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Risk for Recurrent Venous Thromboembolism and Bleeding With Apixaban Compared With Rivaroxaban: An Analysis of Real-World Data

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Background: Apixaban and rivaroxaban are replacing vitamin K antagonists for the treatment of venous thromboembolism (VTE) in adults; however, head-to-head comparisons remain limited.

Objective: To assess the effectiveness and safety of apixaban compared with rivaroxaban in patients with VTE.

Design: Retrospective new-user cohort study.

Setting: U.S.-based commercial health care insurance database from 1 January 2015 to 30 June 2020.

Participants: Adults with VTE who were newly prescribed apixaban or rivaroxaban.

Measurements: The primary effectiveness outcome was recurrent VTE, a composite of deep venous thrombosis and pulmonary embolism. The primary safety outcome was a composite of gastrointestinal and intracranial bleeding.

Results: Of 49 900 eligible patients with VTE, 18 618 were new users of apixaban and 18 618 were new users of rivaroxaban. Median follow-up was 102 days (25th, 75th percentiles: 30, 128 days) among apixaban and 105 days (25th, 75th percentiles: 30, 140 days) among rivaroxaban users. After propensity score matching, apixaban (vs. rivaroxaban) was associated with a lower rate for recurrent VTE (hazard ratio, 0.77 [95% CI, 0.69 to 0.87]) and bleeding (hazard ratio, 0.60 [CI, 0.53 to 0.69]). The absolute reduction in the probability of recurrent VTE with apixaban versus rivaroxaban was 0.006 (CI, 0.005 to 0.011) within 2 months and 0.011 (CI, 0.011 to 0.013) within 6 months of initiation. The absolute reduction in the probability of gastrointestinal and intracranial bleeding with apixaban versus rivaroxaban was 0.011 (CI, 0.010 to 0.011) within 2 months and 0.015 (CI, 0.013 to 0.015) within 6 months of initiation.

Limitation: Short follow-up.

Conclusion: In this population-based cohort study, patients with VTE who were new users of apixaban had lower rates for recurrent VTE and bleeding than new users of rivaroxaban.

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Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep venous thrombosis (DVT), affects 100 persons per 100 000 each year in the United States (1). Approximately 20% to 28% of patients with VTE experience recurrent VTE within 5 years of initial diagnosis (2). Oral anticoagulants, including direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) (such as warfarin), reduce the risk for recurrent VTE and are recommended by national and international treatment guidelines (3, 4).

Compared with warfarin, DOACs have fewer drug–drug interactions, lower bleeding rates, and fixed dosing, and they do not require routine laboratory monitoring. Among DOACs, apixaban and rivaroxaban are increasingly being used and are replacing VKAs (5). To date, there are no head-to-head randomized clinical trials (RCTs) of apixaban versus rivaroxaban in patients with VTE. In the AMPLIFY (Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy) trial, apixaban was noninferior to warfarin (with enoxaparin bridging) for the treatment of acute VTE and was associated with significantly less bleeding (6). In the EINSTEIN DVT and EINSTEIN PE (Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis or Pulmonary Embolism) trials, rivaroxaban was noninferior to warfarin or acenocoumarol (with enoxaparin bridging) and was associated with a similar risk for bleeding (7, 8).

Randomized clinical trials comparing apixaban with rivaroxaban in patients with VTE are under way (for example, COBRRA [Comparison of Bleeding Risk Between Rivaroxaban and Apixaban for the Treatment of Acute Venous Thromboembolism]: NCT03266783). Until the results from these trials become available (the estimated completion date for COBRRA is December 2023), observational studies that use existing data can provide evidence on the effectiveness and safety of these alternatives to inform clinical practice. A limited number of observational studies have compared apixaban and rivaroxaban (9, 10), but these studies had a relatively small sample size (n = 1504 to 3000 for apixaban) or included data up to 2015, a year after apixaban was approved by the U.S. Food and Drug Administration for treatment of VTE. Because apixaban use during its first year of approval may not have reflected treatment uptake in later years, we sought to compare the effectiveness and safety of apixaban and rivaroxaban among adults with VTE in an independent data set of more than 28 000 apixaban users, using data through 2020 and including sociodemographic factors and laboratory measures for a subset of the cohort.

Table 1. Demographic and Clinical Characteristics of New Users of Apixaban and Rivaroxaban Among Patients With VTE

Characteristic	Prematching Cohort			Postmatching Cohort		
	Apixaban (*n* = 28 287)	Rivaroxaban (*n* = 21 613)	Standardized Difference	Apixaban (*n* = 18 618)	Rivaroxaban (*n* = 18 618)	Standardized Difference
Demographic characteristics						
Mean age (SD), *y*	70.3 (14.3)	65.7 (15.6)	0.33	67.4 (15.1)	67.5 (14.8)	0.01
Male sex, *n (%)*	12 729 (45.0)	10 411 (48.2)	0.06	8839 (47.5)	8823 (47.4)	0.00
Division, *n (%)*			0.08			0.00
East North Central	3846 (13.6)	3568 (16.5)	–	2869 (15.4)	2881 (15.5)	–
East South Central	1526 (5.4)	865 (4.0)	–	766 (4.1)	828 (4.4)	–
Middle Atlantic	2111 (7.5)	1771 (8.2)	–	1485 (8.0)	1474 (7.9)	–
Mountain	2627 (9.3)	2508 (11.6)	–	2031 (10.9)	2001 (10.7)	–
New England	897 (3.2)	698 (3.2)	–	626 (3.4)	610 (3.3)	–
Pacific	2629 (9.3)	1946 (9.0)	–	1745 (9.4)	1728 (9.3)	–
South Atlantic	8839 (31.2)	5713 (26.4)	–	5258 (28.2)	5240 (28.1)	–
West North Central	1751 (6.2)	1863 (8.6)	–	1401 (7.5)	1407 (7.6)	–
West South Central	4020 (14.2)	2652 (12.3)	–	2407 (12.9)	2424 (13.0)	–
Unknown	41 (0.1)	29 (0.1)	–	30 (0.2)	25 (0.1)	–
Insurance type, *n (%)*			0.04			0.00
Exclusive provider organization	1015 (3.6)	1001 (4.6)	–	820 (4.4)	805 (4.3)	–
Health maintenance organization	9089 (32.1)	6848 (31.7)	–	6064 (32.6)	6048 (32.5)	–
Indemnity	209 (0.7)	136 (0.6)	–	128 (0.7)	129 (0.7)	–
Other	9578 (33.9)	5186 (24.0)	–	4972 (26.7)	5008 (26.9)	–
Point of service	4838 (17.1)	5888 (27.2)	–	4357 (23.4)	4333 (23.3)	–
Preferred provider organization	3558 (12.6)	2554 (11.8)	–	2277 (12.2)	2295 (12.3)	–
Provider categories, *n (%)*			0.06			0.00
Cardiology	1679 (5.9)	940 (4.3)	–	905 (4.9)	926 (5.0)	–
Emergency medicine	599 (2.1)	797 (3.7)	–	520 (2.8)	536 (2.9)	–
Family practice	4147 (14.7)	2952 (13.7)	–	2659 (14.3)	2630 (14.1)	–
General surgery	185 (0.7)	178 (0.8)	–	145 (0.8)	136 (0.7)	–
Geriatric medicine	109 (0.4)	63 (0.3)	–	61 (0.3)	61 (0.3)	–
Hematology and oncology	1428 (5.0)	1629 (7.5)	–	1226 (6.6)	1239 (6.7)	–
Internal medicine	9067 (32.1)	6315 (29.2)	–	5748 (30.9)	5748 (30.9)	–
Nephrology	187 (0.7)	74 (0.3)	–	72 (0.4)	72 (0.4)	–
Orthopedics	174 (0.6)	409 (1.9)	–	193 (1.0)	170 (0.9)	–
Other nonphysician provider	597 (2.1)	513 (2.4)	–	417 (2.2)	428 (2.3)	–
Other physician specialty	4061 (14.4)	3209 (14.8)	–	2799 (15.0)	2786 (15.0)	–
Physical medicine and rehabilitation	347 (1.2)	202 (0.9)	–	176 (0.9)	183 (1.0)	–
Psychiatry	87 (0.3)	73 (0.3)	–	57 (0.3)	62 (0.3)	–
Pulmonary medicine	498 (1.8)	386 (1.8)	–	340 (1.8)	344 (1.8)	–
Registered nurse	827 (2.9)	543 (2.5)	–	501 (2.7)	495 (2.7)	–
Vascular surgery	209 (0.7)	213 (1.0)	–	164 (0.9)	166 (0.9)	–
Others	878 (3.1)	819 (3.8)	–	2045 (11.0)	2060 (11.1)	–
Unknown	3208 (11.3)	2298 (10.6)	–	590 (3.2)	576 (3.1)	–
Baseline comorbid conditions, *n (%)*						
Alcohol use disorder	1222 (4.3)	896 (4.1)	0.01	793 (4.3)	768 (4.1)	0.01
Anemia	4840 (17.1)	3134 (14.5)	0.07	2819 (15.1)	2796 (15.0)	0.00
Angina	782 (2.8)	471 (2.2)	0.04	433 (2.3)	433 (2.3)	0.00
Cancer	6273 (22.2)	4703 (21.8)	0.01	3979 (21.4)	4171 (22.4)	0.03
Chronic kidney disease	11 551 (40.8)	6042 (28.0)	0.26	5681 (30.5)	5765 (31.0)	0.01
Chronic lung disease	10 127 (35.8)	6577 (30.4)	0.11	5906 (31.7)	5941 (31.9)	0.00
Coronary artery disease	372 (1.3)	249 (1.2)	0.01	224 (1.2)	229 (1.2)	0.00
Diabetes	9937 (35.1)	5871 (27.2)	0.17	5491 (29.5)	5478 (29.4)	0.00
Drug misuse disorder	1490 (5.3)	984 (4.6)	0.03	874 (4.7)	877 (4.7)	0.00
End-stage renal disease	614 (2.2)	81 (0.4)	0.12	279 (1.5)	76 (0.4)	0.09
Heart failure	7752 (27.4)	3746 (17.3)	0.23	3619 (19.4)	3623 (19.5)	0.00
Hemophilia	37 (0.1)	82 (0.4)	0.07	37 (0.2)	35 (0.2)	0.00
HIV infection	123 (0.4)	81 (0.4)	0.01	70 (0.4)	76 (0.4)	0.01
Hyperlipidemia	14 756 (52.2)	9438 (43.7)	0.17	8670 (46.6)	8611 (46.3)	0.01
Hypertension	21 538 (76.1)	14 026 (64.9)	0.26	12 783 (68.7)	12 840 (69.0)	0.01
Liver disease	3489 (12.3)	2320 (10.7)	0.05	2078 (11.2)	2101 (11.3)	0.00
Peripheral vascular disease	7602 (26.9)	3922 (18.1)	0.20	3769 (20.2)	3769 (20.2)	0.00
Stroke	7755 (27.4)	3375 (15.6)	0.26	3604 (19.4)	3255 (17.5)	0.05
Tobacco use	54 (0.2)	16 (0.1)	0.03	16 (0.1)	16 (0.1)	0.00
Transient ischemic attack	3981 (14.1)	3215 (14.9)	0.02	2734 (14.7)	2698 (14.5)	0.01
Ulcer	2663 (9.4)	1358 (6.3)	0.11	1264 (6.8)	1292 (6.9)	0.01

