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Effectiveness and Safety of Apixaban Compared With Rivaroxaban for Patients With Atrial Fibrillation in Routine Practice

A Cohort Study

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Background: Apixaban and rivaroxaban are the most commonly prescribed direct oral anticoagulants for adults with atrial fibrillation, but head-to-head data comparing their safety and effectiveness are lacking.

Objective: To compare the safety and effectiveness of apixaban versus rivaroxaban for patients with nonvalvular atrial fibrillation.

Design: New-user, active-comparator, retrospective cohort study.

Setting: A U.S. nationwide commercial health care claims database from 28 December 2012 to 1 January 2019.

Patients: Adults newly prescribed apixaban (n = 59 172) or rivaroxaban (n = 40 706).

Measurements: The primary effectiveness outcome was a composite of ischemic stroke or systemic embolism. The primary safety outcome was a composite of intracranial hemorrhage or gastrointestinal bleeding.

Results: 39 351 patients newly prescribed apixaban were propensity score matched to 39 351 patients newly prescribed rivaroxaban. Mean age was 69 years, 40% of patients were women, and mean follow-up was 288 days for new apixaban users and 291 days for new rivaroxaban users. The incidence rate of ischemic stroke or systemic embolism was 6.6 per 1000 person-years for adults prescribed apixaban compared with 8.0 per 1000 person-years for those prescribed rivaroxaban (hazard ratio [HR], 0.82 [95% CI, 0.68 to 0.98]; rate difference, 1.4 fewer events per 1000 person-years [CI, 0.0 to 2.7]). Adults prescribed apixaban also had a lower rate of gastrointestinal bleeding or intracranial hemorrhage (12.9 per 1000 person-years) compared with those prescribed rivaroxaban (21.9 per 1000 person-years), corresponding to an HR of 0.58 (CI, 0.52 to 0.66) and a rate difference of 9.0 fewer events per 1000 person-years (CI, 6.9 to 11.1).

Limitation: Unmeasured confounding, incomplete laboratory data.

Conclusion: In routine care, adults with atrial fibrillation prescribed apixaban had a lower rate of both ischemic stroke or systemic embolism and bleeding compared with those prescribed rivaroxaban.

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Approximately 1% of adults in North America have atrial fibrillation (1, 2). Ischemic stroke may affect up to 20% of patients with atrial fibrillation and is associated with substantial disability, morbidity, and mortality (2–4). Oral anticoagulants decrease the risk for stroke and other systemic emboli by up to 70% and are recommended for most patients with atrial fibrillation (5–8). Direct oral anticoagulants (DOACs) are increasingly being recommended over warfarin because of improved efficacy, safety, and ease of use (9, 10). Although 4 DOACs are now approved for treating atrial fibrillation, apixaban and rivaroxaban are the most commonly prescribed (11–13). In the ARISTOTLE (Apixaban Versus Warfarin in Patients With Atrial Fibrillation) trial, patients randomly assigned to apixaban had lower rates of stroke, bleeding, and all-cause mortality (9). In the ROCKET-AF (Rivaroxaban Versus Warfarin in Nonvalvular Atrial Fibrillation) trial, rivaroxaban was noninferior to warfarin for stroke prevention and was associated with a lower risk for intracranial and fatal bleeding (10).

Randomized trials directly comparing apixaban with rivaroxaban have not been completed but are currently under way (14). In mid-2012, one of the first indirect comparisons between apixaban and rivaroxaban in patients with nonvalvular atrial fibrillation was published. That study, based on phase 3 randomized trials, found a possible reduced risk for stroke and embolic events (hazard ratio [HR], 0.77 [95% CI, 0.56 to 1.06]) and a reduced risk for major bleeding (HR, 0.68 [CI, 0.52 to 0.90]) with apixaban (15). Because head-to-head data are lacking and patients included in randomized clinical trials do not necessarily reflect general practice, how the results of meta-analyses apply to patients in routine care is unclear.

Although several observational studies of DOACs were performed previously, they lacked relevant laboratory data (such as baseline hemoglobin levels and renal function measures) (16–19); generally used data up to 2015; and, except for 1 industry-funded study, were relatively small (approximately 5000 apixaban users per study) (16). In the current investigation of more than 90 000 patients, we used data up to 2019, including details on baseline laboratory values for a small subset of the patients, to evaluate the safety and effec-

See also:

Summary for Patients I-16

tiveness of apixaban versus rivaroxaban for patients with atrial fibrillation.

METHODS

Study Design

We conducted a new-user, active-comparator cohort study using the nationwide U.S. commercial insurance claims database Optum Clinformatics ("Optum"). Most patients within Optum are covered by employer-sponsored insurance. Approximately 10% of patients in the database receive health care coverage through Medicare Advantage plans.

Optum provides deidentified, longitudinal, individual-level data on patient demographic characteristics, health care use, medical diagnoses, diagnostic tests, clinical procedures, outpatient laboratory results, provider type, and pharmacy dispensing of drugs for 13 million persons at any given time in the United States. Of note, the database lacks information on other relevant baseline characteristics (including race, socioeconomic status, echocardiographic findings, and duration of atrial fibrillation).

We compared persons older than 18 years who received a diagnosis of atrial fibrillation or atrial flutter and filled a new prescription for apixaban, 5 mg, or rivaroxaban, 20 mg, between 28 December 2012 (date of U.S. approval of apixaban for atrial fibrillation) and 1 January 2019 (most recent data available). Lower dosages of either medication were not included, and we assumed that the dosing was twice daily for apixaban and once daily for rivaroxaban on the basis of their product monographs. Patients with atrial fibrillation or atrial flutter were identified by using the International Classification of Diseases, Ninth Revision and 10th Revision (ICD-9 and ICD-10) codes (ICD9: 427.31, 427.32; ICD10: I48.x) (20, 21). These codes generally have a sensitivity above 80% and a specificity above 99% (20, 21). Cohort entry was defined as the date of the first prescription for apixaban or rivaroxaban. New users were defined as those without a prescription for apixaban, rivaroxaban, dabigatran, or edoxaban in the preceding 180 days.

Patients with any of the following characteristics in the 180 days before cohort entry were excluded: insufficient database enrollment (that is, <180 days), stage 5 chronic kidney disease requiring dialysis, cancer, valvular heart disease, venous thromboembolism, hip surgery, or knee surgery (**Appendix Figure 1**, available at Annals.org).

The Brigham and Women's Hospital Institutional Review Board provided ethics approval, and a valid data use agreement for the Optum database was in place at the Division of Pharmacoepidemiology and Pharmacoeconomics.

Patient Follow-up

Follow-up began the day after cohort entry and continued until the end of the study period (1 January 2019), the end of continuous health plan enrollment, the occurrence of a study outcome, discontinuation of the initial medication, a switch to the comparator, or death. A medication was considered discontinued if 30 days had elapsed after the last prescription's supply expired and the prescription was not refilled.

Study Outcomes

The primary effectiveness outcome was a composite of ischemic stroke or systemic embolism (**Appendix Table 1**, available at Annals.org). The primary safety outcome was a composite of gastrointestinal bleeding or intracranial hemorrhage (**Appendix Table 1**). We also assessed rates of other bleeding. Because most clinical trials included both gastrointestinal bleeding and intracranial hemorrhage in the same category (that is, major bleeding), we followed the same approach in this study. Rates of hepatitis and vasculitis were also assessed, because case reports suggest that rivaroxaban might be associated with an increased risk for both, and neither has been well characterized in a large cohort (22, 23). In the United States, each hospitalization is assigned 1 primary diagnosis as well as several secondary diagnoses. Our primary safety and effectiveness outcomes were defined by using the primary diagnosis code alone.

