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Oral Anticoagulation and Risk of Adverse Clinical Outcomes in Venous Thromboembolism

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IMPORTANCE Over the past decade, there has been a considerable shift in the use of pharmacologic agents for venous thromboembolism (VTE), with direct oral anticoagulants replacing warfarin as the drugs of choice for VTE recurrence prevention; however, evidence from head-to-head comparison studies remains limited.

OBJECTIVE To compare the effectiveness and safety of 3 common oral anticoagulants (apixaban, rivaroxaban, and warfarin) in patients with VTE.

DESIGN, SETTING, AND PARTICIPANTS This population-based cohort study used Medicare and 2 commercial insurance databases from 2016 up to 2024 to identify patients 18 years and older who initiated an oral anticoagulant following VTE and had at least 1 year of continuous insurance enrollment before the index date.

EXPOSURE Initiation of apixaban, rivaroxaban, or warfarin within 30 days after VTE discharge.

MAIN OUTCOMES AND MEASURES The primary effectiveness outcome was hospitalization for recurrent VTE. The primary safety outcome was major bleeding. Patients were followed up from treatment initiation until outcome occurrence, treatment discontinuation/switch, disenrollment, death, or end of available data. Propensity score–matching weights were used to adjust for confounding. Weighted Cox proportional hazard models estimated weighted hazard ratios (HRs) and 95% CIs.

RESULTS Among 163 593 eligible individuals (mean [SD] age, 71.4 [13.5] years; 56.7% female), 58.5% initiated apixaban, 25.7% initiated rivaroxaban, and 15.8% initiated warfarin. Overall, 3270 hospitalizations for recurrent VTE and 4229 hospitalizations for bleeding events occurred. Compared with warfarin, patients taking apixaban (HR, 0.67; 95% CI, 0.61-0.75) and rivaroxaban (HR, 0.77; 95% CI, 0.69-0.87) had a lower risk of recurrent VTE. Apixaban showed a further decrease in risk compared with rivaroxaban (HR, 0.87; 95% CI, 0.78-0.96). Patients taking apixaban also had a lower risk of major bleeding compared with warfarin (HR, 0.70; 95% CI, 0.64-0.76) and rivaroxaban (HR, 0.69; 95% CI, 0.63-0.75). No difference in bleeding risk was observed between rivaroxaban and warfarin (HR, 1.02; 95% CI, 0.92-1.12). These findings were consistent across subgroups defined by age, sex, cancer, chronic kidney disease, bleeding history, and frailty.

CONCLUSIONS AND RELEVANCE In this cohort study of patients with VTE who initiated an oral anticoagulant, apixaban was associated with a lower risk of VTE recurrence and major bleeding compared with rivaroxaban and warfarin. These results provide evidence to guide the selection of appropriate initial oral anticoagulant regimens for adult patients with VTE.

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Supplemental content

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Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common condition, affecting 900 000 patients in the US and leading to 100 000 deaths annually.[1,2] The incidence of the disease increases with age and is associated with a high rate of recurrence, considerable burden on the health care system, and high mortality.[3] Despite available treatments and knowledge of VTE recurrence risk factors, up to 10% of patients experience recurrence within the first 6 months and as many as 30% within the first year.[4]

Oral anticoagulants (OACs) have been shown to substantially reduce the risk of thromboembolic recurrence among patients with VTE.[5-11] Until 2012, warfarin was the only OAC available for patients with VTE. Since then, several direct oral anticoagulants (DOACs) have been approved for secondary VTE prevention and rapidly adopted in clinical practice due to their greater efficacy and convenience.[12-14] In 2021, American College of Chest Physicians guidelines recommended DOACs over warfarin as the initial anticoagulant treatment in patients with VTE.[15] However, the guidelines did not provide recommendations regarding specific DOAC agents due to the lack of evidence on the comparative effectiveness and safety of DOACs in this population. While the Comparison of Bleeding Risk Between Rivaroxaban and Apixaban for the Treatment of Acute VTE (COBRRA) trial comparing apixaban and rivaroxaban is ongoing,[16] there is limited randomized clinical trial (RCT) evidence on the comparative effects of different DOACs to guide clinical practice. Several observational studies compared the effectiveness and safety of newer DOACs to warfarin in patients with VTE.[17-20] However, previous studies have only compared 2 agents at a time, with few studies including data beyond 2016, when apixaban became the anticoagulant of choice among patients with VTE.[21] Moreover, most studies used a single database, limiting the generalizability of their findings and the power to assess the comparative effects in subgroups.

Thus, we aimed to compare the effectiveness and safety of the 3 most commonly used OACs—apixaban, rivaroxaban, and warfarin—using 3 US administrative health care databases, including both publicly and commercially insured individuals, focusing on more recent data. The study period (2016-2024) was chosen to ensure the exchangeability of patients, as early DOAC adopters may have been different from patients who were treated with warfarin, and to ensure consistency in coding in the data, as the US transitioned to the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* in October 2015.

Key Points

Question How do the 3 most commonly used oral anticoagulants for venous thromboembolism (VTE) recurrence prevention—apixaban, rivaroxaban, and warfarin—compare with regard to VTE prevention and bleeding in clinical practice?

Findings In this cohort study of 163 593 patients with VTE, apixaban was associated with a lower risk of hospitalizations for recurrent VTE and major bleeding compared with rivaroxaban or warfarin. While no differences in major bleeding were observed, rivaroxaban was associated with a lower risk of recurrent VTE compared with warfarin.

Meaning These findings support the guideline recommendation to use direct oral anticoagulants as a primary treatment option for patients with VTE; for most patients, apixaban appears to be the most effective and safest choice.