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Table 1–Continued

Characteristic	Prematching Cohort			Postmatching Cohort		
	Apixaban (*n* = 28 287)	Rivaroxaban (*n* = 21 613)	Standardized Difference	Apixaban (*n* = 18 618)	Rivaroxaban (*n* = 18 618)	Standardized Difference
Baseline medications, *n* (%)						
ACE inhibitors	8177 (28.9)	5284 (24.4)	0.10	4835 (26.0)	4832 (26.0)	0.00
Aldosterone antagonists	1411 (5.0)	743 (3.4)	0.07	686 (3.7)	692 (3.7)	0.00
α-Adrenergic blockers	3434 (12.1)	2067 (9.6)	0.08	1915 (10.3)	1931 (10.4)	0.00
Antiplatelet	5008 (17.7)	2438 (11.3)	0.11	2340 (12.6)	2346 (12.6)	0.00
ARBs	6176 (21.8)	3727 (17.2)	0.11	3468 (18.6)	3492 (18.8)	0.00
β-Blockers	9705 (34.3)	5389 (24.9)	0.20	5070 (27.2)	5097 (27.4)	0.00
CCBs	8435 (29.8)	4602 (21.3)	0.19	4305 (23.1)	4358 (23.4)	0.01
Direct vasodilators	1137 (4.0)	383 (1.8)	0.11	390 (2.1)	380 (2.0)	0.00
Loop diuretics	6585 (23.3)	3386 (15.7)	0.18	3271 (17.6)	3216 (17.3)	0.01
NSAIDs	5745 (20.3)	4671 (21.6)	0.03	3943 (21.2)	3924 (21.1)	0.00
Potassium diuretics	1474 (5.2)	774 (3.6)	0.07	711 (3.8)	721 (3.9)	0.00
PPIs	9286 (32.8)	5978 (27.7)	0.11	5404 (29.0)	5416 (29.1)	0.00
SSRIs	5306 (18.8)	3679 (17.0)	0.04	3271 (17.6)	3233 (17.4)	0.01
Statins	13 616 (48.1)	8336 (38.6)	0.19	7721 (41.5)	7723 (41.5)	0.00
Thiazide diuretics	6899 (24.4)	4559 (21.1)	0.08	4145 (22.3)	4155 (22.3)	0.00
Measures of health care use (SD), *n*						
Mean inpatient visits	1.7 (1.6)	1.3 (1.4)	0.24	1.4 (1.3)	1.4 (1.4)	0.00
Mean prescriptions	39.0 (37.6)	32.9 (35.0)	0.16	34.6 (36.0)	34.5 (35.7)	0.02
Mean procedures	1.9 (2.7)	1.8 (2.6)	0.03	1.8 (2.8)	1.8 (2.6)	0.00

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton-pump inhibitor; SSRI = selective serotonin reuptake inhibitor; VTE = venous thromboembolism.

METHODS

Database

We used commercial data from Optum's deidentified Clinformatics Data Mart Database, which captures the health care experience of a privately insured population in the United States. The administrative database includes deidentified individual-level data on enrollment, patient demographics, outpatient claims, inpatient claims, prescription drug claims, and laboratory data for a subset of beneficiaries. At the University of Pennsylvania, studies using the Optum Clinformatics Data Mart Database are categorized as exempt from requiring institutional review board approval.

Study Population

We performed a retrospective new-user cohort study of patients with VTE who had at least 1 prescription dispensed for apixaban or rivaroxaban from 1 January 2015 to 30 June 2020. We assigned the date of the first prescription for apixaban or rivaroxaban as the cohort entry date. We required patients to have 12 months of continuous enrollment before the first eligible prescription to ascertain patients' demographics, comorbid conditions, and prior drug use. We included patients who had a diagnosis of VTE documented in at least 1 inpatient encounter and who initiated treatment with apixaban or rivaroxaban within 30 days of diagnosis (**Appendix Figure 1**, available at Annals.org). International Classification of Diseases, Ninth (or Tenth) Revision, Clinical Modification (ICD-9-CM or ICD-10-CM), codes for VTE in the primary or principal position have a positive predictive value (PPV) of 95% (95% CI, 93% to 97%) (11). We did not consider VTE events in the secondary position because the PPV is substantially lower (PPV, 75% [CI, 71% to 80%]) (11). Similarly, we did not consider VTE cases documented in outpatient claims, because they have poor PPV in identifying incident cases (PPV, 31%) (12). We included new users of apixaban or rivaroxaban aged at least 18 years at cohort entry. Because we were interested in capturing incident rather than prevalent VTE, patients with either a prescription for an anticoagulant during the lookback period or a diagnosis of PE or DVT before their index VTE diagnosis were excluded (**Appendix Table 1**, available at Annals.org).

Exposure Ascertainment

We identified new users of apixaban or rivaroxaban as patients without use during the 12-month lookback period. We excluded patients who initiated both medications on the same date. We considered patients exposed if they refilled prescriptions, allowing a gap between refills of no longer than 7 days.

Outcome Ascertainment

The primary effectiveness outcome was recurrent VTE defined as a composite of DVT and PE identified using ICD-9-CM and ICD-10-CM codes listed in the primary position in the inpatient discharge claims. The primary safety outcome was a composite of intracranial and gastrointestinal bleeding identified using ICD-9-CM and ICD-10-CM codes listed in the primary position in the inpatient discharge claims. Diagnosis codes for bleeding events had a PPV of 89% (CI, 83% to 92%) (13). We did not consider bleeding events documented in the outpatient setting but rather focused on bleeding resulting in hospitalization (14).

Follow-up

Follow-up began on the cohort entry date (that is, initiation of apixaban or rivaroxaban) and ended at the earliest occurrence of an outcome of interest end of the

study period, or censoring due to disenrollment from the health plan for more than 30 days, treatment discontinuation, or initiation of the comparator (for example, apixaban user initiates rivaroxaban).

Confounder Adjustment

We included confounders on the basis of their probability of having an association with VTE or bleeding, including demographics (for example, age [15, 16] and sex), risk factors for VTE (17–19) (for example, cancer), risk factors for bleeding (for example, coagulation defect [20]), baseline medications, and measures of intensity of health care utilization (for example, total number of hospitalizations). We used previously validated definitions of confounders (21, 22). We classified users of apixaban and rivaroxaban on the basis of incident VTE type into 2 groups: VTE provoked by transient risk factors (for example, trauma, pregnancy, postpartum, surgery), and VTE that was either provoked by chronic risk factors (for example, cancer) or unprovoked (23, 24).

