ARTICLE

Comparative effectiveness and safety of extended anticoagulant therapy among Medicare beneficiaries with venous thromboembolism

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Abstract

Guidelines recommend an extended course of anticoagulation therapy for patients who experienced venous thromboembolism (VTE) without transient provocation, however, optimal duration remains uncertain. We assessed effectiveness and safety of extended use of apixaban and warfarin greater than 6 months of initial treatment in patients with VTE. We conducted a retrospective cohort study of Medicare beneficiaries aged greater than or equal to 18 years with deep vein thrombosis or pulmonary embolism. Patients were required to have initiated anticoagulants within 30 days of their first VTE diagnosis, completed 6 months of initial anticoagulant treatment, and received extended phase treatment with apixaban (the apixaban group) or warfarin (the warfarin group) or no extended therapy. Multivariable Cox proportional hazards modeling with inverse probability treatment weighting was used to compare recurrent VTE, mortality, and major bleeding risks among the three groups. Mean extended-treatment duration was up to 10 months and 14 months in apixaban and warfarin groups, respectively. Compared with no extended treatment, apixaban use was associated with decreased risks of recurrent VTE (hazard ratio [HR] = 0.08, [95% confidence interval [CI]: 0.01–0.41]) and mortality (HR = 0.37, [95% CI: 0.27–0.51]) without increased major bleeding risk (HR = 1.29, [95% CI: 0.68–2.45]); warfarin use was associated not with recurrent VTE risk change but with increased major bleeding risk (HR = 2.14, [95% CI: 1.26–3.65]) and decreased mortality risk (HR = 0.39, [95% CI: 0.29–0.51]). Compared with warfarin, apixaban use was associated with decreased recurrent VTE (HR = 0.13, [95% CI: 0.03–0.63]) and major bleeding (HR = 0.56, [95% CI: 0.32–0.98]) risks. Subgroup and sensitivity analyses (e.g., intention-to-treat) findings remained consistent. Compared with warfarin or no extended therapy, extended-apixaban use was associated with reduced risk of recurrent VTE without increased major bleeding risk. Continuing anticoagulant therapy with apixaban greater than 6 months may be effective and safe.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
Extended treatment with warfarin or apixaban beyond 6 months of initial treatment reduces recurrent venous thromboembolism (VTE) compared with placebo. Risk of bleeding is a concern with continuation of anticoagulant therapy, but the optimal duration of anticoagulation treatment remains uncertain.

WHAT QUESTION DID THIS STUDY ADDRESS?
What is the effectiveness and safety of extended use of apixaban and warfarin greater than 6 months of initial treatment compared with no treatment and apixaban versus warfarin greater than 6 months of initial treatment in patients with VTE?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
In this analysis of a large population-based cohort of patients with VTE, the use of apixaban as extended treatment was associated with decreased risk of recurrent VTE and mortality without increasing major bleeding risk compared with no extended treatment and had a better safety profile with significantly fewer recurrent VTEs compared with warfarin.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
This study provides confirmatory evidence on the effectiveness and safety of apixaban as extended therapy in routine care.

INTRODUCTION

Every year in the United States, venous thromboembolism (VTE) may affect as many as 900,000 individuals and cause up to 300,000 deaths.[1,2] Within 5 years of a VTE event, about 25% of individuals experience a recurrence.[3] Individuals have a greater risk of recurrence 6–12 months after an incident VTE.[4] The annual incidence of VTE increases exponentially with age, from 1 per 10,000 in young adults to 1 per 100 in the elderly.[5,6]

Continuing anticoagulation treatment may reduce the risk of recurrent VTE but is associated with increased bleeding risk.[7] Warfarin has been used for 6 decades; however, newer direct-acting oral anticoagulants (DOACs) are increasingly being used in routine clinical practice owing to their conventional dosing and favorable pharmacological profiles. Two large randomized clinical trials, Prolonged Anticoagulation During 18 Months versus Placebo After Initial 6-month Treatment for a First Episode of Idiopathic Pulmonary Embolism (PADIS-PE) and Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy-Extended Treatment (AMPLIFY-EXT), reported that extended treatment with warfarin or apixaban beyond 6 months of initial treatment reduced recurrent VTE without increasing the rate of major bleeding compared with placebo.[8,9] Recent guidelines strongly recommend an

extended course of anticoagulation therapy for patients who experienced VTE without transient provocation.[10]