Methods

Data Source

We used 3 US health care claims databases for the study: (1) fee-for-service Medicare claims, collected by the Centers for Medicare & Medicaid Services, from 2016 to 2020, (2) Merative MarketScan from 2016 to 2022, and (3) Optum's deidentified Clinformatics Data Mart database from 2016 to 2024. These large electronic databases provide longitudinal, deidentified administrative data for diverse populations across different regions and clinical settings in the US. The data include detailed information on enrollment, demographics, inpatient and outpatient diagnoses and procedures, billed laboratory tests, and claims for filled prescription medications. Information on all-cause mortality was available in all databases.[22-25]

This study was approved by the institutional review board of Brigham and Women's Hospital, which granted a waiver of informed consent owing to use of deidentified data. We followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Study Design and Patient Eligibility

The study used a parallel-group, new-user cohort design. The study population included patients who initiated OACs within 30 days of VTE discharge. Eligible patients were 18 years or older (≥65 years for Medicare) and had at least 365 days of continuous insurance coverage. They were required not to have used any OAC (any of apixaban, rivaroxaban, warfarin, edoxaban, or dabigatran) or been hospitalized for VTE in the past year. VTE was defined based on *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes for DVT or PE as the primary discharge diagnosis (eTable 1 in Supplement 1).[26] For patients with multiple VTE hospitalizations, the earliest event in the study period was selected. The date of OAC initiation had to occur between January 1, 2017, and latest available in the data and was set as the index (cohort entry) date. Patients who initiated multiple OACs on the index date, had end-stage kidney disease, or had evidence of hospice or palliative care in the 365 days prior to the index VTE event were excluded from the study (eFigure 1 in Supplement 1). This analysis includes OAC prescriptions initiated within 30 days of VTE diagnosis, including both the treatment phase (first 3 months) and the extended phase (beyond 3 months), which is clinically considered part of secondary prevention for patients with initial VTE event.[15]

Exposures

The exposures of interest were apixaban, rivaroxaban, and warfarin, identified through pharmacy claims that provided details

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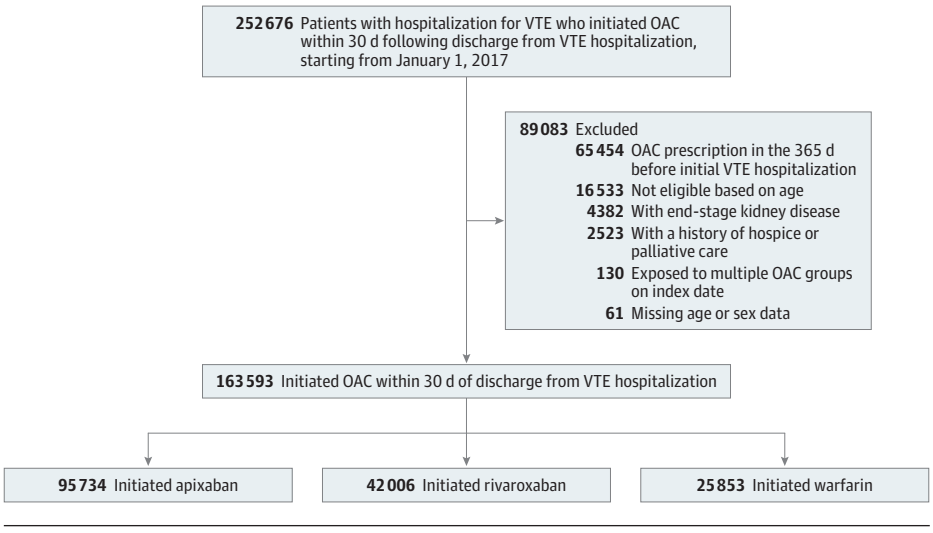
Figure 1. Flowchart of Study Population



OAC indicates oral anticoagulant; VTE, venous thromboembolism.

on the dispensing date, quantity, days covered by the dispensing, and National Drug Code. Patients were assigned to treatment groups based on the first OAC they filled within 30 days following discharge from VTE hospitalization. Continuous exposure was determined based on the days covered by each dispensed prescription, allowing for a gap of up to 14 days for delayed refills. Patients who did not refill their medication within 14 days were considered to have discontinued treatment.[27] As a limited number of patients initiated dabigatran (<1%) or edoxaban (<1%) following VTE discharge, these drugs were not evaluated.

Outcomes and Follow-Up

The primary effectiveness outcome was hospitalization for recurrent DVT or PE (eTable 1 in Supplement 1). The primary safety outcome was hospitalization for major bleeding, which included intracranial, gastrointestinal, or other major bleeding events (eTable 1 in Supplement 1).[26,28] Secondary outcomes included all-cause mortality and a composite end point consisting of hospitalization for recurrent VTE, hospitalization for major bleeding, and all-cause mortality. Patients were followed up from the day after OAC initiation until the first occurrence of an outcome, treatment discontinuation, switching to a different OAC, loss of health insurance coverage, death, or the end of available data.

Covariates

We assessed multiple baseline covariates known or suspected to be risk factors for the outcomes and potentially associated with the exposures. Covariates were assessed during the 365 days before and including OAC initiation date (eFigure 1 in Supplement 1). These included demographic characteristics (age, sex, region, and state), type of index VTE event, prior bleeding history, modified HAS-BLED (hypertension, abnormal kidney/liver function, stroke, bleeding history, labile International Normalized Ratio, elderly [≥65 years old], and drug/alcohol use) score,[22] conditions associated with hypercoagulable state (ie, cancer, pregnancy, use of hormone replacement therapy, surgery), cardiovascular conditions (ie, hypertension, hyperlipidemia, ischemic heart disease, heart failure, stroke), other comorbidities (ie, liver disease, stages of chronic kidney disease,[29] type 2 diabetes), other prescription medications, frailty score,[30-32] combined comorbidity score,[33] and prior health care utilization, including cancer screenings and specialists care (eTable 2 in Supplement 1).