Statistical Analysis

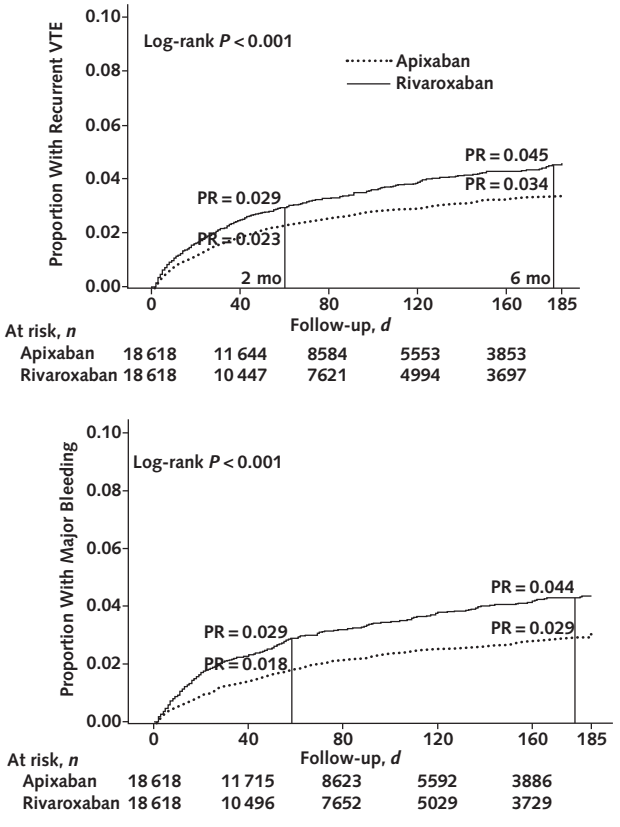
We used propensity score (PS) matching to reduce differences in baseline characteristics between new users of apixaban and rivaroxaban. We selected this method to balance potential confounders because PS allows for the adjustment of a large number of potential confounders by creating 1 summary score; PS matching minimizes the potential for confounding by indication; and unlike regression models, PS matching emulates an RCT, because the study design is separated from the outcome analysis (25). We calculated PS using a logistic regression model (PROC LOGISTIC in SAS; SAS Institute) that predicted the probability of initiating apixaban compared with rivaroxaban as a function of the 45 variables listed in Table 1. We did not include in the PS model sociodemographic factors (that is, education level, race, and income) or laboratory values (that is, creatinine, hemoglobin A_{1c}, cholesterol, and triglyceride levels), because these data were missing for 22% (sociodemographic factors) and 90% (laboratory values) of patients. No other data were missing in our study.

In the primary analysis, we matched without replacement each apixaban user to a rivaroxaban user using 1:1 matching. After randomly sorting the data, we selected the first apixaban user to find its closest rivaroxaban match based on a maximum caliper width of 0.1 of SD of the logit of PS. We used caliper matching because it performed better than optimal or greedy matching when assessed using mean squared error (26). We selected a caliper of 0.2 or less of the SD because prior studies showed that this would eliminate at least 98% of the bias in the crude estimator (27). We used absolute standardized differences, which are not affected by the sample size, to assess the balance before and after PS matching (28). We calculated the incidence rates of effectiveness and safety outcomes per 100 person-years and plotted the incidence in the matched cohort (NEWSURV macro in SAS). We compared the equality of survival curves using a stratified log-rank test (29). We estimated marginal hazard ratios (HRs) and corresponding 95% CI via Cox proportional hazards regression using a robust variance estimator while adjusting for calendar year (29). We used robust variance estimation to account for the lack of independence in outcomes because of the nature of the matched sample (29). We assessed proportional hazards assumptions using Schoenfeld residuals.

Sensitivity and Subgroup Analyses

We conducted several sensitivity analyses to assess the robustness of the primary findings. First, we increased the gap between contiguous refills from 7 days to 15 and 30 days. Second, we symmetrically trimmed the tails of PS to remove extreme observations (<5th and >95th, <15th and >85th, <25th and >75th percentiles). Third, we used inverse probability of treatment weighting (IPTW) average treatment effects (ATE) and average treatment effects on the treated (ATT) as methods of adjustment instead of matching (30). Fourth, we adjusted for PS as a variable in the model instead of matching. Fifth, we used 1:*n* matching with replacement as a method of adjustment. Sixth, we included VTE events occurring in the outpatient setting in the outcome definition. Seventh, we examined the incidence of prostate

Figure. Cumulative incidence curves depicting the risk for recurrent VTE (*top*) and bleeding (*bottom*) in matched cohorts of patients with VTE who were new users of apixaban or rivaroxaban.



PR = probability; VTE = venous thromboembolism.

Table 2. Risk for Recurrent VTE and Bleeding Comparing Apixaban and Rivaroxaban in Patients With VTE*

Outcome	Apixaban				Rivaroxaban				Adjusted Marginal HR (95% CI)
	Patients, n	Events, *n*	PYs of Follow-up	Incidence Rate per 100 PYs	*Patients, n*	Events, *n*	PYs of Follow-up	Incidence Rate per 100 PYs	
Recurrent VTE	18 618	475	5314	8.9	18 618	595	5200	11.4	0.77 (0.69–0.87)
DVT	–	442	5322	8.3	–	501	5223	9.6	0.85 (0.74–0.97)
PE	–	33	5382	0.6	–	94	5276	1.8	0.59 (0.39–0.91)
Bleeding	18 618	386	5344	7.2	18 618	577	5239	11.0	0.60 (0.53–0.69)
GI	–	382	5344	7.0	–	566	5240	10.6	0.60 (0.53–0.69)
Intracranial	–	4	5389	0.2	–	11	5298	0.4	0.54 (0.14–1.20)

DVT = deep venous thrombosis; GI = gastrointestinal; HR = hazard ratio; PE = pulmonary embolism; PY = person-year; VTE = venous thromboembolism.
* Results from Cox proportional hazard models after propensity score 1:1 matching without replacement using a caliper of 0.1 of the SD of the logit of propensity score.

cancer and breast cancer as negative control outcomes. In addition, we assessed residual confounding by examining the distribution of sociodemographic factors and laboratory values before and after matching in a subset of the cohort. We also calculated the E-value to assess the potential for unmeasured confounders (31). The E-value provides, conditional on measured confounders, the minimum needed strength of association among an unmeasured confounder, exposure, and study outcomes to move the observed effect estimates toward the null value of 1 (www.evalue-calculator.com).

We assessed the potential for effect modification within selected subgroups by including an interaction term in the primary models. Clinically relevant subgroups of interest included age, sex, cancer, nonsteroidal anti-inflammatory drug use, antiplatelet use, VTE type (provoked vs. unprovoked), mechanical heart valve, hip or knee replacement, and end-stage renal disease. We performed matching again within each of the selected subgroups and reported the HRs and corresponding CI. We used Bonferroni adjustment to account for multiple testing within subgroup analyses. We considered results statistically significant if the *P* value for interaction was less than or equal to α (that is, 0.05)/*n*, where *n* equals the total number of subgroup analyses (32). We conducted all analyses using SAS, version 9.4.

Role of the Funding Source

No external funding was received for this study.

RESULTS

We identified 28 287 and 21 613 new users of apixaban and rivaroxaban, respectively (**Appendix Figure 2**, available at Annals.org). **Appendix Figure 3** (available at Annals.org) demonstrates a gradual shift in prescribing from warfarin to apixaban and rivaroxaban during the study period. Compared with rivaroxaban users, apixaban users were older (70 vs. 66 years) and had a higher prevalence of chronic kidney disease (41% vs. 28%), diabetes (35% vs. 27%), heart failure (27% vs. 17%), and hypertension (76% vs. 65%) (**Table 1**). After PS matching, we included 18 618 and 18 618 new users of apixaban and rivaroxaban, respectively (**Table 1**). The distribution of PS before and after matching is illustrated in **Appendix Figure 4** (available at Annals.org). All covariates were well balanced after PS matching (standardized difference <0.1) (**Appendix Figure 5**, available at Annals.org). The median follow-up was 102 days (25th, 75th percentiles: 30, 128 days) among apixaban users and 105 days (25th, 75th percentiles: 30, 140 days) among rivaroxaban users. Reasons for censoring were treatment discontinuation (83%; 84% for apixaban and 82% for rivaroxaban), initiation of or switching to the study comparator (13%; 11% for apixaban and 14% for rivaroxaban), and end of enrollment (1.5%; 1.9% for apixaban and 1.2% for rivaroxaban). Among patients with sociodemographic data and after PS matching, 55% had less than a Bachelor's degree, 74% were White, and approximately 30% had an income less than $40 000 per year (**Appendix Table 2**, available at Annals.org). Despite the PS model not including sociodemographic factors and laboratory values (that is, creatinine, hemoglobin A_{1c}, cholesterol, and triglyceride levels), these variables were well balanced after PS matching (**Appendix Tables 2 and 3**, available at Annals.org). Patients' demographics and clinical characteristics were similar between those with and without laboratory values.

Rate of Recurrent VTE

In the matched sample, 475 patients had recurrent VTE among 18 618 apixaban users (8.9 events per 100 person-years) compared with 595 among 18 618 rivaroxaban users (11.4 events per 100 person-years) (HR, 0.77 [CI, 0.69 to 0.87]) (**Figure**, *top*). The absolute reduction in the probability of recurrent VTE with apixaban compared with rivaroxaban was 0.006 (CI, 0.005 to 0.011) within 2 months and 0.011 (CI, 0.011 to 0.013) within 6 months of treatment initiation. Results were consistent for apixaban (vs. rivaroxaban) for DVT (HR, 0.85 [CI, 0.74 to 0.97]) and PE (HR, 0.59 [CI, 0.39 to 0.91]) (**Table 2**).

