




ORIGINAL ARTICLE

Venous thrombosis recurrence risk according to warfarin versus direct oral anticoagulants for the secondary prevention of venous thrombosis

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Abstract

Background: Venous thromboembolism (VTE) affects nearly 1 million Americans annually, and many benefit from continued anticoagulation after the initial 3- to 6-month treatment period (secondary prevention).

Objectives: To determine whether warfarin, apixaban, or rivaroxaban is associated with reduced recurrent VTE hospitalization in the secondary prevention of VTE.

Patients/Methods: We performed a retrospective cohort study of participants enrolled in the MarketScan Insurance Database between 2013 and 2017 in those with an incident VTE. In those individuals who continued oral anticoagulation (warfarin, apixaban, or rivaroxaban) beyond 6 months, we determined the relative rate of recurrent VTE hospitalization.

Results: Among 119 964 individuals with VTE, 25 419 remained on anticoagulation after 6 months and were matched successfully by age, sex, and date. After adjusting for a propensity score, apixaban versus rivaroxaban (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.45-0.94) and apixaban versus warfarin (HR, 0.68; 95% CI, 0.47-1.00) had a reduced risk of recurrent VTE hospitalization, and rivaroxaban versus warfarin (HR, 1.12; 95% CI, 0.94-1.33) had equivalent rates. For the rivaroxaban versus warfarin comparison there was a significant interaction by renal function ($P < .01$) where rivaroxaban was associated with a lower risk of recurrent VTE hospitalization (HR, 0.65; 95% CI, 0.41-1.03) in those with kidney disease and increased risk in those without kidney disease (HR, 1.24; 95% CI, 1.02-1.50).

Conclusions: These data suggest that apixaban has a lower recurrent VTE hospitalization rate than rivaroxaban during the secondary prevention of VTE, and further study of diverse patient populations, especially by kidney function, is warranted.

KEYWORDS

anticoagulants, factor Xa inhibitors, secondary prevention, venous thromboembolism, warfarin

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Essentials

- There are few direct comparisons of anticoagulants for the secondary prevention of venous thromboembolism (VTE).
- We compared recurrent VTE hospitalization in commercially insured people on oral anticoagulants.
- Apixaban had the lowest risk of recurrent VTE hospitalization versus rivaroxaban or warfarin.
- Risk of recurrent VTE hospitalization for rivaroxaban versus warfarin was lower with kidney disease.

1 | INTRODUCTION

Venous thromboembolism (VTE), consisting of deep vein thrombosis and pulmonary embolism, affects approximately 1 million people per year in the United States.¹ Standard treatment after initial stabilization is anticoagulation for 3 to 6 months to prevent progression of the initial thrombosis and allow restoration of normal blood flow in the venous or pulmonary arterial vasculature (primary treatment).² In recognition of a high recurrence rate,³ individuals are then assessed for the best approach to prevent future VTE events (secondary prevention).² Secondary prevention can consist of pharmacologic or nonpharmacologic prophylaxis during periods of risk (hospitalization, surgery, fracture, immobilization, etc) or continued anticoagulation at full or reduced (prophylactic) doses.²

The decision to offer an individual anticoagulation for secondary prevention requires incorporating patient preferences with clinical judgment on the balance of bleeding and recurrent thrombosis risk.^{2,4} There are no firm guidelines as to who should be on secondary prevention with anticoagulation. Anticoagulation, however, is a common approach for secondary prevention of VTE, especially for those with a VTE event not associated with a transient risk factor such as surgery, trauma, hospitalization, or immobility.² Before 2012, the only oral options for anticoagulation for secondary prevention of VTE were vitamin K antagonists⁵ (warfarin in the United States); however, since then, several direct oral anticoagulants (DOACs) are commercially available and approved for secondary prevention of VTE after an initial treatment period (apixaban,⁶ dabigatran,⁷ and rivaroxaban⁸).

Anticoagulation for the secondary prevention of VTE compared to no secondary prevention is highly effective, with a low incidence of recurrent VTE.⁹ Thus, a randomized clinical trial would need to be large to compare the effectiveness of secondary prevention anticoagulation strategies.⁵⁻⁸ Further, real-world clinical conditions such as need for monitoring (warfarin) and once-daily (warfarin or rivaroxaban) versus twice-daily dosing (apixaban or dabigatran) influence adherence and thus efficacy. These considerations may not be apparent in controlled clinical trials, since trials are often conducted among healthier and highly motivated people. To help clinicians determine the optimal anticoagulation strategy for secondary prevention of VTE, we used administrative "healthcare claims" data (IBM MarketScan) to assess the comparative effectiveness of secondary prevention anticoagulation strategies on the recurrence of VTE hospitalization. While a clinical trial would help define the best option under ideal circumstances, understanding how care translates into a real-world clinical setting is essential for clinicians caring for people with VTE.

