





BRIEF REPORT

Impact of oral anticoagulant choice for the secondary prevention of venous thromboembolism on the risk of inpatient bleeding

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Abstract

Background: Randomized trials suggest that direct oral anticoagulants (DOACs) are at least as effective as warfarin for primary treatment of VTE and that bleeding risk may be lower for some DOACs relative to warfarin. However, there is very little information regarding potential bleeding risks for DOACs versus warfarin in secondary prevention of VTE.

Objective: The aim of this study was to compare rates of bleeding events resulting in inpatient admissions between individuals taking apixaban, rivaroxaban, and warfarin for secondary prevention of VTE during the period 2013-2017.

Methods: We used the IBM MarketScan Commercial Claims and Encounters Database and Medicare Supplemental and Coordination of Benefits Database (IBM Watson Health, Ann Arbor, MI) to establish a retrospective cohort. Initial venous thrombolism events were defined from medical claims, and follow-up for this cohort began 6 months after the initial event. Bleeding events resulting in inpatient admission were identified from claims data over the subsequent year of secondary prevention.

Results: A total of 69 264 individuals were identified for the cohort, with 567 bleeding events. The crude rate of bleeding was highest among warfarin users (1.47/100 person-years; 95% confidence interval [CI], 1.24-1.74) and lower among those on either apixaban (1.00/100 person-years; 95% CI, 0.65-1.54) or rivaroxaban (0.84/100 person-years; 95% CI, 0.66-1.08). In multivariable adjusted Cox models, those on apixaban (hazard ratio [HR], 0.80; 95% CI, 0.50-1.29) and rivaroxaban (HR, 0.81; 95% CI, 0.59-1.09) had somewhat lower rates of bleeding events relative to those on warfarin.

Conclusions: We found modest evidence of decreased risk of bleeding for apixaban and rivaroxaban. These estimates were relatively imprecise.

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Essentials

- We estimated bleeding event rates for individuals taking apixaban, rivaroxaban, and warfarin.
- We established a retrospective cohort of 69 264 in the secondary prevention phase of treatment.
- In adjusted models, apixaban and rivaroxaban had slightly lower, though imprecise, bleeding rates.
- We found modest evidence of decreased risk of bleeding for apixaban and rivaroxaban.

1 | INTRODUCTION

Venous thromboembolism (VTE) affects >1 million people in the United States per year.¹ There are substantial costs with such a highly prevalent condition. With a case fatality of 10%-30%, as many as 100 000 people per year may die as a result of VTE.^{2,3} The economic burden associated with VTE is at least \$10 billion per year, and the surgeon general has issued a "Call to Action" to prevent VTE.^{2,3}

Management of VTE is divided into three phases: the acute phase, beginning with the initial VTE event, lasting for 5-10 days; primary treatment, beginning after the acute phase and lasting the first 3-6 months; and secondary prevention, beginning at 6 months after the VTE event and continuing for a person's life regardless of whether they are on an anticoagulant or not. While warfarin has proven to be highly effective for primary treatment and secondary prevention of VTE,^{4,5} newer direct oral anticoagulants (DOACs) have been less studied despite being widely used in clinical care.⁶ There is evidence from randomized trials as well as observational studies that DOACs are at least as effective as warfarin for primary treatment of VTE.⁷⁻¹¹ Further, bleeding risk may be lower for some DOACs relative to warfarin in primary treatment.^{12,13} However, there is very little information regarding potential bleeding risks for DOACs versus warfarin in secondary prevention.¹⁴

We used data from the MarketScan administrative databases to examine bleeding events related to DOAC use in secondary prevention of VTE. In particular, we compared the rate of bleeding events resulting in inpatient admissions between individuals taking apixaban, rivaroxaban, and warfarin for secondary prevention during the period 2013-2017. Dabigatran and edoxaban were not evaluated, as they were infrequently used.⁶ Potential interactions between DOAC treatment and age, kidney disease, and sex were evaluated.

2 | METHODS

IBM MarketScan Commercial Claims and Encounters Database and the Medicare Supplemental and Coordination of Benefits Database (IBM Watson Health, Ann Arbor, MI) were used to establish a retrospective cohort.¹⁵ MarketScan includes enrollment information, inpatient and outpatient claims, and pharmaceutical reimbursements. We used claims data between January 1, 2013, and December 31, 2017.