However, the optimal duration of anticoagulation treatment remains uncertain, and the risk of bleeding is a concern with continuation of anticoagulant therapy.[11–13] Several studies have shown the benefits of long-term anticoagulation therapy to reduce recurrent VTE risk even among individuals with transient provoked VTE.[10,12,14] By contrast, a meta-analysis of clinical trials found that the extended use of anticoagulation not only did not lower the risk of recurrent VTE but also increased the risk of bleeding approximately 2.5-fold,[15,16] suggesting that treatment should be determined by balancing the risks of recurrent VTE and major bleeding to avoid unnecessary risk of bleeding with extended anticoagulation therapy.[12,17]

To fill these unsettling gaps in evidence assessing the real-world effectiveness and safety of extended anticoagulation therapy beyond 6 months of initial treatment for patients with VTE, we compared the safety and effectiveness of no treatment with extended treatments of apixaban and warfarin using real-world data from the national Medicare insurance database. We also performed a head-to-head comparison of the extended therapies of warfarin and apixaban on the risk of recurrent VTE, major bleeding events, and mortality in patients who completed 6 months of anticoagulant therapy for VTE.

METHODS

Study design and data source

We conducted a retrospective cohort study using a random 5% sample of 2014–2015 Medicare claims data and a random 15% sample of 2016–2018 Medicare claims data. The data included beneficiaries' information on demographic characteristics, medical and pharmacy enrollment status, inpatient and outpatient medical service utilization, outpatient pharmacy dispensing information, and death. The University of Florida Institutional Review Board approved this study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Study population

Using a previously validated method, we identified adult (≥18 years) fee-for-service beneficiaries for whom the first VTE in their inpatient claims occurred during the period of January 1, 2014 to December 31, 2018 using International Classification of Diseases, Ninth (ICD-9-CM) or Tenth (ICD-10-CM) Revision, Clinical Modification to discern primary or secondary diagnosis codes for pulmonary embolism (PE) or deep vein thrombosis (DVT; Table S1).[18,19] To establish the incident VTE cohort, we excluded beneficiaries who had a VTE diagnosis or anticoagulant treatment within 12 months before their first VTE diagnosis. We required the initiation of oral anticoagulant treatment (i.e., apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin) be within the 30-day period following the first VTE and that during the initial treatment period of 6 months the oral anticoagulant treatment last a minimum of 5 months (proportion of days covered ≥83%) without any major bleeding or recurrent VTE events. During the 6-month initial treatment period, patients were allowed to switch between oral anticoagulants.

We further required beneficiaries to have extended phase medication therapy either with apixaban (apixaban group), with warfarin (warfarin group), or to not have had an extended phase therapy phase (no-treatment group) based on prescriptions during the 30-day period before and the period following the sixth month after the date of the initial oral anticoagulant prescription. The index date for the apixaban and warfarin groups was the date of either the apixaban or warfarin prescription nearest to the end date of the sixth month. The index date for the no-treatment group was the day after an anticoagulant prescription's last fill date plus the days' supply. We required patients to have been continuously enrolled in Medicare Parts A, B, and D for a 12-month baseline period before the index date. We established three pairwise comparisons of patients termed cohort 1 (apixaban vs. no treatment), cohort 2 (warfarin vs. no treatment), and cohort 3 (apixaban vs. warfarin).