2 | METHODS

2.1 | Study population/MarketScan

The IBM MarketScan Commercial Claims and Encounters Database and Medicare Supplemental Database (IBM Watson Health, Ann Arbor, MI, USA) contain detailed healthcare claims from ≈43.6 million Americans per year. We conducted a retrospective cohort study using data from January 1, 2013, to December 31, 2017, by combining individual-level enrollment information, healthcare claims (ie, inpatient, outpatient, and procedure claims) and pharmacy prescription fills information from the MarketScan databases. We defined the patients' initial VTE as one inpatient or two outpatient claims for VTE 7 to 184 days apart with at least one confirmatory outpatient anticoagulation prescription within 31 days of the VTE date.¹⁰ VTE codes were defined from International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes or Tenth Revision (ICD-10-CM) codes in any position and are found in Table S1. The positive predictive value for defining VTE using ICD codes was 91% in a previous validation study using similar inpatient, outpatient, and prescription criteria.¹¹

After excluding those with ≤3 months of continuous enrollment and those aged <18 or >99 years from the sample, there were 119 964 patients with VTE. Since the focus of this article is on risk of recurrent hospitalization for VTE following secondary prevention, we also required that patients had been prescribed warfarin, apixaban, or rivaroxaban between 6 and 7 months after their initial VTE. Users of dabigatran and edoxaban were not considered for this analysis due to their limited usage during the study period.¹² The 6- to 7-month time window was selected to ensure a true secondary prevention population. Since clinical guidelines recommend an initial 3- to 6-month period of OACs for initial VTE treatment,² any continued anticoagulation beyond 6 months would be considered secondary prevention. The eligible analytic sample included 29 351 individuals who received OACs for secondary prevention. Overall participant flow is provided in Figure 1, and a graphical depiction of the cohort study based on methods developed by Schneeweiss et al¹³ for pharmacoepidemiologic studies can be found in Figure 2.

2.2 | Secondary prevention – anticoagulant use

Patient exposure was categorized as the first DOAC prescribed between 6 and 7 months succeeding the initial VTE, as warfarin, rivaroxaban, or apixaban. A previous study determined the validity of

FIGURE 1 Flowchart for sample selection of patients with venous thromboembolism (VTE) receiving oral anticoagulation for secondary prevention of VTE

