486 (17.0%)
Liver disease	661 (10.6%)	660 (10.6%)	276 (9.7%)	296 (10.3%)
Malignancy	1,347 (21.6%)	1,308 (20.9%)	582 (20.3%)	563 (19.7%)
Obesity	2,010 (32.2%)	2,037 (32.6%)	1,046 (36.6%)	1,032 (36.1%)
Peptic ulcer	278 (4.5%)	275 (4.4%)	139 (4.9%)	133 (4.7%)
Smoking	2,830 (45.3%)	2,897 (46.4%)	1,284 (44.9%)	1,263 (44.2%)
Cardiovascular medications				
ACE inhibitors	1,546 (24.8%)	1,562 (25.0%)	730 (25.5%)	729 (25.5%)
Angiotensin II receptor blockers	677 (10.8%)	699 (11.2%)	364 (12.7%)	391 (13.7%)
Antiarrhythmic agents	1,314 (21.0%)	1,320 (21.1%)	688 (24.1%)	688 (24.1%)

(Continued)

Table 1 (Cont'd). Selected Baseline Characteristics of Patients With Atrial Fibrillation and Nondialysis CKD Stage 4/5 Initiating Warfarin Versus Apixaban or Rivaroxaban Versus Apixaban After 1:1 Propensity-Score Matching

	Warfarin vs Apixaban Cohort		Rivaroxaban vs Apixaban Cohort	
Characteristic	Apixaban (n = 6,244)	Warfarin (n = 6,244)	Rivaroxaban (n = 2,860)	Apixaban (n = 2,860)
Anticoagulants, injectable	85 (1.4%)	89 (1.4%)	33 (1.2%)	29 (1.0%)
Antiplatelet agent	1,520 (24.3%)	1,543 (24.7%)	658 (23.0%)	699 (24.4%)
β-Blockers	4,973 (79.6%)	4,978 (79.7%)	2,140 (74.8%)	2,187 (76.5%)
Calcium channel blockers	346 (5.5%)	346 (5.5%)	120 (4.2%)	133 (4.7%)
Diuretics	5,090 (81.5%)	5,087 (81.5%)	2,291 (80.1%)	2,311 (80.8%)
Fibrates	522 (8.4%)	524 (8.4%)	277 (9.7%)	272 (9.5%)
Statins	4,718 (75.6%)	4,752 (76.1%)	2,127 (74.4%)	2,145 (75.0%)
Nitrates	1,761 (28.2%)	1,770 (28.3%)	733 (25.6%)	723 (25.3%)
Other medications				
Anticonvulsants	1,480 (23.7%)	1,483 (23.8%)	793 (27.7%)	794 (27.8%)
Antidepressants–SSRI/SNRI	1,418 (22.7%)	1,435 (23.0%)	733 (25.6%)	722 (25.2%)
Antidepressants–tricyclics	203 (3.3%)	207 (3.3%)	114 (4.0%)	107 (3.7%)
Antidepressants–other	674 (10.8%)	711 (11.4%)	347 (12.1%)	364 (12.7%)
Antipsychotic agents	201 (3.2%)	227 (3.6%)	140 (4.9%)	134 (4.7%)
Anxiolytics–benzodiazepines	1,019 (16.3%)	1,020 (16.3%)	576 (20.1%)	574 (20.1%)
Anxiolytics (except benzodiazepine)	81 (1.3%)	87 (1.4%)	49 (1.7%)	57 (2.0%)
Bronchodilators	1,533 (24.6%)	1,557 (24.9%)	835 (29.2%)	788 (27.6%)
Corticosteroids, inhaled	1,444 (23.1%)	1,453 (23.3%)	772 (27.0%)	754 (26.4%)
Corticosteroids, oral	2,358 (37.8%)	2,382 (38.1%)	1,159 (40.5%)	1,162 (40.6%)
Dementia drugs	285 (4.6%)	279 (4.5%)	153 (5.3%)	162 (5.7%)
Diabetes agents–insulin	1,659 (26.6%)	1,660 (26.6%)	755 (26.4%)	750 (26.2%)
Diabetes agents–metformin	425 (6.8%)	431 (6.9%)	211 (7.4%)	226 (7.9%)
Diabetes agents–other	761 (12.2%)	768 (12.3%)	440 (15.4%)	437 (15.3%)
Diabetes agents–sulfonylurea	1,202 (19.3%)	1,173 (18.8%)	542 (19.0%)	534 (18.7%)
Estrogen	97 (1.6%)	96 (1.5%)	42 (1.5%)	58 (2.0%)
GI–H2 blockers	722 (11.6%)	721 (11.5%)	399 (14.0%)	378 (13.2%)
GI–proton pump inhibitors	2,543 (40.7%)	2,543 (40.7%)	1,254 (43.8%)	1,217 (42.6%)
GI–sucralfate	178 (2.9%)	187 (3.0%)	97 (3.4%)	95 (3.3%)
Hypnotics	538 (8.6%)	559 (9.0%)	273 (9.5%)	302 (10.6%)
NSAIDs	394 (6.3%)	411 (6.6%)	266 (9.3%)	249 (8.7%)
Opioids	2,859 (45.8%)	2,847 (45.6%)	1,417 (49.5%)	1,402 (49.0%)
Parkinsonism drugs	284 (4.5%)	287 (4.6%)	172 (6.0%)	180 (6.3%)
Thyroid hormone replacement	1,775 (28.4%)	1,782 (28.5%)	830 (29.0%)	858 (30.0%)
Healthcare use				
Emergency department visits	3,354 (53.7%)	3,318 (53.1%)	1,577 (55.1%)	1,598 (55.9%)
Home Health Day	1,749 (28.0%)	1,774 (28.4%)	819 (28.6%)	809 (28.3%)
Home oxygen use	470 (7.5%)	489 (7.8%)	275 (9.6%)	257 (9.0%)
Hospitalizations	4,662 (74.7%)	4,740 (75.9%)	1,990 (69.6%)	1,986 (69.4%)
Geographic region[a]				
Northeast	1,209 (19.4%)	1,227 (19.7%)	426 (14.9%)	400 (14.0%)
Midwest	1,770 (28.3%)	1,733 (27.8%)	690 (24.1%)	697 (24.4%)
South	2,176 (34.8%)	2,175 (34.8%)	1,139 (39.8%)	1,152 (40.3%)
West	1,089 (17.4%)	1,109 (17.8%)	605 (21.2%)	611 (21.4%)