Study outcomes

The incidence rate of recurrent VTE and all-cause mortality was the effectiveness outcome. Recurrent VTE was defined as the presence of inpatient primary discharge diagnoses codes (ICD-9-CM or ICD-10-CM) that have been validated previously and for which the positive predictive value was 83%.[19] The incidence rate of major bleeding events was the safety outcome. This was defined by identifying bleeding-related hospitalizations related to oral anticoagulant use using Cunningham's algorithm, which has an estimated positive predictive value equaling 89%–99%.[20] The algorithm discerns hospitalizations related to serious bleeding events, including gastrointestinal or genitourinary bleeding, intracranial hemorrhage, and bleeding at other sites using diagnosis and procedure codes.[20] We followed patients from their index date until (1) their earliest date of an occurrence of each outcome, (2) they switched to any different anticoagulant therapy (or when a patient in the no-treatment group initiated an anticoagulant), (3) they discontinued their extended phase treatment (>7-day gap between prescription fills), (4) their Medicare benefit enrollment ended, (5) or December 31, 2018 (i.e., the end of the study period; Figure S1).

Covariates

On the basis of prior studies assessing risk factors for developing VTE or bleeding events,[21–25] we considered a priori a defined set of covariates during the baseline period, including demographic characteristics (age, sex, race and ethnicity, receipt of low-income subsidy, and disability status) and presence of comorbidities (cancer, surgery, trauma, hyperlipidemia, abnormal coagulation, tobacco use, respiratory diseases, liver diseases, chronic kidney disease, anemia, alcohol use disorder, drug use disorder, history of bleeding, ischemic heart disease, myocardial infarction, atrial fibrillation, stroke, heart failure, varicose veins, thrombocytopenia, hypercoagulable state, and obesity; Tables S1 and S2). Additionally, we took prior medication use during the baseline period into account (angiotensin-converting enzyme inhibitors, antiplatelet therapy, aspirin, β-blockers, calcium channel blockers, corticosteroids, cyclooxygenase-2 inhibitors, loop diuretics, estrogens, nonsteroidal anti-inflammatory drugs, potassium-sparing diuretics,

proton pump inhibitors,[26] selective serotonin reuptake inhibitors, thiazide diuretics, and vasodilators). We classified the incident VTE type for each beneficiary into provoked or unprovoked.[22] Beneficiaries were considered to have provoked VTE if they had a VTE associated with malignant neoplasm (i.e., any diagnosis of cancer occurring during the 6-month period preceding the VTE; and active cancer), or had any of the following within 3 months preceding the VTE: VTE related to pregnancy, surgery, or trauma; or a hospital admission of greater than or equal to 3 consecutive days.[27,28] Furthermore, we calculated the bleeding risk score, Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile, Elderly, and Drugs (HAS-BLED) score, which is a commonly used measure validated in patients with VTE receiving anticoagulation treatment.[29] The HAS-BLED score is calculated according to the presence of the following components: age greater than 65 years; ICD-9-CM or ICD-10-CM codes for abnormal kidney function, abnormal liver function, alcohol use disorder, bleeding, drug use disorder, hypertension, and stroke; and prescription records for antiplatelets or nonsteroidal anti-inflammatory drugs.

Statistical analysis

We summarized demographic and clinical characteristics using proportions for categorical variables and means and SDs for continuous variables for the three cohorts. To adjust for differences in baseline characteristics and disease risk factors, we used the stabilized inverse probability treatment weighting (IPTW) method. The propensity score (predicted probability of extended treatment initiation) for the treatment that each patient received was estimated using logistic regression given the baseline covariates of demographic characteristics, presence of comorbidities, HAS-BLED score, initial presentation of VTE (provoked or unprovoked; DVT, PE, or both), and prior medication use. We used the standardized mean difference to assess the balance among the groups and considered statistical significance to be >0.1.[30] Crude incidence rates were reported for major bleeding events, mortality, and recurrent VTE (number of events/100 person-years). After applying IPTW, Cox proportional hazards models to further adjust for covariates that that persistently differed among the groups. We presented hazard ratios (HRs) and 95% confidence intervals (95% CIs) for each outcome. The proportional hazard assumption was tested using Schoenfeld residuals. For recurrent VTE and major bleeding outcomes, we used cause-specific hazard modeling to adjust for the competing risk for death.