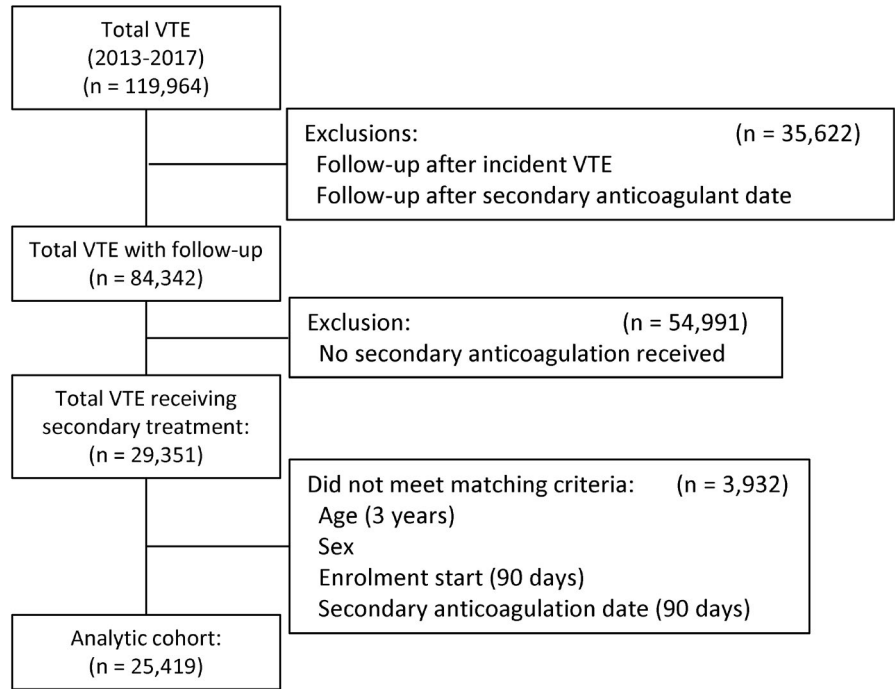
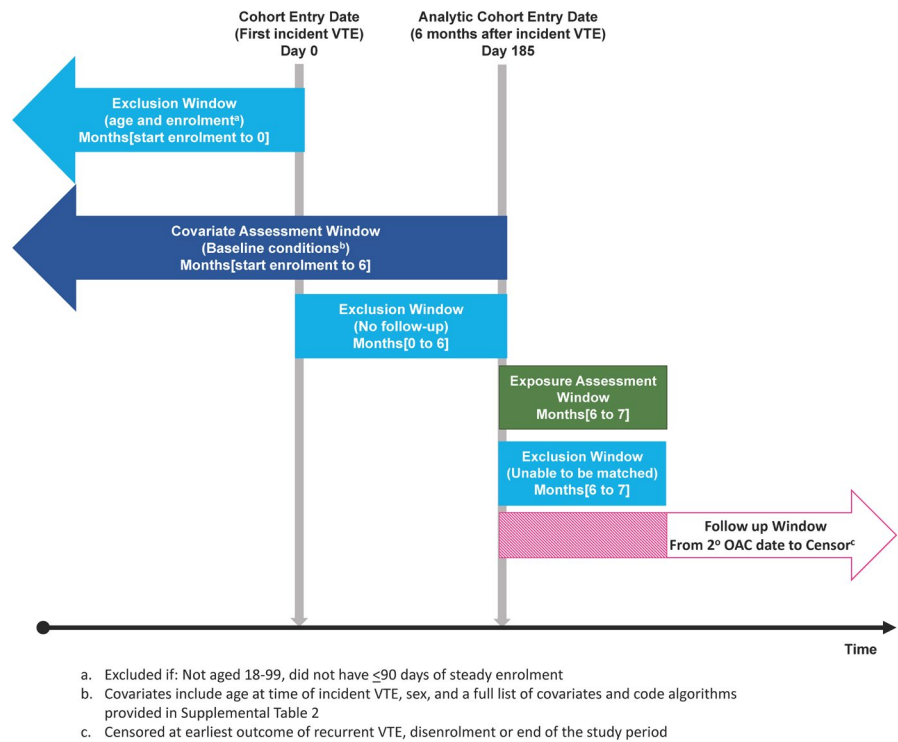


FIGURE 2 Graphical visualization of retrospective cohort study design. DOAC, direct oral anticoagulant



warfarin claims from administrative databases to be excellent, with a sensitivity of 94% and a positive predictive value of 99%.¹⁴ The validity of claims for rivaroxaban and apixaban has not yet been established.

2.3 | Outcome ascertainment

We defined recurrent VTE as a hospitalization for VTE, with the same ICD-9-CM and ICD-10-CM codes used to define initial VTE in

the first position, among individuals continuing anticoagulation after 6 months of initial anticoagulation.

2.4 | Risk factors

Potential confounders were defined via validated algorithms based on inpatient, outpatient, and pharmacy claims occurring before the start of secondary anticoagulation.¹⁵ Table S2 reports the administrative codes used to define risk factors including kidney disease.

2.5 | Statistical analysis

Cox proportional hazards regression models were used to estimate the association between secondary anticoagulation choice and the time to recurrent VTE hospitalization.¹⁶ Start of follow-up was defined as the date of secondary anticoagulation initiation and ended when any of the following first occurred: (i) first recurrent hospitalized VTE, (ii) health plan disenrollment, or (iii) the end of study follow-up (December 31, 2017). We performed three comparisons: rivaroxaban versus warfarin (reference), apixaban versus warfarin (reference), and apixaban versus rivaroxaban (reference). Logistic regression models were used to calculate propensity scores to predict anticoagulant choice, based on 28 a priori defined comorbidities and medications (listed in Table 1).¹⁷ Separate propensity scores were calculated for each comparison.

Participants from each reference OAC category were matched with up to five opposing secondary prevention OAC initiators by age (± 3 years), sex, starting date of database enrollment (± 90 days), and date of secondary OAC initiation (± 90 days). Matching was done separately for each comparison using a greedy matching algorithm.¹⁸ The Cox proportional hazards regression models were adjusted for age, sex, calendar year, and the relevant propensity score. Finally, multiplicative interaction was evaluated between secondary prevention OAC choice and age (<65 years vs ≥ 65 years), sex, and prevalent kidney disease status (yes vs no).

The individual-level enrollment, inpatient, outpatient, and medical claims provided by IBM MarketScan are all deidentified and compliant with the Health Insurance Portability and Accountability Act. The University of Minnesota Institutional Review Board deemed this analysis exempt from review. All data management and analyses were done using SAS v 9.4 (SAS Institute Inc., Cary, NC).