Baseline Characteristics

All baseline covariates were assessed by using information from up to 180 days preceding the date of cohort entry. For each patient, data were collected reflecting diagnoses and procedures recorded during health encounters, including chronic medical conditions (such as hypertension and coronary artery disease), overall health care use (such as a recent hospitalization or an emergency department visit), and medications (such as antihypertensives and diuretics). Data on hemoglobin (26%) and creatinine (33%) levels were available for approximately one third of patients. We also included whether the provider seen within 3 days of the patient's index prescription (if one was seen) was a general internist or cardiologist, because these are the most common providers treating patients with atrial fibrillation (24). These covariates were selected on the basis of previous literature, clinical experience, and expert opinion (19, 24, 25).

Statistical Analysis

Propensity score matching was used to adjust for confounding. The propensity score for initiating apixaban treatment was calculated through a multivariable logistic regression model that contained all baseline covariates except laboratory values (that is, hemoglobin and creatinine levels). Laboratory data were not included, because these data were missing for a substantial proportion of patients. Thus, the laboratory values provided additional, granular details about a subset of the included patients and also allowed us to assess how balanced these values were before as well as after matching. No other data were missing in our study.

The propensity score was used for 1:1 matching of adults prescribed apixaban with those prescribed rivaroxaban (**Figures 1** and **2**). Nearest-neighbor matching without replacement was performed by using a caliper of 0.05 on the propensity score scale (26). The nearest-

neighbor approach identified and formed the best match (defined by smallest difference in propensity score values) among all possible pairs of apixaban and rivaroxaban initiators. After removing both patients in this pair from the pool of potential matches, the best remaining match (that is, apixaban–rivaroxaban patient pair) was identified and formed. This process was repeated until the best possible remaining match had propensity score values that exceeded the caliper of 0.05 on the propensity score scale.

The propensity score was re-estimated for the subgroup analysis of patients older than 70 years. A cutoff of 70 years of age was chosen a priori, because the prevalence of atrial fibrillation increases substantially in this age group (2). Covariate balance within the matched cohorts was assessed with standardized differences. A standardized difference of 0.1 or less indicates adequate balance between groups (27).

After propensity score matching, Cox proportional hazards models were used to estimate the incidence rate, HRs, and 95% CIs for the primary outcome. Because propensity score matching accounts for confounding, no further adjustment was performed in the Cox models. Schoenfeld residuals were plotted and reviewed to assess the proportional hazards assumption for both the primary effectiveness and primary safety outcomes. To estimate rate differences, we used a Poisson model. To obtain the 95% CI, we used the following formula for the SE of the rate difference: sqrt ((e1/(t1*t1)) + (e2/(t2*t2))), where e1 and e2 are the numbers of events for apixaban and rivaroxaban, and t1 and t2 are the amounts of person-time.

We performed a predefined sensitivity analysis in which the censoring criteria of drug discontinuation or switching were removed and all patients were followed for up to 365 days, unless they reached the end of the study period, disenrolled, experienced a study outcome, or died. As a negative control, we assessed the risk for heart failure, which should be similar for rivaroxaban and apixaban. All analyses were performed by using the Aetion Evidence Platform, version 3.11, with R, version 3.4.2 (The R Foundation) (**Appendix Table 2**, available at Annals.org), which was scientifically validated previously by accurately repeating a range of published studies and by replicating or predicting clinical trial findings (28–30).

We also performed several post hoc analyses. First, we analyzed our primary effectiveness and safety outcomes by stratifying patients by deciles of the propensity score rather than through 1:1 matching. To further reduce confounding in the stratified analysis, we symmetrically trimmed the propensity score. To be specific, patients with propensity scores below the 2.5th percentile or above the 97.5th percentile of the overall propensity score distribution were excluded. Second, to account for competing risks, we created an overall com-

Figure 1. Kaplan–Meier curve for stroke or systemic embolism among propensity score–matched patients.

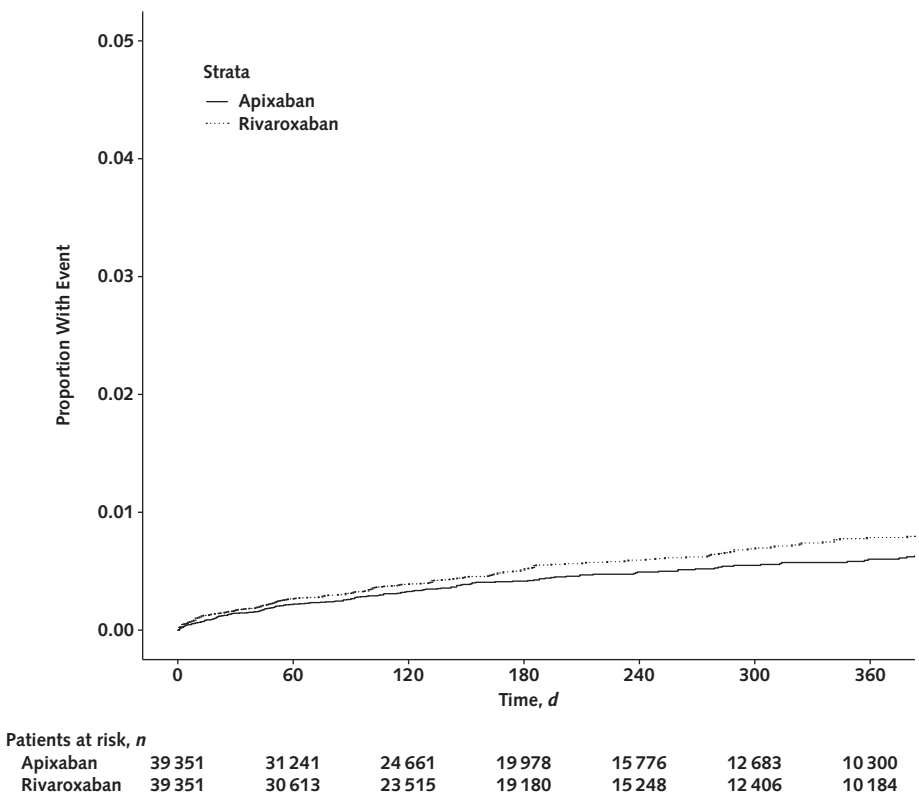
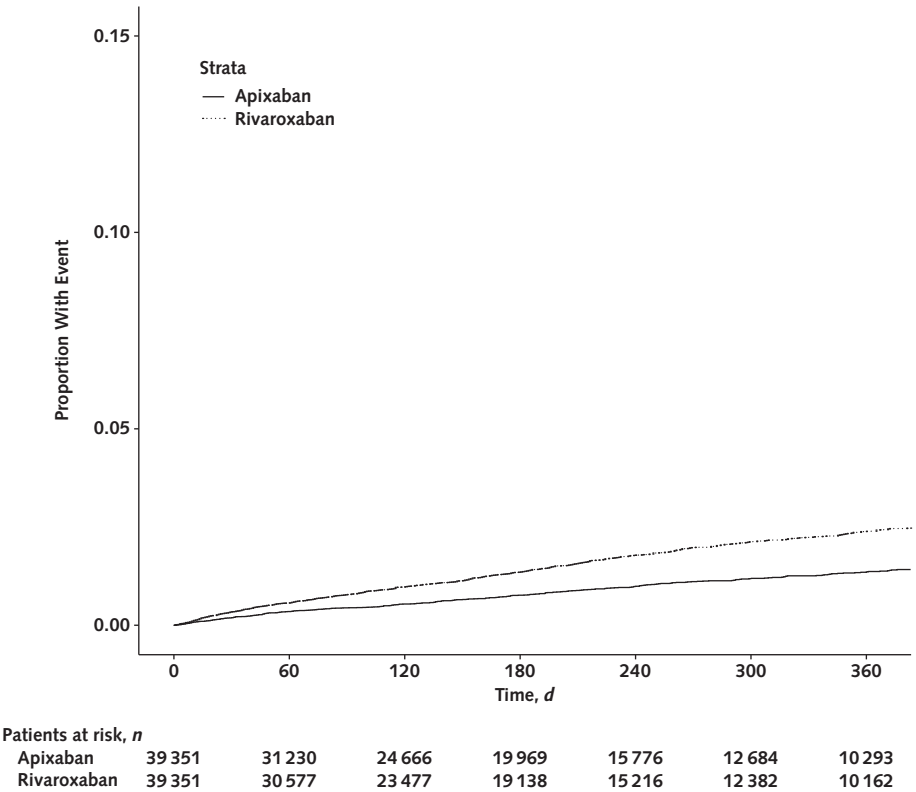


Figure 2. Kaplan–Meier curve for intracranial hemorrhage or gastrointestinal bleeding among propensity score–matched patients.



posite outcome including stroke, systemic embolism, gastrointestinal bleeding, or intracranial hemorrhage. This overall composite outcome was analyzed by using 1:1 propensity score matching.

