Comparative Clinical and Economic Outcomes Associated with Warfarin Versus Apixaban in the Treatment of Patients with Venous Thromboembolism in a Large U.S. Commercial Claims Database

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ABSTRACT

BACKGROUND: Venous thromboembolism (VTE), constituting deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common cause of vascular-related morbidity and mortality, resulting in a significant clinical and economic burden in the United States each year. Clinical guidelines recommend that patients with DVT and PE without cancer should be initiated on anticoagulation therapy with a direct oral anticoagulant over a vitamin K antagonist. Yet there is limited real-world evidence comparing the economic burden of warfarin and apixaban in treating VTE patients in a large commercially insured population.

OBJECTIVE: To compare safety and effectiveness of warfarin and apixaban and evaluate associated economic burden in treating VTE patients in a large U.S. commercial health care claims database.

METHODS: The PharMetrics Plus database was used to identify oral anticoagulant (OAC)-naïve patients aged ≥ 18 years who initiated apixaban or warfarin within 30 days of a qualifying VTE encounter and had continuous health plan enrollment with medical and pharmacy benefits for 6 months before treatment initiation. Apixaban initiators and warfarin initiators were matched using the propensity score matching (PSM) technique. Cox proportional hazard models were used to assess and compare the risk of major bleeding (MB), clinically relevant nonmajor (CRNM) bleeding, and recurrent VTE. Generalized linear models were used to assess and compare the all-cause health care costs. A 2-part model with bootstrapping was used to evaluate MB- and recurrent VTE-related medical costs.

RESULTS: Among 25,193 prematched patients, 13,421 (53.3%) were prescribed warfarin and 11,772 (46.7%) were prescribed apixaban. After 1:1 PSM, 8,858 matched warfarin-apixaban pairs were selected with a mean follow-up of 109 days and 103 days, respectively. Warfarin was associated with a significantly higher risk of MB (HR = 1.52, 95% CI = 1.14-2.04), CRNM bleeding (HR = 1.27, 95% CI = 1.017-1.40), and recurrent VTE (HR = 1.50, 95% CI = 1.24-1.82) compared with apixaban. Warfarin patients had significantly higher all-cause medical costs per patient per month (PPPM; \$2,333 vs. \$1,992; $P=0.001$), MB-related costs PPPM (\$112 vs. \$65; $P=0.020$), and recurrent VTE-related costs PPPM (\$287 vs. \$206; $P=0.014$) compared with apixaban patients. Warfarin patients had similar all-cause total health care costs PPPM (\$2,630 vs. \$2,420; $P=0.051$) compared with apixaban patients.

CONCLUSIONS: Warfarin use was associated with a higher risk of MB, CRNM bleeding, and recurrent VTE compared with apixaban. Warfarin use was also associated with higher all-cause medical costs, MB-related medical costs, and recurrent VTE-related costs PPPM compared with apixaban.

J Manag Care Spec Pharm. 2020;26(8):1017-26

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What is already known about this subject

- Venous thromboembolism (VTE) is the third most common cause of vascular-related death, and the overall economic burden of VTE ranges between \$13.5 and \$27.2 billion per year in the United States.
- According to the American College of Chest Physician guidelines, VTE patients who do not have cancer should be initiated on anticoagulation therapy with a direct oral anticoagulant over a vitamin K antagonist.
- Supportive real-world evidence regarding the economic benefits of warfarin versus apixaban use with corresponding clinical outcomes in a commercially insured population is lacking.

What this study adds

- This study evaluated the clinical and economic burdens of VTE treatment in warfarin initiators compared with apixaban initiators in a commercially insured population.
- Warfarin initiators were associated with an approximately 1.5 times higher risk of major bleeding (MB), clinically relevant non-major (CRNM) bleeding, and recurrent VTE.
- Warfarin initiators also had \$341 per patient per month (PPPM) higher all-cause medical costs, \$47 PPPM higher MB-related medical costs, and \$82 PPPM higher recurrent VTE-related medical costs compared with apixaban initiators.

Venous thromboembolism (VTE) can be classified into deep vein thrombosis (DVT) and pulmonary embolism (PE), with approximately one third of affected patients presenting with PE and two thirds with DVT.¹ VTE is the third most common cause of vascular-related death, following myocardial infarction (MI) and stroke.² Patients with comorbid conditions such as extremity trauma, cancer, surgery, prolonged immobilization, and hormone therapy are at a greater risk for VTE.³⁻⁸ These comorbidities are also strongly related to VTE recurrence, resulting in higher inpatient, outpatient, and pharmacy costs compared with those without recurrent VTE among commercially insured VTE patients.⁹ Incident cases of VTE along with subsequent complications reportedly result

in an average incremental direct medical cost of \$18,000 to \$23,000 per incident case among survivors.¹⁰ Overall, the economic burden of VTE ranges between \$13.5 and \$27.2 billion per year (in 2011 U.S. dollars) in the United States.¹¹

According to the American College of Chest Physician guidelines, DVT and PE patients without evidence of cancer should be initiated on anticoagulation therapy with a direct oral anticoagulant (DOAC: dabigatran, rivaroxaban, apixaban, or edoxaban) over a vitamin K antagonist (VKA) such as warfarin.¹² This recommendation is supported with evidence from the AMPLIFY randomized clinical trial program that demonstrated that a 5-mg twice-daily fixed-dose oral regimen of apixaban alone (after administering apixaban 10 mg twice daily for 7 days) was noninferior to conventional therapy (subcutaneous enoxaparin, overlapped and followed by warfarin) and was associated with significantly less bleeding in VTE patients.¹³

Similar to other DOACs, treatment with apixaban reduces the complexity of VTE treatment by eliminating the need for an initial parenteral anticoagulant (PAC) as required in conventional therapy.¹⁴ A recent large-scale, real-world evaluation of VTE patients receiving outpatient treatment with apixaban or warfarin in U.S. clinical practice reported that patients treated with apixaban had a significantly lower risk of major bleeding (MB), clinically relevant nonmajor (CRNM) bleeding, and recurrent VTE compared with those treated with warfarin over a mean of 152-day follow-up but without economic assessment.¹⁵ Furthermore, studies regarding the economic burden of VTE have been conducted but solely within the Medicare fee-for-service population.¹⁶

The economic burden of warfarin versus apixaban in treatment of VTE has not been well established using commercially insured data in the literature. Therefore, the aim of this study was to compare safety and effectiveness of warfarin versus apixaban and evaluate the associated economic burden in treating VTE patients in a large, commercially insured U.S. population.

Methods

Data Source

This retrospective cohort study used the IQVIA PharMetrics Real-World Data Adjudicated Claims (PharMetrics Plus, PMTX+) database from March 1, 2014, to September 30, 2018. PMTX+ data were selected primarily due to national representativeness of the data over other available commercial claims databases.¹⁷ It provides fully adjudicated health plan claims information for 150 million nonidentified lives in the United States, sourcing information from several commercial health plans in 50 states. It includes patients with 97% commercial, 2% Medicare Advantage, and 1% Medicaid coverage.