3 | RESULTS

We identified 119 964 individuals who met our definition for incident VTE (ie, ICD codes indicating incident VTE and an DOAC prescription fill) from 2013 to 2017. After excluding individuals with <7 months of follow-up ($n = 35\ 622$) and those who were not continued on a DOAC for >6 months after the initial VTE ($n = 54\ 991$), we identified 29 351 individuals who continued on a DOAC for secondary prevention (Figures 1 and 2). Of the 29 351 individuals, a total of 25 419 were included in the primary analyses after matching (10 208 warfarin users, 11 403 rivaroxaban users, 3808 apixaban users).

Table 1 presents the matched cohort by anticoagulant comparison: apixaban versus warfarin, rivaroxaban versus warfarin, and apixaban versus rivaroxaban. In the matched comparisons, warfarin users tended to have a slightly greater burden of comorbid conditions. In the matched rivaroxaban versus apixaban comparison, rivaroxaban users tended to have fewer comorbid conditions than matched apixaban users (Table 1).

Among the 25 419 patients with VTE included in the matched analysis, the average follow-up was 16.8 (standard deviation, 12.8)

months, and a total of 608 (2.4%) experienced a recurrent VTE hospitalization. Table 2 presents the multivariable adjusted association of DOAC use with recurrent VTE hospitalization. After adjusting for age-, sex-, enrollment date, DOAC prescription date, and the propensity-score, apixaban had a lower hazard of recurrent VTE hospitalization versus rivaroxaban (hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.45-0.94) or warfarin (HR, 0.68; 95% CI, 0.47-1.00). There was no difference in the hazard of recurrent VTE hospitalization for rivaroxaban versus warfarin (HR, 1.12; 95% CI, 0.94-1.33). In a sensitivity analysis, excluding individuals with cancer did not change interpretation of the results (Table S3).

When assessing for a differential association (effect modification) on the multiplicative scale by age, sex, or kidney disease status (Figure 3), there was no evidence of interaction for apixaban versus rivaroxaban or apixaban versus warfarin (all P interactions ≥ 0.1). For rivaroxaban versus warfarin, there was no interaction by sex or age category. However, there was evidence of a multiplicative interaction by kidney disease status (P interaction <0.01). In those with kidney disease, there was a reduced hazard of recurrent VTE hospitalization for rivaroxaban versus warfarin (HR, 0.65; 95% CI, 0.41-1.03), and an increased hazard of recurrent VTE hospitalization for those without kidney disease (HR, 1.24; 95% CI, 1.02-1.50). Table 3 presents the effect of anticoagulant dose on recurrent VTE hospitalization risk, comparing doses among rivaroxaban users and among apixaban users, respectively. For rivaroxaban, those prescribed 15 mg versus 20 mg daily had an increased risk of recurrent VTE hospitalization (HR, 1.91; 95% CI, 1.36-2.69) but not those prescribed 10 mg versus 20 mg (HR, 0.88; 95% CI, 0.36-2.13), albeit with marked imprecision. The baseline characteristics of those on rivaroxaban 20 mg, 15 mg, and 10 mg daily are presented in Table S4 and demonstrate a much higher prevalence of kidney disease in the rivaroxaban 15 mg daily group. For apixaban, the point estimate was lower for VTE hospitalization for the 2.5 mg versus the 5 mg dose but with a wide CI (HR, 0.69; 95% CI, 0.26-1.80).

4 | DISCUSSION

In this analysis of claims data, apixaban was associated with a lower risk of recurrent VTE hospitalization than rivaroxaban or warfarin when used for secondary prevention of VTE. When comparing rivaroxaban to warfarin, while there was no overall association with recurrent VTE hospitalization, there was evidence that of effect modification by kidney disease status. Individuals without kidney disease had a higher risk of recurrent VTE hospitalization with rivaroxaban versus warfarin, and individuals with kidney disease had a lower risk of recurrent VTE hospitalization. These observational data suggest that apixaban may have a lower recurrent VTE hospitalization risk than rivaroxaban or warfarin and that the association of rivaroxaban with recurrent VTE hospitalization may be dependent on renal function.