Data presented as mean ± standard deviation where applicable. Abbreviations: ACE, angiotensin-converting enzyme; CCI, combined comorbidity; CFI, claims-based frailty index; CHA_2DS_2-VASc, Congestive Heart failure (or left ventricular systolic dysfunction), Hypertension (blood pressure consistently >140/90 mm Hg or treated with medication), Age (≥75 y), Diabetes mellitus, Prior Stroke or transient ischemic attack or thromboembolism, Vascular disease (eg, peripheral artery disease, myocardial infarction, aortic plaque), Age 65-74 y, Sex category (ie, female sex); CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 y), Drugs/alcohol concomitantly; NSAID, nonsteroidal anti-inflammatory drug; PVD, peripheral vascular disease; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a]Northeast (Connecticut, Massachusetts, Maine, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont); South (Alabama; Arkansas; Delaware; Florida; Georgia; Kentucky; Louisiana; Maryland; Mississippi; North Carolina; Oklahoma; South Carolina; Tennessee; Texas; Virginia; Washington, DC; West Virginia); Midwest (Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, Wisconsin); West (Alaska, Arizona, California, Colorado, Hawaii, Idaho, Montana, New Mexico, Nevada, Oregon, Utah, Washington, Wyoming).

Table 2. Comparative Safety and Effectiveness of Warfarin Versus Apixaban in Patients With Atrial Fibrillation and Nondialysis CKD Stage 4/5 Before and After 1:1 Propensity-Score Matching Under As-Treated Follow-up

	Before 1:1 Propensity-Score Matching		After 1:1 Propensity-Score Matching	
	Warfarin (n = 9,717)	Apixaban (n = 14,699)	Warfarin (n = 6,244)	Apixaban (n = 6,244)
Major bleeding				
Total events	659	564	428	273
Follow-up, PYs	6,771	10,818	4,166	5,386
Incidence rate per 1,000 PYs	97.3 (90.0 to 105.1)	52.1 (47.9 to 56.6)	102.7 (93.2 to 113.0)	50.7 (44.9 to 57.1)
Rate difference per 1,000 PYs	45.2 (36.6 to 53.8)	Reference	52.0 (40.6 to 63.5)	Reference
HR	1.79 (1.60 to 2.00)	Reference	1.85 (1.59 to 2.15)	Reference
Ischemic stroke				
Total events	111	170	75	76
Follow-up, PYs	6,901	10,902	4,247	5,426
Incidence rate per 1,000 PYs	16.1 (13.2 to 19.4)	15.6 (13.3 to 18.1)	17.7 (14.0 to 22.1)	14.0 (11.0 to 17.5)
Rate difference per 1,000 PYs	0.5 (−3.3 to 4.3)	Reference	3.7 (−1.4 to 8.7)	Reference
HR	1.04 (0.81 to 1.32)	Reference	1.14 (0.83 to 1.57)	Reference
All-cause mortality				
Total events	1,384	1,995	880	975
Follow-up, PYs	5,732	8,100	3,546	4,542
Incidence rate per 1,000 PYs	241.5 (228.9 to 254.5)	246.3 (235.6 to 257.4)	248.2 (232.0 to 265.1)	214.7 (201.4 to 228.6)
Rate difference per 1,000 PYs	−4.8 (−21.5 to 11.9)	Reference	33.5 (12.3 to 54.7)	Reference
HR	0.96 (0.89 to 1.02)	Reference	1.08 (0.98 to 1.18)	Reference
Major gastrointestinal bleeding				
Total events	401	354	278	175
Follow-up, PYs	6,839	10,869	4,202	5,412
Incidence rate per 1,000 PYs	58.6 (53.0 to 64.7)	32.6 (29.3 to 36.2)	66.2 (58.6 to 74.4)	32.3 (27.7 to 37.5)
Rate difference per 1,000 PYs	26.1 (19.4 to 32.7)	Reference	33.8 (24.7 to 43.0)	Reference
HR	1.71 (1.48 to 1.98)	Reference	1.86 (1.53 to 2.25)	Reference
Intracranial bleeding				
Total events	120	102	74	49
Follow-up, PYs	6,926	10,948	4,265	5,451
Incidence rate per 1,000 PYs	17.3 (14.4 to 20.7)	9.3 (7.6 to 11.3)	17.4 (13.6 to 21.8)	9.00 (6.7 to 11.9)
Rate difference per 1,000 PYs	8.0 (4.4 to 11.6)	Reference	8.4 (3.7 to 13.1)	Reference
HR	1.94 (1.43 to 2.63)	Reference	2.15 (1.42 to 3.25)	Reference

Values in parentheses are 95% confidence intervals. Mortality estimates were based on Medicare only. We pooled database-specific IR and IR differences based on pooled event number and PYs and used the standard error formulas. The database-specific HRs were pooled using random effects meta-analysis. Abbreviations: CKD, chronic kidney disease; HR, hazard ratio; IR, incidence rate; PY, person-year.