We first identified 347 046 people aged 18-99 with at least 1 inpatient or 2 outpatient claims for VTE between 7 and 365 days apart. VTE events were identified using *International Classification*

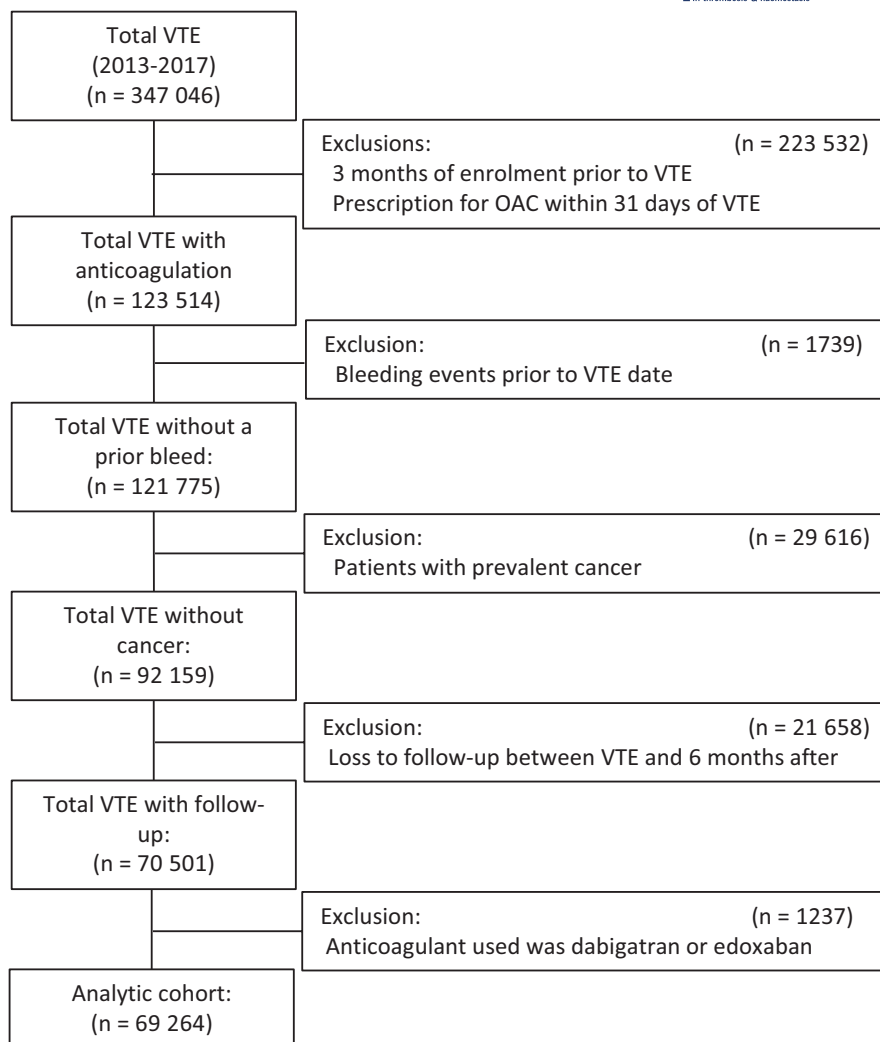
of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) and Tenth Revision, Clinical Modification (ICD-10-CM) codes in any position on the inpatient or outpatient claims. ICD-9-CM and ICD-10-CM codes used in this analysis have been previously published.¹³ We further required that individuals have a prescription for an oral anticoagulant (OAC) within 31 days of the VTE event and have 3 months of continuous enrollment before their VTE event, limiting the available sample size to 123 514. This prescription could fall between the two dates for VTE events classified from outpatient claims. We further eliminated anyone with ICD codes for bleeding before their VTE event, leaving 121 775 individuals. Patients with prevalent cancer were excluded due to their unique etiology and differing treatment recommendations. After excluding anyone with prevalent cancer, there were 92 159 individuals. A total of 21 658 dropped out of the MarketScan database between their initial VTE event and 6 months (baseline for this analysis), and we further excluded participants taking an infrequently used OAC (ie, dabigatran, edoxaban) at the beginning of 6 months ($N = 1237$), leaving a final analytic database of 69 264 (Figure 1). Of note, patients with atrial fibrillation were included in this population if they met inclusion criteria and experienced a VTE.

MarketScan outpatient pharmaceutical claims were used to identify anticoagulant use 6 months following the initial VTE event. The treatment at the beginning of the secondary prevention phase (6 months after VTE event) was assumed to be the first OAC claim that was filled during the 6 month following their index VTE event. Patients who did not fill a prescription in this time were assumed not to be on an OAC for secondary prevention.