Patient Selection

Patients with a VTE diagnosis claim in any position in inpatient and outpatient (including emergency room) settings were identified from September 1, 2014, to September 30, 2018. The date of the first VTE encounter was designated as the index VTE encounter date. Patients who were aged ≥ 18 years were selected if they had ≥ 1 pharmacy claim for warfarin or apixaban on or within the 30-day period following the index VTE encounter. The first warfarin or apixaban prescription date was designated as the index date. Patients were required to have continuous health plan enrollment with medical and pharmacy benefits for 6 months before the index VTE encounter date and during the time between the index VTE encounter and index date. The baseline period was defined as 6 months before the index VTE encounter including the index date.

Patients were excluded if they had atrial fibrillation/atrial flutter or a mechanical heart valve during the baseline period, received oral anticoagulant (OAC) or PAC (unless the therapy was administered prophylactically), or had a VTE diagnosis 6 months before the index VTE encounter. Patients were also excluded if they had evidence of active malignancy (defined as ≥ 2 medical claims for cancer diagnosis or 1 claim for cancer diagnosis and ≥ 1 claim for cancer treatment) 6 months before until 30 days after the index VTE encounter, a claim for inferior vena cava filter or pregnancy during the study period or evidence of nonindex OAC use on the index date or a nonindex OAC during the period between the index VTE encounter and the index date. Finally, warfarin patients with their index VTE encounter in the outpatient setting were excluded if they did not have evidence of PAC use (i.e., bridging therapy) within ± 14 days of the index date or if they received PAC treatment beyond the 14-day period after the index date. Warfarin patients with an inpatient index VTE event were assumed to have bridged therapy with PAC (Figure 1).

The follow-up period was variable and was defined from the day after the index date through the earliest of the following: (a) end of the subsequent 6-month period, (b) health plan disenrollment, (c) index therapy discontinuation, (d) switch to nonindex OAC/PAC treatment, or (e) study end. Discontinuation was defined as no evidence of index warfarin or apixaban use for 30 days from the day of the last supply of the last filled prescription. Switch was defined as a prescription for a nonindex OAC/PAC within 30 days before or after the discontinuation date.

Demographic and clinical characteristics (comorbidities and medication use) and all-cause health care resource utilization and costs were evaluated during the baseline period. Additionally, VTE-related variables, including site of index VTE encounter (inpatient vs. outpatient), VTE diagnosis (DVT

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FIGURE 1 Patient Selection Criteria

OAC = oral anticoagulant; PAC = parenteral anticoagulant; VTE = venous thromboembolism.

only vs. PE with or without DVT), position of VTE diagnosis (primary vs. secondary) and VTE etiology (provoked vs. unprovoked) were measured during the index VTE encounter. Provoked VTE was defined as events that are preceded by hormone therapy, fracture/trauma involving lower extremities, pelvic/orthopedic surgery, or hospitalization for any reason for ≥3 days during the 3-month pre-index VTE encounter period¹⁸; unprovoked VTE was defined as all events not classified as provoked events.¹⁸

Outcome Measures

Clinical Outcomes. The clinical outcomes evaluated in this study were MB, CRNM bleeding, recurrent VTE, and all-cause hospitalization. MB was identified using an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) or *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) diagnosis or procedure code as the primary diagnosis in the inpatient setting and was stratified by gastrointestinal (GI) bleeding;

intracranial hemorrhage (ICH); and bleeding at other key sites (e.g., hepatic, splenic, and ocular hemorrhage; Appendix A, available in online article).¹⁹ CRNM bleeding was identified using secondary diagnosis codes in the inpatient setting for non-critical sites for bleeding (not including patients with MB in the inpatient setting) or a diagnosis code for GI bleeding or other bleeding in the outpatient setting.¹⁶ Recurrent VTE was defined by primary diagnosis in an inpatient setting, excluding admissions that occurred within 7 days of the index VTE encounter.¹⁵ All-cause hospitalization was defined as an acute inpatient stay related to any cause at any time during the follow-up period.

Economic Outcomes. Economic outcomes, including all-cause inpatient costs, all-cause emergency room (ER) costs, all-cause office visits costs, all-cause outpatient costs, all-cause medical costs, all-cause pharmacy costs, all-cause health care costs, MB-related costs, and VTE-related costs were evaluated in this study. All-cause inpatient, ER, and office costs were defined as costs related to any inpatient, ER, or office stay respectively during the follow-up. All-cause outpatient costs were defined as the sum of costs in the outpatient, ER, or office setting during the follow-up. All-cause medical costs were defined as the sum of costs in inpatient and outpatient setting during the follow-up. All-cause pharmacy costs included costs for all prescriptions during the follow-up, not just for OAC medications. All-cause health care costs were defined as the sum of medical and pharmacy costs during the follow-up. MB-related medical costs were defined as hospitalization costs associated with the first MB event plus all subsequent bleeding costs occurring in the inpatient or outpatient setting (primary and secondary diagnoses). Recurrent VTE-related medical costs were defined as the hospitalization costs associated with the first recurrent VTE event plus all subsequent VTE costs in the inpatient or outpatient (primary and secondary diagnoses) setting. Because a fixed follow-up was not used, the total costs were calculated per patient per month (PPPM) and adjusted to 2018 U.S. dollars. The numerator for PPPM calculation was the aggregate of all costs in each category, and the denominator was the aggregated patient-months.

Statistical Methods

Bivariate comparisons of baseline characteristics were conducted using t-tests and chi-square tests. Propensity score matching (PSM) without replacement was conducted between the warfarin and apixaban cohorts to balance the patient characteristics between cohorts. Patients were matched 1:1 based on the propensity scores generated by logistic regression. Some of the baseline variables included in the PSM were demographics, VTE-related variables, Deyo-Charlson Comorbidity Index (CCI) score, baseline comorbidities, selected surgeries, and baseline

medication use (Appendix B, available in online article).²⁰ The nearest neighbor method with a caliper of 0.01 was used to match patients.

Covariate balance was checked through standardized differences, with a threshold of 10%; covariates with a standardized difference greater than 10% were considered unbalanced.²¹ The incidence rates for the clinical outcomes were calculated as the number of events per 100 person-years. The first event per patient for each clinical outcome was included in the calculation. As all variables were balanced after PSM, OAC was the only independent variable included in the models. Cox proportional models were conducted to compare the risk of MB, CRNM bleeding, recurrent VTE, and all-cause hospitalization among the postmatch warfarin and apixaban cohorts.

The all-cause health care costs among the postmatched population were evaluated using generalized linear models with log-link and gamma distribution, wherein cost was the dependent variable.