Rate of Bleeding Events

In the matched sample, 386 patients had gastrointestinal and intracranial bleeding events among 18 618 apixaban users (7.2 events per 100 person-years) compared with 577 among 18 618 rivaroxaban users (11.0 events per 100 person-years) (HR, 0.60 [CI, 0.53 to 0.69]) (**Figure**, *bottom*). The absolute reduction in the probability of gastrointestinal and intracranial bleeding with apixaban compared with rivaroxaban was 0.011 (CI, 0.010 to

0.011) within 2 months and 0.015 (CI, 0.013 to 0.015) within 6 months of treatment initiation. Results were consistent for apixaban (vs. rivaroxaban) for gastrointestinal (HR, 0.60 [CI, 0.53 to 0.69]) and intracranial (HR, 0.54 [CI, 0.14 to 1.20]) bleeding (Table 2).

Results From Sensitivity Analyses

Sensitivity analyses yielded results similar to the primary findings, including when using IPTW ATT and IPTW ATE (Table 3). Analysis of the negative control outcomes resulted in nonsignificant association (HR, 1.01 [CI, 0.90 to 1.15]). The E-value corresponding to the lower bound for the effectiveness outcome was 1.56 (E-value for the point estimate, 1.92) and for the safety outcome was 2.26 (E-value for the point estimate, 2.72) (Appendix Figure 6, available at Annals.org). The observed CI for recurrent VTE could be moved to include the null value of 1 by an unmeasured confounder that was associated with both exposure and the effectiveness outcome by a risk ratio of 1.56-fold each, above and beyond the measured confounders included in the PS model, but weaker confounding could not do so. The observed CI for intracranial and gastrointestinal bleeding could be moved to include the null value of 1 by an unmeasured confounder that was associated with both exposure and bleeding events by a risk ratio of 2.26-fold each, above and beyond the measured confounders included in the PS model.

Results From Subgroup Analyses

The results from the subgroup analyses were consistent with the primary findings for both the effectiveness and safety outcome, suggesting an absence of effect modification (Table 4).

Discussion

In this population-based, matched cohort study of approximately 37 000 patients with VTE in the United States, the use of apixaban was associated with a lower rate of recurrent VTE and bleeding events compared with rivaroxaban. Results from subgroup and sensitivity analyses using different analytic approaches were consistent with the primary analysis, including comparing patients with VTE provoked by a transient risk factor versus VTE that was unprovoked or provoked by a chronic risk factor. These findings support superior effectiveness and safety of apixaban for the prevention of recurrent VTE relative to rivaroxaban.

In the AMPLIFY trial, 10 mg of apixaban twice daily for 7 days followed by 5 mg twice daily for 6 months was compared with conventional subcutaneous enoxaparin therapy followed by warfarin in 5244 adults with acute VTE (6). The trial found that a fixed-dose regimen of apixaban was noninferior to conventional therapy for the treatment of acute VTE and was associated with significantly less major bleeding and clinically relevant nonmajor bleeding (relative risk [RR], 0.44 [CI, 0.36 to 0.55]; $P < 0.001$). In the EINSTEIN trial, 15 mg of rivaroxaban for the first 3 weeks, followed by 20 mg once daily for 3, 6, or 12 months of treatment, was compared with standard therapy (subcutaneous enoxaparin and either warfarin or acenocoumarol) in 3449 adults with acute DVT (7). The trial found that rivaroxaban was noninferior to standard therapy and was associated with a similar risk for bleeding (7). Although these trials did not include a direct comparison of apixaban and rivaroxaban, they were followed by several meta-analyses of RCTs and observational studies (33–35).

Cohen and colleagues (34) performed a network meta-analysis of RCTs of DOACs. The study reported no difference in the composite of recurrent VTE– and VTE-related deaths but found a lower risk for bleeding with apixaban compared with rivaroxaban. This was followed by another meta-analysis of the same RCTs, which reported similar findings (35). The discordant findings for the effectiveness outcome in the current study relative to the meta-analyses may be explained by the small number of events in the clinical trials ($n = 59$) (36). Compared with the meta-analysis by Cohen and colleagues, our point estimate and CI for the effectiveness outcome fall completely within their results (HR, 0.75 [CI, 0.66 to 0.86], vs. RR, 0.93 [CI, 0.59 to 1.46]), suggesting that the meta-analysis was likely underpowered to detect a difference for the efficacy end point. However, the meta-analysis had more power for bleeding

Table 3. Summary of Results From Sensitivity Analysis

Variable	Patients, *n*		aHR for Apixaban vs. Rivaroxaban (95% CI)	
	Apixaban	Rivaroxaban	Recurrent VTE	Bleeding Events
Increasing permissible grace period between consecutive refills from 7 to 15 d	18 618	18 618	0.81 (0.71–0.92)	0.60 (0.52–0.68)
Increasing permissible grace period between consecutive refills from 7 to 30 d	18 618	18 618	0.82 (0.73–0.93)	0.63 (0.55–0.71)
Trimming PS distribution tail to 95th and 5th percentile	18 618	18 618	0.78 (0.69–0.89)	0.60 (0.52–0.68)
Trimming PS distribution tail to 85th and 15th percentile	18 545	18 545	0.78 (0.69–0.89)	0.60 (0.52–0.68)
Trimming PS distribution tail to 75th and 25th percentile	17 644	17 644	0.80 (0.70–0.91)	0.61 (0.53–0.70)
Adjustment using IPTW ATE	28 287	21 613	0.80 (0.72–0.89)	0.60 (0.54–0.67)
Adjustment using IPTW ATT	28 287	21 613	0.80 (0.73–0.89)	0.59 (0.54–0.65)
Adjustment for PS in the primary outcome model	28 287	21 613	0.80 (0.71–0.89)	0.61 (0.55–0.69)
1:*n* matching with replacement	18 618	27 616	0.80 (0.76–0.85)	0.69 (0.59–0.80)
Changing caliper width from 0.1 to 0.2 of the SD of the logit of PS	18 656	18 656	0.78 (0.69–0.88)	0.61 (0.54–0.70)
Changing caliper width from 0.1 to 0.01 of the SD of the logit of PS	18 419	18 419	0.77 (0.68–0.87)	0.63 (0.55–0.72)
Changing caliper width from 0.1 to 0.02 of the SD of the logit of PS	18 580	18 580	0.77 (0.68–0.87)	0.63 (0.55–0.72)
Including recurrent VTE occurring in the outpatient setting in the outcome definition	18 618	18 618	0.78 (0.69–0.89)	–
Prostate and breast cancer as negative control outcome	18 618	18 618	1.01 (0.90–1.15)	–

aHR = adjusted hazard ratio; ATE = average treatment effects; ATT = average treatment effects on the treated; IPTW = inverse probability of treatment weighting; PS = propensity score; VTE = venous thromboembolism.

Table 4. Summary of Results From Subgroup Analysis*

Variable	Patients, *n*		Recurrent VTE		Bleeding Events	
	Apixaban	Rivaroxaban	aHR for Apixaban vs. Rivaroxaban (95% CI)	*P* Value for Interaction	aHR for Apixaban vs. Rivaroxaban (95% CI)	*P* Value for Interaction
Age				0.84		0.03
<65 y	6791	6791	0.80 (0.65–0.99)		0.71 (0.52–0.96)	
≥65 y	11 613	11 613	0.79 (0.68–0.91)		0.62 (0.54–0.72)	
Sex				0.16		0.80
Male	8871	8 871	0.86 (0.72–1.02)		0.66 (0.54–0.79)	
Female	9689	9 689	0.74 (0.63–0.87)		0.62 (0.52–0.74)	
Cancer				0.01		0.11
With	4069	4 069	0.96 (0.76–1.23)		0.71 (0.56–0.89)	
Without	14 396	14 396	0.71 (0.61–0.81)		0.60 (0.51–0.70)	
NSAIDs				0.18		0.53
With	3904	3904	0.90 (0.69–1.17)		0.58 (0.43–0.80)	
Without	14 656	14 656	0.70 (0.61–0.80)		0.58 (0.50–0.67)	
Antiplatelet				0.43		0.50
With	1116	1116	0.73 (0.47–1.13)		0.59 (0.41–0.85)	
Without	17 422	17 422	0.82 (0.73–0.93)		0.62 (0.54–0.71)	
VTE type†				0.52		0.32
Provoked	7860	7860	0.72 (0.59–0.88)		0.64 (0.54–0.80)	
Unprovoked	10 525	10 525	0.82 (0.69–0.97)		0.61 (0.50–0.75)	
Mechanical heart valve				0.57		0.37
With	90	90	1.40 (0.24–8.21)		0.36 (0.08–1.76)	
Without	18 470	18 470	0.83 (0.73–0.93)		0.58 (0.51–0.67)	
Hip or knee replacement				0.92		0.85
With	37	37	‡		‡	
Without	18 515	18 515	0.80 (0.71–0.90)		0.61 (0.54–0.70)	
End-stage renal disease				0.50		0.76
With	53	53	2.86 (0.30–27.71)		1.28 (0.32–5.17)	
Without	18 545	18 545	0.77 (0.68–0.87)		0.60 (0.52–0.68)	

aHR = adjusted hazard ratio; NSAID = nonsteroidal anti-inflammatory drug; PS = propensity score; VTE = venous thromboembolism.
* We used Bonferroni adjustment to account for multiple testing. Results were considered statistically significant if the corresponding *P* value was ≤ α (that is, 0.05)/*n*, where *n* equals total number of subgroup analyses.
† VTE was categorized into provoked by transient risk factors vs. provoked by chronic risk factors or unprovoked VTE. Transient risk factors included pregnancy, postpartum, trauma, or surgery within 90 d preceding VTE, or hospital admission within the 60 d preceding VTE and with a length of stay exceeding 3 d.
‡ Estimates could not be obtained because of the lack of power.

outcomes and produced similar findings (HR, 0.63 [CI, 0.53 to 0.76], vs. RR, 0.69 [CI, 0.36 to 0.62]).