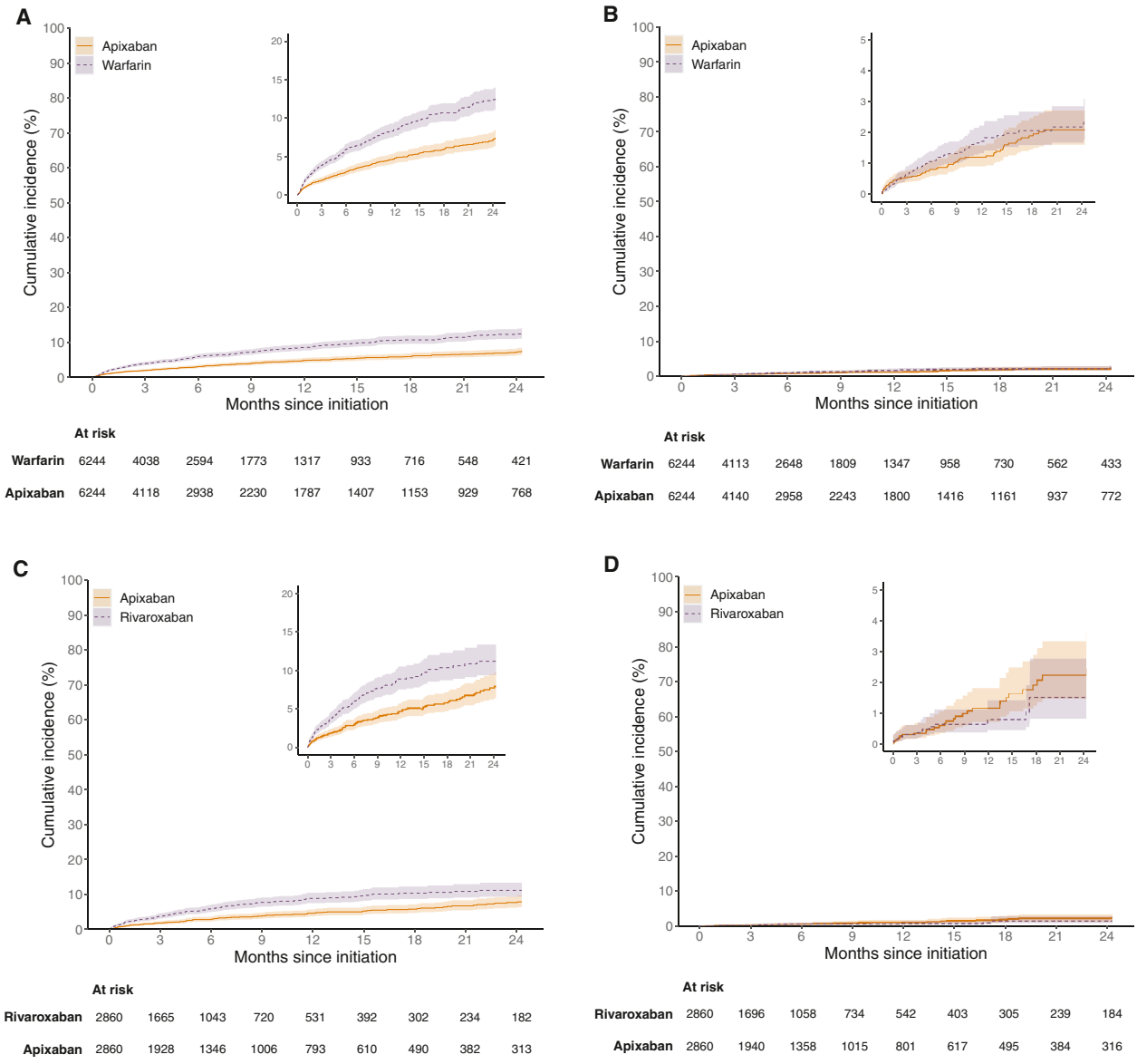

Figure 1. Cumulative incidence curves for major bleeding (A) and ischemic stroke (B) for warfarin versus apixaban and for major bleeding (C) and ischemic stroke (D) for rivaroxaban versus apixaban.

Clinical Outcomes Associated With Warfarin Versus Apixaban

Mean follow-up was 276.6 (standard deviation, 332.4) days in the overall 1:1 PS-matched cohort population (Table S4). In the PS-matched cohort with CKD stage 4/5, the IR for major bleeding was 102.7 (95% CI, 93.2-113.0) per 1,000 person-years for warfarin initiators, compared with 50.7 (95% CI, 44.9-57.1) for apixaban initiators. The adjusted HR for warfarin versus apixaban was 1.85 (95% CI, 1.59-2.15), and the IRD was 52.0 (95% CI, 40.6-63.5) per 1,000 person-years. Warfarin initiation was also associated with higher rates of major gastrointestinal and intracranial bleeding, with HRs of 1.86 (95% CI, 1.53-2.25) and 2.15 (95% CI, 1.42-3.25), respectively. For ischemic stroke, IRs in the PS-matched cohort were 17.7 (95% CI, 14.0-22.1) per 1,000 person-years for warfarin and 14.0 (95% CI, 11.0-17.5) for apixaban, corresponding to an HR of 1.14 (95% CI, 0.83-1.57) and an IRD of 3.7 (95% CI, −1.4 to 8.7) per 1,000 person-years. IRs for all-cause mortality (only in the Medicare dataset) were 248.2 (95% CI, 232.0-265.1) for warfarin and 214.7 (95% CI, 201.4-228.6) for apixaban, corresponding to an HR of 1.08 (95% CI, 0.98-1.18) and an IRD of 33.5 (95% CI, 12.3-54.7) per 1,000 person-years (Table 2). Cumulative incidence curves in the matched cohort are shown in Fig 1A and B, showing that the lower risk of major bleeding occurred early during follow-up. The absolute risks at 2 years of follow-up for major bleeding were 12.3% among warfarin initiators and 7.2% among apixaban initiators, corresponding to an absolute risk

Table 3. Comparative Effectiveness and Safety of Rivaroxaban Versus Apixaban in Patients With Atrial Fibrillation and Nondialysis CKD Stage 4/5 Before and After 1:1 Propensity Score Matching Under As-Treated Follow-up