Finally, we calculated an E-value to assess the impact of unmeasured confounding (31). The E-value indicates how strongly an unmeasured confounder would have to be associated with both the use of apixaban and rivaroxaban and the outcomes of interest to reduce the observed effect to the null, conditional on the measured covariates.

Role of the Funding Source

This study was funded by internal resources in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital. The authors had complete control over the design, conduct, and analysis of the study and the decision to submit the manuscript for publication.

RESULTS

We identified 99 878 patients eligible for the analysis (**Appendix Figure 2**, available at Annals.org). Patients newly prescribed apixaban (n = 59 172) were slightly older, were more likely to have a diagnosis of kidney or cardiovascular disease, and were receiving slightly more medications at baseline (**Table 1** and **Appendix Table 3**, available at Annals.org). Patients newly prescribed rivaroxaban (n = 40 706) were less likely to have a history of smoking or hyperlipidemia and were slightly more likely to have received warfarin in the preceding 30 days (**Table 1**). The vast majority of other baseline characteristics were well balanced (standardized differences <0.1) before propensity score matching.

After 1:1 propensity score matching, we retained 39 351 patients newly prescribed apixaban and 39 351 patients newly prescribed rivaroxaban (**Table 1**). All baseline characteristics were well balanced after propensity score matching, including baseline hemoglobin and creatinine values. Mean follow-up was 288 days (SD, 298.0) for new apixaban users and 291 days (SD, 324.0) for new rivaroxaban users. The most common reason for censoring was treatment discontinuation (60% for apixaban, 66% for rivaroxaban), and switching to the comparator medication was rare (1% for apixaban, 2% for rivaroxaban) (**Appendix Table 4**, available at Annals.org).

Rate of Stroke or Systemic Embolism

In the unmatched analysis, 342 adults had a stroke or systemic embolism among 59 172 new apixaban users (7.5 events per 1000 person-years), compared with 255 among 40 706 new rivaroxaban users (7.9 events per 1000 person-years) (HR, 0.94 [CI, 0.80 to 1.10]). After propensity score matching, 206 adults had a

stroke or systemic embolism among 39 351 new apixaban users (6.6 events per 1000 person-years), compared with 251 among 39 351 new rivaroxaban users (8.0 events per 1000 person-years) (HR, 0.82 [CI, 0.68 to 0.98]). The resulting estimand from this analysis is close to the average treatment effect among the treated patients but deviates slightly. That is, because almost all the rivaroxaban patients are included, the estimand is close to the average treatment effect among the treated patients but does not apply to those who would not have been candidates for both rivaroxaban and apixaban (32). Visual inspection of the Schoenfeld residual plot suggests that the proportional hazards assumption was not violated (Appendix Figure 3, available at Annals.org). Results are also available for the individual outcomes of stroke or systemic embolism (Table 2).

In the propensity score–matched analysis restricted to patients older than 70 years, 132 patients newly prescribed apixaban had a stroke or systemic embolism

Table 1. Baseline Characteristics Before and After Propensity Score Matching*

Characteristic	Unmatched			Propensity Matched		
	Rivaroxaban Group (*n* = 40 706)	Apixaban Group (*n* = 59 172)	Standardized Difference	Rivaroxaban Group (*n* = 39 351)	Apixaban Group (*n* = 39 351)	Standardized Difference
Female, *n (%)*	15 791 (38.8)	25 823 (43.6)	0.099	15 577 (39.6)	15 603 (39.7)	0.003
Mean age (SD), *y*	68.9 (10.9)	70.8 (10.0)	0.181	69.3 (10.6)	69.4 (10.5)	0.004
Comorbid conditions, *n (%)*						
$CHADS_2$ score						
0	5350 (13.1)	5899 (10.0)	0.099	4904 (12.5)	5015 (12.7)	0.008
1	17 583 (43.2)	22 562 (38.1)	0.103	16 944 (43.1)	16 672 (42.4)	0.014
≥2	17 773 (43.7)	30 711 (51.9)	0.166	17 503 (44.5)	17 664 (44.9)	0.002
Hypertension	32 287 (79.3)	49 224 (83.2)	0.099	31 479 (80.0)	31 492 (80.0)	0.001
Hyperlipidemia	25 518 (62.7)	39 975 (67.6)	0.102	24 983 (63.5)	24 947 (63.4)	0.002
Ischemic stroke or TIA	3678 (9.0)	6715 (11.3)	0.076	3627 (9.2)	3678 (9.3)	0.004
ICH	249 (0.6)	563 (1.0)	0.039	248 (0.6)	246 (0.6)	0.001
Heart failure	8706 (21.4)	15 129 (25.6)	0.099	8518 (21.6)	8482 (21.6)	0.002
Ischemic heart disease	15 421 (37.9)	27 517 (46.5)	0.175	15 282 (38.8)	15 299 (38.9)	0.001
Chronic kidney disease (stage 3 or 4)	2534 (6.2)	6621 (11.2)	0.177	2533 (6.4)	2455 (6.2)	0.008
Bleeding						
GI	1159 (2.8)	2039 (3.4)	0.034	1138 (2.9)	1133 (2.9)	0.001
Other	2593 (6.4)	4115 (7.0)	0.023	2523 (6.4)	2516 (6.4)	0.001
Liver disease	297 (0.7)	522 (0.9)	0.017	291 (0.7)	278 (0.7)	0.004
Smoking	8137 (20.0)	15 120 (25.6)	0.133	8071 (20.5)	8076 (20.5)	0
Obesity or overweight	11 372 (27.9)	19 977 (33.8)	0.126	11 219 (28.5)	11 222 (28.5)	0
Medications						
Antiplatelets, *n (%)*	3812 (9.4)	6881 (11.6)	0.074	3777 (9.6)	3806 (9.7)	0.002
Warfarin, *n (%)*						
Remote use†	5649 (13.9)	6367 (10.8)	0.095	5102 (13.0)	5098 (13.0)	0
Recent use‡	5352 (13.1)	5523 (9.3)	0.121	4743 (12.1)	4724 (12.0)	0.001
Proton-pump inhibitors, *n (%)*	9432 (23.2)	15 383 (26.0)	0.066	9251 (23.5)	9148 (23.2)	0.006
Angiotensin-converting enzyme inhibitors, *n (%)*	13 848 (34.0)	20 578 (34.8)	0.016	13 421 (34.1)	13 364 (34.0)	0.003
β-Blockers, *n (%)*	26 607 (65.4)	40 610 (68.6)	0.07	25 914 (65.9)	25 930 (65.9)	0.001
Statins, *n (%)*	21 624 (53.1)	34 369 (58.1)	0.1	21 171 (53.8)	21 179 (53.8)	0
Oral steroids, *n (%)*	6128 (15.1)	9942 (16.8)	0.048	5979 (15.2)	5995 (15.2)	0.001
Mean total medications (SD), *n*	9.2 (5.1)	9.9 (5.3)	0.136	9.3 (5.1)	9.3 (5.1)	0.001
Laboratory values						
Mean creatinine level (SD)						
mg/dL	0.98 (0.26)	1.03 (0.34)	0.158	0.98 (0.26)	1.01 (0.30)	0.077
μmol/L	86.6 (23.0)	91.1 (30.1)	–	86.6 (23.0)	89.3 (26.5)	–
Missing, *n (%)*	27 807 (68.3)	38 646 (65.3)	–	26 771 (68.0)	26 300 (66.8)	–
Mean hemoglobin level (SD), *g/L*	139.1 (1.73)	137.0 (1.75)	0.123	138.9 (1.73)	138.9 (1.73)	0.001
Missing, *n (%)*	30 867 (75.8)	43 529 (73.6)	–	29 756 (75.6)	29 382 (74.7)	–
Health care use						
General internist visits, *n (%)*§	7704 (18.9)	11 771 (19.9)	0.024	7492 (19.0)	7434 (18.9)	0.004
Cardiologist visits, *n (%)*§	13 219 (32.5)	19 181 (32.4)	0.001	12 750 (32.4)	12 666 (32.2)	0.005
Mean ED visits (SD), *n*	5.3 (17.6)	7.0 (18.7)	0.096	5.4 (17.8)	5.5 (15.6)	0.006
Mean outpatient visits (SD), *n*	5.5 (4.2)	5.7 (4.2)	0.056	5.5 (4.2)	5.5 (4.1)	0.003