Subgroup and sensitivity analyses

Subgroup analyses were conducted in the following selected subgroups of patients with VTE to examine the potential heterogeneity of treatment effects: age (>65 vs. ≤65 years), cancer, chronic kidney disease, hypercoagulable state, obesity, sex (male vs. female), and type of first VTE (provoked vs. unprovoked). In sensitivity analyses, we extended the exposure effect windows until 30 and 60 days after the end of the last prescription's supply and conducted an intention-to-treat (ITT) analysis. We further conducted analyses for 12-month and 24-month study periods. A p value of >0.05 for interactions was considered an indicator of significant differences between groups. All analyses were performed using SAS, version 9.4. (SAS Institute).

Patient and public involvement

This study used de-identified data; thus, informed consent was waived. Patients were not involved in the development of the research question, outcome measures, or in the development of the study recruitment strategy, design, and implementation. We did not seek advice from patients on interpreting or documenting the results. We do not plan to disseminate the results to the study participants or the patient community.

RESULTS

Study cohort and patient characteristics

Before IPTW, we identified 2303 beneficiaries with apixaban extended therapy, 2764 patients with warfarin extended therapy, and 2332 beneficiaries having no extended therapy (Figure 1 and Table S3). The study populations for the three pairwise comparisons of patients initiated with apixaban or warfarin as extended phase therapy or with no treatment after IPTW are shown in Table 1. After IPTW, all standardized mean differences were less than or equal to 0.1 from each pairwise comparison indicating that patient demographic and clinical characteristics were balanced among the groups. Regardless of the study group, adherence to the initial 6 months of anticoagulant therapy was high (mean monthly proportion of days covered, 0.97). In the pairwise comparison for apixaban and warfarin (cohort 3), the mean extended therapy duration was 4.5–9.7 months (maximum duration 47.8 months), and 4.5–13.6 months (maximum duration 55 months) during a mean follow-up of 12.8 and 22.0 months in addition to the 6 months
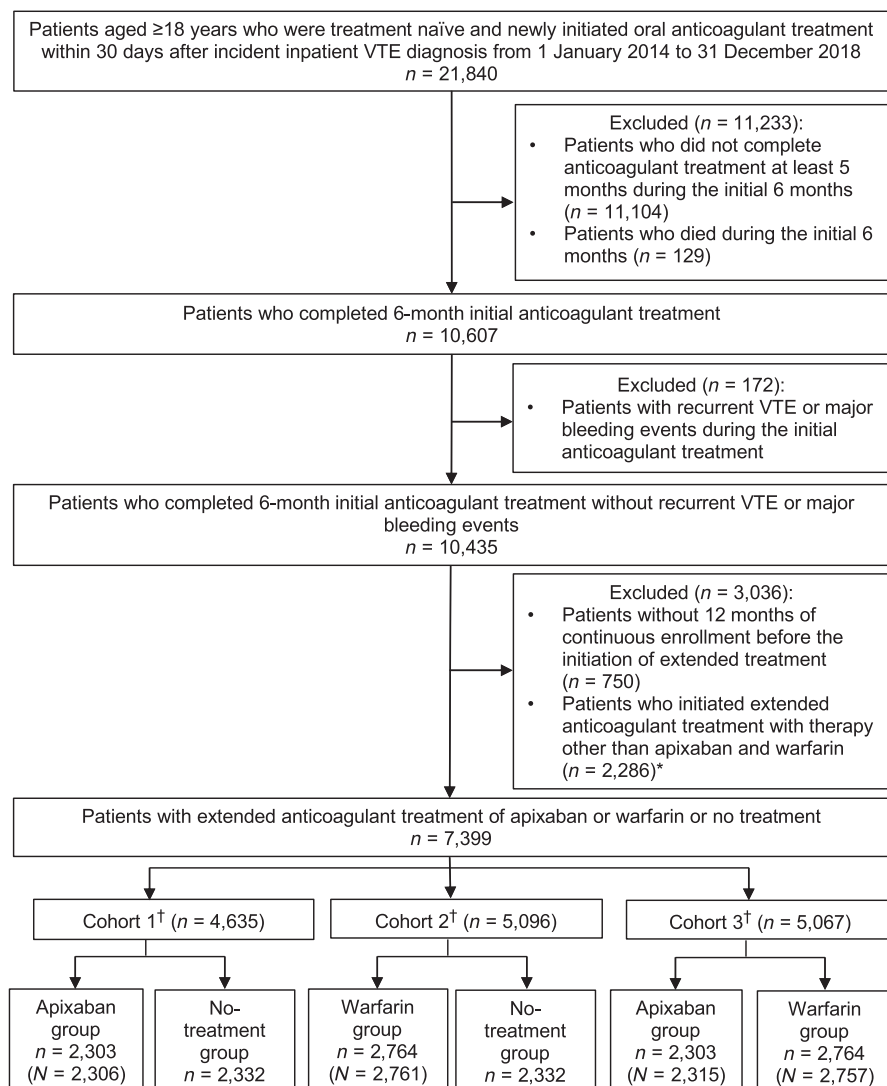
FIGURE 1 Flowchart of study population selection. *Included 2165 rivaroxaban users, 118 dabigatran users, and less than 10 edoxaban users. †Patients who met inclusion criteria could contribute to multiple different cohorts. n, unweighted number of patients; N, weighted number of patients; VTE, venous thromboembolism