Hospitalized bleeding events were defined according to *ICD-9-CM* and *ICD-10-CM* codes on inpatient claims following the beginning of an eligible individual's secondary treatment phase. Our definition of bleeding events has been thoroughly described elsewhere and consisted of intracranial hemorrhage (from a primary discharge diagnosis on an inpatient claim), gastrointestinal bleeding, or other major bleeding events (from primary and secondary diagnoses and inpatient claims and the presence of transfusion codes) and are based on the Cunningham algorithm.^{13,16} Clinical covariates of interest as potential confounding factors were identified from inpatient and outpatient claims. These demographic characteristics and comorbid conditions are given in Table 1, and *ICD* codes used to identify these conditions have been previously published.¹³

Primary analyses used Cox proportional hazards models to estimate the association between OAC group and time to secondary bleed. Individuals were followed from the beginning of secondary prevention (6 months after their initial VTE event) until a hospitalized bleeding event (primary outcome). Individuals were censored

FIGURE 1 Patient flowchart documenting exclusions from the final analytic cohort using MarketScan, 2013-2017. OAC, oral anticoagulant; VTE, venous thromboembolism



when they were no longer enrolled in a health plan contained in the MarketScan databases or at the end of 1 year of follow-up after secondary prevention. Cox models were adjusted for the demographic and clinical conditions given in Table 1, as well as whether individuals experienced a bleeding event in the initial VTE primary treatment phase and year of VTE event. Clinical conditions were assessed on the basis of ICD codes at any time before the beginning of the secondary prevention phase.

To understand individual-level patterns of OAC use across time, we also cross-classified OAC use at the start of the secondary prevention period by the OAC used in primary treatment (Table 2). This informed evaluation of the impact of treatment switching, which we examined in two ways. First, we restricted our analyses to only those patients who did not switch treatments between the primary and secondary treatment phase. Second, we restricted an analysis to individuals who were warfarin users in the primary treatment period; this was the only primary OAC treatment group with sufficient numbers to examine the association of treatment switching and bleeding. We estimated the association between secondary OAC treatment and bleeding among those for whom warfarin was their primary treatment. Additive interactions between OAC and sex, age >60, and chronic kidney disease were examined. As a sensitivity analysis, we repeated all analyses without excluding patients who

had evidence of bleeding before their incident VTE. The total analytic sample size for this analysis was N=69 998.

3 | RESULTS AND DISCUSSION

Comorbid conditions and demographic characteristics by secondary treatment are shown in Table 1. Overall, 66.5% of the sample was not on a treatment regimen during the secondary treatment phase, 15.5% were prescribed warfarin, 4.5% apixaban, and 13.5% rivaroxaban. Differences in comorbidity among the four groups were generally small in magnitude; however, apixaban users were more likely to have comorbid conditions, on average. Apixaban users had a higher prevalence of pulmonary disease, peripheral arterial disease, and hypertension relative to warfarin users, rivaroxaban users, and individuals who took no medication for secondary prevention. Among individuals on warfarin, apixaban, rivaroxaban, or no anticoagulant at the beginning of secondary prevention, approximately 70% had switched OAC status from primary treatment phases, with 65% switching to no OAC (Table 2).

Crude rates (Table 3) of hospitalized bleeding events in the secondary prevention period were highest among warfarin users and lowest among those who were not on OACs. In Cox models, those

	Warfarin N = 10 714	Apixaban N = 3113	Rivaroxaban N = 9371	None N = 46 066
Age, y	59.2 (15.8)	59.4 (15.4)	55.4 (14.4)	55.5 (16.2)
Female	5112 (47.7)	1498 (48.1)	4212 (45.0)	23 712 (51.8)
Chronic pulmonary disease	3469 (32.4)	1108 (35.6)	2938 (31.4)	13 367 (29.0)
Dementia	347 (3.2)	129 (4.1)	190 (2.0)	952 (2.1)
Depression	2125 (19.8)	731 (23.5)	1864 (19.9)	9699 (21.1)
Diabetes	2907 (27.1)	837 (26.9)	2117 (22.6)	10 128 (22.0)
Hematologic disorders	3063 (28.6)	807 (25.9)	2350 (25.1)	10 486 (22.8)
Hypertension	6955 (64.9)	2097 (67.4)	5504 (58.7)	25 990 (56.4)
Ischemic stroke	1632 (15.2)	496 (15.9)	1106 (11.8)	5799 (12.7)
Kidney disease	1571 (14.7)	421 (13.5)	722 (7.7)	4839 (10.5)
Liver disease	1059 (9.9)	393 (12.6)	957 (10.2)	4400 (9.6)
Myocardial infarction	918 (8.6)	285 (9.2)	626 (6.7)	3011 (6.5)
Peripheral arterial disease	1918 (17.9)	600 (19.3)	1316 (14.0)	6651 (14.4)

Note: Variables are reported as n (%).