ED = emergency department; GI = gastrointestinal; ICH = intracranial hemorrhage; TIA = transient ischemic attack.
* Baseline characteristics were assessed up to 180 d before the index date unless otherwise specified.
† Days 90–180 before index date.
‡ Days 1–30 before index date.
§ Up to 3 d before and including index date.

Table 2. Rate of Subsequent Stroke, Systemic Embolism, or Bleeding

Outcome*	Unmatched		Propensity Matched	
	Rivaroxaban Group	Apixaban Group	Rivaroxaban Group	Apixaban Group
Pooled stroke or systemic emboli				
Patients, *n*	40 706	59 172	39 351	39 351
PY, *n*	32 444	45 358	31 323	31 011
Events, *n*	255	342	251	206
Rate per 1000 PY	7.86	7.54	8.01	6.64
Rate difference per 1000 PY (95% CI)	−0.32 (−1.57 to 0.93)		−1.37 (−2.71 to −0.03)	
HR (95% CI)	0.94 (0.80 to 1.10)		0.82 (0.68 to 0.98)	
Stroke				
Patients, *n*	40 706	59 172	39 351	39 351
PY, *n*	32 450	45 363	31 329	31 016
Events, *n*	236	327	232	198
Rate per 1000 PY	7.27	7.21	7.41	6.38
Rate difference per 1000 PY (95% CI)	−0.06 (−1.28 to 1.15)		−1.02 (−2.32 to 0.28)	
HR (95% CI)	0.97 (0.82 to 1.15)		0.85 (0.70 to 1.03)	
Systemic embolism				
Patients, *n*	40 706	59 172	39 351	39 351
PY, *n*	32 549	45 488	31 423	31 099
Events, *n*	19	16	19	9
Rate per 1000 PY	0.58	0.35	0.60	0.29
Rate difference per 1000 PY (95% CI)	−0.23 (−0.55 to 0.08)		−0.32 (−0.65 to 0.02)	
HR (95% CI)	0.58 (0.30 to 1.14)		0.47 (0.21 to 1.04)	
Pooled GI bleeding or ICH				
Patients, *n*	40 706	59 172	39 351	39 351
PY, *n*	32 375	45 276	31 257	30 985
Events, *n*	697	727	685	401
Rate per 1000 PY	21.53	16.06	21.92	12.94
Rate difference per 1000 PY (95% CI)	−5.47 (−7.47 to −3.49)		−8.97 (−11.05 to −6.90)	
HR (95% CI)	0.73 (0.66 to 0.81)		0.58 (0.52 to 0.66)	
GI bleeding				
Patients, *n*	40 706	59 172	39 351	39 351
PY, *n*	32 399	45 314	31 281	31 004
Events, *n*	572	544	561	290
Rate per 1000 PY	17.65	12.00	17.93	9.35
Rate difference per 1000 PY (95% CI)	−5.65 (−7.41 to −3.89)		−8.58 (−10.41 to −6.75)	
HR (95% CI)	0.67 (0.59 to 0.75)		0.52 (0.45 to 0.59)	
ICH				
Patients, *n*	40 706	59 172	39 351	39 351
PY, *n*	32 531	45 455	31 406	31 085
Events, *n*	125	186	124	113
Rate per 1000 PY	3.84	4.09	3.95	3.64
Rate difference per 1000 PY (95% CI)	0.25 (−0.64 to 1.14)		−0.31 (−1.28 to 0.65)	
HR (95% CI)	1.05 (0.84 to 1.32)		0.91 (0.71 to 1.18)	
Other bleeding				
Patients, *n*	40 706	59 172	39 351	39 351
PY, *n*	32 497	45 435	31 372	31 065
Events, *n*	168	159	165	96
Rate per 1000 PY	5.17	3.50	5.26	3.09
Rate difference per 1000 PY (95% CI)	−1.67 (−2.62 to −0.72)		−2.17 (−3.18 to −1.16)	
HR (95% CI)	0.66 (0.53 to 0.83)		0.58 (0.45 to 0.75)	

GI = gastrointestinal; HR = hazard ratio; ICH = intracranial hemorrhage; PY = person-years.
* HRs and rate differences are for apixaban relative to rivaroxaban. Rate differences were calculated by using a Poisson model.

(8.3 events per 1000 person-years) compared with 165 newly prescribed rivaroxaban (10.5 events per 1000 person-years), corresponding to an HR of 0.79 (CI, 0.63 to 0.99) (Table 3).

Rate of Bleeding

In the unmatched analysis, 727 adults had a major bleeding episode among 59 172 newly prescribed apixaban (16.1 events per 1000 person-years), compared with 697 adults among 40 706 newly prescribed rivaroxaban (21.5 events per 1000 person-years) (HR, 0.73 [CI, 0.66 to 0.81]). After propensity score matching, the rate of major bleeding was 12.9 per 1000 person-years for adults newly prescribed apixaban and 21.9 per 1000 person-years for those newly prescribed

rivaroxaban (HR, 0.58 [CI, 0.52 to 0.66]). Visual inspection of the Schoenfeld residual plot suggests that the proportional hazards assumption was not violated (Appendix Figure 3). Estimates for each outcome are also presented separately and indicate that the decreased bleeding risk was driven mainly by a reduction in gastrointestinal bleeding events (Table 2). A reduced rate of nongastrointestinal or intracranial bleeding also was observed (Table 2). Similar results were seen for patients older than 70 years (Table 3).

Rate of Hepatitis or Vasculitis

Hepatitis was diagnosed in 403 adults among 39 351 propensity score–matched patients newly pre-

Table 3. Rate of Subsequent Stroke, Systemic Embolism, or Bleeding in Patients Older Than 70 Years