	Before 1:1 Propensity-Score Matching		After 1:1 Propensity-Score Matching	
	Rivaroxaban (n = 3,048)	Apixaban (n = 14,745)	Rivaroxaban (n = 2,860)	Apixaban (n = 2,860)
Major bleeding				
Total events	184	566	171	124
Follow-up, PY	1,918	10,846	1,779	2,348
Incidence rate per 1,000 PYs	95.9 (82.6 to 110.8)	52.2 (48.0 to 56.7)	96.1 (82.3 to 111.7)	52.8 (43.9 to 63.0)
Rate difference per 1,000 PYs	43.7 (29.2 to 58.3)	Reference	43.3 (26.2 to 60.5)	Reference
HR	1.74 (1.47 to 2.05)	Reference	1.69 (1.33 to 2.15)	Reference
Ischemic stroke				
Total events	19	170	19	34
Follow-up, PY	1,953	10,928	1,813	2,372
Incidence rate per 1,000 PYs	9.7 (5.9 to 15.2)	15.6 (13.3 to 18.1)	10.5 (6.3 to 16.4)	14.3 (9.9 to 20.0)
Rate difference per 1,000 PYs	−5.8 (−10.8 to −0.9)	Reference	−3.9 (−10.6 to 2.9)	Reference
HR	0.62 (0.39 to 0.99)	Reference	0.71 (0.40 to 1.24)	Reference
All-cause mortality				
Total events	310	2,001	284	385
Follow-up, PY	1,506	8,115	1392	1,901
Incidence rate per 1,000 PYs	205.8 (183.6 to 230.1)	246.6 (235.9 to 257.6)	204.0 (181.0 to 229.2)	202.5 (182.8 to 223.8)
Rate difference per 1,000 PYs	−40.7 (−66.1 to −15.4)	Reference	1.5 (−29.7 to 32.7)	Reference
HR	0.79 (0.70 to 0.90)	Reference	0.94 (0.81 to 1.10)	Reference
Major gastrointestinal bleeding				
Total events	136	358	130	89
Follow-up, PYs	1,924	10,895	1,784	2,360
Incidence rate per 1,000 PYs	70.7 (59.3 to 83.6)	32.9 (29.5 to 36.5)	72.9 (60.9 to 86.5)	37.7 (30.3 to 46.4)
Rate difference per 1,000 PYs	37.8 (25.5, 50.2)	Reference	35.2 (20.4, 49.9)	Reference
HR	2.02 (1.66 to 2.46)	Reference	1.77 (1.35 to 2.32)	Reference
Intracranial bleeding				
Total events	23	101	20	15
ollow-up, PYs	1,955	10,976	1,814	2,384
Incidence rate per 1,000 PYs	11.8 (7.5 to 17.7)	9.2 (7.5 to 11.2)	11.0 (6.7 to 17.0)	6.3 (3.5 to 10.4)
Rate difference per 1,000 PYs	2.6 (−2.6 to 7.7)	Reference	4.7 (−1.1 to 10.5)	Reference
HR	1.00 (0.31 to 3.21)	Reference	1.33 (0.30 to 5.94)	Reference

Values in parentheses are 95% confidence intervals. Mortality estimates were based on Medicare only. We pooled database-specific IR and IR differences based on pooled event number and PYs and used the standard error formulas. The database-specific HRs were pooled using random effects meta-analysis. Abbreviations: CKD, chronic kidney disease; HR, hazard ratio; IR, incidence rate; PY, person-year.

difference of 5.1% (95% CI, 3.4%-6.9%; Table S5). Furthermore, 2-year absolute risks for ischemic stroke were 2.2% for warfarin and 2.1% for apixaban, with an absolute risk difference of 0.1% (95% CI, −0.7% to 0.9%).

Clinical Outcomes Associated With Rivaroxaban Versus Apixaban

Mean follow-up was 266.8 (standard deviation, 336.7) days in the 1:1 PS-matched cohort population of rivaroxaban versus apixaban initiators (Table S4). Rivaroxaban initiation was associated with a higher rate of major bleeding compared with apixaban, with respective IRs of 96.1 (95% CI, 82.3-111.7) and 52.8 (95% CI, 43.9-63.0) per 1,000 person-years. The HR for major bleeding was 1.69 (95% CI, 1.33-2.15), and the IRD was 43.3 (95% CI, 26.2-60.5) per 1,000 person-years. The higher rate of major bleeding was driven by major gastrointestinal bleeding (HR, 1.77; 95% CI, 1.35-2.32) rather than intracranial bleeding (HR, 1.33; 95% CI, 0.30-5.94). Few ischemic stroke events occurred during follow-up among rivaroxaban and apixaban initiators (19 vs 34), with an HR of 0.71 (95% CI, 0.40-1.24) and an IRD of −3.9 (95% CI, −10.6 to 2.9) per 1,000 person-years. Respective IRs for all-cause mortality (only in the Medicare dataset) were 204.0 (95% CI, 181.0-229.2) and 202.5 (95% CI, 182.8-223.8), with an adjusted HR of 0.94 (95% CI, 0.81-1.10) and an IRD of 1.5 (95% CI, −29.7 to 32.7) per 1,000 person-years (Table 3). Cumulative incidence curves in the matched cohort are shown in Fig 1C and D. At 2 years of follow-up, the absolute risk for major bleeding was 11.2% (95% CI, 9.3%-13.4%) for rivaroxaban, compared with 7.7% (95% CI, 6.2%-9.5%) for apixaban, with an absolute risk difference of 3.5% (95% CI, 0.9%-6.1%). The respective 2-year absolute risks for ischemic stroke were 1.5% (95% CI, 0.8%-2.8%) and 2.2% (95% CI, 1.5%-3.3%), corresponding to an absolute risk difference of −0.7% (95% CI, −2.0% to 0.6%).

Additional and Sensitivity Analyses

For our positive control cohort of patients with CKD stage 3, after 1:1 PS matching, we included 20,623 PS-matched warfarin and apixaban initiators and 19,569 PS-matched rivaroxaban and apixaban initiators (Tables S6 and S7). Most baseline characteristics were balanced before PS matching. For warfarin versus apixaban, the HRs were 1.67 (95% CI, 1.50-1.84) for major bleeding, 1.18 (95% CI, 0.98-1.42) for ischemic stroke, and 1.13 (95% CI, 1.06-1.20) for all-cause mortality (Table S8). For rivaroxaban versus apixaban, the HRs were 1.64 (95% CI, 1.37-1.96) for major bleeding, 1.25 (95% CI, 0.95-1.65) for ischemic stroke, and 1.00 (95% CI, 0.94-1.07) for all-cause mortality (Table S9). For our primary study cohort (non–dialysis-dependent CKD stage 4/5), the findings were generally consistent when adjusting for an HDPS, when using different gaps (15 and 45 days) to define treatment discontinuation in as-treated analyses, when implementing a 183-day intention-to-treat follow-up, when investigating renal and nonrenal doses, when excluding patients with a recent stroke or those admitted to a skilled nursing facility, when using PS overlap weighting instead of matching, and when using a Fine and Gray model (Tables S10 and S11).