A limited number of observational studies have rigorously evaluated apixaban compared with rivaroxaban in the VTE population. An analysis in the Truven MarketScan database found that patients starting apixaban had a lower rate of recurrent VTE and major bleeding events than patients starting rivaroxaban (9). Notably, compared with our study, the prior analysis reported lower rates of recurrent VTE (8.5 and 12.9 vs. 3 and 7 events per 100 person-years) in the apixaban and rivaroxaban groups, respectively. These differences can be explained by population characteristics. Unlike the prior study, which was conducted during the first year of apixaban approval, the patients enrolled in our study were older (mean age, 69 vs. 62 years) and had a higher prevalence of comorbid conditions, including hyperlipidemia (49% vs. 45%), chronic kidney disease (19% vs. 17%), and liver disease (12% vs. 3%). Nonetheless, both studies observed superior effectiveness and safety of apixaban versus rivaroxaban for treatment of recurrent VTE.

It is unknown why apixaban may be more effective and safer than rivaroxaban. One possible explanation is pharmacokinetics. A randomized crossover study that compared the pharmacokinetics and pharmacodynamics of both drugs found that apixaban had significantly less fluctuation in plasma concentrations, a lower peak-to-trough ratio, and less variability in pharmacokinetic variables (that is, maximum concentration and area under the curve) compared with rivaroxaban (37), potentially accounting for its superior effectiveness and safety. In the absence of data from RCTs, the benefits of apixaban (vs. rivaroxaban) observed in the current study can be used to guide treatment selection in clinical practice along with other factors that may affect treatment choice, including patient preference for once- versus twice-daily dosing, cost, and insurance coverage.

Strengths of our study include the use of PS matching and large sample size. We also had access to sociodemographic factors and laboratory results for a subset of the cohort, which allowed us to examine the distribution of several measures that are often not captured in claims databases. However, our study has several limitations. First, unmeasured confounding is possible, because the current data did not have information on body mass index, lifestyle variables, or over-the-counter medications such as aspirin. Geographic information was available at the census division but not at the state level. Laboratory values were available only for a small subset of the patients. However, our examination of several laboratory measures in a subset of the matched cohort revealed a well-balanced distribution of baseline laboratory measures, including creatinine, cholesterol, triglyceride, and hemoglobin A_{1c} levels. Although PS method does not guarantee balance in unmeasured confounders, a recent analysis that linked claims databases to electronic health records (38) found that a new-users active comparator design led to balance on several variables not available from claims data, such as prescriber specialty, aspirin use, body mass index, and alcohol use. Second, exposure misclassification is possible because some patients may overstock medications and take a longer time to pick up their next prescription from an outpatient pharmacy. Although such patients would have been censored from the primary analysis, the results were consistent in the sensitivity analysis, allowing a longer permissible gap between refills. Third, outcome misclassification is possible because we relied on diagnostic codes that are used for billing purposes. However, because we used the same validated outcome definitions in both groups, misclassification is likely nondifferential. Fourth, only severe outcomes resulting in hospitalization were included and not those presenting in the outpatient setting. Fifth, although we lacked information on adherence, the study results remained robust when we modified the permissible gap between contiguous refills from 7 days to 15 and 30 days.

Finally, our cohort was restricted to commercially insured patients with VTE, which limited the generalizability to other populations, such as those with governmental insurance or uninsured individuals. Because PS matching resulted in the loss of participants, the estimated effect may not generalize to the unmatched population. However, study results were consistent when using other methods of adjustment (that is, IPTW ATT, IPTW ATE, adjustment for PS in the outcome model).

In this comparative effectiveness and safety study using real-world data, adults with VTE who initiated apixaban had a lower rate of recurrent VTE and intracranial and gastrointestinal bleeding events compared with rivaroxaban. These findings suggest that apixaban has superior effectiveness and safety compared with rivaroxaban and may provide guidance to clinicians and patients regarding selection of an anticoagulant for treatment of VTE.

From University of Pennsylvania, Philadelphia, Pennsylvania (G.K.D., C.E.L., J.D.L., A.C.).

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Reproducible Research Statement: *Study protocol:* Not available. *Statistical code:* Available from Dr. Dawwas (e-mail, gkdawwas@pennmedicine.upenn.edu). *Data set:* Not available.

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References

1. **White RH.** The epidemiology of venous thromboembolism. Circulation. 2003;107:I4-8. [PMID: 12814979]
2. **Hansson PO, Sörbo J, Eriksson H.** Recurrent venous thromboembolism after deep vein thrombosis: incidence and risk factors. Arch Intern Med. 2000;160:769-74. [PMID: 10737276]
3. **Ortel TL, Neumann I, Ageno W, et al.** American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020;4:4693-738. [PMID: 33007077] doi:10.1182/bloodadvances.2020001830
4. **Konstantinides SV, Meyer G, Becattini C, et al; ESC Scientific Document Group.** 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J. 2020;41:543-603. [PMID: 31504429] doi:10.1093/eurheartj/ehz405
5. **Zhu J, Alexander GC, Nazarian S, et al.** Trends and variation in oral anticoagulant choice in patients with atrial fibrillation, 2010-2017. Pharmacotherapy. 2018;38:907-20. [PMID: 29920705] doi:10.1002/phar.2158
6. **Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators.** Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369:799-808. [PMID: 23808982] doi:10.1056/NEJMoa1302507
7. **Bauersachs R, Berkowitz SD, Brenner B, et al; EINSTEIN Investigators.** Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363:2499-510. [PMID: 21128814] doi:10.1056/NEJMoa1007903
8. **Büller HR, Prins MH, Lensin AW, et al; EINSTEIN–PE Investigators.** Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366:1287-97. [PMID: 22449293] doi:10.1056/NEJMoa1113572
9. **Dawwas GK, Brown J, Dietrich E, et al.** Effectiveness and safety of apixaban versus rivaroxaban for prevention of recurrent venous thromboembolism and adverse bleeding events in patients with venous thromboembolism: a retrospective population-based cohort analysis. Lancet Haematol. 2019;6:e20-8. [PMID: 30558988] doi:10.1016/S2352-3026(18)30191-1
10. **Sindet-Pedersen C, Staerk L, Pallisgaard JL, et al.** Safety and effectiveness of rivaroxaban and apixaban in patients with venous thromboembolism: a nationwide study. Eur Heart J Cardiovasc Pharmacother. 2018;4:220-7. [PMID: 29945162] doi:10.1093/ehjcvp/pvy021
11. **White RH, Garcia M, Sadeghi B, et al.** Evaluation of the predictive value of ICD-9-CM coded administrative data for venous thromboembolism in the United States. Thromb Res. 2010;126:61-7. [PMID: 20430419] doi:10.1016/j.thromres.2010.03.009
12. **Fang MC, Fan D, Sung SH, et al.** Validity of using inpatient and outpatient administrative codes to identify acute venous thromboembolism: the CVRN VTE study. Med Care. 2017;55:e137-e143. [PMID: 29135777] doi:10.1097/MLR.0000000000000524