Two-part models with bootstrapping were implemented for MB and recurrent VTE-related costs to account for a large number of zeros (\$0) because very few patients had MB or recurrent VTE event costs. In the 2-part models, the first part was a logistic regression for the occurrence of the event (MB or recurrent VTE) and the second part was a generalized linear model regression of cost, conditional on the event.²² To mitigate the impact of extreme cost outliers in the data, MB and recurrent VTE-related costs were adjusted using the winsorization method. Winsorization transforms the cost of the outliers to the preestablished percentile of the data.^{23,24} Therefore, the event-related cost values below the 5th percentile were winsorized to costs in the 5th percentile, and costs above the 95th percentile were transformed to costs in the 95th percentile.

Sensitivity Analysis

There is variation in the literature surrounding the definition of recurrent VTE.^{9,16,25-28} Therefore, to test the robustness of our findings, 3 sensitivity analyses were conducted surrounding the definition of recurrent VTE for both clinical and economic outcomes. First, recurrent VTE was defined to include events occurring within 7 days of the qualifying index VTE encounter.²⁶ Second, recurrent VTE was defined to include encounters in the inpatient and emergency room (ER) settings, excluding events within 7 days of the index VTE encounter.²⁸ Third, recurrent VTE was defined to include both encounters within 7 days of the index VTE encounter and those occurring in the ER setting.¹⁶

Results

Baseline Characteristics

Among 25,193 prematched patients, 13,421 (53.3%) were prescribed warfarin, and 11,772 (46.7%) were prescribed apixaban

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TABLE 1 Prematched and Postmatched Descriptive Baseline Characteristics Among VTE Patients Prescribed Warfarin Versus Apixaban

	Prematched			Postmatched		
	Apixaban Cohort (Reference)	Warfarin Cohort	STD ^a	Apixaban Cohort (Reference)	Warfarin Cohort	STD ^a
Sample size	11,772	13,421		8,858	8,858	
Age, years, mean (SD)	52.7 (12.7)	52.4 (13.1)	1.90	52.6 (12.9)	52.5 (12.9)	0.84
Age, years, n (%)						
18-54	5,956 (50.6)	6,946 (51.8)	2.33	4,527 (51.1)	4,538 (51.2)	0.25
55-64	4,252 (36.1)	4,698 (35.0)	2.34	3,162 (35.7)	3,157 (35.6)	0.12
65-74	1,144 (9.7)	1,214 (9.0)	2.30	815 (9.2)	830 (9.4)	0.58
75-79	155 (1.3)	206 (1.5)	1.84	130 (1.5)	120 (1.4)	0.96
≥80	265 (2.3)	357 (2.7)	2.64	224 (2.5)	213 (2.4)	0.80
Gender, n (%)						
Male	6,554 (55.7)	7,214 (53.8)	3.85	4,907 (55.4)	4,910 (55.4)	0.07
Female	5,218 (44.3)	6,207 (46.2)	3.87	3,951 (44.6)	3,948 (44.6)	0.07
Geographic region, n (%)						
Northeast	2,281 (19.4)	2,713 (20.2)	2.11	1,993 (22.5)	1,918 (21.7)	2.04
North Central	2,756 (23.4)	4,348 (32.4)	20.12	2,631 (29.7)	2,643 (29.8)	0.30
South	5,216 (44.3)	3,194 (23.8)	44.32	2,732 (30.8)	2,815 (31.8)	2.02
West	1,427 (12.1)	2,990 (22.3)	27.16	1,413 (16.0)	1,401 (15.8)	0.37
Other	92 (0.8)	176 (1.3)	5.21	89 (1.0)	81 (0.9)	0.93
Type of index VTE encounter, n (%)						
Inpatient	4,568 (38.8)	7,494 (55.8)	34.61	4,017 (45.3)	4,113 (46.4)	2.17
Outpatient	7,204 (61.2)	5,927 (44.2)	34.61	4,841 (54.7)	4,745 (53.6)	2.17
Index VTE diagnosis, n (%)						
DVT only	6,455 (54.8)	7,443 (55.5)	1.26	4,947 (55.8)	4,879 (55.1)	1.54
PE with or without DVT	5,317 (45.2)	5,978 (44.5)	1.26	3,911 (44.2)	3,979 (44.9)	1.54
Index VTE etiology, n (%)						
Provoked	3,545 (30.1)	4,335 (32.3)	4.73	2,709 (30.6)	2,741 (30.9)	0.78
Unprovoked	8,227 (69.9)	9,086 (67.7)	4.73	6,149 (69.4)	6,117 (69.1)	0.78
Deyo-Charlson Comorbidity Index, mean (SD)	0.8 (1.4)	1.0 (1.6)	13.60	0.8 (1.5)	0.8 (1.5)	0.90
Baseline comorbidity, n (%)						
Anemia	1,720 (14.6)	2,715 (20.2)	14.83	1,417 (16.0)	1,422 (16.1)	0.15
Central venous catheter	721 (6.1)	1,253 (9.3)	12.05	628 (7.1)	633 (7.1)	0.22
Cerebrovascular disease	547 (4.6)	979 (7.3)	11.19	461 (5.2)	456 (5.1)	0.25
Ischemic heart/coronary artery disease	1,467 (12.5)	1,746 (13.0)	1.65	1,068 (12.1)	1,076 (12.1)	0.28
Dyspepsia or stomach discomfort	2,236 (19.0)	2,929 (21.8)	7.03	1,732 (19.6)	1,732 (19.6)	0.00
Hyperlipidemia	3,498 (29.7)	3,819 (28.5)	2.77	2,519 (28.4)	2,523 (28.5)	0.10
Obesity	3,246 (27.6)	3,814 (28.4)	1.87	2,403 (27.1)	2,451 (27.7)	1.21
Pneumonia	1,211 (10.3)	1,612 (12.0)	5.45	914 (10.3)	939 (10.6)	0.92
Sleep apnea	1,432 (12.2)	1,728 (12.9)	2.15	1,084 (12.2)	1,089 (12.3)	0.17
Thrombophilia	537 (4.6)	908 (6.8)	9.55	468 (5.3)	475 (5.4)	0.35
Congestive heart failure	794 (6.7)	1,200 (8.9)	8.14	634 (7.2)	656 (7.4)	0.96
Diabetes	2,023 (17.2)	2,679 (20.0)	7.15	1,569 (17.7)	1,563 (17.6)	0.18
Hypertension	5,509 (46.8)	6,479 (48.3)	2.97	4,055 (45.8)	4,062 (45.9)	0.16
Renal disease	977 (8.3)	1,500 (11.2)	9.72	795 (9.0)	824 (9.3)	1.14
Liver disease	864 (7.3)	1,169 (8.7)	5.05	656 (7.4)	668 (7.5)	0.52
COPD	912 (7.7)	1,199 (8.9)	4.29	720 (8.1)	703 (7.9)	0.71
Peripheral vascular disease	870 (7.4)	1,302 (9.7)	8.27	692 (7.8)	702 (7.9)	0.42
Baseline bleed	1,612 (13.7)	2,677 (19.9)	16.78	1,362 (15.4)	1,366 (15.4)	0.13
Fracture/trauma involving lower extremities, n (%)	1,532 (13.0)	1,783 (13.3)	0.81	1,157 (13.1)	1,182 (13.3)	0.83
Selected surgeries, n (%)	2,528 (21.5)	3,540 (26.4)	11.51	1,992 (22.5)	2,037 (23.0)	1.21

^aSTD: standardized difference = $100 \times (\text{actual STD})$. A standardized difference greater than 10 is considered significant.