Discussion

In this nationwide US cohort study of individuals with CKD stage 4/5 initiating warfarin or direct oral anticoagulant treatment, we found that rivaroxaban and warfarin use were associated with higher rates of major bleeding compared with apixaban use. Furthermore, we found no statistically significant differences in the rates of ischemic stroke, even though the CIs were wide as a result of the small number of events. All-cause mortality was generally similar across different oral anticoagulant user groups. These observations were consistent in a number of sensitivity analyses.

Despite their high risk for adverse outcomes, there is surprisingly little evidence to guide anticoagulant treatment in patients with advanced CKD. The large randomized trials that compared direct oral anticoagulants versus warfarin in patients with AF systematically excluded persons with a creatinine clearance <25 mL/min. Our results among patients with CKD stage 4/5 align with a small subgroup analysis of the ARISTOTLE trial.[11] In that analysis, apixaban caused less major bleeding than warfarin (HR, 0.34; 95% CI, 0.14-0.80) among 269 patients with a creatinine clearance between 25 and 30 mL/min.[11] One observational study using Australian and Canadian data compared 1,827 PS-matched direct oral anticoagulant initiators versus warfarin initiators and found no difference in the rates of ischemic stroke or transient ischemic attack (HR, 1.08; 95% CI, 0.69-1.70) and lower rates of major bleeding (HR, 0.71; 95% CI, 0.52-0.99) and all-cause mortality (HR, 0.84; 95% CI, 0.73-0.95) among those with an eGFR <30 mL/min/1.73 m^2.[36] However, no stratification by individual anticoagulants was performed. A subsequent analysis using the same databases specifically compared rivaroxaban versus warfarin and found a lower rate of major bleeding with rivaroxaban (HR, 0.63; 95% CI, 0.37-1.09), albeit with imprecise estimates, and a lower rate of all-cause mortality (HR, 0.76; 95% CI, 0.59-0.97).[37] Furthermore, results for ischemic stroke or transient ischemic attack (HR, 0.99; 95% CI, 0.45-2.17) were inconclusive as a result of wide CIs.[37] However, these results are not directly comparable with ours because we compared warfarin with apixaban. Other observational studies reported results in patients with CKD but did not specifically focus on patients with advanced CKD.[38]

None of the randomized trials have performed a head-to-head comparison between different direct oral anticoagulants, let alone in patients with advanced CKD. A number of observational studies have compared different direct oral anticoagulants, but these did not focus on

patients with CKD.[39-41] A recent observational study found that the risk of gastrointestinal bleeding was lower with apixaban than with rivaroxaban or dabigatran in the subgroup of patients with CKD, with similar risks observed for ischemic stroke or systemic embolism, intracranial hemorrhage, and all-cause mortality. However, no results stratified by specific CKD stage, including stage 4/5, were reported.[42]

Our findings suggest that apixaban should be the preferred anticoagulant in patients with CKD stage 4/5 who are currently receiving warfarin or rivaroxaban because of its better safety profile and lower associated rate of major bleeding. We did not find major differences in the rates of ischemic stroke or all-cause mortality, but few ischemic stroke events occurred and the CIs were wide. Another important finding to highlight is the high incidence of adverse outcomes observed in this vulnerable population compared with general-population cohorts. For instance, the IR of major bleeding among rivaroxaban initiators in our study was more than 4 times that in previously published observational studies (96.1 vs 21.5 events per 1,000 person-years).[39] A better safety profile of apixaban versus warfarin has also been observed in the general population, which may be due to a lower propensity for drug and food interactions as well as the ease of use of direct oral anticoagulants, which can be administered in fixed doses and do not require routine coagulation monitoring. Furthermore, individuals with an eGFR <30 mL/min/1.73 m^2 who are undergoing dialysis experience greater fluctuations in International Normalized Ratio (an indicator of coagulation) and spend less time in the target range.[43,44] A randomized cross-over trial of 14 healthy participants compared apixaban 2.5 mg twice daily versus rivaroxaban 10 mg once daily and found that apixaban showed lower peak anti–factor Xa levels, which may explain the lower risk of bleeding observed for apixaban.[45] Finally, apixaban has a lower renal clearance than rivaroxaban (27% vs 35%).[46]

Strengths of our study include the use of large, nationally representative cohorts and an active-comparator, new-user design, which mitigates common biases such as immortal time bias and prevalent user bias[47]; adjustment for 80 confounders, including validated frailty index and stroke and bleeding risk; and numerous sensitivity analyses with consistent findings. Our study also has several limitations. First, we cannot rule out potential residual confounding. For instance, we did not have data on over-the-counter aspirin use. However, the warfarin and apixaban initiators had very similar baseline characteristics even before PS matching, indicating no major differences in measured characteristics. Also, similar results were obtained when using an HDPS. Second, we were unable to study dabigatran or edoxaban because few persons with advanced CKD in our data set initiated the use of these drugs. However, because of the low use of these agents in the United States in recent years,[18] this limitation should not reduce the impact of our findings on current practice. Third, even though we adjusted for predicted anticoagulation control quality score, we had no data on the quality of warfarin control. Previous observational studies have shown lower anticoagulation control quality during warfarin treatment among persons with advanced CKD compared with those with higher kidney function.[48] This may partly mediate the higher risk of bleeding with warfarin versus apixaban observed in our study. Nevertheless, the lack of necessity for frequent International Normalized Ratio monitoring is considered one of the advantages of direct oral anticoagulants.[46] Fourth, we relied on diagnosis codes to ascertain CKD stage 4/5 rather than using eGFR.[49] Although our internal validation study suggested that the majority of people (>75%) with 2 diagnosis codes for CKD stage 4/5 had an eGFR <30 mL/min/1.73 m^2, a proportion may have had an eGFR between 30 and 60 mL/min/1.73 m^2. Fifth, even though we used large nationwide databases, the number of ischemic stroke events was relatively low, leading to wide CIs. Finally, for the mortality outcome, we used data from only the Medicare database because death ascertainment in the CDM database is merely based on discharge status and therefore considered incomplete.