initial anticoagulant treatment in the apixaban and warfarin groups, respectively (Table S4).

Recurrent VTE

Table 2 and Figure S2 show the risk of recurrent VTE in the three comparison cohorts. The recurrent VTE crude incidence rates were 0.24 for apixaban, 1.41 for warfarin, and 1.44 and no-treatment per 100 person-years. In comparisons with the no-treatment group using Cox proportional hazards models after IPTW, the extended use of apixaban (HR, 0.08 [CI, 0.01 to 0.41]) but not warfarin (HR, 0.62 [CI, 0.32 to 1.21]) was associated with lower risk of recurrent VTE. Compared with the use of warfarin, the use of apixaban was associated with decreased risk of recurrent VTE (HR, 0.13 [CI, 0.03 to 0.63]). Our findings remained consistent when we conducted an ITT analysis as well as an analysis of the extended exposure effect window after patients discontinued their medication up to 60 days

(Table S5). Results from subgroup analyses were consistent with the main findings' results except for patients with a hypercoagulable condition or obesity in cohort 2 (warfarin vs. no treatment). When comparing warfarin users to the no-treatment group, the risk of recurrent VTE was significantly higher for individuals with versus without a hypercoagulable state (P-interaction = 0.016) and among individuals with versus without obesity (P-interaction = 0.031; Table S6).

All-cause mortality

Table 3 shows that the number of deaths in the apixaban, warfarin, and no-treatment groups were 50 of 2306, 76 of 2761, and 231 of 2326 and crude incidence rates of mortality were 5.97, 7.14, and 11.02 per 100 person-years, respectively. In the Cox proportional hazards model after IPTW, the extended use of apixaban (HR, 0.37 [CI, 0.27 to 0.51]) and warfarin (HR, 0.39 [CI, 0.29 to 0.51]) were associated

TABLE 1 Baseline characteristics of patients with venous thromboembolism who received extended treatment with apixaban or warfarin or had no extended therapy, after inverse probability treatment weighting