COPD = chronic obstructive pulmonary disease; DVT = deep vein thrombosis; PE = pulmonary embolism; SD = standard deviation; VTE = venous thromboembolism.

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FIGURE 2 Propensity Score-Matched Incidence Rates and Hazard Ratios of Major Bleeding, CRNM Bleeding, Recurrent VTE, and All-Cause Hospitalization for Warfarin Versus Apixaban

Note: In this figure, apixaban was used as the reference.

CI=confidence interval; CRNM=clinically relevant nonmajor; GI=gastrointestinal; ICH=intracranial hemorrhage; VTE=venous thromboembolism.

(Figure 1). Patients prescribed warfarin had higher mean CCI scores, more selected surgeries, and more history of falls during the baseline period compared with apixaban in the prematched population (Appendix B, available in online article). After 1:1 PSM, 8,858 warfarin-apixaban pairs were selected with a mean follow-up of 109 days and 103 days, respectively (Table 1).

After PSM, the standardized differences of the means of the matched variables were less than 10%, indicating that the covariates were balanced between treatment groups at baseline. Apixaban- and warfarin-matched patients had a mean age of 52.5 years and a mean CCI score of 0.8. Approximately 46% of patients had an index VTE encounter in the inpatient setting, 55% of patients had a diagnosis of DVT only, and 31% of patients had a provoked VTE diagnosis (Table 1).

Clinical Outcomes

In the PSM-matched population, the incidence rates of MB (4.4 vs. 3.0 per 100 person-years), CRNM bleeding (34.6 vs. 28.2 per 100 person-years), and recurrent VTE (9.9 vs. 7.0 per 100 person-years; Figure 2) were higher for warfarin compared with apixaban. Warfarin and apixaban patients had a similar incidence of all-cause hospitalization during the follow-up period (38.0 vs. 36.0 per 100 person-years).

Warfarin was associated with a significantly higher risk of MB (hazard ratio [HR]=1.52, 95% confidence interval

[CI]=1.14-2.04; $P=0.005$), CRNM bleeding (HR=1.27, 95% CI=1.15-1.40; $P<0.001$), and recurrent VTE (HR=1.50, 95% CI=1.24-1.82; $P<0.001$) compared with apixaban. The risk of all-cause hospitalization was similar for warfarin patients compared with apixaban patients (HR=1.08, 95% CI=0.98-1.18; $P=0.113$; Figure 2).

Economic Outcomes

Warfarin patients had significantly higher all-cause medical costs PPPM (\$2,333 vs. \$1,992; $P=0.001$) compared with apixaban patients. After pharmacy costs were included, warfarin patients had similar all-cause total health care costs PPPM (\$2,630 vs. \$2,420; $P=0.051$; Table 2) compared with apixaban patients. Warfarin was however associated with significantly higher MB-related medical costs PPPM (\$112 vs. \$65; difference=\$47, 95% CI=\$8-\$90; $P=0.020$; Table 2) and recurrent VTE-related medical costs PPPM (\$287 vs. \$206; difference=\$82, 95% CI=\$17-\$145; $P=0.014$) compared with apixaban patients.

Sensitivity Analyses

Both the clinical and economic outcomes from all 3 sensitivity analyses were consistent with the main analysis (Table 3). Recurrent VTE incidence and recurrent VTE-related costs were significantly higher in warfarin patients compared with apixaban patients when recurrent VTE was defined to include events

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TABLE 2 All-Cause Health Care Costs in the Propensity Score-Matched Cohorts

	Apixaban (Reference)			Warfarin			Difference Between Marginal Effects	95% CI for Difference Between Marginal Effect	P Value	
	Marginal Effect	95% CI for Marginal Effect		Marginal Effect	95% CI for Marginal Effect					
All-cause health care costs (PPPM), USD										
ER visit costs	73	71	74	102	97	108	30	15	43	<0.001
Office visit costs	160	157	163	187	178	196	27	21	32	<0.001
Other outpatient costs	829	812	846	974	926	1,024	145	56	233	0.001
Total outpatient costs (ER + office + other)	1,062	1,040	1,084	1,263	1,201	1,328	201	106	294	<0.001
Inpatient stay costs	930	910	949	1,070	1,017	1,125	140	−33	314	0.112
Total medical costs (outpatient + inpatient)	1,992	1,951	2,034	2,333	2,218	2,453	341	134	548	0.001
Pharmacy costs	429	420	438	297	283	312	−132	−162	−102	<0.001
Total health care costs (outpatient + inpatient + pharmacy)	2,420	2,371	2,471	2,630	2,501	2,766	210	−1	419	0.051
Major bleeding-related medical costs (PPPM), USD	65	63	67	112	109	116	47	8	90	0.020
Recurrent VTE-related medical costs (PPPM), USD	206	203	209	287	283	292	82	17	145	0.014

Note: The costs have been adjusted to 2018 USD.

CI = confidence interval; ER = emergency room; PPPM = per patient per month; USD = U.S. dollar; VTE = venous thromboembolism.

within 7 days of the index VTE encounter, events in the ER setting, and events both within 7 days of index VTE encounter and the ER setting in aggregate.

Discussion

This retrospective cohort analysis evaluated the clinical and economic burden associated with VTE among patients treated with warfarin and apixaban in a younger, commercially insured population compared with the published literature.^{15,16} Warfarin was associated with a higher risk of MB, CRNM bleeding, and recurrent VTE among VTE patients compared with patients prescribed apixaban. In addition to observed clinical benefit, warfarin use was also associated with higher all-cause medical costs PPPM, and MB- and recurrent VTE-related costs PPPM compared with apixaban use. All-cause health care costs were similar among warfarin and apixaban patients.

The results from this study add evidence to supplement results from the AMPLIFY trial where a benefit of reduced risk of MB (0.6% vs. 1.8%; relative risk = 0.31 [0.17-0.55]) and CRNM bleeding (3.8% vs. 8.0%; relative risk = 0.48 [0.38-0.60]) was observed when patients were treated with apixaban compared with conventional therapy (subcutaneous enoxaparin followed by warfarin).¹³ The trial also reported a reduced risk of recurrent VTE in apixaban patients; however, the association was not statistically significant (HR = 0.84, 95% CI = 0.60-1.18). In this study, in addition to MB and CRNM bleeding, recurrent VTE was also significantly higher for warfarin- compared with

apixaban-treated patients. The inconsistency in the recurrent VTE risk could be attributed to study setting (controlled trial vs. real world), differences in the methods employed to identify eligible VTE patients (diagnoses via imaging techniques vs. ICD-9-CM and ICD-10-CM codes), and variable follow-up periods. and definition of recurrent VTE (clinical assessment including fatal and nonfatal VTE vs. a primary diagnosis in an inpatient setting). Additionally, the AMPLIFY trial was designed to assess noninferiority in a clinical trial setting, whereas the present real-world study has a much larger sample size for detecting association.