Statistical Analysis

We used propensity score–matching weights to adjust for confounding due to the nonrandom assignment of patients to treatment groups.[34,35] To estimate the weights, we used a multinomial logistic regression model, including all covariates, to predict each patient's probability of initiating apixaban, rivaroxaban, or warfarin (ie, propensity scores). The matching weights were calculated by dividing the smallest of the 3 propensity scores by the probability of the treatment the patient actually received. Propensity scores and matching weights were estimated within each database. Covariate balance between treatment groups was assessed using standardized differences, with absolute values greater than 0.1 considered as an indication of imbalance.[36,37]

Analyses were conducted in the data pooled across 3 databases. We reported both crude and weighted incidence rates (IRs) and IR differences (IRDs) per 1000 person-years for each outcome by treatment group. Nonparametric bootstrapping with 1000 resamples was used to compute 95% CIs for IRDs.[38] Weighted Cox proportional hazard models, stratified on database, estimated hazard ratios (HRs) with robust variance estimators to account for weighting.[39] Cumulative incidence curves were plotted for the weighted population, and log-rank tests were performed. Cohorts were created using Aetion Evidence Platform, version 4.53; analyses were conducted using SAS statistical software, version 9.4 (SAS Institute).

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Table 1. Selected Baseline Characteristics of Study Population

Characteristics	Patients, No. (%)					
	Unweighted			Weighted[a]		
	Apixaban (n = 95 734)	Rivaroxaban (n = 42 006)	Warfarin (n = 25 853)	Apixaban (n = 20 947)	Rivaroxaban (n = 20 872)	Warfarin (n = 20 969)
Age, mean (SD), y	71.9 (13.4)	69.1 (14.0)	73.1 (12.7)	72.1 (12.9)	72 (12.8)	72.1 (12.8)
Sex						
Female	54 817 (57.3)	22 908 (54.5)	15 075 (58.3)	11 972 (57.2)	12 001 (57.5)	12 055 (57.5)
Male	40 917 (42.7)	19 098 (45.5)	10 778 (41.7)	8975 (42.8)	8871 (42.5)	8914 (42.5)
Index event						
Deep vein thrombosis	25 807 (27.0)	11 456 (27.3)	8830 (34.2)	6573 (31.4)	6455 (30.9)	6569 (31.3)
Pulmonary embolism	69 927 (73.0)	30 550 (72.7)	17 023 (65.8)	14 374 (68.6)	14 417 (69.1)	14 400 (68.7)
Comorbidities						
Modified HAS-BLED score, mean (SD)	2.1 (1.0)	1.9 (1.0)	2.3 (0.9)	2.2 (0.9)	2.2 (0.9)	2.2 (0.9)
Frailty score, mean (SD)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)	0.2 (0.1)
Combined comorbidity score, mean (SD)	5.1 (3.4)	4.4 (3.2)	5.0 (3.3)	4.7 (3.2)	4.7 (3.2)	4.7 (3.2)
Cancer, excluding nonmelanoma	20 854 (21.8)	8892 (21.2)	4906 (19.0)	4092 (19.5)	4109 (19.7)	4096 (19.5)
Any prior bleeding	27160 (28.4)	10823 (25.8)	8369 (32.4)	6178 (29.5)	6187 (29.6)	6225 (29.7)
Major surgery	8630 (9.0)	3098 (7.4)	2235 (8.6)	1671 (8.0)	1649 (7.9)	1698 (8.1)
Atrial fibrillation or flutter	15 296 (16.0)	5304 (12.6)	4729 (18.3)	3435 (16.4)	3400 (16.3)	3434 (16.4)
Valvular heart disease	29 709 (31.0)	11 008 (26.2)	7484 (28.9)	5849 (27.9)	5789 (27.7)	5809 (27.7)
Fracture	9410 (9.8)	3479 (8.3)	2346 (9.1)	1823 (8.7)	1817 (8.7)	1838 (8.8)
Chronic kidney disease, stage 3	19 045 (19.9)	5954 (14.2)	7051 (27.3)	4485 (21.4)	4409 (21.1)	4455 (21.2)
Chronic kidney disease, stage 4	2640 (2.8)	402 (1.0)	1518 (5.9)	393 (1.9)	390 (1.9)	401 (1.9)
Acute MI	7263 (7.6)	2485 (5.9)	1842 (7.1)	1402 (6.7)	1387 (6.6)	1389 (6.6)
Cerebrovascular disease	15 711 (16.4)	5512 (13.1)	4704 (18.2)	3457 (16.5)	3462 (16.6)	3504 (16.7)
Ischemic heart disease	36 230 (37.8)	13 536 (32.2)	10 188 (39.4)	7773 (37.1)	7754 (37.2)	7788 (37.1)
Peripheral vascular disease	16 249 (17.0)	5958 (14.2)	4774 (18.5)	3542 (16.9)	3521 (16.9)	3582 (17.1)
Congestive heart failure	26 074 (27.2)	8922 (21.2)	7982 (30.9)	5716 (27.3)	5697 (27.3)	5741 (27.4)
Anemia	36 285 (37.9)	13 573 (32.3)	10 783 (41.7)	7956 (38.0)	7940 (38.0)	7999 (38.1)
Chronic liver disease	11 665 (12.2)	4847 (11.5)	3023 (11.7)	2396 (11.4)	2424 (11.6)	2422 (11.5)
Dementia	11 559 (12.1)	3734 (8.9)	3258 (12.6)	2419 (11.5)	2422 (11.6)	2452 (11.7)
Diabetes	31 620 (33.0)	12 318 (29.3)	9299 (36.0)	7081 (33.8)	7049 (33.8)	7097 (33.8)
Peptic ulcer disease	2984 (3.1)	1048 (2.5)	941 (3.6)	644 (3.1)	656 (3.1)	660 (3.1)
Obstructive lung disorder	32 866 (34.3)	13 446 (32.0)	9386 (36.3)	7313 (34.9)	7384 (35.4)	7410 (35.3)
Any COVID-19[b]	6033 (6.3)	1108 (2.6)	282 (1.1)	262 (1.2)	265 (1.3)	262 (1.2)

(continued)

Sensitivity and Subgroup Analyses

We conducted several sensitivity analyses to confirm the robustness of the findings. First, we conducted a 1-year intention-to-treat analysis, where patients were followed up from the day after OAC initiation until the first occurrence of outcome, loss of health insurance coverage, death, end of available data, or 365 days after OAC initiation. Second, we modified the definition of continuous exposure by extending the allowable gap between dispensings from 14 to 30 days. Third, to minimize the possibility of misclassification of bleeding outcomes, we required all diagnostic codes to occur in the primary position of the discharge summary. Fourth, we excluded patients with an outpatient VTE diagnosis in any position during the baseline period prior to improve the precision of incident VTE cohort selection.