The most effective anticoagulant strategy to prevent recurrent VTE after 3 to 6 months of primary anticoagulation treatment

TABLE 1 Age-, sex-, enrollment date-, and anticoagulation date-matched cohort: MarketScan 2013–2017

	Comparisons					
	Rivaroxaban	Apixaban	Warfarin	Apixaban	Warfarin	Rivaroxaban
Number	5675	3701	5082	3064	9627	9627
Matching ratio	2	1	3	1	1	1
Person-years follow-up (mean)	5701 (1.0)	3402 (0.9)	6227 (1.2)	3131 (1.0)	15,021 (1.6)	14,940 (1.6)
Recurrent VTE, n (%)	107 (1.9)	41 (1.1)	112 (2.2)	37 (1.2)	250 (2.6)	273 (2.8)
Recurrent VTE per 1000 person-years (95% CI)	18.8 (15.5, 22.6)	12.1 (8.8, 16.2)	18.0 (14.9, 21.6)	11.8 (8.4, 16.1)	16.6 (14.7, 18.8)	18.3 (16.2, 20.5)
Age, y (SD)	58.8 (13.9)	60.1 (14.4)	61.5 (15.2)	61.1 (15.0)	58.1 (14.4)	58.0 (14.5)
Female, n (%)	2675 (47.1)	1775 (48.0)	2476 (48.7)	1477 (48.2)	4491 (46.7)	4491 (46.7)
Baseline comorbid conditions, n (%)						
Hypertension	3614 (63.7)	2571 (69.5)	3593 (70.7)	2155 (70.3)	6295 (65.0)	5975 (62.1)
Cancer	1229 (21.7)	799 (21.6)	1024 (20.2)	665 (21.7)	1801 (18.7)	1962 (20.4)
Diabetes	1421 (25.0)	1051 (28.4)	1572 (30.9)	871 (28.4)	2693 (28.0)	2315 (24.1)
Myocardial infarction	437 (7.7)	357 (9.7)	533 (10.5)	307 (10.0)	855 (8.9)	683 (7.1)
Heart failure	843 (15.8)	725 (20.7)	1112 (22.6)	638 (21.9)	1719 (18.1)	1428 (15.1)
Ischemic stroke	848 (14.9)	636 (17.2)	1014 (20.0)	540 (17.6)	1501 (15.6)	1341 (13.9)
Kidney disease	579 (10.2)	548 (14.8)	993 (19.5)	478 (15.6)	1462 (15.2)	872 (9.1)
Chronic pulmonary disease	1984 (35.0)	1401 (37.9)	1936 (38.1)	1175 (38.4)	3238 (33.6)	3202 (33.3)
Liver disease	818 (14.4)	553 (14.9)	712 (14.0)	448 (14.6)	1216 (12.6)	1226 (12.7)
Depression	1246 (22.0)	907 (24.5)	1208 (23.8)	723 (23.6)	2027 (21.1)	1953 (20.3)
Alcohol abuse	113 (2.0)	84 (2.3)	102 (2.0)	55 (1.8)	120 (1.3)	100 (1.0)
Gastrointestinal bleeding	1887 (33.3)	1287 (34.8)	1842 (36.3)	1045 (34.1)	2950 (30.6)	2803 (29.1)
Other bleeding	2402 (42.3)	1688 (45.6)	2563 (50.4)	1414 (46.2)	4435 (46.1)	3870 (40.2)
Medication use, n (%)						
Antiplatelet medication	78 (1.4)	73 (2.0)	87 (1.7)	58 (1.9)	140 (1.5)	125 (1.3)
Statins	2141 (37.7)	1594 (43.1)	2217 (43.6)	1334 (43.5)	3720 (38.6)	3412 (35.4)
Selective serotonin reuptake inhibitors	1971 (34.7)	1348 (36.4)	1780 (35.0)	1098 (35.8)	3189 (33.1)	3159 (32.8)

Abbreviations: CI, confidence interval; SD, standard deviation; VTE, venous thromboembolism.

is unknown due to the lack of randomized controlled trials directly comparing anticoagulation options. The RE-MEDY trial is the only published randomized trial comparing different anticoagulants for the secondary prevention of VTE. The trial reported dabigatran (150 mg twice daily) equivalent to standard-intensity warfarin for VTE recurrence risk.⁷ However, in our population, few people used dabigatran (or edoxaban) for secondary prevention of VTE, likely reflecting lack of use for the primary treatment of VTE in this population.¹² While it is logical to assume VTE recurrence and bleeding risk should be proportional to the degree of anticoagulation, existing evidence suggests this assumption is inaccurate. As seen with warfarin, reduced-intensity warfarin (international normalized ratio [INR] goal, 1.5–2.0) versus standard-intensity warfarin (INR goal, 2.0–3.0) increased VTE recurrence risk and did not reduce bleeding risk.⁵ A similar impact of anticoagulation intensity on VTE recurrence or

bleeding risk during secondary prevention was not seen with either apixaban or rivaroxaban in randomized trials where low-dose versus conventional-dose arms had equivalent VTE recurrence and bleeding risks.^{6,8} We did see an increased risk of recurrent VTE hospitalization in the 15-mg rivaroxaban dose; however, this is a nonstandard dose for primary treatment or secondary prevention, and it is unclear clinically why this dose was selected for these patients, making accounting for confounding nearly impossible in this situation.