In conclusion, in this large, US population–based analysis of patients with AF and CKD stage 4/5, we found that rivaroxaban and warfarin were associated with higher rates of major bleeding than apixaban. In contrast, no significant differences in the rates of ischemic stroke were found across oral anticoagulant users in this population. Our findings lend support to the use of apixaban in patients with AF and advanced CKD who are not yet receiving dialysis.

Supplementary Material

Supplementary File 1 (PDF)

Figure S1: Cohort formation for the warfarin versus apixaban and rivaroxaban versus apixaban cohorts.

Figure S2: Cohort formation for the internal validation study.

Figure S3: Flow chart of patient inclusion for the warfarin versus apixaban cohort (A) and the rivaroxaban versus apixaban cohort (B) pooled across the Medicare fee-for-service and Optum Clinformatics Data Mart databases.

Figure S4: Propensity score distribution before and after 1:1 propensity-score matching for warfarin versus apixaban (A and B) and rivaroxaban versus apixaban (C and D) in the Medicare fee-for-service database.

Item S1: Additional details of the internal validation study for CKD stage definition.

Table S1: Baseline characteristics of patients with atrial fibrillation and non–dialysis-dependent CKD stage 4/5 initiating warfarin versus apixaban before and after 1:1 propensity score matching, pooled across Medicare fee-for-service and Optum Clinformatics Data Mart databases.

Table S2: Baseline characteristics of patients with atrial fibrillation and non–dialysis-dependent CKD stage 4/5 initiating rivaroxaban versus apixaban before and after 1:1 propensity-score matching, pooled across Medicare fee-for-service and Optum Clinformatics Data Mart databases.

Table S3: Number of individuals initiating a reduced dose of apixaban or rivaroxaban in non–dialysis-dependent CKD stage 4/5 cohorts before and after 1:1 propensity-score matching, pooled across Medicare fee-for-service and Optum Clinformatics Data Mart databases.

Table S4: Follow-up and reasons for censoring after 1:1 propensity-score matching for the warfarin versus apixaban and rivaroxaban versus apixaban cohorts, pooled across Medicare fee-for-service and Optum Clinformatics Data Mart databases.

Table S5: Absolute risks at 6, 12, 18, and 24 months of follow-up for warfarin versus apixaban and rivaroxaban versus apixaban for outcomes of major bleeding and ischemic stroke.

Table S6: Baseline characteristics of patients in positive control cohort with atrial fibrillation and CKD stage 3 initiating warfarin versus apixaban before and after 1:1 propensity-score matching, pooled across Medicare fee-for-service and Optum Clinformatics Data Mart databases.

Table S7: Baseline characteristics of patients in the positive control cohort with atrial fibrillation and CKD stage 3 initiating rivaroxaban versus apixaban before and after 1:1 propensity-score matching pooled across Medicare fee-for-service and Optum Clinformatics Data Mart databases.

Table S8: Comparative safety and effectiveness of warfarin versus apixaban in the positive control cohort of patients with atrial fibrillation and CKD stage 3 before and after 1:1 propensity score matching, pooled across Medicare fee-for-service and Optum Clinformatics Data Mart databases.

Table S9: Comparative safety and effectiveness of rivaroxaban versus apixaban in the positive control cohort of patients with atrial fibrillation and CKD stage 3 before and after 1:1 propensity score matching, pooled across Medicare fee-for-service and Optum Clinformatics Data Mart databases.

Table S10: Sensitivity analyses for warfarin versus apixaban in the Medicare fee-for-service population for CKD stage 4/5.

Table S11: Sensitivity analyses for rivaroxaban versus apixaban in the Medicare fee-for-service population for CKD stage 4/5.

Supplementary File 2 (PDF)

Variable definitions.

Article Information

Authors' Full Names and Academic Degrees: Edouard L. Fu, PhD, Rishi J. Desai, PhD, Julie M. Paik, MD, MPH, ScD, Dae Hyun Kim, MD, ScD, Yichi Zhang, MS, Julianna M. Mastrorilli, BS, Alexander Cervone, BA, and Kueiyu Joshua Lin, MD, ScD.

Authors' Affiliations: Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School (ELF, RJD, JMP, YZ, JMM, AC, KJL), Division of Renal Medicine, Department of Medicine, Brigham and Women's Hospital (JMP), New England Geriatric Research Education and Clinical Center, VA Boston Healthcare System (JMP), Hinda and Arthur Marcus Institute for Aging Research, Hebrew SeniorLife and Harvard Medical School (DHK), Division of Gerontology, Department of Medicine, Beth Israel Deaconess Medical Center and Harvard Medical School (DHK), and Division of General Internal Medicine, Department of Medicine, Massachusetts General Hospital and Harvard Medical School (DHK, KJL), Boston, Massachusetts.

Address for Correspondence: Kueiyu Joshua Lin, MD, ScD, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 1620 Tremont St, Suite 3030, Boston, MA 02120. Email: jklin@bwh.harvard.edu

Authors' Contributions: Research idea and study design: ELF, KJL; data acquisition: KJL; data analysis/interpretation: all authors; statistical analysis: ELF, YZ, JMM, AC, KJL; supervision or mentorship: KJL. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

Support: This study was funded by the National Institute on Aging (RF1AG063381-01 and R01 AG075335). Dr Fu is supported by a Rubicon Grant from the Netherlands Organization for Scientific Research. The funder had no role in the design, collection, analysis, interpretation of the data, or the decision to submit the manuscript for publication.

Financial Disclosure: Dr Kim reports personal fees from Alosa Health and VillageMD for unrelated work. The other authors declare that they have no relevant financial interests.

Peer Review: Received June 30, 2023. Evaluated by 2 external peer reviewers, with direct editorial input from a Statistics/Methods Editor, an Associate Editor, and the Editor-in-Chief. Accepted in revised form August 26, 2023.