We performed several prespecified subgroup analyses based on age (<65 years, ≥65 years), sex, active cancer (defined as presence of cancer treatment [eg, chemotherapy, radiation, cancer surgery] or diagnosis of metastatic cancer during the year before index date), chronic kidney disease, history of bleeding, and categories of frailty (nonfrail: frailty index, <0.15; prefrail: frailty index, 0.15-0.24; frail: frailty index, ≥0.25).[30,31] Propensity scores and weights were reestimated within each subgroup and then pooled across databases to ensure control within each subgroup.[40,41] Analyses were conducted in the subgroup data with the same approach as in the primary analyses. We aimed for valid treatment effect estimation within subgroups, not *P* value–based hypothesis testing; therefore, no statistical testing of treatment effect heterogeneity was completed.

Results

Baseline Characteristics

A total of 163 593 eligible individuals (mean [SD] age, 71.4 [13.5] years; 56.7% female) initiated 1 of the OACs of interest within

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Table 1. Selected Baseline Characteristics of Study Population (continued)

Characteristics	Patients, No. (%)					
	Unweighted			Weighted[a]		
	Apixaban (n = 95 734)	Rivaroxaban (n = 42 006)	Warfarin (n = 25 853)	Apixaban (n = 20 947)	Rivaroxaban (n = 20 872)	Warfarin (n = 20 969)
Comedications						
COPD and asthma medications	22922 (23.9)	10262 (24.4)	6286 (24.3)	5115 (24.4)	5172 (24.8)	5188 (24.7)
Estrogen	4350 (4.5)	2119 (5.0)	840 (3.2)	743 (3.5)	754 (3.6)	734 (3.5)
ACE inhibitors	26 516 (27.7)	11 335 (27.0)	7990 (30.9)	6317 (30.2)	6261 (30.0)	6332 (30.2)
ARBs	22 601 (23.6)	8798 (20.9)	5736 (22.2)	4589 (21.9)	4641 (22.2)	4629 (22.1)
Antiarrhythmic agents	2501 (2.6)	847 (2.0)	806 (3.1)	591 (2.8)	558 (2.7)	568 (2.7)
Antiplatelet agents	9167 (9.6)	3365 (8.0)	2723 (10.5)	2001 (9.6)	2032 (9.7)	2029 (9.7)
β-Blockers	38 760 (40.5)	14 894 (35.5)	11 781 (45.6)	8875 (42.4)	8814 (42.2)	8898 (42.4)
Calcium channel blockers	19 085 (19.9)	8628 (20.5)	6722 (26.0)	5142 (24.5)	5137 (24.6)	5134 (24.5)
Loop diuretics	22 332 (23.3)	7841 (18.7)	7560 (29.2)	5204 (24.8)	5249 (25.1)	5303 (25.3)
Thiazide diuretics	12 321 (12.9)	5164 (12.3)	3555 (13.8)	2771 (13.2)	2835 (13.6)	2823 (13.5)
Potassium-sparing diuretics	4946 (5.2)	1772 (4.2)	1602 (6.2)	1124 (5.4)	1127 (5.4)	1145 (5.5)
Statins	46 832 (48.9)	18 853 (44.9)	12 823 (49.6)	10 113 (48.3)	10 104 (48.4)	10 155 (48.4)
Proton-pump inhibitors	33 439 (34.9)	13 283 (31.6)	9690 (37.5)	7397 (35.3)	7438 (35.6)	7470 (35.6)
NSAIDs	23 047 (24.1)	10 528 (25.1)	5578 (21.6)	4786 (22.8)	4832 (23.2)	4833 (23.0)
Opioids	45 401 (47.4)	20 861 (49.7)	12 761 (49.4)	10 311 (49.2)	10 321 (49.5)	10 388 (49.5)
Health care utilization						
No. of hospitalizations, mean (SD)	1.6 (1.1)	1.5 (1.0)	1.7 (1.2)	1.6 (1.1)	1.7 (1.1)	1.7 (1.1)
No. of emergency department visits, mean (SD)	1.1 (2.2)	0.9 (3.5)	1.1 (2.2)	1.0 (2.1)	1.0 (2.0)	1.0 (2.2)
Cardiologist visit	72 653 (75.9)	31 244 (74.4)	20 385 (78.8)	16 289 (77.8)	16 257 (77.9)	16 305 (77.8)
Nephrologist visit	9327 (9.7)	2713 (6.5)	3512 (13.6)	2004 (9.6)	2018 (9.7)	2016 (9.6)

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a] After matching weights were applied, all covariates were balanced with a standardized difference of 0.1 or less.

[b] Any COVID-19–related inpatient and outpatient diagnoses or medications (eg, nirmatrelvir/ritonavir, remdesivir, molnupiravir).

30 days of VTE discharge between 2017 and 2024 (**Figure 1**). Of these, 58.5% initiated apixaban, 25.7% initiated rivaroxaban, and 15.8% initiated warfarin (Figure 1). Before propensity score weighting, patients taking warfarin were older (mean [SD] age across groups: apixaban, 71.9 [13.4] years; rivaroxaban, 69.1 [14.0] years; warfarin: 73.1 [12.7] years) and more likely to present with DVT as the index event (apixaban, 27.0%; rivaroxaban, 27.3%; warfarin, 34.2%), have stage 3 chronic kidney disease (apixaban, 19.9%; rivaroxaban, 14.2%; warfarin, 27.3%), and any prior bleeding episodes (apixaban, 28.4%; rivaroxaban, 25.8%; warfarin, 32.4%). After weighting, all baseline covariates were well balanced across the 3 OAC groups (**Table 1** and eTables 2-5 and eFigure 2-4 in Supplement 1).