Outcome*	Unmatched		Propensity Matched	
	Rivaroxaban Group	Apixaban Group	Rivaroxaban Group	Apixaban Group
Pooled stroke or systemic emboli				
Patients, *n*	19 415	32 712	19 124	19 124
PY, *n*	16 083	25 945	15 779	15 922
Events, *n*	168	233	165	132
Rate per 1000 PY	10.45	8.98	10.46	8.29
Rate difference per 1000 PY (95% CI)	−1.47 (−3.42 to 0.49)		−2.17 (−4.30 to −0.03)	
HR (95% CI)	0.84 (0.69 to 1.02)		0.79 (0.63 to 0.99)	
Stroke				
Patients, *n*	19 415	32 712	19 124	19 124
PY, *n*	16 089	25 947	15 785	15 924
Events, *n*	156	225	153	126
Rate per 1000 PY	9.70	8.67	9.69	7.91
Rate difference per 1000 PY (95% CI)	−1.02 (−2.92 to 0.87)		−1.78 (−3.85 to 0.29)	
HR (95% CI)	0.87 (0.71 to 1.07)		0.81 (0.64 to 1.03)	
Systemic embolism				
Patients, *n*	19 415	32 712	19 124	19 124
PY, *n*	16 163	26 046	15 858	15 981
Events, *n*	12	8	12	6
Rate per 1000 PY	0.74	0.31	0.76	0.38
Rate difference per 1000 PY (95% CI)	−0.44 (−0.91 to 0.04)		−0.38 (−0.90 to 0.14)	
HR (95% CI)	0.40 (0.16 to 0.99)		0.49 (0.18 to 1.31)	
Pooled GI bleeding or ICH				
Patients, *n*	19 415	32 712	19 124	19 124
PY, *n*	16 056	25 905	15 757	15 907
Events, *n*	481	516	473	272
Rate per 1000 PY	29.96	19.92	30.02	17.10
Rate difference per 1000 PY (95% CI)	−10.04 (−13.22 to −6.86)		−12.92 (−16.30 to −9.54)	
HR (95% CI)	0.65 (0.58 to 0.74)		0.57 (0.49 to 0.66)	
GI bleeding				
Patients, *n*	19 415	32 712	19 124	19 124
PY, *n*	16 074	25 930	15 776	15 924
Events, *n*	387	391	379	192
Rate per 1000 PY	24.08	15.08	24.02	12.06
Rate difference per 1000 PY (95% CI)	−9.00 (−11.82 to −6.17)		−11.97 (−14.93 to −9.01)	
HR (95% CI)	0.61 (0.53 to 0.70)		0.50 (0.42 to 0.59)	
ICH				
Patients, *n*	19 415	32 712	19 124	19 124
PY, *n*	16 150	26 023	15 845	15 965
Events, *n*	94	128	94	81
Rate per 1000 PY	5.82	4.92	5.93	5.07
Rate difference per 1000 PY (95% CI)	−0.90 (−2.35 to 0.55)		−0.86 (−2.49 to 0.77)	
HR (95% CI)	0.84 (0.64 to 1.09)		0.85 (0.63 to 1.15)	
Other bleeding				
Patients, *n*	19 415	32 712	19 124	19 124
PY, *n*	16 125	26 013	15 820	15 965
Events, *n*	110	103	107	52
Rate per 1000 PY	6.82	3.96	6.76	3.26
Rate difference per 1000 PY (95% CI)	−2.86 (−4.35 to −1.38)		−3.51 (−5.06 to −1.95)	
HR (95% CI)	0.57 (0.43 to 0.74)		0.48 (0.34 to 0.67)	

GI = gastrointestinal; HR = hazard ratio; ICH = intracranial hemorrhage; PY = person-years.
* HRs and rate differences are for apixaban relative to rivaroxaban. Rate differences were calculated by using a Poisson model.

Table 4. Rate of Subsequent Hepatitis, Vasculitis, and Heart Failure Exacerbation

Event*	Unmatched		Propensity Matched	
	Rivaroxaban Group	Apixaban Group	Rivaroxaban Group	Apixaban Group
Hepatitis or transaminitis				
Patients, *n*	40 706	59 172	39 351	39 351
PY, *n*	32 247	45 107	31 129	30 843
Events, *n*	394	621	384	403
Rate per 1000 PY	12.22	13.77	12.34	13.07
Rate difference per 1000 PY (95% CI)	1.55 (−0.07 to 3.17)		0.73 (−1.04 to 2.51)	
HR (95% CI)	1.10 (0.97 to 1.25)		1.05 (0.91 to 1.20)	
Vasculitis				
Patients, *n*	40 706	59 172	39 351	39 351
PY, *n*	32 527	45 455	31 402	31 075
Events, *n*	38	55	38	33
Rate per 1000 PY	1.17	1.21	1.21	1.06
Rate difference per 1000 PY (95% CI)	0.04 (−0.45 to 0.53)		−0.15 (−0.68 to 0.38)	
HR (95% CI)	1.00 (0.66 to 1.52)		0.86 (0.54 to 1.37)	
Heart failure hospitalization				
Patients, *n*	40 706	59 172	39 351	39 351
PY, *n*	31 198	43 089	30 110	29 739
Events, *n*	2768	4888	2712	2703
Rate per 1000 PY	88.72	113.44	90.07	90.89
Rate difference per 1000 PY (95% CI)	24.71 (20.13 to 29.30)		0.82 (−4.00 to 5.64)	
HR (95% CI)	1.25 (1.19 to 1.31)		1.00 (0.95 to 1.05)	

HR = hazard ratio; PY = person-years.
* HRs and rate differences are for apixaban relative to rivaroxaban. Rate differences were calculated by using a Poisson model.

scribed apixaban (13.1 events per 1000 person-years), compared with 384 among 39 351 patients newly prescribed rivaroxaban (12.3 events per 1000 person-years). This corresponded to a similar rate of hepatitis with apixaban versus rivaroxaban (HR, 1.05 [CI, 0.91 to 1.20]). The rate of vasculitis was slightly lower for patients prescribed apixaban, albeit with wide CIs (HR, 0.86 [CI, 0.54 to 1.37]) that included the possibility of a null effect (Table 4).

Sensitivity Analyses

In the analysis that did not censor on treatment discontinuation and followed patients for up to 365 days after the index date, propensity score–matched results were consistent with our primary findings, suggesting a lower rate of stroke or systemic embolism (HR, 0.80 [CI, 0.68 to 0.94]) and gastrointestinal or intracranial bleeding (HR, 0.61 [CI, 0.54 to 0.68]) with apixaban relative to rivaroxaban.

In the analysis that stratified on the propensity score, the HRs for stroke or systemic embolism (HR, 0.79 [CI, 0.67 to 0.94]) and major bleeding (HR, 0.61 [CI, 0.54 to 0.68]) were lower for apixaban than rivaroxaban and the point estimates were similar to the results from our primary analysis. For the composite outcome that included both stroke or systemic embolism and major bleeding, the rate was lower for apixaban than rivaroxaban (19.4 vs. 29.5 per 1000 person-years) and corresponded to an HR of 0.65 (CI, 0.59 to 0.72).

Assessing the Impact of Unmeasured Confounding

The E-value corresponding to the lower bound for our main effectiveness outcome was 1.16 (E-value for point estimate, 1.74), and that for our main safety outcome was 2.40 (E-value for point estimate, 2.84). Thus, our observed HR for the effectiveness outcome could be explained away by an unmeasured confounder that occurs 1.16 times more often in the rivaroxaban group, increases the rate of the effectiveness outcome by 16%, and is not correlated with the measured confounders we included in the propensity score. Likewise, our observed HR for the main safety outcome could be explained away by an unmeasured confounder that was associated with rivaroxaban versus apixaban use and major bleeding by a risk ratio of 2.40-fold each, above and beyond the measured confounders included in the propensity score.

Negative Control

Within the propensity score–matched population, the rate of heart failure hospitalization was 91 per 1000 person-years with apixaban and 90 per 1000 person-years with rivaroxaban. As anticipated, this corresponded to a similar rate for the 2 groups (HR, 1.00 [CI, 0.95 to 1.05]).

DISCUSSION

In this study of more than 90 000 patients with atrial fibrillation in the United States, apixaban was associated with a lower rate of stroke or systemic embolism, as well as bleeding, compared with rivaroxaban. Findings were robust across several subgroup and sensitivity analyses, including a population restricted to patients older than 70 years. As a negative control, we also assessed the rate of heart failure hospitalization

and found that it was similar for patients prescribed apixaban and those prescribed rivaroxaban (HR, 1.00 [CI, 0.95 to 1.05]). This finding provides reassurance that our analyses were internally valid but, of course, does not guarantee it because the risk factors for heart failure and our study outcomes may differ.

The results of our study are concordant with those of the first indirect comparison among randomized controlled trials suggesting that apixaban was safer than rivaroxaban and with those of subsequent network meta-analyses (15, 33). Of the 21 available network meta-analyses, 16 found a lower rate of major bleeding with apixaban compared with rivaroxaban (33, 34). The relative reduction in the bleeding rate was about 30%, which is similar to our findings (33). Although the definition of major bleeding varied among the network meta-analyses, most definitions were a composite that included both intracranial hemorrhage and gastrointestinal bleeding (33).