Other retrospective studies comparing DOACs to warfarin have shown similar results.^{15,19} Using a commercial pooled database, VTE patients who initiated apixaban were associated with a significantly lower risk of MB (HR = 0.75, 95% CI = 0.64-0.87), CRNM bleeding (HR = 0.77, 95% CI = 0.71-0.83), and recurrent VTE (HR = 0.80, 95% CI = 0.70-0.91) compared with warfarin patients, which is consistent with our study.¹⁵ In another study using a Medicare population, warfarin was associated with a significantly higher risk of MB (HR = 1.31, 95% CI = 1.10-1.57) and CRNM bleeding (HR = 1.31, 95% CI = 1.19-1.43; $P < 0.001$), but a similar risk of recurrent VTE (HR = 0.96, 95% CI = 0.70-1.33; $P = 0.825$), compared with apixaban patients.¹⁹ Although the MB and CRNM bleeding risks are consistent with the Medicare study, the risk of recurrent VTE is not. This could be attributed to the different health insurances (i.e., Medicare vs. commercial insurance) or the differences in

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TABLE 3 Sensitivity Analysis for Clinical and Economic Outcomes for Recurrent VTE

	Clinical Outcomes		Economic Outcomes ^a			
	HR (95% CI) for Warfarin vs. Apixaban	P Value	Mean Costs for Warfarin vs. Apixaban, USD	Difference Between Marginal Effects, USD (95% CI for difference)	P Value	
Recurrent VTE (including 7 days)	1.44 (1.21-1.71)	<0.001	353 vs. 247	106 (33-182)	0.005	
Recurrent VTE (including ER)	1.50 (1.28-1.75)	<0.001	256 vs. 177	79 (29-129)	0.002	
Recurrent VTE (including 7 days+ER)	1.46 (1.28-1.65)	<0.001	328 vs. 240	88 (32-145)	0.002	

Note: In this table, apixaban was used as the reference.

^aThe costs have been adjusted to 2018 USD.

CI=confidence interval; ER=emergency room; HR=hazard ratio; USD=U.S. dollar; VTE=venous thromboembolism.

the data structure. The Medicare study also included higher-risk older patients with a mean age of 78 years, compared with a younger population with a mean age of 52 years in this study. Additionally, the current study used more recent data (until September 2018) compared with the Medicare study (until December 2016), which could have affected the outcomes.

Fewer studies have evaluated the economic burden as well as the impact of complications including recurrence of VTE and MB among patients who initiated oral anticoagulants in a younger, commercially insured VTE population. Lin et al. (2014) found that among Medicare and commercially insured VTE patients, recurrent VTE rates were relatively high (11.4% and 15.4%, respectively).⁹ A systematic review had estimated that managing an initial episode of acute VTE costs between \$12,000 and \$15,000, with subsequent complications increasing costs to between \$18,000 and 23,000 per incident case.¹⁰ Additionally, the authors found that the primary driver for health care costs was the use of inpatient care, which is similar to the findings of the present study.¹⁰ They concluded that among the VTE patient population, the total health care costs for patients with a recurrent VTE event were approximately triple those for patients who did not experience a recurrent VTE event.⁹ The above-mentioned study using the Medicare population found that all-cause (\$3,267 vs. \$3,033; $P<0.001$) and MB-related costs (\$147 vs. \$75; $P=0.003$) were significantly higher for warfarin patients whereas recurrent VTE related costs were similar (\$30 vs. \$36; $P=0.516$) compared with apixaban patients.¹⁹ In this study, warfarin patients had significantly higher MB- and recurrent VTE-related costs compared with apixaban patients using winsorization. A similar trend was seen without applying winsorization; warfarin trended toward higher MB- and recurrent VTE-related costs; however, the MB-related costs were not significant. One likely reason for this may be due to the extreme cost outliers and the smaller sample size associated with MB and recurrent VTE events.

Limitations

To the best of our knowledge, this retrospective analysis is the first study that evaluated economic burden associated with VTE and recurrence of VTE in a commercially insured population. It provides a comprehensive picture of how medications are used by clinicians in routine practice. One of the main strengths of the study is that it has a wide geographic U.S. representation and can be generalized to the U.S. commercially insured population younger than aged 65 years.

There are some inherent limitations to this study and the nature of observational research. Causal relationships cannot be reported; only associations could be assessed. Additionally, administrative claims data are collected for purposes other than research, and the analysis is constrained by diagnosis and procedure codes. The presence of a diagnosis code on a medical claim is not a positive indication of the presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. Over-the-counter use of medications such as aspirin could not be captured which could affect the treatment patterns associated with the study anticoagulants.

This study used ICD-9-CM and ICD-10-CM codes to identify DVT and PE, which is different from the imaging assessments used in clinical trials; this may lead to differences in patient populations. Also, although cohorts were matched using PSM, there remains the potential for residual confounding, such as warfarin dose adjustment and over-the-counter use of aspirin, which was not available in the database. Finally, these results may not be generalizable to those who are uninsured, the Medicare population, or other segments of the U.S. population.

Conclusions

In this commercially insured population, warfarin use among VTE patients was associated with higher risk of MB, CRNM bleeding, and recurrent VTE compared with apixaban use.

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These results are largely consistent with available clinical trial and recently published real-world data. Warfarin was also associated with higher medical health care costs, higher MB-related costs, and higher recurrent VTE-related costs compared with apixaban. These results may help clinicians, stakeholders, and decision makers in identifying safe and effective treatment for VTE as well as potentially reducing economic burden.

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DISCLOSURES

This study was funded by Bristol Myers Squibb and Pfizer, which were also involved in the study design, as well as writing and revising of the manuscript. Guo, Rajpura, Okano, and Rosenblatt are employees of Bristol Myers Squibb. Hlavacek, Mardekian, and Russ are employees of Pfizer. Keshishian, Sah, Delinger, and Mu are employees of SIMR, LLC, which received funding from the study sponsors to conduct this study.

ACKNOWLEDGMENTS

The editorial support provided by Christopher Haddelsey at SIMR, LLC, was funded by Bristol Myers Squibb and Pfizer.