13. **Cunningham A, Stein CM, Chung CP, et al.** An automated database case definition for serious bleeding related to oral anticoagulant use. Pharmacoepidemiol Drug Saf. 2011;20:560-6. [PMID: 21387461] doi:10.1002/pds.2109
14. **Shehab N, Ziemba R, Campbell KN, et al.** Assessment of ICD-10-CM code assignment validity for case finding of outpatient anticoagulant-related bleeding among Medicare beneficiaries. Pharmacoepidemiol Drug Saf. 2019;28:951-64. [PMID: 31144403] doi:10.1002/pds.4783
15. **Gregson J, Kaptoge S, Bolton T, et al; Emerging Risk Factors Collaboration.** Cardiovascular risk factors associated with venous thromboembolism. JAMA Cardiol. 2019;4:163-73. [PMID: 30649175] doi:10.1001/jamacardio.2018.4537
16. **Alikhan R, Cohen AT, Combe S, et al; MEDENOX Study.** Risk factors for venous thromboembolism in hospitalized patients with acute medical illness: analysis of the MEDENOX Study. Arch Intern Med. 2004;164:963-8. [PMID: 15136304]
17. **Anderson FA Jr, Spencer FA.** Risk factors for venous thromboembolism. Circulation. 2003;107:I9-16. [PMID: 12814980]
18. **Holst AG, Jensen G, Prescott E.** Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. Circulation. 2010;121:1896-903. [PMID: 20404252] doi:10.1161/CIRCULATIONAHA.109.921460
19. **Ageno W, Becattini C, Brighton T, et al.** Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation. 2008;117:93-102. [PMID: 18086925]
20. **Fitzmaurice DA, Blann AD, Lip GY.** Bleeding risks of antithrombotic therapy. BMJ. 2002;325:828-31. [PMID: 12376447]
21. **Tonelli M, Wiebe N, Fortin M, et al; Alberta Kidney Disease Network.** Methods for identifying 30 chronic conditions: application to administrative data. BMC Med Inform Decis Mak. 2015;15:31. [PMID: 25886580] doi:10.1186/s12911-015-0155-5
22. **Quan H, Li B, Saunders LD, et al; IMECCHI Investigators.** Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. Health Serv Res. 2008;43:1424-41. [PMID: 18756617]
23. **Puhr HC, Eischer L, Sõinkovec H, et al.** Circumstances of provoked recurrent venous thromboembolism: the Austrian study on recurrent venous thromboembolism. J Thromb Thrombolysis. 2020;49:505-10. [PMID: 31625082] doi:10.1007/s11239-019-01965-z
24. **Kearon C, Ageno W, Cannegieter SC, et al; Subcommittees on Control of Anticoagulation, and Predictive and Diagnostic Variables in Thrombotic Disease.** Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. J Thromb Haemost. 2016;14:1480-3. [PMID: 27428935] doi:10.1111/jth.13336
25. **Benedetto U, Head SJ, Angelini GD, et al.** Statistical primer: propensity score matching and its alternatives. Eur J Cardiothorac Surg. 2018;53:1112-7. [PMID: 29684154] doi:10.1093/ejcts/ezy167
26. **Austin PC.** A comparison of 12 algorithms for matching on the propensity score. Stat Med. 2014;33:1057-69. [PMID: 24123228] doi:10.1002/sim.6004
27. **Austin PC.** Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat. 2011;10:150-61. [PMID: 20925139] doi:10.1002/pst.433
28. **Austin PC.** Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28:3083-107. [PMID: 19757444] doi:10.1002/sim.3697
29. **Austin PC.** The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med. 2014;33:1242-58. [PMID: 24122911] doi:10.1002/sim.5984
30. **Austin PC.** Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. Stat Med. 2016;35:5642-55. [PMID: 27549016] doi:10.1002/sim.7084
31. **VanderWeele TJ, Ding P.** Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med. 2017;167:268-74. [PMID: 28693043] doi:10.7326/M16-2607
32. **Noble WS.** How does multiple testing correction work. Nat Biotechnol. 2009;27:1135-7. [PMID: 20010596] doi:10.1038/nbt1209-1135
33. **Aryal MR, Gosain R, Donato A, et al.** Systematic review and meta-analysis of the efficacy and safety of apixaban compared to rivaroxaban in acute VTE in the real world. Blood Adv. 2019;3:2381-7. [PMID: 31405948] doi:10.1182/bloodadvances.2019000572
34. **Cohen AT, Hamilton M, Mitchell SA, et al.** Comparison of the novel oral anticoagulants apixaban, dabigatran, edoxaban, and rivaroxaban in the initial and long-term treatment and prevention of venous thromboembolism: systematic review and network meta-analysis. PLoS One. 2015;10:e0144856. [PMID: 26716830] doi:10.1371/journal.pone.0144856
35. **Mantha S, Ansell J.** Indirect comparison of dabigatran, rivaroxaban, apixaban and edoxaban for the treatment of acute venous thromboembolism. J Thromb Thrombolysis. 2015;39:155-65. [PMID: 24989022] doi:10.1007/s11239-014-1102-5
36. **Mantha S, Ansell J.** Indirect comparison of dabigatran, rivaroxaban, apixaban and edoxaban for the treatment of acute venous thromboembolism. J Thromb Thrombolysis. 2015;39:155-65. [PMID: 24989022] doi:10.1007/s11239-014-1102-5
37. **Frost C, Song Y, Barrett YC, et al.** A randomized direct comparison of the pharmacokinetics and pharmacodynamics of apixaban and rivaroxaban. Clin Pharmacol. 2014;6:179-87. [PMID: 25419161] doi:10.2147/CPAA.S61131
38. **Huybrechts KF, Gopalakrishnan C, Franklin JM, et al.** Claims data studies of direct oral anticoagulants can achieve balance in important clinical parameters only observable in electronic health records. Clin Pharmacol Ther. 2019;105:979-993. [PMID: 30341980] doi:10.1002/cpt.1256

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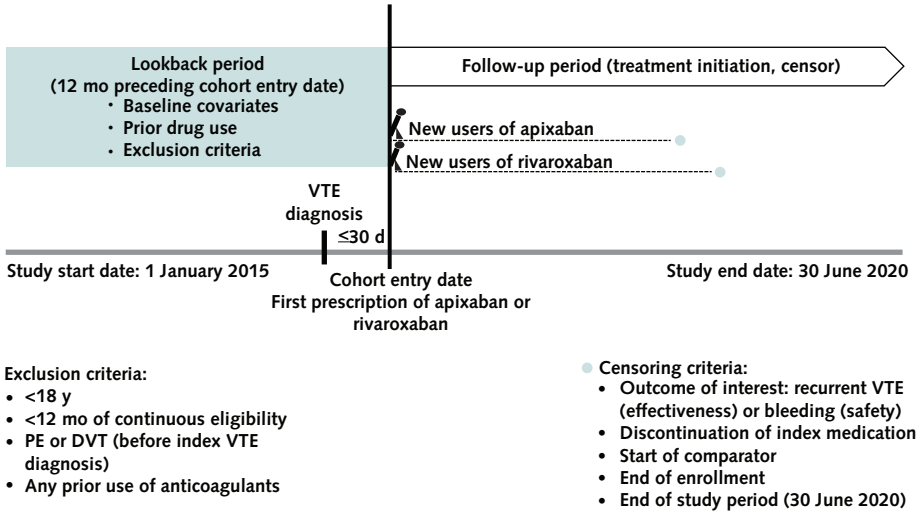
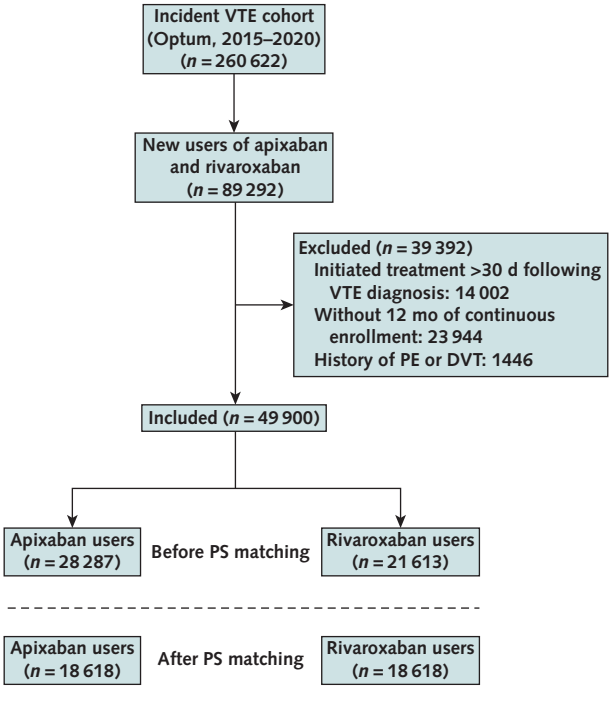
Appendix Figure 1. Study design.



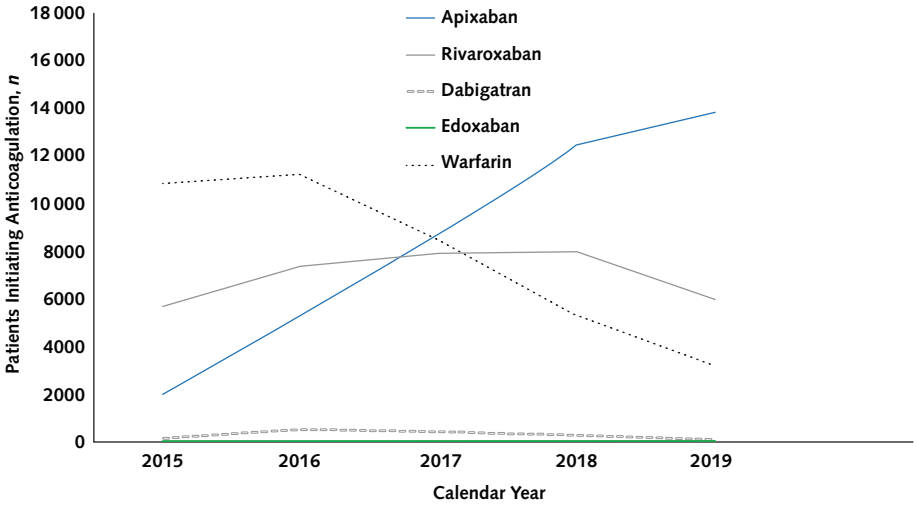
The study cohort included persons aged ≥18 y who newly initiated treatment with apixaban or rivaroxaban, had no prior use of anticoagulants during the 12-mo lookback period preceding cohort entry date, and had a diagnosis of VTE during 30 d preceding treatment initiation. DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

Appendix Figure 2. Study flow diagram.