Characteristic	Cohort 1		Cohort 2		Cohort 3		Max SMD[a]
	Apixaban (n = 2306)	No treatment (n = 2325)	Warfarin (n = 2761)	No treatment (n = 2326)	Apixaban (n = 2315)	Warfarin (n = 2757)	
Weighted number of patients							
Age, mean (SD), years	73.2 (11.5)	73.2 (11.0)	72.6 (12.2)	72.6 (11.6)	73.5 (11.9)	73.3 (12)	0.016
Female n (%)	1352 (58.7)	1363 (58.6)	1625 (58.9)	1372 (58.9)	1396 (60.3)	1652 (59.9)	0.008
Race and ethnicity, n (%)							
White	1958 (84.9)	1971 (84.8)	2317 (83.9)	1947 (83.7)	1949 (84.2)	2309 (83.8)	<0.001
Black	244 (10.6)	246 (10.6)	333 (12.1)	285 (12.3)	279 (12.1)	342 (12.4)	
Other	103 (4.5)	108 (4.6)	111 (4)	94 (4.0)	87 (3.8)	107 (3.9)	
LIS receipt, n (%)	700 (30.4)	710 (30.5)	908 (32.9)	759 (32.6)	786 (34.0)	962 (34.9)	0.020
Disability, n (%)	520 (22.5)	528 (22.7)	690 (25.0)	583 (25.1)	558 (24.1)	685 (24.8)	0.017
Dual eligibility, n (%)	635 (27.5)	645 (27.7)	834 (30.2)	697 (30.0)	719 (31.1)	885 (32.1)	0.023
Metropolitan residence, n (%)	1867 (81)	1886 (81.1)	2165 (78.4)	1824 (78.4)	1817 (78.5)	2152 (78.1)	0.011
Comorbidities, n (%)							
Cancer	584 (25.3)	579 (24.9)	646 (23.4)	543 (23.4)	561 (24.3)	654 (23.7)	0.012
Surgery	710 (30.8)	711 (30.6)	886 (32.1)	744 (32.0)	652 (28.2)	761 (27.6)	0.013
Trauma	125 (5.4)	121 (5.2)	246 (8.9)	206 (8.9)	171 (7.4)	183 (6.6)	0.029
Hyperlipidemia	1619 (70.2)	1629 (70.1)	1950 (70.6)	1644 (70.7)	1635 (70.6)	1951 (70.8)	0.003
Abnormal coagulation	595 (25.8)	593 (25.5)	760 (27.5)	643 (27.6)	620 (26.8)	711 (25.8)	0.022
Tobacco use	353 (15.3)	351 (15.1)	431 (15.6)	364 (15.6)	370 (16.0)	435 (15.8)	0.007
Respiratory tract disease	1265 (54.9)	1270 (54.6)	1510 (54.7)	1273 (54.7)	1302 (56.2)	1515 (55.0)	0.026
Liver disease	286 (12.4)	291 (12.5)	393 (14.2)	329 (14.1)	281 (12.1)	332 (12.0)	0.004
Chronic kidney disease	502 (21.8)	508 (21.8)	621 (22.5)	525 (22.6)	546 (23.6)	642 (23.3)	0.007
Anemia	991 (43.0)	999 (43.0)	1324 (48.0)	1116 (48.0)	1052 (45.5)	1246 (45.2)	0.005
Alcohol use disorder	94 (4.1)	96 (4.1)	119 (4.3)	98 (4.2)	80 (3.5)	100 (3.6)	0.008
Drug use disorder	135 (5.9)	135 (5.8)	188 (6.8)	155 (6.7)	139 (6.0)	171 (6.2)	0.008
History of bleeding	822 (35.6)	822 (35.4)	1091 (39.5)	918 (39.5)	852 (36.8)	986 (35.8)	0.022
Ischemic heart disease	1142 (49.5)	1150 (49.5)	1343 (48.6)	1134 (48.8)	1168 (50.5)	1377 (49.9)	0.011
Myocardial infarction	449 (19.5)	455 (19.6)	546 (19.8)	468 (20.1)	454 (19.6)	547 (19.8)	0.009
Atrial fibrillation	615 (26.7)	630 (27.1)	811 (29.4)	683 (29.4)	711 (30.7)	843 (30.6)	0.010
Stroke	169 (7.3)	176 (7.6)	236 (8.5)	201 (8.6)	182 (7.9)	226 (8.2)	0.012

(Continues)

TABLE 1 (Continued)