In the context of secondary VTE prevention, there have been no direct comparisons between apixaban and rivaroxaban or between these agents and warfarin. In a placebo-controlled trial of secondary VTE prevention (AMPLIFY-EXT), apixaban was associated with ≈80% reduced hazard of VTE (either the 2.5 mg or 5 mg twice-daily dose) compared with placebo.⁶ Likewise, in a randomized trial of rivaroxaban (either 20 mg or 10 mg daily) versus aspirin

Comparison	Recurrent VTE	
Apixaban vs rivaroxaban (1:2 matching)	Rivaroxaban	Apixaban
Number matched	5675	3701
Number recurrent VTE hospitalizations	107	41
Person-years follow-up	5701	3402
Hazard ratio ^a (95% CI)	1 (reference)	0.65 (0.45-0.94)
Apixaban vs warfarin (1:3 matching)	Warfarin	Apixaban
Number matched	5082	3064
Number recurrent VTE hospitalizations	112	37
Person-years follow-up	6227	3131
Hazard ratio ^a (95% CI)	1 (reference)	0.68 (0.47-1.00)
Rivaroxaban vs warfarin (1:1 matching)	Warfarin	Rivaroxaban
Number matched	9627	9627
Number recurrent VTE hospitalizations	250	273
Person-years follow-up	15,020	14,940
Hazard ratio ^a (95% CI)	1 (reference)	1.12 (0.94-1.33)

TABLE 2 Association of anticoagulant choice for secondary prevention with VTE hospitalization: MarketScan 2013–2017

Abbreviations: CI, confidence interval; VTE, venous thromboembolism.

^aAdjusted for age, sex, year of VTE and propensity score.