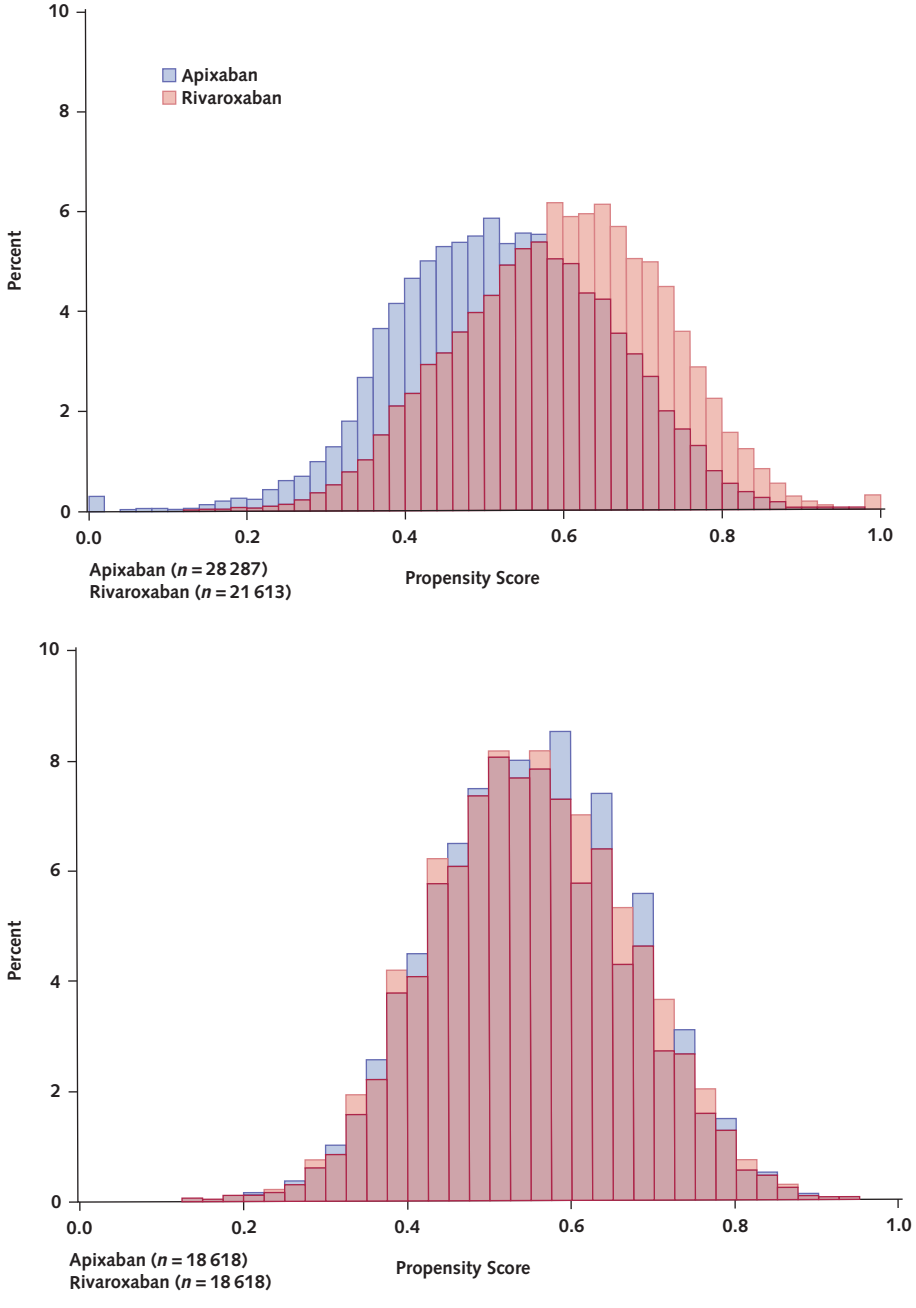
DVT = deep venous thrombosis; PE = pulmonary embolism; PS = propensity score; VTE = venous thromboembolism.

Appendix Figure 3. Distribution of treatment initiation year, before propensity score matching, among patients with VTE who initiated anticoagulants during the study period.



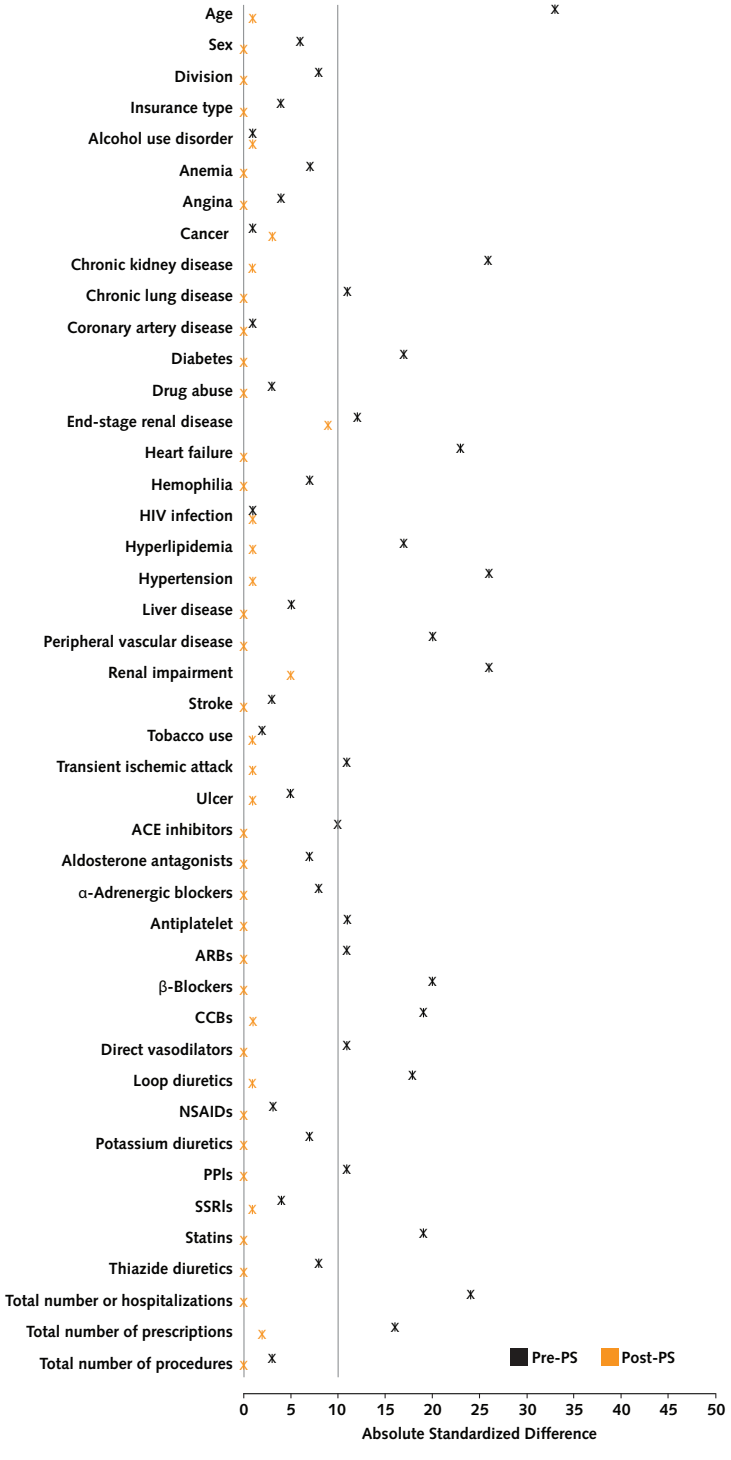
Data up to December 2019 only were included because data from 2020 were limited to June 2020. VTE = venous thromboembolism.

Appendix Figure 4. Distribution of propensity score before (*top*) and after (*bottom*) matching.