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APPENDIX A Codes for Identifying Clinical Outcomes

Category	ICD-9 Codes	ICD-10 Codes
Major bleeding		
Gastrointestinal	ICD-9-CM codes: 456.0x, 456.20, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x	ICD-10-CM codes: I8501, I8511, K2211, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K2901, K2921, K2931, K2941, K2951, K2961, K2971, K2981, K2991, K31811, K3182, K5521, K5701, K5711, K5713, K5721, K5731, K5733, K5741, K5751, K5753, K5781, K5791, K5793, K625, K6381, K661, K920, K921, K922, K9161, K9162, K91840, K91841
	ICD-9-PCS codes: 44.43	ICD-10-PCS codes: no codes
Intracranial	430.xx, 431.xx, 432.xx, 852.0x, 852.2x, 852.4x, 853.0x	I6000, I6001, I6002, I6010, I6011, I6012, I602, I6030, I6031, I6032, I604, I6050, I6051, I6052, I606, I607, I608, I609, I610, I611, I612, I613, I614, I615, I616, I618, I619, I6200, I6201, I6202, I6203, I621, I629, S06340A, S06341A, S06342A, S06343A, S06344A, S06345A, S06346A, S06347A, S06348A, S06349A, S06350A, S06351A, S06352A, S06353A, S06354A, S06355A, S06356A, S06357A, S06358A, S06359A, S06360A, S06361A, S06362A, S06363A, S06364A, S06365A, S06366A, S06367A, S06368A, S06369A, S064X0A, S064X1A, S064X2A, S064X3A, S064X4A, S064X5A, S064X6A, S064X7A, S064X8A, S064X9A, S065X0A, S065X1A, S065X2A, S065X3A, S065X4A, S065X5A, S065X6A, S065X7A, S065X8A, S065X9A, S066X0A, S066X1A, S066X2A, S066X3A, S066X4A, S066X5A, S066X6A, S066X7A, S066X8A, S066X9A
Other major bleeding	ICD-9-Diagnosis: 285.1, 360.43, 362.43, 362.81, 363.61, 363.62, 363.72, 364.41, 372.72, 374.81, 376.32, 377.42, 379.23, 423.0x, 596.7x, 599.7x, 602.1x, 620.1, 621.4, 626.2, 626.5, 626.7, 626.8, 626.9, 719.1x, 782.7, 784.7, 784.8, 786.3x, 958.2, 997.02, 998.11	ICD-10-CM codes: D62, D7801, D7802, D7821, D7822, E3601, E3602, E89810, E89811, G9731, G9732, G9751, G9752, H05231, H05232, H05233, H05239, H1130, H1131, H1132, H1133, H2100, H2101, H2102, H2103, H31301, H31302, H31303, H31309, H31311, H31312, H31313, H31319, H31411, H31412, H31413, H31419, H3560, H3561, H3562, H3563, H35731, H35732, H35733, H35739, H4310, H4311, H4312, H4313, H44811, H44812, H44813, H44819, H47021, H47022, H47023, H47029, H59111, H59112, H59113, H59119, H59121, H59122, H59123, H59129, H59311, H59312, H59313, H59319, H59321, H59322, H59323, H59329, H9521, H9522, H9541, H9542, I312, I97410, I97411, I97418, I9742, I97610, I97611, I97618, I97620, J9561, J9562, J95830, J95831, L7601, L7602, L7621, L7622, M2500, M25011, M25012, M25019, M25021, M25022, M25029, M25031, M25032, M25039, M25041, M25042, M25049, M25051, M25052, M25059, M25061, M25062, M25069, M25071, M25072, M25073, M25074, M25075, M25076, M2508, M96810, M96811, M96830, M96831, N421, N857, N897, N920, N923, N930, N938, N939, N9961, N9962, N99820, N99821, R040, R041, R042, R0489, R049, R233, R310, R319, R58, T792XXA
	ICD-9 procedure: 99.04	ICD-10 PCS codes: 30230N1, 30230P1, 30233N1, 30233P1, 30240N1, 30240P1, 30243N1, 30243P1, 30250N1, 30250P1, 30253N1, 30253P1, 30260N1, 30260P1, 30263N1, 30263P1
Clinically relevant nonmajor bleeding		
Gastrointestinal	ICD-9-CM codes: 456.0x, 456.20, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 578.x	ICD-10-CM codes: I8501, I8511, K2211, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K2901, K2921, K2931, K2941, K2951, K2961, K2971, K2981, K2991, K31811, K3182, K5521, K5701, K5711, K5713, K5721, K5731, K5733, K5741, K5751, K5753, K5781, K5791, K5793, K625, K6381, K920, K921, K922, K9161, K9162, K91840, K91841
	ICD-9-PCS codes: 44.43	ICD-10-PCS codes: no codes
Other major bleeding	ICD-9-Diagnosis: 285.1, 372.72, 374.81, 596.7x, 599.7x, 602.1x, 620.1, 621.4, 626.2, 626.5, 626.7, 626.8, 626.9, 782.7, 784.7, 784.8, 786.3x, 958.2	ICD-10-CM codes: D62, E89810, E89811, H0289, H1130, H1131, H1132, H1133, J9561, J9562, J95830, J95831, L7601, L7602, L7621, L7622, M96810, M96811, M96830, M96831, N421, N857, N897, N920, N923, N930, N938, N939, N9961, N9962, N99820, N99821, R040, R041, R042, R0489, R049, R233, R310, R319, R58, T792XXA
	ICD-9 procedure: 99.04	ICD-10-PCS codes: 30230N1, 30230P1, 30233N1, 30233P1, 30240N1, 30240P1, 30243N1, 30243P1, 30250N1, 30250P1, 30253N1, 30253P1, 30260N1, 30260P1, 30263N1, 30263P1
Recurrent VTE^a		
VTE	PE: 415.11, 415.13, 415.19	PE: I2692, I2699
	DVT: 451.11, 451.19, 451.2, 451.81, 451.83, 451.84, 451.9, 453.1, 453.2, 453.4, 453.82, 453.83, 453.84, 453.85, 453.86, 453.87, 453.89, 453.9	DVT: I801, I802, I803, I809, I821, I82210, I82220, I82290, I8240, I8241, I8242, I8243, I8244, I8249, I824Y, I824Z, I8260, I8262, I82A1, I82B1, I82C1, I82890, I8290

^aThe same codes were used to identify VTE patients for study inclusion.

DVT=deep vein 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.

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APPENDIX B Descriptive Baseline Characteristics Among VTE Patients Prescribed Warfarin Versus Apixaban