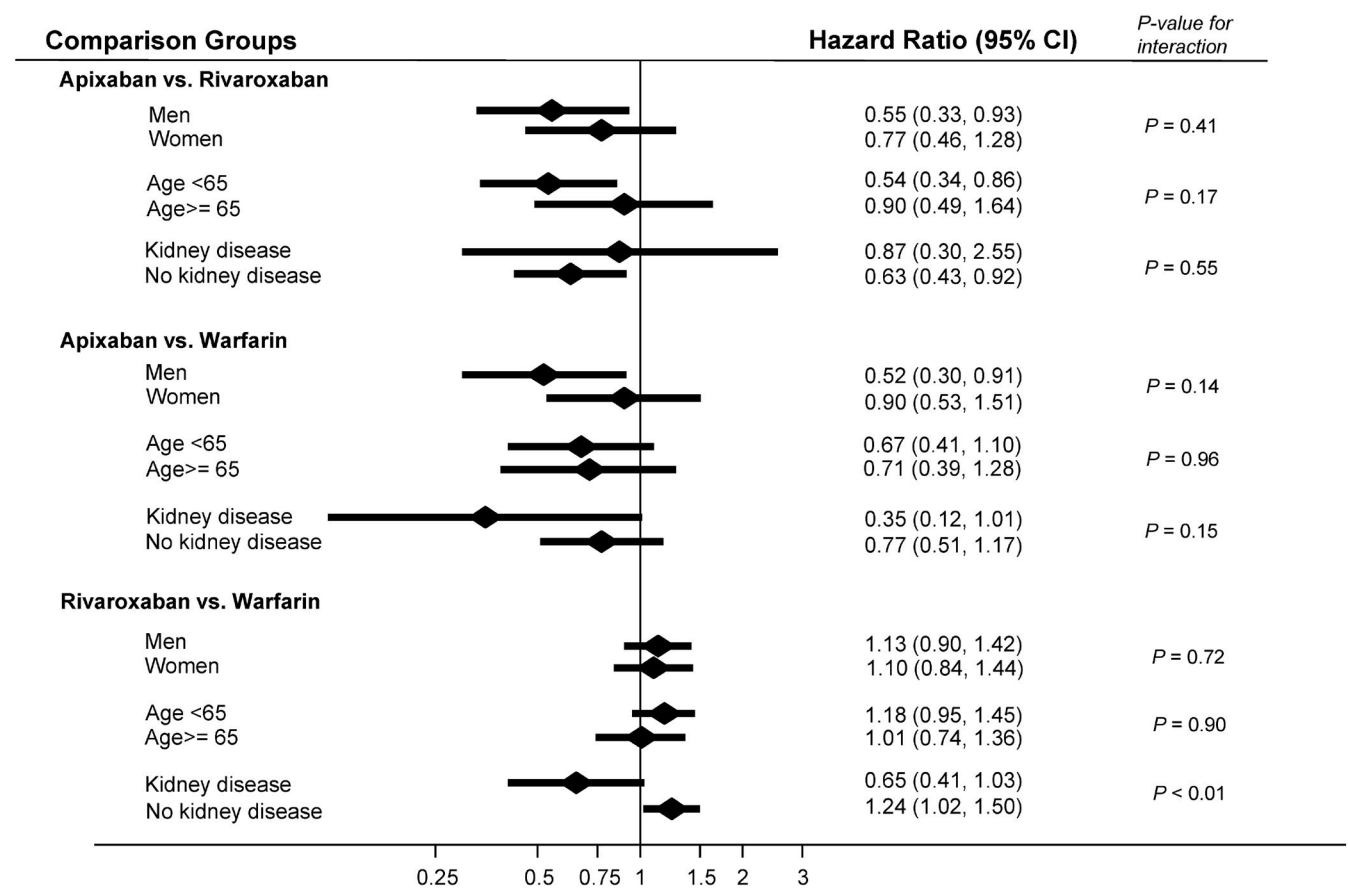


FIGURE 3 Association of anticoagulant choice for secondary prevention of venous thromboembolism (VTE) stratified by age, sex, and kidney disease status: MarketScan 2013–2017. CI, confidence interval

for secondary prevention of VTE (EINSTEIN Choice), rivaroxaban was associated with ≈70% reduction in recurrent VTE compared with aspirin.⁸ Direct comparisons between the point estimates of

recurrent VTE are challenging, as each trial has different inclusion and exclusion criteria, and one had aspirin as the control arm and the other a placebo. Further, as the AMPLIFY-EXT and EINSTEIN

TABLE 3 Association of direct anticoagulant strength for secondary prevention of VTE hospitalization: MarketScan 2013–2017

Comparison	Recurrent VTE		
	Rivaroxaban 20 mg	Rivaroxaban 15 mg	Rivaroxaban 10 mg
Rivaroxaban 10 vs 15 vs 20			
Number	10 474	802	255
Number recurrent VTE	265	40	5
Person-years follow-up	15 128	1176	327
Hazard ratio ^a (95% CI)	1 (reference)	1.91 (1.36-2.69)	0.88 (0.36-2.13)
Apixaban 2.5 vs 5.0	Apixaban 5.0 mg	Apixaban 2.5 mg	
Number	3407	587	
Number recurrent VTE	37	5	
Person-years follow-up	3033	552	
Hazard ratio ^a (95% CI)	1 (reference)	0.69 (0.26-1.80)	

^aAdjusted for age, sex, year of VTE, and propensity score.

Choice studies each had a nonanticoagulant arm, these participants had to have a low enough risk for recurrent VTE to justify potentially randomizing them to a nonanticoagulant treatment. To address some of these challenges, investigators have conducted a network meta-analysis of randomized controlled trials of anticoagulants for secondary prevention of VTE.⁹ The main findings were that all of the anticoagulation approaches except for reduced-intensity warfarin were equivalent in efficacy to prevent recurrent VTE after an initial 3- to 12-month treatment period. However, the CIs were wide, and the number of recurrent VTE events were lower than reported here. Furthermore, since the randomized controlled trial populations were at low-enough recurrence risk to be randomized to the non-DOAC arm, they are not representative of the general VTE patient population in which extended DOAC is generally indicated. A previously reported analysis of the MarketScan Commercial Claims and Encounters Database and Medicare Supplemental Database by Dawwas et al¹⁹ comparing apixaban and rivaroxaban for recurrent VTE risk demonstrated a dramatic reduction in recurrence risk with apixaban versus rivaroxaban (HR, 0.37; 95% CI, 0.24-0.55). The magnitude of the findings are much greater than those reported here and in the network analysis of clinical trials.^{9,20} The present analysis focuses on a different patient population from that of Dawwas – those who have completed the primary treatment of VTE versus a combination of primary- and secondary-treatment patient populations. Further, while inpatient VTE ICD codes have good predictive value for VTE, the analysis by Dawwas required only one outpatient VTE ICD code, different from the validated definition used in the current analysis.¹¹