Hospitalizations for Recurrent VTE

Over a median (IQR) follow-up of 169 (66-339) days, 3270 hospitalizations for recurrent VTE were identified. The weighted IRs of recurrent VTE hospitalizations per 1000 person-years were 23.3 (95% CI, 21.0-25.7) for apixaban, 26.8 (95% CI, 24.4-29.5) for rivaroxaban, and 38.3 (95% CI, 35.1-41.6) for warfarin. Compared with warfarin, patients who received apixaban had lower risk of recurrent VTE, with a weighted IRD of −15.0 (95% CI, −18.4 to −11.3) per 1000 person-years and a weighted HR of 0.67 (95% CI, 0.61-0.75). Patients who initiated rivaroxaban also had lower risk of recurrent VTE compared with warfarin, with a weighted IRD of −11.5 (95% CI, −15.2 to −7.7) per 1000 person-years and a weighted HR of 0.77 (95% CI, 0.69-0.87). Patients taking apixaban had lower risk than patients taking rivaroxaban, with a weighted IRD of −3.5 (95% CI, −6.3 to −0.9) per 1000 person-years and a weighted HR of 0.87 (95% CI, 0.78-0.96) (**Table 2**, **Figure 2**, and eTables 6-11 in Supplement 1).

Hospitalizations for Major Bleeding

Over a median (IQR) follow-up of 169 (67-339) days, 4229 hospitalizations for major bleeding were identified (Table 2). The weighted IRs for major bleeding per 1000 person-years were 30.6 (95% CI, 28.0-33.3) for apixaban, 44.6 (95% CI, 41.4-47.9) for rivaroxaban, and 47.2 (95% CI, 43.7-50.9) for warfarin. Patients who received apixaban had lower risk of major bleeding than patients taking warfarin, with a weighted IRD of −16.6 (95% CI, −20.2 to −12.9) per 1000 person-years and a weighted HR of 0.70 (95% CI, 0.64-0.76). No substantial differences were observed between patients taking rivaroxaban and warfarin, with a weighted IRD of −2.6 (95% CI, −6.9 to 1.5) per 1000 person-years and a weighted HR of 1.02 (95% CI, 0.92-1.12). Comparison of apixaban and rivaroxaban yielded a weighted IRD of −14.0 (95% CI, −17.4 to −10.7) per 1000 person-years and a weighted HR of 0.69 (95% CI, 0.63- 0.75) (Table 2, Figure 2, and eTables 6-11 in Supplement 1).

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Table 2. Comparative Effectiveness and Safety Between Apixaban, Rivaroxaban, and Warfarin Among Patients With Venous Thromboembolism (VTE)

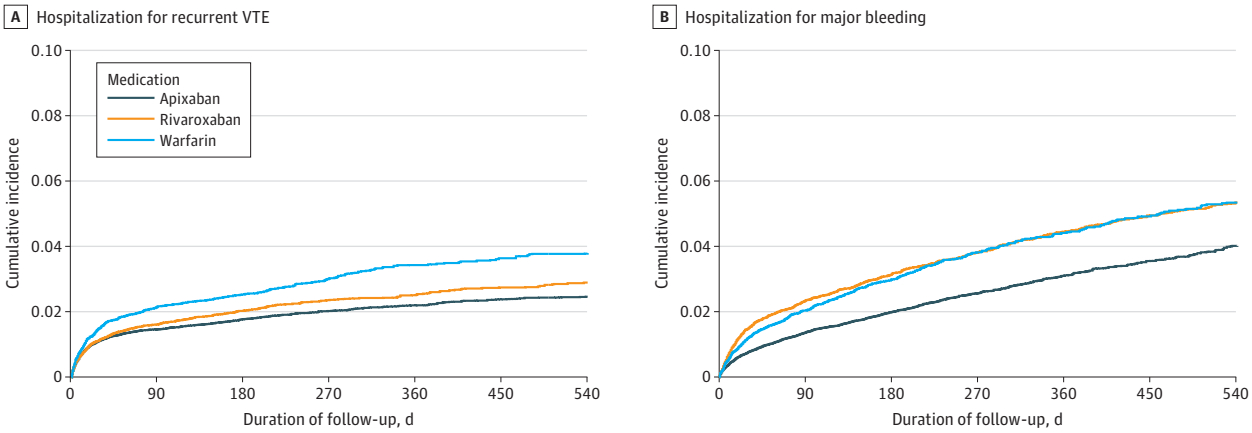
Outcome	No. of events[a]			Weighted IR per 1000 person-years (95% CI)			Weighted IRD per 1000 person-years (95% CI)			Weighted hazard ratio (95% CI)		
	Apixaban (n = 95 734)	Rivaroxaban (n = 42 006)	Warfarin (n = 25 853)	Apixaban	Rivaroxaban	Warfarin	Apixaban vs warfarin	Rivaroxaban vs warfarin	Apixaban vs rivaroxaban	Apixaban vs warfarin	Rivaroxaban vs warfarin	Apixaban vs rivaroxaban
Primary												
Hospitalization for recurrent VTE	1755	844	671	23.3 (21.0 to 25.7)	26.8 (24.4 to 29.5)	38.3 (35.1 to 41.6)	−15.0 (−18.4 to −11.3)	−11.5 (−15.2 to −7.7)	−3.5 (−6.3 to −0.9)	0.67 (0.61 to 0.75)	0.77 (0.69 to 0.87)	0.87 (0.78 to 0.96)
Hospitalization for major bleeding	2081	1207	941	30.6 (28.0 to 33.3)	44.6 (41.4 to 47.9)	47.2 (43.7 to 50.9)	−16.6 (−20.2 to −12.9)	−2.6 (−6.9 to 1.5)	−14.0 (−17.4 to −10.7)	0.70 (0.64 to 0.76)	1.02 (0.92 to 1.12)	0.69 (0.63 to 0.75)
Secondary												
All-cause mortality	6343	2228	1618	80.9 (76.7 to 85.3)	76.8 (72.7 to 81.2)	82.4 (77.8 to 87.3)	−1.5 (−6.7 to 3.5)	−5.6 (−11.4 to 0.5)	4.1 (−0.4 to 8.7)	1.05 (0.98 to 1.11)	1.00 (0.93 to 1.07)	1.05 (0.99 to 1.11)
Composite outcome[b]	9450	3980	2966	127.4 (122.0 to 132.9)	140.4 (134.7 to 146.3)	157.9 (151.4 to 164.7)	−30.5 (−37.6 to −22.5)	−17.5 (−26.4 to −9.6)	−13.0 (−19.5 to −6.5)	0.87 (0.83 to 0.91)	0.96 (0.91 to 1.01)	0.91 (0.87 to 0.95)

Abbreviations: IR, incidence rate; IRD, incidence rate difference.