Several observational studies indirectly compared apixaban with rivaroxaban through a common comparator group that received warfarin (35–40). Other observational studies directly compared patients receiving apixaban with those receiving rivaroxaban. One study found a decreased risk for major bleeding with apixaban relative to rivaroxaban. It did not identify a difference in the rate of stroke or systemic embolism; however, the study's small sample size (n = 6565 receiving apixaban) may have resulted in it being underpowered to detect this difference (19). An industry-funded observational study of patients covered by Medicare or private insurance also reported a decreased risk for major bleeding with apixaban, as well as a decreased risk for stroke, with a point estimate similar to our findings (16). Finally, a study of patients covered by Medicare identified a lower risk for bleeding with apixaban versus rivaroxaban but a similar risk for thromboembolic stroke (17).

As a result of the large sample of patients included in our study, we were also able to assess the rate of potential rare adverse events with rivaroxaban. For example, recent case reports suggest that rivaroxaban might be associated with hepatitis and leukocytoclastic vasculitis (22, 23). Similar to the clinical trial literature, we determined that hepatitis occurs relatively commonly in this patient population (about 12 cases per 1000 person-years); however, we did not identify a higher rate for patients prescribed rivaroxaban. We also assessed the rate of vasculitis and determined it to be low (about 1 per 1000 person-years), and although a slightly lower rate was found for apixaban, the CIs are wide and include the possibility of null effect.

Our observational study had several limitations. First, we were unable to balance unmeasured confounding factors. For example, we lacked information on over-the-counter prescriptions (such as aspirin) (37), and we could not include laboratory values in our propensity score because of missing data. However, using propensity score matching, we could effectively balance other measured confounders, and we were able to balance laboratory values among the subset of matched patients for whom data were available. Although this does not guarantee that other unmeasured variables (such as body mass index and providers' therapeutic preference) were balanced after matching, the ability to balance other unmeasured variables is supported by a recent study demonstrating that propensity score matching within a claims database balanced unmeasured variables that were subsequently available through linking the claims database to electronic health records (41). These variables included body mass index, tobacco and alcohol use, duration of atrial fibrillation, and HAS-BLED bleeding risk scores (41).

Second, our outcomes were defined by using ICD-9 and ICD-10 diagnosis codes rather than outcome adjudication. However, these codes generally have adequate positive predictive value, and the quality of the codes probably would not differ between treatment groups (20, 21, 42). Third, as in randomized trials comparing these drugs to warfarin, we did not account for time-varying confounders that might affect a patient's risk for either stroke or bleeding. However, we do not expect time-varying confounding in this study. Fourth, we did not adjust for other provider types (such as emergency medicine physicians and nurse practitioners) or the setting in which the patient was seen for the index prescription (for example, inpatient hospitalization, emergency department, or outpatient clinic). This might result in unmeasured confounding, although we do not anticipate that these factors have a large impact on a patient's risk for systemic embolism or bleeding. Finally, because we had a shorter follow-up relative to the clinical trials of DOACs, we cannot comment on longer-term outcomes. However, bleeding risk with oral anticoagulants is time varying, with the highest risk in the first 30 days after initiation of treatment (43, 44).

Apixaban and rivaroxaban both act through direct, selective, and reversible inhibition of free and clot-bound factor Xa (45). Anti–factor Xa levels may be used to estimate the plasma concentration of rivaroxaban or apixaban, with higher levels indicating higher drug concentrations (46, 47). A randomized study of healthy participants found that apixaban (5 mg twice daily), compared with rivaroxaban (20 mg once daily), was associated with more consistent and stable anti–factor Xa activity (that is, higher trough anti–factor Xa activity and lower peak anti–factor Xa activity) (48). The lower peak anti–factor Xa levels in patients receiving apixaban might account for the lower rates of major bleeding, whereas the higher trough levels may explain the lower rates of stroke and systemic embolism. These proposed mechanisms are supported further by a recent study of patients with nonvalvular atrial fibrillation that showed lower peak prothrombin time (a measure associated with anticoagulant activity) and higher trough prothrombin time with apixaban compared with rivaroxaban (46).

Apixaban may be safer and more effective than rivaroxaban for treating nonvalvular atrial fibrillation. Until head-to-head clinical trial data are available, the results of our study, which included a large sample of patients seen in routine care, provides updated evi-

dence in support of apixaban for treating nonvalvular atrial fibrillation.

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Reproducible Research Statement: *Study protocol and statistical code:* Available from Dr. Fralick (e-mail, mike.fralick@mail.utoronto.ca). *Data set:* Available by license through Optum (e-mail, connected@optum.com).

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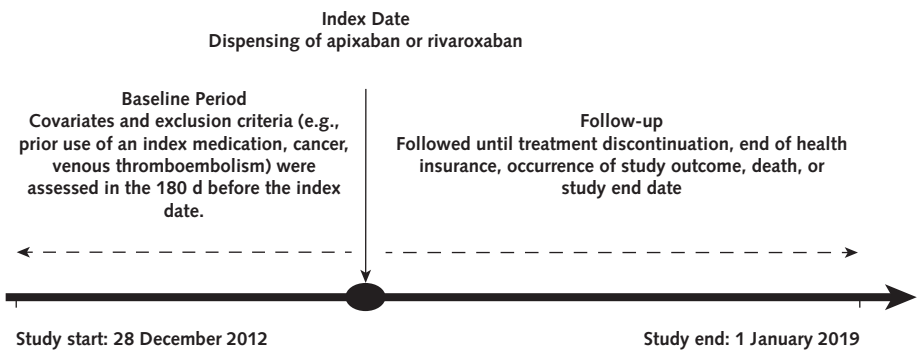
Appendix Figure 1. Cohort creation diagram.



Covariates include chronic medical conditions, health care use, laboratory values, medications, and recent visits to a cardiologist or general internist (within 3 days of the index date).

Appendix Table 1. Study Outcome Definitions

Outcome	Codes
Stroke or systemic embolism	
ICD-9	433.x1, 434.x1, 436, 444.x, 362.3x
ICD-10	I63.x, I67.81, I67.82, I67.89, H34.0x, H34.1x, H34.2x, I74.x
ICH	
ICD-9	430.x, 431.x, 432.x, 852.0x, 852.2x, 852.4x, 853.x
ICD-10	I60.x, I61.x, I62.0x, I62.1, I62.9, S06.6x, S06.5x, S06.4x, S06.36x
GI bleeding	
ICD-9	456.0, 456.20, 530.21, 530.7, 530.82, 531.00, 531.01, 531.20, 531.21, 531.40, 531.41, 531.60, 531.61, 532.00, 532.01, 532.20, 532.21, 532.40, 532.41, 532.60, 532.61, 533.00, 533.01, 533.20, 533.21, 533.40 533.41, 533.60, 533.61, 534.00, 534.01, 534.20, 534.21, 534.40, 534.41, 534.60, 534.61, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 569.86, 578.0, 578.1, 578.9
ICD-10	I85.01, I85.11, K22.11, K22.6, K22.8, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.01, K29.41, K29.51, K29.61, K29.21, K29.71, K29.91, K29.81, K31.811, K31.82, K57.01, K57.11, K57.13, K57.41, K57.51, K57.53, K57.81, K57.93, K57.21, K57.31, K57.91, K57.33, K66.1, K62.5, K55.21, K63.81, K92.0, K92.1, K92.2
Other bleeding	
ICD-9	078.6, 246.3, 285.1, 286.5, 336.1, 388.69, 360.43, 362.43, 362.81, 363.61, 363.62, 363.72, 364.41, 372.72, 376.32, 377.42, 379.23, 423.0, 459.0, 599.7, 599.70, 599.71, 602.1, 621.4, 626.2, 626.5, 626.7, 626.8, 626.9, 640.8x, 641.8x, 641.9x, 641.3x, 641.1x, 666.1x, 719.1x, 782.7, 784.7, 784.8, 866.01, 866.11, 790.01, 958.2, 998.1, 998.11, 998.12
ICD-10	A98.5, D62, D68.312, D68.318, D68.32, G95.19, H92.2x, H44.81x, H35.73x, H35.6x, H31.30x, H31.31x, H31.41x, H21.0x, H11.3x, H05.23x, H47.02x, H43.1x, I31.2, R58, R31.9, R31.0, N42.1, N85.7, N92.0, N92.3, N93.0, N93.8, N92.6, N93.9, O20.8x, O46.x, O72.x, M25.0x, R23.3, R04.0, R04.1, S37.019, S37.029, S37.019, S37.029, R71.0, T79.2x, D78.2x, E36.0x, E89.1x, G97.3x, G97.5x, H59.1x, H59.3x, H95.2x, H95.4x, I97.4x, I97.6x, J95.6x, J95.83x, K91.6x, K91.84x, L76.0x, L76.2x, M96.8x, N99.6x, N99.82x
Vasculitis	
ICD-9	446.2, 446.29, 709.1, 447.6, 287.0
ICD-10	M31.0, L95.8, L95.9, I77.6, D69.0
Hepatitis	
ICD-9	573.3, 790.4, 794.8
ICD-10	K71.2, K71.9, R74.0, R94.5