One intriguing finding was the interaction by kidney disease when comparing the effectiveness of rivaroxaban versus warfarin on recurrence prevention whereby rivaroxaban was associated with lower risk among participants with kidney disease but higher risk among those without evidence of kidney disease. While this could be a chance finding, there is precedent for differential effects of DOACs by renal function status. Edoxaban in the ENGAGE AF-TIMI 48 trial demonstrated reduced efficacy in preventing thromboembolic complications of atrial fibrillation among individuals with

normal renal function, which is reflected in the package insert.^{21,22} Compared with apixaban, rivaroxaban has a shorter half-life (despite being only dosed once daily) and has increased renal clearance (35% vs 25%).²³ In theory, with normal renal function, individuals may have less anticoagulant exposure than with warfarin (where the anticoagulant intensity is titrated on the basis of a laboratory test). However, in a prior analysis, we did not find an interaction by kidney function for bleeding risk for the primary treatment (first 6 months) of VTE.¹⁰ There were too few recipients of renal allografts to meaningfully affect the results (n = 127; 0.5%). The interaction by kidney function status should be considered hypothesis generating given the number of comparisons made but must be addressed in future observational and interventional studies.

Large administrative databases, such as used in the present analysis, reflect real-world conditions patients and providers face with treatment. Randomized controlled trials often have restrictive inclusion criteria and thus do not include patients with complex comorbidities that are present in usual clinical practice. Also, while seemingly a straightforward assumption that there will be greater compliance with use of an anticoagulant lacking monthly monitoring and prescribed at a fixed-dose regimen (ie, rivaroxaban or apixaban), translation into real-world practice is not so straightforward. Despite the “inconvenience” of monitoring the anticoagulant effect of warfarin, the ability and requirement to monitor anticoagulation levels may result in more compliance with therapy and more documentation of noncompliance.^{4,24,25} Another important consideration is the consequence of missed doses. While never ideal, occasional missed doses of warfarin (with a long half-life and long anticoagulant effect) and missed doses of twice-daily apixaban may have fewer consequences than a missed dose of rivaroxaban with a short half-life and once-daily dosing.²⁴ Another consideration here is that time in therapeutic range for warfarin has important implications for VTE recurrence and cannot be assessed using administrative data. These real-world considerations are critical for providers and patients when deciding the most appropriate anticoagulation strategies.

The strengths and the weaknesses of our analyses are inherent to the use of administrative data. We cannot validate our VTE events through medical record review, we must rely on administrative data

definitions of key risk factors, and some potentially relevant covariate information is lacking. There is no validated definition of recurrent VTE for analyses using administrative databases. We chose a conservative definition: a hospitalization with a VTE ICD code in the first position with a concurrent anticoagulation prescription occurring ≥ 6 months after the initial VTE event. The validity of our definition is based on two assumptions: (i) that recurrent VTEs in patients on anticoagulation result in hospitalization, and (ii) that any misclassification of VTE events that occurred is nondifferential by DOAC prescribed. For the first assumption, despite multiple studies suggesting the safety of outpatient VTE treatment, a majority of people with VTEs are treated as inpatients in the United States.^{2,26} While there is no consensus on how to treat recurrent VTE for patients on anticoagulation, most situations would result in hospitalization.²⁷ For the second assumption, there is no obvious hypothesis why recurrent thrombosis occurring from one DOAC versus another would result in a differential frequency of hospitalization. While, ideally, we would conduct a randomized, multiarmed active comparator-controlled blinded trial of all anticoagulant options and monitor prospectively for outcomes, this approach will take time and substantial resources. The small absolute differences in VTE hospitalization (1%) seen here suggest that clinical trials would need tens of thousands of individuals per arm to detect differences in recurrent VTE rates. The Comparison of Oral Anticoagulant for Extended Venous Thromboembolism study (COVET; NCT03196349) was to address the very question posed here; however, the trial was terminated in December 2019 due to lack of enrollment.

In summary, apixaban seems more efficacious than rivaroxaban or warfarin for the prevention of recurrent VTE hospitalization after an initial period of anticoagulation. While preliminary, the impact of renal function on the relative efficacy must be addressed in future observational and randomized trials. These data should not dictate anticoagulant choice for secondary prevention but should serve to help inform providers and patients about anticoagulation options for secondary prevention. However, these data highlight the need to specifically recruit individuals with a wide range of renal function and comorbid conditions into clinical trials when evaluating the safety and efficacy of DOACs for the secondary prevention of VTE.

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RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Drafted manuscript: NAZ. Statistical analyses: RFW, RFM, PLL. Obtained funding: PLL, AA. Concept and design: NAZ, PLL.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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