References

1. Soliman EZ, Prineas RJ, Go AS, et al. Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). *Am Heart J*. 2010;159(6):1102-1107. doi:10.1016/j.ahj.2010.03.027
2. McManus DD, Corteville DC, Shlipak MG, Whooley MA, Ix JH. Relation of kidney function and albuminuria with atrial fibrillation (from the Heart and Soul Study). *Am J Cardiol*. 2009;104(11):1551-1555. doi:10.1016/j.amjcard.2009.07.026
3. Carrero JJ, Evans M, Szummer K, et al. Warfarin, kidney dysfunction, and outcomes following acute myocardial infarction in patients with atrial fibrillation. *JAMA*. 2014;311(9):919-928. doi:10.1001/jama.2014.1334
4. Ocak G, Khairoun M, Khairoun O, et al. Chronic kidney disease and atrial fibrillation: a dangerous combination. *PLoS One*. 2022;17(4):e0266046. doi:10.1371/journal.pone.0266046
5. de Jong Y, Fu EL, van Diepen M, et al. Validation of risk scores for ischaemic stroke in atrial fibrillation across the spectrum of kidney function. *Eur Heart J*. 2021;42(15):1476-1485. doi:10.1093/eurheartj/ehab059
6. Providencia R, Marijon E, Boveda S, et al. Meta-analysis of the influence of chronic kidney disease on the risk of thromboembolism among patients with nonvalvular atrial fibrillation. *Am J Cardiol*. 2014;114(4):646-653. doi:10.1016/j.amjcard.2014.05.048
7. Olesen JB, Lip GY, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med*. 2012;367(7):625-635. doi:10.1056/NEJMoa1105594
8. Go AS, Fang MC, Udaltsova N, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. *Circulation*. 2009;119(10):1363-1369. doi:10.1161/CIRCULATIONAHA.108.816082
9. Ishigami J, Grams ME, Naik RP, Coresh J, Matsushita K. Chronic kidney disease and risk for gastrointestinal bleeding in the community: the Atherosclerosis Risk in Communities

(ARIC) study. *Clin J Am Soc Nephrol*. 2016;11(10):1735-1743. doi:10.2215/CJN.02170216
10. Ha JT, Neuen BL, Cheng LP, et al. Benefits and harms of oral anticoagulant therapy in chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2019;171(3):181-189. doi:10.7326/M19-0087
11. Stanifer JW, Pokorney SD, Chertow GM, et al. Apixaban versus warfarin in patients with atrial fibrillation and advanced chronic kidney disease. *Circulation*. 2020;141(17):1384-1392. doi:10.1161/CIRCULATIONAHA.119.044059
12. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151. doi:10.1056/NEJMoa0905561
13. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-992. doi:10.1056/NEJMoa1107039
14. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-2104. doi:10.1056/NEJMoa1310907
15. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-891. doi:10.1056/NEJMoa1009638
16. Konstantinidis I, Nadkarni GN, Yacoub R, et al. Representation of patients with kidney disease in trials of cardiovascular interventions: an updated systematic review. *JAMA Intern Med*. 2016;176(1):121-124. doi:10.1001/jamainternmed.2015.6102
17. Fu EL, van Diepen M, Xu Y, et al. Pharmacoepidemiology for nephrologists (part 2): potential biases and how to overcome them. *Clin Kidney J*. 2021;14(5):1317-1326. doi:10.1093/ckj/sfaa242
18. Ko D, Lin KJ, Bessette LG, et al. Trends in use of oral anticoagulants in older adults with newly diagnosed atrial fibrillation, 2010-2020. *JAMA Netw Open*. 2022;5(11):e2242964. doi:10.1001/jamanetworkopen.2022.42964
19. Turakhia MP, Blankestijn PJ, Carrero JJ, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. *Eur Heart J*. 2018;39(24):2314-2325. doi:10.1093/eurheartj/ehy060
20. Tirschwell DL, Longstreth WT Jr. Validating administrative data in stroke research. *Stroke*. 2002;33(10):2465-2470. doi:10.1161/01.str.0000032240.28636.bd
21. Roumie CL, Mitchel E, Gideon PS, Varas-Lorenzo C, Castellsague J, Griffin MR. Validation of ICD-9 codes with a high positive predictive value for incident strokes resulting in hospitalization using Medicaid health data. *Pharmacoepidemiol Drug Saf*. 2008;17(1):20-26. doi:10.1002/pds.1518
22. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. *Pharmacoepidemiol Drug Saf*. 2011;20(6):560-566. doi:10.1002/pds.2109
23. 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(2):263-272. doi:10.1378/chest.09-1584
24. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33(12):1500-1510. doi:10.1093/eurheartj/ehr488
25. 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(5):1093-1100. doi:10.1378/chest.10-0134
26. Gagne JJ, Glynn RJ, Avorn J, Levin R, Schneeweiss S. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol*. 2011;64(7):749-759. doi:10.1016/j.jclinepi.2010.10.004
27. Kim DH, Schneeweiss S, Glynn RJ, Lipsitz LA, Rockwood K, Avorn J. Measuring frailty in Medicare data: development and validation of a claims-based frailty index. *J Gerontol A Biol Sci Med Sci*. 2018;73(7):980-987. doi:10.1093/gerona/glx229
28. Kim DH, Patorno E, Pawar A, Lee H, Schneeweiss S, Glynn RJ. Measuring frailty in administrative claims data: comparative performance of four claims-based frailty measures in the U.S. Medicare data. *J Gerontol A Biol Sci Med Sci*. 2020;75(6):1120-1125. doi:10.1093/gerona/glz224
29. Gautam N, Bessette L, Pawar A, Levin R, Kim DH. Updating International Classification of Diseases 9th Revision to 10th Revision of a claims-based frailty index. *J Gerontol A Biol Sci Med Sci*. 2021;76(7):1316-1317. doi:10.1093/gerona/glaa150
30. Lin KJ, Singer DE, Glynn RJ, et al. Prediction score for anticoagulation control quality among older adults. *J Am Heart Assoc*. 2017;6(10):e006814. doi:10.1161/JAHA.117.006814
31. Fu EL, Groenwold RHH, Zoccali C, Jager KJ, van Diepen M, Dekker FW. Merits and caveats of propensity scores to adjust for confounding. *Nephrol Dial Transplant*. 2019;34(10):1629-1635. doi:10.1093/ndt/gfy283
32. Hohnloser SH, Hijazi Z, Thomas L, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J*. 2012;33(22):2821-2830. doi:10.1093/eurheartj/ehs274
33. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology*. 2009;20(4):512-522. doi:10.1097/EDE.0b013e3181a663cc
34. Lin KJ, Schneeweiss S, Pawar A, Singer DE, Liu J, Gagne JJ. Using a simple prescription gap to determine warfarin discontinuation can lead to substantial misclassification. *Thromb Haemost*. 2022;122(3):386-393. doi:10.1055/a-1508-8187
35. Zhuo M, Paik JM, Tsacogianis TN, Desai RJ. Use of anticoagulants and dosing appropriateness of apixaban for new-onset atrial fibrillation among hemodialysis patients. *Am J Kidney Dis*. 2022;79(6):909-912. doi:10.1053/j.ajkd.2021.08.014
36. Jun M, Scaria A, Andrade J, et al. Kidney function and the comparative effectiveness and safety of direct oral anticoagulants vs. warfarin in adults with atrial fibrillation: a multicenter observational study. *Eur Heart J Qual Care Clin Outcomes*. 2022. doi:10.1093/ehjqcco/qcac069
37. Ha JT, Scaria A, Andrade J, et al. Safety and effectiveness of rivaroxaban versus warfarin across GFR levels in atrial fibrillation: a population-based study in Australia and Canada. *Kidney Med*. 2023;5(7):100675. doi:10.1016/j.xkme.2023.100675
38. Trevisan M, Hjemdahl P, Clase CM, et al. Cardiorenal outcomes among patients with atrial fibrillation treated with oral anticoagulants. *Am J Kidney Dis*. 2022;81(3):307-317. doi:10.1053/j.ajkd.2022.07.017
39. Fralick M, Colacci M, Schneeweiss S, Huybrechts KF, Lin KJ, Gagne JJ. Effectiveness and safety of apixaban compared with rivaroxaban for patients with atrial fibrillation in routine practice: a cohort study. *Ann Intern Med*. 2020;172(7):463-473. doi:10.7326/M19-2522
40. Lip GYH, Keshishian A, Li X, et al. Effectiveness and safety of oral anticoagulants among nonvalvular atrial fibrillation patients.