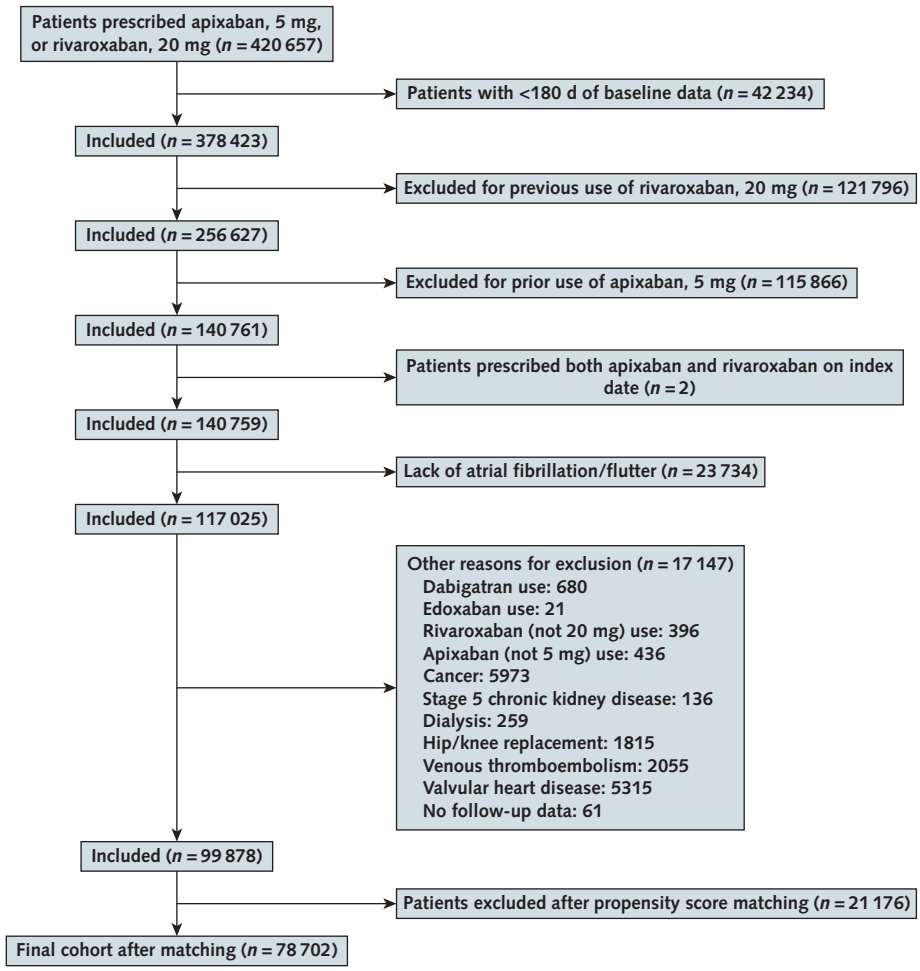
GI = gastrointestinal; ICD-9 = International Classification of Diseases, Ninth Revision; ICD-10 = International Classification of Diseases, 10th Revision; ICH = intracranial hemorrhage.

Appendix Table 2. Statistical Packages

Results	Statistical Function/Package
Aetion*	
Logistic regression	lrm function within rms package
Propensity score matching	Propensity score generated by using the glm() function from the stats package. Propensity score matching was performed by using an in-house algorithm developed by Aetion. Matchit is a commonly used package available in R that closely mirrors this.
Cox proportional hazards model	The coxph() function from the survival package and the cph() function from the rms package
Poisson model	To estimate rate differences, we used a Poisson model. To obtain the 95% CI, we used the following formula for the SE of the rate difference: sqrt((e1/(t1*t1)) + (e2/(t2*t2))), where e1 and e2 are the numbers of events for apixaban and rivaroxaban, and t1 and t2 are the amounts of person-time.
Creation of tables	Performed by using an in-house algorithm developed by Aetion. Tableone is a commonly used package that closely mirrors this.
Kaplan–Meier curves	Survminer, survival, ggplot2

* Aetion used R, version 3.4.2 (The R Foundation).

Appendix Figure 2. Study diagram.