	Prematched			Postmatched		
	Apixaban Cohort (Reference)	Warfarin Cohort	STD ^a	Apixaban Cohort (Reference)	Warfarin Cohort	STD ^a
Sample size, n	11,772	13,421		8,858	8,858	
Age, mean (SD)	52.7 (12.7)	52.4 (13.1)	1.89	52.6 (12.9)	52.5 (12.9)	0.84
Age, ^b years, n (%)						
18-54	5,956 (50.6)	6,946 (51.8)	2.33	4,527 (51.1)	4,538 (51.2)	0.25
55-64	4,252 (36.1)	4,698 (35.0)	2.34	3,162 (35.7)	3,157 (35.6)	0.12
65-74	1,144 (9.7)	1,214 (9.0)	2.30	815 (9.2)	830 (9.4)	0.58
75-79	155 (1.3)	206 (1.5)	1.84	130 (1.5)	120 (1.4)	0.96
≥80	265 (2.3)	357 (2.7)	2.64	224 (2.5)	213 (2.4)	0.80
Gender, ^b n (%)						
Male	6,554 (55.7)	7,214 (53.8)	3.85	4,907 (55.4)	4,910 (55.4)	0.07
Female	5,218 (44.3)	6,207 (46.2)	3.87	3,951 (44.6)	3,948 (44.6)	0.07
Geographic region, ^b n (%)						
Northeast	2,281 (19.4)	2,713 (20.2)	2.11	1,993 (22.5)	1,918 (21.7)	2.04
North Central	2,756 (23.4)	4,348 (32.4)	20.12	2,631 (29.7)	2,643 (29.8)	0.30
South	5,216 (44.3)	3,194 (23.8)	44.32	2,732 (30.8)	2,815 (31.8)	2.02
West	1,427 (12.1)	2,990 (22.3)	27.16	1,413 (16.0)	1,401 (15.8)	0.37
Other	92 (0.8)	176 (1.3)	5.21	89 (1.0)	81 (0.9)	0.93
Plan type, n (%)						
Commercial	5,437 (46.2)	7,165 (53.4)	14.43	4,014 (45.3)	4,881 (55.1)	19.67
Medicaid	256 (2.2)	1,408 (10.5)	34.65	217 (2.4)	659 (7.4)	23.17
Medicare Advantage	174 (1.5)	337 (2.5)	7.39	166 (1.9)	188 (2.1)	1.77
Self-insured	3,168 (26.9)	3,774 (28.1)	2.71	2,406 (27.2)	2,642 (29.8)	5.90
Medicare Supplemental	11 (0.1)	108 (0.8)	10.65	8 (0.1)	69 (0.8)	10.48
Other/missing	2,816 (23.9)	767 (5.7)	53.01	2,114 (23.9)	510 (5.8)	52.72
Index year, ^c n (%)						
2014	158 (1.3)	2,094 (15.6)	52.97	127 (1.4)	1,407 (15.9)	53.16
2015	1,667 (14.2)	5,472 (40.8)	62.46	1,240 (14.0)	3,635 (41.0)	63.52
2016	3,419 (29.0)	3,443 (25.7)	7.61	2,614 (29.5)	2,207 (24.9)	10.34
2017	4,263 (36.2)	1,885 (14.0)	52.86	3,187 (36.0)	1,264 (14.3)	51.69
2018	2,265 (19.2)	527 (3.9)	49.28	1,690 (19.1)	345 (3.9)	49.03
Type of index VTE encounter, ^b n (%)						
Inpatient	4,568 (38.8)	7,494 (55.8)	34.61	4,017 (45.3)	4,113 (46.4)	2.17
Outpatient	7,204 (61.2)	5,927 (44.2)	34.61	4,841 (54.7)	4,745 (53.6)	2.17
ER	3,613 (30.7)	3,141 (23.4)	16.46	2,410 (27.2)	2,492 (28.1)	2.07
Index VTE diagnosis, ^b n (%)						
DVT only	6,455 (54.8)	7,443 (55.5)	1.26	4,947 (55.9)	4,879 (55.1)	1.54
PE with DVT	1,874 (15.9)	2,126 (15.8)	0.23	1,457 (16.4)	1,338 (15.1)	3.69
PE without DVT	3,443 (29.3)	3,852 (28.7)	1.20	2,454 (27.7)	2,641 (29.8)	4.66
Position of index VTE diagnosis, ^b n (%)						
Primary	10,399 (88.3)	11,716 (87.3)	3.18	7,835 (88.5)	7,841 (88.5)	0.21
Secondary	1,373 (11.7)	1,705 (12.7)	3.18	1,023 (11.5)	1,017 (11.5)	0.21
Index VTE etiology, ^b n (%)						
Provoked	3,545 (30.1)	4,335 (32.3)	4.73	2,709 (30.6)	2,741 (30.9)	0.78
Unprovoked	8,227 (69.9)	9,086 (67.7)	4.73	6,149 (69.4)	6,117 (69.1)	0.78
Deyo-Charlson Comorbidity Index, mean (SD)	0.8 (1.4)	1.0 (1.6)	13.55	0.8 (1.5)	0.8 (1.5)	0.93
Baseline comorbidity, ^b n (%)						
AIDS	57 (0.5)	77 (0.6)	1.23	44 (0.5)	41 (0.5)	0.49
Alcohol abuse	393 (3.3)	645 (4.8)	7.43	318 (3.6)	343 (3.9)	1.49
Anemia	1,720 (14.6)	2,715 (20.2)	14.83	1,417 (16.0)	1,422 (16.1)	0.15
Central venous catheter	721 (6.1)	1,253 (9.3)	12.05	628 (7.1)	633 (7.1)	0.22
Cerebrovascular disease	547 (4.6)	979 (7.3)	11.19	461 (5.2)	456 (5.1)	0.25

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**Comparative Clinical and Economic Outcomes Associated with Warfarin Versus Apixaban
in the Treatment of Patients with Venous Thromboembolism in a Large U.S. Commercial Claims Database**

APPENDIX B Descriptive Baseline Characteristics Among VTE Patients Prescribed Warfarin Versus Apixaban
(continued)