[a] Unweighted number of events and number of patients.

[b] Composite outcome that comprised hospitalization for recurrent VTE, hospitalization for major bleeding, and all-cause mortality.

Figure 2. Weighted Cumulative Incidence of Outcomes



VTE indicates venous thromboembolism.

Secondary Outcomes: All-Cause Mortality and Composite Outcome

For all-cause mortality, all 3 OACs had comparable weighted IRs (Table 2). The weighted HRs were 1.05 (95% CI, 0.98-1.11) for apixaban vs warfarin, 1.00 (95% CI, 0.93-1.07) for rivaroxaban vs warfarin, and 1.05 (95% CI, 0.99-1.11) for apixaban vs rivaroxaban (Table 2 and eTables 6-11 and eFigure 5 in Supplement 1). For the composite outcome that included VTE recurrence, major bleeding, and all-cause mortality, patients taking apixaban had lower weighted IR than patients taking either rivaroxaban or warfarin (Table 2). The weighted HRs were 0.87 (95% CI, 0.83-0.91) for apixaban vs warfarin, 0.96 (95% CI, 0.91-1.01) for rivaroxaban vs warfarin, and 0.91 (95% CI, 0.87-0.95) for apixaban vs rivaroxaban (Table 2 and eTables 6-11 and eFigure 5 in Supplement 1).

Sensitivity and Subgroup Analyses

In the sensitivity analyses, the results remained consistent with the primary findings when applying an intention-to-treat approach, a continuous exposure definition with a gap between refills of up to 30 days, or excluding those with a prior outpatient diagnosis of VTE (eTables 12-14 in Supplement 1). Sensitivity analysis excluding individuals with an outpatient VTE diagnosis during the baseline period (n = 5153) yielded the same results as the main analyses (eTable 14 in Supplement 1). Restricted definition of major bleeding yielded weighted HR of 0.57 (95% CI, 0.51-0.63) for apixaban vs warfarin, 0.89 (95% CI, 0.80-1.00) for rivaroxaban vs warfarin, and 0.63 (95% CI, 0.57-0.70) for apixaban vs rivaroxaban (eTable 15 in Supplement 1).

The VTE results were generally consistent across subgroups (**Figure 3** and eTable 16 in Supplement 1). For bleeding,

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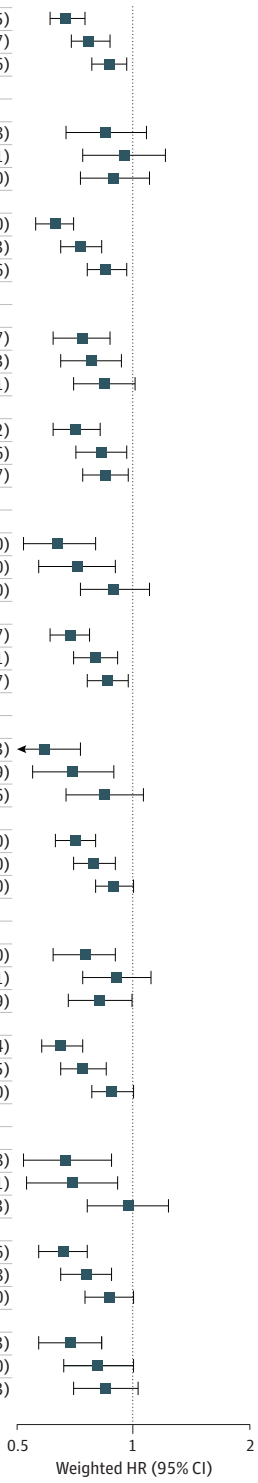
Figure 3. Results of Subgroup Analyses