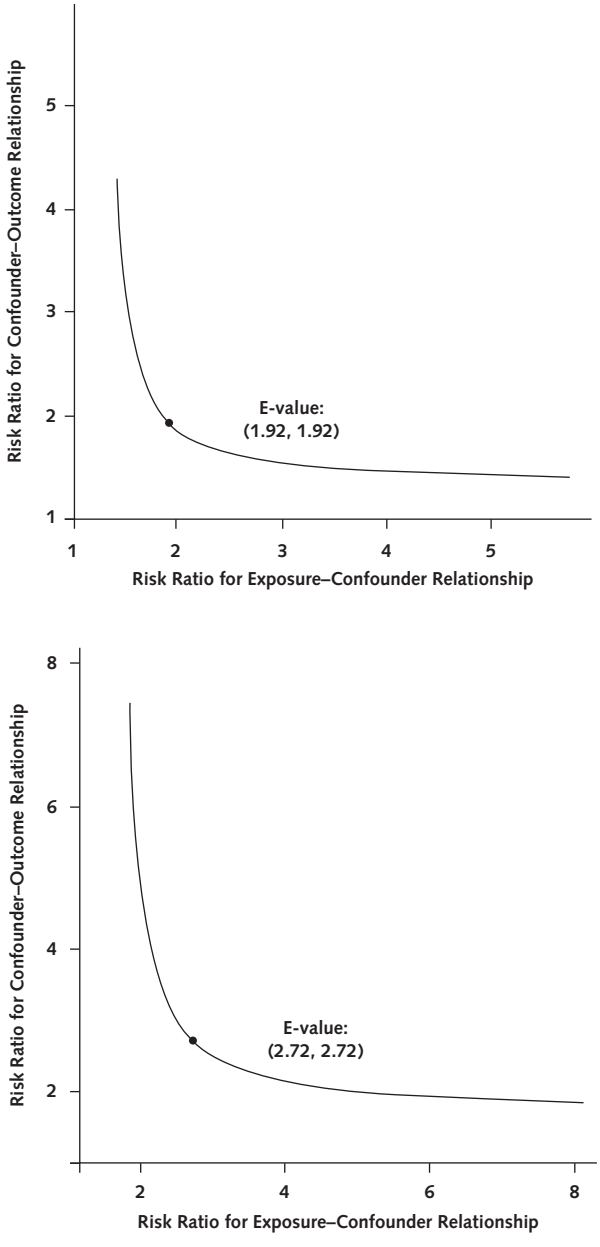
The propensity score was modeled using a logistic regression model (PROC LOGISTIC in SAS).

Appendix Figure 5. Absolute standardized differences comparing the balance of covariates before and after PS matching among patients with VTE who were new users of apixaban or rivaroxaban.



ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CCB = calcium-channel blocker; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton-pump inhibitor; PS = propensity score; SSRI = selective serotonin reuptake inhibitor; VTE= venous thromboembolism.

Appendix Figure 6. E-value representing the joint minimum strength of association on the risk ratio scale that an unmeasured confounder must have with the use of apixaban or rivaroxaban, recurrent VTE (*top*), and bleeding outcome (*bottom*) to fully explain away an observed treatment–outcome hazard ratio of 0.77 (recurrent VTE) and 0.61 (bleeding outcome).



Generated using www.evalue-calculator.com. VTE = venous thromboembolism.

Appendix Table 1. Study Design, Inclusion and Exclusion Criteria, and Outcome Definitions

Study Characteristic	Description
Design	New-user active comparator cohort design
Source population	Optum Insight Clinformatics Database, a commercial insurance database in the United States from 1 January 2015 to 30 June 2020
Target population	Adults (age ≥18 years) with a diagnosis of VTE who initiated treatment with apixaban or rivaroxaban within 30 days after incident VTE diagnosis
Inclusion criteria	
Initiated treatment with apixaban or rivaroxaban within 30 days after incident VTE diagnosis	Absence of prior use of any anticoagulants during a 12-month lookback period before treatment initiation
Age ≥18 years	Defined at cohort entry
Diagnosis of VTE during 30-day period preceding their first prescription	Defined based on inpatient claims, based on the following ICD-9 and ICD-10 codes: 415.1, 453.8, 453.2, 451.2, 451.9, 453.1, 453.2, 453.8, 453.9, 451.2, 451.9, I82.4, I82.9, I26.0, I26.9, 451.19, 451.81, 451.83, 451.89, 451.11, 451.19, 451.81, 451.83, 451.89
Exclusion criteria	Less than 12 months of continuous enrollment before cohort entry History of prior dispensing of any anticoagulant during the 12-month lookback period preceding cohort entry date History of DVT or PE during the lookback period
Primary study outcomes	
Primary effectiveness outcome was recurrent VTE defined as a composite of PE and DVT, based on inpatient discharge diagnosis primary position only	ICD-9-CM and ICD-10-CM: 415.1, 453.8, 453.2, 451.2, 451.9, 453.1, 453.2, 453.8, 453.9, 451.2, 451.9, I82.4, I82.9, I26.0, I26.9, 451.19, 451.81, 451.83, 451.89, 451.11, 451.19, 451.81, 451.83, 451.89
Primary safety outcome was a composite of gastrointestinal and intracranial bleeding, based on inpatient discharge diagnosis primary position only	ICD-9-CM and ICD-10-CM: 430, 431, 432, 853, I61, 456.0, 530.7, 569.3, 578.0, 578.1, 578.9, 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, K66.1, K62.5, K28.2, K28.4, K28.6, K92.0, K92.1, K92.2, 852.0, 852.2, 852.4, I62.0, I62.1, I62.9, SO6.6, S06.5, S06.4, 456.20, 530.21, 530.82, 531.00, 531.00, 531.01, 531.20, 531.21, 531.40, 531.41, 531.60, 53.161, 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, 534.2, 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, 569.85, 569.86, I85.01, I85.11, K22.11, K29.41, K29.51, K29.61, K29.21, K29.91, K29.81, 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, K55.21, K63.81, S06.36, K31.811, KK2.901

DVT = deep venous thrombosis; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM = International Classification of Diseases, Tenth Revision, Clinical Modification; PE = pulmonary embolism; VTE = venous thromboembolism.

Appendix Table 2. Distribution of Sociodemographic Factors Within a Subset of Patients With VTE Who Were New Users of Apixaban or Rivaroxaban

Factor	Prematching Cohort					Postmatching Cohort				
	Apixaban (*n* = 21 813), *n* (%)		Rivaroxaban (*n* = 17 253), *n* (%)		Standardized Difference	Apixaban (*n* = 14 711), *n* (%)		Rivaroxaban (*n* = 14 711), *n* (%)		Standardized Difference
Education level*	–	–	–	–	0.11	–	–	–	–	0.03
<12th grade	104	(0.4)	71	(0.4)	–	57	(0.4)	65	(0.4)	–
High school diploma	6852	(31.4)	4655	(26.9)	–	4268	(29.0)	4122	(28.0)	–
<Bachelor's degree	11 818	(54.1)	9642	(55.8)	–	8151	(55.4)	8143	(55.4)	–
≥Bachelor's degree	3039	(13.9)	2885	(16.7)	–	2235	(15.2)	2381	(16.2)	–
Race*	–	–	–	–	0.08	–	–	–	–	0.00
Asian American	421	(1.9)	337	(1.9)	–	287	(1.9)	281	(1.9)	–
Black	3647	(16.7)	2440	(14.1)	–	2171	(14.8)	2193	(14.9)	–
Hispanic	2217	(10.1)	1509	(8.7)	–	1379	(9.4)	1307	(8.9)	–
White	15 528	(71.1)	12 967	(75.1)	–	10 874	(73.9)	10 930	(74.3)	–
Income*	–	–	–	–	0.16	–	–	–	–	0.02
<$40 000	7358	(33.7)	4853	(28.1)	–	4443	(30.2)	4329	(29.4)	–
$40 000–$49 000	1912	(8.7)	1376	(7.9)	–	1223	(8.3)	1214	(8.3)	–
$50 000–$59 000	1947	(8.9)	1443	(8.3)	–	1274	(8.7)	1263	(8.6)	–
$60 000–$74 000	2540	(11.6)	2031	(11.7)	–	1761	(11.9)	1775	(12.1)	–
$75 000–$99 000	3209	(14.7)	2733	(15.8)	–	2303	(15.7)	2298	(15.6)	–
$100 000 +	4847	(22.2)	4817	(27.9)	–	3707	(25.2)	3832	(26.0)	–

VTE = venous thromboembolism.
* Race, education level, and income were not included in the propensity score model; sociodemographic variables were based on census block level.

Appendix Table 3. Information on Laboratory Values in a Subset of Patients With VTE Who Were New Users of Apixaban or Rivaroxaban

Laboratory Measure*	Prematching Cohort					Postmatching Cohort				
	Apixaban (*n* = 4738)		Rivaroxaban (*n* = 2984)		Standardized Difference	Apixaban (*n* = 2550)		Rivaroxaban (*n* = 2550)		Standardized Difference
Mean hemoglobin A_{1c} (SD), %	6.5	(1.5)	6.4	(1.4)	0.06	6.5	(1.5)	6.5	(1.4)	0.00
Mean cholesterol level (SD)	–	–	–	–	0.06	–	–	–	–	0.01
mmol/L	4.50	(1.08)	4.57	(1.05)	–	4.56	(1.09)	4.55	(1.06)	–
mg/dL	174.1	(41.8)	176.7	(40.7)	–	176.4	(42.2)	175.9	(40.8)	–
Mean triglyceride level (SD)	–	–	–	–	0.03	–	–	–	–	0.03
mmol/L	1.60	(1.00)	1.62	(1.06)	–	1.59	(0.99)	1.62	(1.07)	–
mg/dL	141.4	(88.3)	143.8	(93.8)	–	140.7	(87.9)	143.6	(94.6)	–
Mean creatinine level (SD)	–	–	–	–	0.04	–	–	–	–	0.08
μmol/L	106.08	(97.24)	97.24	(79.56)	–	97.24	(97.24)	97.24	(79.56)	–
mg/dL	1.2	(1.1)	1.1	(0.9)	–	1.1	(1.1)	1.1	(0.9)	–

VTE = venous thromboembolism.
* Laboratory measures were not included in the propensity score model.