Stroke. 2018;49(12):2933-2944. doi:10.1161/STROKEAHA.118.020232

41. Dawwas GK, Cuker A, Barnes GD, Lewis JD, Hennessy S. Apixaban versus rivaroxaban in patients with atrial fibrillation and valvular heart disease: a population-based study. *Ann Intern Med*. 2022;175(11):1506-1514. doi:10.7326/m22-0318
42. Lau WCY, Torre CO, Man KKC, et al. Comparative effectiveness and safety between apixaban, dabigatran, edoxaban, and rivaroxaban among patients with atrial fibrillation: a multinational population-based cohort study. *Ann Intern Med*. 2022;175(11):1515-1524. doi:10.7326/m22-0511
43. Limdi NA, Beasley TM, Baird MF, et al. Kidney function influences warfarin responsiveness and hemorrhagic complications. *J Am Soc Nephrol*. 2009;20(4):912-921. doi:10.1681/ASN.2008070802
44. Yang F, Hellyer JA, Than C, et al. Warfarin utilisation and anticoagulation control in patients with atrial fibrillation and chronic kidney disease. *Heart*. 2017;103(11):818-826. doi:10.1136/heartjnl-2016-309266
45. Frost C, Song Y, Barrett YC, et al. A randomized direct comparison of the pharmacokinetics and pharmacodynamics of apixaban and rivaroxaban. *Clin Pharmacol*. 2014;6:179-187. doi:10.2147/CPAA.S61131
46. Steffel J, Collins R, Antz M, et al. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Europace*. 2021;23(10):1612-1676. doi:10.1093/europace/euab065
47. Fu EL. Target trial emulation to improve causal inference from observational data: what, why, and how? *J Am Soc Nephrol*. 2023;34(8):1305-1314. doi:10.1681/ASN.0000000000000152
48. Szummer K, Gasparini A, Eliasson S, et al. Time in therapeutic range and outcomes after warfarin initiation in newly diagnosed atrial fibrillation patients with renal dysfunction. *J Am Heart Assoc*. 2017;6(3):e004925. doi:10.1161/JAHA.116.004925
49. Carrero JJ, Fu EL, Vestergaard SV, et al. Defining measures of kidney function in observational studies using routine health care data: methodological and reporting considerations. *Kidney Int*. 2023;103(1):53-69. doi:10.1016/j.kint.2022.09.020

Comparative Safety and Effectiveness of Warfarin or Rivaroxaban Versus Apixaban in Patients With Advanced CKD and Atrial Fibrillation

Setting & Participants

Propensity score matched cohort study

2 nationwide US claims databases, 2013-2022

Patients with atrial fibrillation (AF) and CKD stages 4-5 newly initiated on:

Warfarin vs apixaban	Rivaroxaban vs apixaban
(N = 12,488)	(N = 5,720)

Findings

	Warfarin vs Apixaban HR (95% CI)	Rivaroxaban vs Apixaban HR (95% CI)
Major bleeding	1.85 (1.59-2.15)	1.69 (1.33-2.15)
Ischemic stroke	1.14 (0.83-1.57)	0.71 (0.40-1.24)
All-cause mortality	1.08 (0.98-1.18)	0.94 (0.81-1.10)

CONCLUSION: In patients with AF and advanced CKD, rivaroxaban and warfarin were associated with a higher rate of major bleeding compared with apixaban.

Edouard L. Fu, Rishi J. Desai, Julie M. Paik, et al

@AJKDonline | DOI: 10.1053/j.ajkd.2023.08.017