	N	Secondary prevention			
		Warfarin N = 10 454	Apixaban N = 2981	Rivaroxaban N = 8999	No anticoagulant ^a N = 42 418
Primary Treatment					
Warfarin	32 749	9875 (30.2)	366 (1.1)	1537 (4.7)	20 971 (64.0)
Apixaban	7080	91 (1.3)	2373 (33.5)	86 (1.2)	4530 (64.0)
Rivaroxaban	25 023	488 (2.0)	242 (1.0)	7376 (29.5)	16 917 (67.5)

Note: Variables are reported as n (%).

^aIndividuals in this group could have taken aspirin.

^bPrimary treatments of dabigatran or other anticoagulants not reported.

on apixaban (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.50-1.29) and rivaroxaban (HR, 0.81; 95% CI, 0.59-1.09) had somewhat lower rates of bleeding events relative to those on warfarin. Combining DOAC categories resulted in similar estimates. In sensitivity analyses among patients who did not change OACs between primary and secondary treatment, results were generally consistent with the main model (apixaban vs warfarin: HR, 0.83; 95% CI, 0.45-1.51; rivaroxaban vs warfarin: HR, 0.55; 95% CI, 0.37-0.82; any DOAC vs warfarin: HR, 0.60; 95% CI, 0.42-0.86). Among patients who switched to rivaroxaban from initial use of warfarin (relative to remaining on warfarin), there was a notable increase in hospitalized bleeding risk (HR, 1.65; 95% CI, 1.07-2.54). There was no evidence of additive interactions (assessed with interaction contrast ratios) with age, sex, or chronic kidney disease. We conducted a sensitivity analysis that did not exclude patients with prior bleeding events. Results were very similar to those in the main analysis (Tables S1-S3). A final sensitivity analysis that controlled for selective serotonin reuptake

TABLE 1 Patient characteristics before secondary prevention period by secondary treatment regimen, MarketScan data 2013-2017 (N = 69 264)

TABLE 2 Primary and secondary treatment regimens among patients with a venous thromboembolism who were initially treated with warfarin, apixaban, or rivaroxaban, MarketScan data 2013-2017 (N=64 852)^b

inhibitor and antiplatelet agent use among participants did not alter effect estimates (see Table S4).

In this large claims database, ≈65% of those who were treated with either warfarin, apixaban, or rivaroxaban in the primary treatment phase did not have a pharmaceutical claim for an OAC at the beginning of the secondary prevention time frame. We found modest evidence of decreased rates of hospitalized bleeding among users of apixaban or rivaroxaban relative to warfarin users during the secondary prevention of VTE. Because the overall rate of hospitalized bleeding during secondary prevention was relatively low, these results were somewhat imprecise particularly among apixaban users.

These results add important information to the sparse existing literature on bleeding risk in secondary prevention of VTE. While numerous studies have looked at the impact of DOAC treatment versus warfarin with regard to prevention of recurrent VTE, relatively few studies have had the power to look at adverse bleeding events in the secondary treatment period. Randomized controlled trials

TABLE 3 Hazard ratios and 95% confidence intervals for inpatient bleeding during secondary treatment for venous thromboembolism in MarketScan, 2013–2017 (N=69 264)

	Warfarin (N = 10 714)	Apixaban (N = 3113)	Rivaroxaban (N = 9371)	None (N = 46 066)	DOAC ^d (N = 12 484)
Number of bleeding events	129	21	62	272	83
Incidence rate ^a (95% CI)	1.47 (1.24-1.74)	1.00 (0.65-1.54)	0.84 (0.66-1.08)	0.78 (0.69-0.88)	0.88 (0.71-1.09)
Crude HR (95% CI)	Reference	0.67 (0.42-1.05)	0.57 (0.42-0.77)	0.53 (0.43-0.65)	0.59 (0.45-0.78)
Adjusted HR (95% CI)	Reference	0.80 (0.50-1.29)	0.81 (0.59-1.09)	0.66 (0.53-0.82)	0.80 (0.61-1.07)
Consistent users ^b Adjusted HR (95% CI)	Reference	0.83 (0.45-1.51)	0.55 (0.37-0.82)	N/A	0.60 (0.42-0.86)
Primary warfarin ^c Adjusted HR (95% CI)	Reference	0.88 (0.32-2.41)	1.65 (1.07-2.54)	0.71 (0.56-0.91)	1.47 (0.98-2.22)

Abbreviations: CI, confidence interval; DOAC, direct oral anticoagulant; HR, hazard ratio; N/A, not applicable; OAC, oral anticoagulant.