Appendix Table 3. Complete Baseline Characteristics*

Characteristic	Before Matching			After Matching		
	Rivaroxaban Group (*n* = 40 706)	Apixaban Group (*n* = 59 172)	Standardized Difference	Rivaroxaban Group (*n* = 39 351)	Apixaban Group (*n* = 39 351)	Standardized Difference
Quarter of cohort entry date, *n* (%)						
First	10 395 (25.5)	14 099 (23.8)	0.073	9920 (25.2)	9957 (25.3)	0.003
Second	9640 (23.7)	13 057 (22.1)	–	9202 (23.4)	9206 (23.4)	–
Third	10 396 (25.5)	15 443 (26.1)	–	10 112 (25.7)	10 118 (25.7)	–
Fourth	10 275 (25.2)	16 573 (28.0)	–	10 117 (25.7)	10 070 (25.6)	–
Sex, *n* (%)			0.099			0.003
Male	24 909 (61.2)	33 344 (56.4)	–	23 770 (60.4)	23 743 (60.3)	–
Female	15 791 (38.8)	25 823 (43.6)	–	15 577 (39.6)	15 603 (39.7)	–
Unknown	6 (0.0)	5 (0.0)	–	4 (0.0)	5 (0.0)	–
Mean age (SD), *y*	68.9 (10.9)	70.8 (10.0)	0.181	69.3 (10.6)	69.4 (10.5)	0.004
Comorbid conditions, *n* (%)						
Ischemic stroke or TIA	3678 (9.0)	6715 (11.3)	0.076	3627 (9.2)	3678 (9.3)	0.004
Intracranial hemorrhage	249 (0.6)	563 (1.0)	0.039	248 (0.6)	246 (0.6)	0.001
Heart failure	8706 (21.4)	15 129 (25.6)	0.099	8518 (21.6)	8482 (21.6)	0.002
$CHADS_2$ score						
0	5350 (13.1)	5899 (10.0)	0.099	4904 (12.5)	5015 (12.7)	0.008
1	17 583 (43.2)	22 562 (38.1)	0.103	16 944 (43.1)	16 672 (42.4)	0.014
≥2	17 773 (43.7)	30 711 (51.9)	0.166	17 503 (44.5)	17 664 (44.9)	0.002
Ischemic heart disease	15 421 (37.9)	27 517 (46.5)	0.175	15 282 (38.8)	15 299 (38.9)	0.001
CABG or PCI	3645 (9.0)	7395 (12.5)	0.115	3635 (9.2)	3665 (9.3)	0.003
Hypertension	32 287 (79.3)	49 224 (83.2)	0.099	31 479 (80.0)	31 492 (80.0)	0.001
Hyperlipidemia	25 518 (62.7)	39 975 (67.6)	0.102	24 983 (63.5)	24 947 (63.4)	0.002
Peripheral vascular disease	4884 (12.0)	9551 (16.1)	0.119	4848 (12.3)	4827 (12.3)	0.002
Acute kidney injury	2101 (5.2)	5278 (8.9)	0.147	2094 (5.3)	2130 (5.4)	0.004
Chronic kidney injury	4264 (10.5)	9591 (16.2)	0.169	4236 (10.8)	4171 (10.6)	0.005
Chronic kidney disease (stage 3 or 4)	2534 (6.2)	6621 (11.2)	0.177	2533 (6.4)	2455 (6.2)	0.008
Bleeding						
GI	1159 (2.8)	2039 (3.4)	0.034	1138 (2.9)	1133 (2.9)	0.001
Other	2593 (6.4)	4115 (7.0)	0.023	2523 (6.4)	2516 (6.4)	0.001
Liver disease	297 (0.7)	522 (0.9)	0.017	291 (0.7)	278 (0.7)	0.004
Smoking	8137 (20.0)	15 120 (25.6)	0.133	8071 (20.5)	8076 (20.5)	0
Obesity or overweight	11 372 (27.9)	19 977 (33.8)	0.126	11 219 (28.5)	11 222 (28.5)	0
Syncope	2763 (6.8)	4740 (8.0)	0.047	2720 (6.9)	2728 (6.9)	0.001
Glaucoma or cataracts	7128 (17.5)	11 246 (19.0)	0.039	6985 (17.8)	7019 (17.8)	0.002
Medications, *n* (%)						
Antiplatelets	3812 (9.4)	6881 (11.6)	0.074	3777 (9.6)	3806 (9.7)	0.002
Nonsteroidal anti-inflammatory drugs	5237 (12.9)	7791 (13.2)	0.009	5099 (13.0)	5095 (12.9)	0
Warfarin						
90–180 d before index date	5649 (13.9)	6367 (10.8)	0.095	5102 (13.0)	5098 (13.0)	0
31–89 d before index date	5671 (13.9)	6343 (10.7)	0.098	5126 (13.0)	5123 (13.0)	0
1–30 d before index date	5352 (13.1)	5523 (9.3)	0.121	4743 (12.1)	4724 (12.0)	0.001
Proton-pump inhibitors	9432 (23.2)	15 383 (26.0)	0.066	9251 (23.5)	9148 (23.2)	0.006
Angiotensin-converting enzyme inhibitors	13 848 (34.0)	20 578 (34.8)	0.016	13 421 (34.1)	13 364 (34.0)	0.003
Angiotensin II–receptor blockers	8997 (22.1)	14 396 (24.3)	0.053	8810 (22.4)	8821 (22.4)	0.001
β-Blockers	26 607 (65.4)	40 610 (68.6)	0.07	25 914 (65.9)	25 930 (65.9)	0.001
Calcium-channel blockers	8076 (19.8)	13 556 (22.9)	0.075	7942 (20.2)	7914 (20.1)	0.002
Nitrates	2676 (6.6)	4942 (8.4)	0.068	2650 (6.7)	2668 (6.8)	0.002
Antiarrhythmics	7521 (18.5)	11 804 (19.9)	0.037	7311 (18.6)	7296 (18.5)	0.001
Digoxin	3656 (9.0)	4354 (7.4)	0.059	3343 (8.5)	3341 (8.5)	0
Statins	21 624 (53.1)	34 369 (58.1)	0.1	21 171 (53.8)	21 179 (53.8)	0
Other lipid-lowering drugs	1876 (4.6)	2909 (4.9)	0.014	1830 (4.7)	1817 (4.6)	0.002
Diuretics	13 447 (33.0)	22 228 (37.6)	0.095	13 152 (33.4)	13 100 (33.3)	0.003
Older-generation antihypertensives	2298 (5.6)	4041 (6.8)	0.049	2257 (5.7)	2155 (5.5)	0.011
Metformin	6722 (16.5)	10 249 (17.3)	0.022	6560 (16.7)	6579 (16.7)	0.001
Insulin	2734 (6.7)	4833 (8.2)	0.055	2675 (6.8)	2656 (6.7)	0.002
Opioids	9912 (24.4)	14 964 (25.3)	0.022	9572 (24.3)	9532 (24.2)	0.002
Anxiolytics	6748 (16.6)	9948 (16.8)	0.006	6517 (16.6)	6486 (16.5)	0.002
Oral steroids	6128 (15.1)	9942 (16.8)	0.048	5979 (15.2)	5995 (15.2)	0.001
Bisphosphonates	1201 (3.0)	1686 (2.8)	0.006	1163 (3.0)	1177 (3.0)	0.002
Antidepressants	8770 (21.5)	13 991 (23.6)	0.05	8545 (21.7)	8523 (21.7)	0.001

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Appendix Table 3–Continued

Characteristic	Before Matching			After Matching		
	Rivaroxaban Group (*n* = 40 706)	Apixaban Group (*n* = 59 172)	Standardized Difference	Rivaroxaban Group (*n* = 39 351)	Apixaban Group (*n* = 39 351)	Standardized Difference
Mean total medications (SD), *n*	9.2 (5.1)	9.9 (5.3)	0.136	9.3 (5.1)	9.3 (5.1)	0.001
Laboratory values						
Creatinine level						
Mean (SD)						
mg/dL	0.98 (0.26)	1.03 (0.34)	0.158	0.98 (0.26)	1.01 (0.30)	0.077
μmol/L	86.6 (23.0)	91.1 (30.1)	–	86.6 (23.0)	89.3 (26.5)	–
Missing, *n (%)*	27 807 (68.3)	38 646 (65.3)	–	26 771 (68.0)	26 300 (66.8)	–
Hemoglobin level						
Mean (SD), *g/L*	139.1 (1.73)	137.0 (1.75)	0.123	138.9 (1.73)	138.9 (1.73)	0.001
Missing, *n (%)*	30 867 (75.8)	43 529 (73.6)	–	29 756 (75.6)	29 382 (74.7)	–
Health care use						
General internist visits, *n (%)*†	7704 (18.9)	11 771 (19.9)	0.024	7492 (19.0)	7434 (18.9)	0.004
Cardiologist visits, *n (%)*†	13 219 (32.5)	19 181 (32.4)	0.001	12 750 (32.4)	12 666 (32.2)	0.005
Mean ED visits (SD), *n*	5.3 (17.6)	7.0 (18.7)	0.096	5.4 (17.8)	5.5 (15.6)	0.006
Mean outpatient visits (SD), *n*	5.5 (4.2)	5.7 (4.2)	0.056	5.5 (4.2)	5.5 (4.1)	0.003
Ordering of metabolic panel, *n (%)*‡	21 217 (52.1)	33 842 (57.2)	0.102	20 819 (52.9)	20 835 (52.9)	0.001
Ordering of CRP test, *n (%)*	1350 (3.3)	2226 (3.8)	0.024	1327 (3.4)	1340 (3.4)	0.002
Ordering of albumin test, *n (%)*	426 (1.0)	676 (1.1)	0.009	417 (1.1)	406 (1.0)	0.003
Preventive health measures, *n (%)*	15 923 (39.1)	23 143 (39.1)	0	15 477 (39.3)	15 499 (39.4)	0.001

CABG = coronary artery bypass grafting; CRP = C-reactive protein; ED = emergency department; GI = gastrointestinal; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.
* Baseline characteristics were assessed up to 180 d before the index date unless otherwise specified.
† Up to 3 d before and including index date.
‡ Metabolic panel generally includes serum creatinine and electrolytes.

Appendix Table 4. Reasons for Censoring Among Propensity Score–Matched Population

Reason	Apixaban Group, *n (%)*	Rivaroxaban Group, *n (%)*
End of insurance coverage*	5094 (12.9)	5872 (14.9)
End of available data	9912 (25.2)	6295 (16.0)
Medication discontinuation	23 634 (60.1)	25 978 (66.0)
Switching to comparator medication	505 (1.3)	955 (2.4)
Study outcome	206 (0.5)	251 (0.6)
Total	39 351	39 351

* Includes death.

Appendix Figure 3. Schoenfeld residual plot for the primary effectiveness outcome (*top*) and primary safety outcome (*bottom*).