	Prematched			Postmatched		
	Apixaban Cohort (Reference)	Warfarin Cohort	STD ^a	Apixaban Cohort (Reference)	Warfarin Cohort	STD ^a
Baseline comorbidity, ^b n (%)						
Coagulopathy	176 (1.5)	336 (2.5)	7.21	154 (1.7)	153 (1.7)	0.09
Ischemic heart/coronary artery disease	1,467 (12.5)	1,746 (13.0)	1.65	1,068 (12.1)	1,076 (12.1)	0.28
Dementia	76 (0.6)	93 (0.7)	0.58	59 (0.7)	62 (0.7)	0.41
Dyspepsia or stomach discomfort	2,236 (19.0)	2,929 (21.8)	7.03	1,732 (19.6)	1,732 (19.6)	0.00
Hemiplegia or paraplegia	124 (1.1)	240 (1.8)	6.21	110 (1.2)	113 (1.3)	0.30
Hyperlipidemia	3,498 (29.7)	3,819 (28.5)	2.77	2,519 (28.4)	2,523 (28.5)	0.10
Obesity	3,246 (27.6)	3,814 (28.4)	1.87	2,403 (27.1)	2,451 (27.7)	1.21
Pneumonia	1,211 (10.3)	1,612 (12.0)	5.45	914 (10.3)	939 (10.6)	0.92
Rheumatologic disease	300 (2.5)	357 (2.7)	0.70	226 (2.6)	219 (2.5)	0.50
Sleep apnea	1,432 (12.2)	1,728 (12.9)	2.15	1,084 (12.2)	1,089 (12.3)	0.17
Spinal cord injury	19 (0.2)	38 (0.3)	2.59	18 (0.2)	16 (0.2)	0.52
Thrombocytopenia	375 (3.2)	650 (4.8)	8.45	329 (3.7)	333 (3.8)	0.24
Thrombophilia	537 (4.6)	908 (6.8)	9.55	468 (5.3)	475 (5.4)	0.35
Varicose veins	499 (4.2)	423 (3.2)	5.76	303 (3.4)	317 (3.6)	0.86
Congestive heart failure	794 (6.7)	1,200 (8.9)	8.14	634 (7.2)	656 (7.4)	0.96
Diabetes	2,023 (17.2)	2,679 (20.0)	7.15	1,569 (17.7)	1,563 (17.6)	0.18
Hypertension	5,509 (46.8)	6,479 (48.3)	2.97	4,055 (45.8)	4,062 (45.9)	0.16
Renal disease	977 (8.3)	1,500 (11.2)	9.72	795 (9.0)	824 (9.3)	1.14
Liver disease	864 (7.3)	1,169 (8.7)	5.05	656 (7.4)	668 (7.5)	0.52
COPD	912 (7.7)	1,199 (8.9)	4.29	720 (8.1)	703 (7.9)	0.71
Peptic ulcer disease	139 (1.2)	218 (1.6)	3.77	119 (1.3)	122 (1.4)	0.29
Inflammatory bowel disease	203 (1.7)	325 (2.4)	4.90	179 (2.0)	172 (1.9)	0.57
Peripheral vascular disease	870 (7.4)	1,302 (9.7)	8.27	692 (7.8)	702 (7.9)	0.42
Baseline bleed	1,612 (13.7)	2,677 (19.9)	16.78	1,362 (15.4)	1,366 (15.4)	0.13
Recent history of falls, ^b n (%)	369 (3.1)	483 (3.6)	2.58	296 (3.3)	286 (3.2)	0.63
Fracture/trauma involving lower extremities, ^b n (%)	1,532 (13.0)	1,783 (13.3)	0.81	1,157 (13.1)	1,182 (13.3)	0.83
Selected surgeries, ^b n (%)	2,528 (21.5)	3,540 (26.4)	11.51	1,992 (22.5)	2,037 (23.0)	1.21
Baseline medication use, ^b n (%)						
Antiarrhythmic	920 (7.8)	1,053 (7.8)	0.12	654 (7.4)	655 (7.4)	0.04
Statins	2,605 (22.1)	2,957 (22.0)	0.23	1,903 (21.5)	1,894 (21.4)	0.25
Antiplatelets	331 (2.8)	452 (3.4)	3.22	261 (2.9)	258 (2.9)	0.20
Beta blockers	2,160 (18.3)	2,836 (21.1)	7.00	1,652 (18.6)	1,691 (19.1)	1.13
Gastroprotective agents	2,903 (24.7)	3,303 (24.6)	0.11	2,151 (24.3)	2,082 (23.5)	1.83
SERMS	53 (0.5)	28 (0.2)	4.22	25 (0.3)	26 (0.3)	0.21
NSAIDs	3,442 (29.2)	3,721 (27.7)	3.35	2,484 (28.0)	2,476 (28.0)	0.20
Hormone therapy	1,215 (10.3)	1,164 (8.7)	5.62	856 (9.7)	839 (9.5)	0.65
Baseline all-cause health care utilization						
Any ER visit, n (%)	6,135 (52.1)	6,792 (50.6)	3.01	4,448 (50.2)	4,587 (51.8)	3.14
Any office visit, n (%)	10,292 (87.4)	11,047 (82.3)	14.32	7,687 (86.8)	7,377 (83.3)	9.82
Any outpatient visit, n (%)	11,604 (98.6)	13,054 (97.3)	9.17	8,711 (98.3)	8,657 (97.7)	4.39
Any inpatient admission, n (%)	6,466 (54.9)	9,173 (68.3)	27.86	5,212 (58.8)	5,456 (61.6)	5.63
Any pharmacy visit, n (%)	11,772 (100.0)	13,421 (100.0)	0.00	8,858 (100.0)	8,858 (100.0)	0.00
ER visits (PPPM), n, mean (SD)	0.1 (0.2)	0.1 (0.2)	2.10	0.1 (0.2)	0.1 (0.2)	4.93
Office visits (PPPM), n, mean (SD)	0.8 (1.0)	0.7 (0.9)	7.99	0.8 (1.0)	0.7 (0.9)	8.18
Outpatient visits (PPPM), n, mean (SD)	1.7 (1.8)	1.8 (1.9)	2.06	1.7 (1.8)	1.7 (1.8)	1.55
Inpatient admission (PPPM), n, mean (SD)	0.1 (0.1)	0.2 (0.2)	27.89	0.1 (0.2)	0.1 (0.2)	5.94
Length (in days) of inpatient stay (PPPM), n, mean (SD)	0.6 (1.6)	1.2 (2.4)	26.54	0.7 (1.7)	0.9 (1.9)	9.98
Pharmacy visits (PPPM), n, mean (SD)	1.5 (1.3)	1.5 (1.4)	3.16	1.5 (1.3)	1.5 (1.3)	0.25

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APPENDIX B Descriptive Baseline Characteristics Among VTE Patients Prescribed Warfarin Versus Apixaban
(continued)

	Prematched			Postmatched		
	Apixaban Cohort (Reference)	Warfarin Cohort	STD ^a	Apixaban Cohort (Reference)	Warfarin Cohort	STD ^a
Baseline all-cause health care costs (PPPM), mean (SD)						
ER visit costs	95 (241)	92 (208)	1.26	87 (196)	90 (183)	1.53
Office visit costs	91 (111)	88 (111)	2.71	92 (115)	87 (107)	4.61
Other outpatient costs	796 (2,002)	795 (1,918)	0.02	784 (2,170)	777 (1,813)	0.34
<i>Total outpatient costs (ER + office + other)</i>	982 (2,068)	975 (1,990)	0.31	963 (2,225)	954 (1,875)	0.43
Inpatient stay costs	2,527 (5,818)	4,072 (8,911)	20.53	2,805 (6,267)	3,198 (7,156)	5.83
<i>Total medical costs (outpatient + inpatient)</i>	3,509 (6,301)	5,048 (9,311)	19.35	3,768 (6,790)	4,152 (7,560)	5.34
Pharmacy costs	292 (812)	273 (696)	2.47	296 (867)	256 (629)	5.30
<i>Total health care costs (outpatient + inpatient + pharmacy)</i>	3,801 (6,404)	5,321 (9,379)	18.92	4,065 (6,896)	4,408 (7,632)	4.72

^aSTD: standardized difference = $100 \times (\text{actual STD})$. A standardized difference greater than 10 is considered significant.

^bVariables that were included in 1:1 propensity score matching between warfarin and apixaban patients.

^cDefined as the year in which patients had their index date.

AIDS = acquired immunodeficiency syndrome; COPD = chronic obstructive pulmonary disease; DVT = deep vein thrombosis; ER = emergency room; NSAIDS = nonsteroidal anti-inflammatory drug; PE = pulmonary embolism; PPPM = per patient per month; SD = standard deviation; SERMS = selective estrogen receptor modulator; STD = standardized difference; VTE = venous thromboembolism.