^aPer 100 person-years.

^bConsistent users were those who took the same OAC in the primary and secondary treatment phase

^cPrimary warfarin users were those who took warfarin in primary treatment and anything in secondary treatment.

^dUsers of either apixaban or rivaroxaban.

(RCTs) have examined OACs for secondary prevention, but they had relatively few bleeding events and typically used as the comparator either placebo or aspirin. The notable exception is the RCT by Schulman et al¹⁴ examining the effect of extended OAC treatment among patients who had already completed at least 3 months of treatment by randomizing participants to dabigatran or warfarin at 3 months and then following them prospectively; they found decreased risk of major bleeding events for patients on dabigatran relative to warfarin. Dabigatran is infrequently prescribed in patients with VTE included in the MarketScan database, and as such we did not have the power to examine it in the present analysis.⁶ Secondary prevention RCTs have been conducted comparing apixaban to placebo and rivaroxaban to aspirin.^{17,18} In both instances, bleeding rates were similar, though precision was poor. In a network meta-analysis of the published RCTs, low- and standard-dose warfarin increased major bleeding risk as compared to DOACs and aspirin.¹⁹ A systematic review of extended treatment found no increase in major bleeding events when comparing warfarin to DOACs.²⁰ Overall, the existing data suggest that DOACs in general could have lower bleeding risk than warfarin. Further, the suggestion of a reduced risk of bleeding among users of rivaroxaban and apixaban is consistent with studies examining the risk of bleeding during VTE primary treatment, where multiple studies have suggested either decreased or no elevated risk of bleeding events relative to warfarin.^{7,8,13}

Observed associations were generally similar when analyses were restricted to users who did not switch anticoagulants between primary and secondary treatments. Only warfarin users had a large enough number of patients who switched treatments to allow analyses of head-to-head OAC comparisons among switchers. Among that group, those who switched to rivaroxaban had higher bleeding rates than those who stayed on warfarin, though estimates were

imprecise, particularly when estimating the association among the group that switched to apixaban. This finding may be an indication that patients who switch OACs are generally sicker or more prone to bleeds than those who do not. In fact, bleeding during the primary treatment period may have prompted the switch from warfarin to an alternate OAC.

The primary strength of the study is the large sample size provided by using MarketScan data, which allowed us to examine associations that have not been explored previously. Secondary bleeding events were somewhat rare, and precision of effect estimates was sometimes low. Poor precision among apixaban users is not entirely unexpected, as apixaban had a later approval date (April 7, 2014) than rivaroxaban (November 2, 2012), and there were fewer apixaban users in our study period. External validity is difficult to assess since information on insurance plans in MarketScan is limited. Misclassification is a concern in claims data. A similar VTE algorithm to ours, defining VTE based on ICD codes and evidence of treatment, has been shown to have relatively high positive and negative predictive power (91% and 95%) in a previous study.²¹ Anticoagulants are also subject to misclassification; however, a previous study found high sensitivity for warfarin claims (94%).²² Our definition for anticoagulant use was determined by usage in the previous month. If patients had a prescription filled for longer than a month, it would potentially be misclassified. Because our analysis follows up those who are alive at the beginning of secondary prevention, selection bias is a concern; however, we adjusted for many potential predictors of selection. Finally, despite adjusting for factors that influence secondary treatment, confounding by indication remains a concern. Sensitivity analyses that are limited to patients who do or do not switch treatments are potentially biased due to confounding by indication if the reason for switching treatment is not adequately controlled for by measured confounders.

This study is one of the largest observational studies examining the association between OAC options for VTE secondary prevention and risk of hospitalized bleeding events. We found modest evidence of decreased risk of bleeding for apixaban and rivaroxaban; however, these estimates were relatively imprecise, and additional studies that evaluate larger numbers of participants are necessary to reliably determine whether DOACs decrease the risk of bleeding events.

RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Concept and design of the research project: RFM, PLL, and NAZ; acquisition of data: RFM, PLL, and RFW; statistical analysis: RFM and PLL; critical review of manuscript: RFM, AA, PLL, NAZ, and TA.

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SUPPORTING INFORMATION

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

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