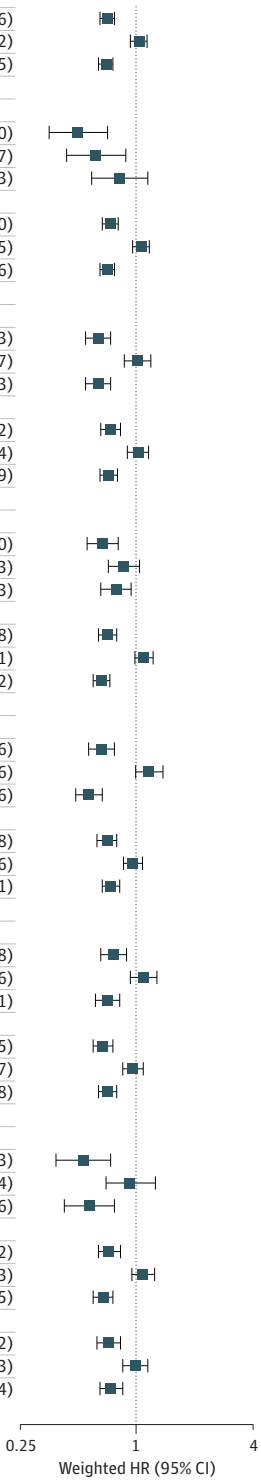
A Hospitalization for recurrent VTE

Subgroup	Weighted HR (95% CI)
Primary analysis	
Apixaban vs warfarin	0.67 (0.61-0.75)
Rivaroxaban vs warfarin	0.77 (0.69-0.87)
Apixaban vs rivaroxaban	0.87 (0.78-0.96)
Age	
<65 y	
Apixaban vs warfarin	0.85 (0.67-1.08)
Rivaroxaban vs warfarin	0.95 (0.74-1.21)
Apixaban vs rivaroxaban	0.89 (0.73-1.10)
≥65 y	
Apixaban vs warfarin	0.63 (0.56-0.70)
Rivaroxaban vs warfarin	0.73 (0.65-0.83)
Apixaban vs rivaroxaban	0.85 (0.76-0.96)
Sex	
Male	
Apixaban vs warfarin	0.74 (0.62-0.87)
Rivaroxaban vs warfarin	0.78 (0.65-0.93)
Apixaban vs rivaroxaban	0.84 (0.70-1.01)
Female	
Apixaban vs warfarin	0.71 (0.62-0.82)
Rivaroxaban vs warfarin	0.83 (0.71-0.96)
Apixaban vs rivaroxaban	0.85 (0.74-0.97)
Active cancer	
Yes	
Apixaban vs warfarin	0.64 (0.52-0.80)
Rivaroxaban vs warfarin	0.72 (0.57-0.90)
Apixaban vs rivaroxaban	0.89 (0.73-1.10)
No	
Apixaban vs warfarin	0.69 (0.61-0.77)
Rivaroxaban vs warfarin	0.80 (0.70-0.91)
Apixaban vs rivaroxaban	0.86 (0.76-0.97)
Chronic kidney disease	
Yes	
Apixaban vs warfarin	0.59 (0.48-0.73)
Rivaroxaban vs warfarin	0.70 (0.55-0.89)
Apixaban vs rivaroxaban	0.84 (0.67-1.06)
No	
Apixaban vs warfarin	0.71 (0.63-0.80)
Rivaroxaban vs warfarin	0.79 (0.70-0.90)
Apixaban vs rivaroxaban	0.89 (0.80-1.00)
History of bleeding	
Yes	
Apixaban vs warfarin	0.75 (0.62-0.90)
Rivaroxaban vs warfarin	0.91 (0.74-1.11)
Apixaban vs rivaroxaban	0.82 (0.68-0.99)
No	
Apixaban vs warfarin	0.65 (0.58-0.74)
Rivaroxaban vs warfarin	0.74 (0.65-0.85)
Apixaban vs rivaroxaban	0.88 (0.78-1.00)
Degree of frailty	
Nonfrail	
Apixaban vs warfarin	0.67 (0.52-0.88)
Rivaroxaban vs warfarin	0.70 (0.53-0.91)
Apixaban vs rivaroxaban	0.97 (0.76-1.23)
Prefrail	
Apixaban vs warfarin	0.66 (0.57-0.76)
Rivaroxaban vs warfarin	0.76 (0.65-0.88)
Apixaban vs rivaroxaban	0.87 (0.75-1.00)
Frail	
Apixaban vs warfarin	0.69 (0.57-0.83)
Rivaroxaban vs warfarin	0.81 (0.66-1.00)
Apixaban vs rivaroxaban	0.85 (0.70-1.03)



B Hospitalization for major bleeding

Subgroup	Weighted HR (95% CI)
Primary analysis	
Apixaban vs warfarin	0.70 (0.64-0.76)
Rivaroxaban vs warfarin	1.02 (0.92-1.12)
Apixaban vs rivaroxaban	0.69 (0.63-0.75)
Age	
<65 y	
Apixaban vs warfarin	0.49 (0.35-0.70)
Rivaroxaban vs warfarin	0.61 (0.43-0.87)
Apixaban vs rivaroxaban	0.81 (0.58-1.13)
≥65 y	
Apixaban vs warfarin	0.73 (0.66-0.80)
Rivaroxaban vs warfarin	1.05 (0.95-1.15)
Apixaban vs rivaroxaban	0.70 (0.64-0.76)
Sex	
Male	
Apixaban vs warfarin	0.63 (0.54-0.73)
Rivaroxaban vs warfarin	1.00 (0.86-1.17)
Apixaban vs rivaroxaban	0.63 (0.54-0.73)
Female	
Apixaban vs warfarin	0.73 (0.65-0.82)
Rivaroxaban vs warfarin	1.01 (0.89-1.14)
Apixaban vs rivaroxaban	0.71 (0.64-0.79)
Active cancer	
Yes	
Apixaban vs warfarin	0.66 (0.55-0.80)
Rivaroxaban vs warfarin	0.85 (0.71-1.03)
Apixaban vs rivaroxaban	0.78 (0.65-0.93)
No	
Apixaban vs warfarin	0.70 (0.63-0.78)
Rivaroxaban vs warfarin	1.08 (0.97-1.21)
Apixaban vs rivaroxaban	0.65 (0.59-0.72)
Chronic kidney disease	
Yes	
Apixaban vs warfarin	0.65 (0.56-0.76)
Rivaroxaban vs warfarin	1.15 (0.98-1.36)
Apixaban vs rivaroxaban	0.56 (0.48-0.66)
No	
Apixaban vs warfarin	0.70 (0.62-0.78)
Rivaroxaban vs warfarin	0.95 (0.85-1.06)
Apixaban vs rivaroxaban	0.73 (0.66-0.81)
History of bleeding	
Yes	
Apixaban vs warfarin	0.75 (0.65-0.88)
Rivaroxaban vs warfarin	1.08 (0.92-1.26)
Apixaban vs rivaroxaban	0.70 (0.61-0.81)
No	
Apixaban vs warfarin	0.66 (0.59-0.75)
Rivaroxaban vs warfarin	0.95 (0.84-1.07)
Apixaban vs rivaroxaban	0.70 (0.63-0.78)
Degree of frailty	
Nonfrail	
Apixaban vs warfarin	0.53 (0.38-0.73)
Rivaroxaban vs warfarin	0.92 (0.69-1.24)
Apixaban vs rivaroxaban	0.57 (0.42-0.76)
Prefrail	
Apixaban vs warfarin	0.71 (0.63-0.82)
Rivaroxaban vs warfarin	1.07 (0.94-1.23)
Apixaban vs rivaroxaban	0.67 (0.59-0.75)
Frail	
Apixaban vs warfarin	0.71 (0.62-0.82)
Rivaroxaban vs warfarin	0.98 (0.84-1.13)
Apixaban vs rivaroxaban	0.73 (0.64-0.84)



HR indicates hazard ratio; VTE, venous thromboembolism.

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the findings were consistent across subgroups of sex and frailty categories (Figure 3 and eTable 17 in Supplement 1); however, more pronounced results of rivaroxaban, relative to warfarin, were observed in patients younger than 65 years (HR, 0.61; 95% CI, 0.43-0.87) than in patients 65 years and older (HR, 1.05; 95% CI, 0.95-1.15). Subgroup analyses of all-cause mortality revealed that, compared with warfarin, apixaban and rivaroxaban were associated with increased mortality in patients with active cancer; however, in patients without cancer, there were no differences across the 3 medications. In the prefrail subgroup, mortality of apixaban was higher compared with rivaroxaban (eTables 18 and 19 and eFigure 6 in Supplement 1).

Discussion

In this population-based study of 163 593 patients who initiated 1 of the 3 most commonly used anticoagulants for VTE recurrence prevention, apixaban was associated with a lower risk of hospitalizations for recurrent VTE and major bleeding events than rivaroxaban or warfarin. These findings were consistent across subgroups defined by age, sex, cancer, chronic kidney disease, bleeding history, and frailty. While we did not observe a substantial difference in mortality rates, patients taking apixaban also had lower rates of a composite event that included VTE recurrence, major bleeding, and all-cause mortality than patients taking warfarin or rivaroxaban. Patients taking rivaroxaban had a lower risk of recurrent VTE than patients taking warfarin; however, no difference in major bleeding was observed.

These findings are consistent with existing evidence on the comparative effectiveness and safety of these medications in patients with VTE. RCTs such as EINSTEIN-DVT,[7] EINSTEIN-PE,[8] and AMPLIFY,[5] demonstrated the noninferiority of rivaroxaban and apixaban, respectively, compared with the standard treatment at the time, warfarin, in terms of efficacy. These RCTs also showed a statistically significant reduction in major bleeding risk for DOACs compared with warfarin (EINSTEIN-PE: HR, 0.49; 95% CI, 0.31-0.79; AMPLIFY: relative risk, 0.31; 95% CI, 0.17-0.55).[16] An observational cohort study by Dawwas et al[18] found that in a commercially insured US population, apixaban was associated with lower rates of recurrent VTE (HR, 0.77; 95% CI, 0.69-0.87) and bleeding (HR, 0.60; 95% CI, 0.53-0.69) compared with rivaroxaban. The present study leveraged 3 large US health care databases that included both commercially and publicly insured individuals. This allowed us to generate findings that are more generalizable to everyday clinical practice, particularly for populations that are often underrepresented in commercially insured cohorts, such as older adults and patients with lower socioeconomic status. We also focused on more recent data (2017 onward) that reflect contemporary treatment decisions. Taken together, this study further confirmed these findings in the overall VTE population, as well as across clinically high-risk subgroups, including older adults and patients with cancer, chronic kidney disease, or history of bleeding, offering clinically actionable insights.

Some differences between subgroups were noted that merit further investigation. Younger adults (<65 years) taking rivaroxaban had lower rates of major bleeding rates than those taking warfarin. However, no differences in bleeding risk between rivaroxaban and warfarin were observed in older adults or any other subgroups. Moreover, in patients with active cancer in this study, apixaban and rivaroxaban were associated with increased mortality compared with warfarin, though residual confounding cannot be excluded. While we adjusted for several cancer-related variables, claims data lack information on important cancer-related predictors of mortality, such as cancer stage. No differences in mortality among the 3 agents were observed in the subgroup without cancer. The results from the these analyses provide important and much-needed evidence on the comparative effectiveness and safety of OACs in subgroups; however, they should be considered exploratory and hypothesis generating. While the study had statistical power to detect or exclude large differences between subgroups, it was not powered to detect small but clinically meaningful differences. For that reason, no statistical tests for treatment effect heterogeneity were conducted. Overall, the results from the subgroup analyses confirmed that for most patients, apixaban initiation was associated with fewer VTE recurrences and bleeding events than warfarin or rivaroxaban.

Limitations

These findings have several limitations to consider. First, administrative claims databases do not provide information on key patient characteristics, such as socioeconomic status, differences in insurance coverage, body mass index, laboratory results (eg, International Normalized Ratio values for warfarin users), cancer severity, or over-the-counter medication use, that could confound the results. We used proxies where possible for these unavailable variables. Previous research has shown that adjusting for the many variables available in claims data often results in balance for unmeasured patient characteristics.[42] However, residual confounding cannot be ruled out. Second, claims-based outcomes may be misclassified. Although we required hospitalizations for all outcomes, not all hospitalizations with a bleeding diagnosis may have been due to major bleeding. Still, our alternative, more specific bleeding definition yielded similar results. Third, while the data provide reliable information on pharmacy dispensing, reducing the risk of exposure misclassification, we lack information on patient adherence and whether they discontinued the medication prematurely. Fourth, in this study, we focused on patients who were hospitalized for VTE and evaluated outcomes that required hospitalization. We acknowledge that some cases of VTE can be treated in the ambulatory setting. Restricting these analyses to hospitalized events increased the internal validity of the study, as hospitalized events usually have high specificity, which is essential for unbiased estimates. Lastly, this study evaluated OAC treatments as they are implemented in clinical practice, including medically necessary dose adjustments. Future research focusing on dosing strategies and adjustments could provide further insight into their impact on OAC treatment outcomes.

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Conclusions

In this large-scale cohort study comparing the 3 most frequently prescribed OACs—apixaban, rivaroxaban, and warfarin—we observed that patients with VTE who initiated apixaban had lower rates of hospitalization for recurrent VTE and major bleeding than patients who initiated rivaroxaban or warfarin. These findings were consistent across various patient subgroups. These results provide evidence to guide the selection of appropriate initial OAC regimens for adult patients with VTE in the everyday setting.

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Acquisition, analysis, or interpretation of data: Bea, Iyer, Kim, Lin, Zakoul, Tesfaye, Bykov.
Drafting of the manuscript: Bea, Zakoul.
Critical review of the manuscript for important intellectual content: Iyer, Kim, Lin, Zhang, Tesfaye, Bykov.
Statistical analysis: Bea, Lin, Bykov.
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Supervision: Iyer, Lin, Bykov.

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