Characteristic	Cohort 1		Cohort 2		Cohort 3		Max SMD[a]
Weighted number of patients	Apixaban (n = 2306)	No treatment (n = 2325)	Warfarin (n = 2761)	No treatment (n = 2326)	Apixaban (n = 2315)	Warfarin (n = 2757)	
Heart failure	833 (36.1)	840 (36.1)	1039 (37.6)	878 (37.8)	934 (40.3)	1110 (40.3)	0.003
Varicose veins	34 (1.5)	37 (1.6)	90 (3.3)	75 (3.2)	64 (2.8)	73 (2.6)	0.010
Thrombocytopenia	256 (11.1)	252 (10.8)	322 (11.7)	269 (11.6)	245 (10.6)	289 (10.5)	0.008
Hypercoagulable state	351 (15.2)	348 (15)	486 (17.6)	412 (17.7)	398 (17.2)	456 (16.5)	0.017
Obesity	989 (42.9)	1003 (43.1)	1134 (41.1)	958 (41.2)	968 (41.8)	1159 (42.0)	0.005
HAS-BLED score, mean (SD)	3 (1.1)	3 (1.1)	3.1 (1.1)	3.1 (1.1)	3.1 (1.1)	3 (1.1)	0.013
Initial presentation of VTE, n (%)							
DVT and PE	128 (5.6)	124 (5.3)	271 (9.8)	226 (9.7)	188 (8.1)	218 (7.9)	0.044
DVT only	249 (10.8)	247 (10.6)	471 (17.1)	395 (17.0)	331 (14.3)	376 (13.6)	
PE only	1928 (83.6)	1954 (84.0)	2019 (73.1)	1706 (73.3)	1796 (77.6)	2163 (78.5)	
Provoked VTE[b]	650 (28.2)	656 (28.2)	826 (29.9)	695 (29.9)	635 (27.4)	755 (27.4)	0.001
Unprovoked VTE	1656 (71.8)	1670 (71.8)	1936 (70.1)	1631 (70.1)	1680 (72.6)	2002 (72.6)	
Prior use of medication, n (%)							
Antiplatelet therapy	360 (15.6)	363 (15.6)	459 (16.6)	388 (16.7)	401 (17.3)	455 (16.5)	0.022
Corticosteroids	1741 (75.5)	1755 (75.5)	2086 (75.6)	1762 (75.8)	1761 (76.1)	2090 (75.8)	0.006
NSAIDs	1055 (45.8)	1061 (45.6)	1271 (46.0)	1067 (45.9)	1059 (45.7)	1250 (45.3)	0.008
ACE inhibitors	897 (38.9)	907 (39.0)	1173 (42.5)	991 (42.6)	954 (41.2)	1158 (42.0)	0.016
Aspirin	19 (0.8)	21 (0.9)	30 (1.1)	26 (1.1)	22 (1.0)	29 (1.1)	0.012
Beta-blockers	1337 (58)	1345 (57.8)	1662 (60.2)	1403 (60.3)	1394 (60.2)	1659 (60.2)	0.003
CCBs	1005 (43.6)	1018 (43.8)	1236 (44.8)	1051 (45.2)	1033 (44.6)	1248 (45.3)	0.013
SSRIs	782 (33.9)	780 (33.5)	961 (34.8)	804 (34.6)	846 (36.5)	995 (36.1)	0.010
PPIs	1271 (55.1)	1284 (55.2)	1551 (56.2)	1309 (56.2)	1306 (56.4)	1552 (56.3)	0.003
Loop diuretics	946 (41.0)	950 (40.9)	1256 (45.5)	1058 (45.5)	1108 (47.9)	1314 (47.7)	0.004
Potassium-sparing diuretics	333 (14.4)	331 (14.2)	409 (14.8)	343 (14.7)	343 (14.8)	413 (15.0)	0.006
Thiazide diuretics	524 (22.7)	526 (22.6)	673 (24.4)	567 (24.4)	549 (23.7)	652 (23.6)	0.003
Vasodilators	366 (15.9)	371 (16.0)	486 (17.6)	413 (17.7)	406 (17.5)	488 (17.7)	0.004
Estrogens	117 (5.1)	118 (5.1)	146 (5.3)	123 (5.3)	122 (5.3)	136 (4.9)	0.016
Cox-2 inhibitors	151 (6.5)	151 (6.5)	180 (6.5)	152 (6.5)	157 (6.8)	176 (6.4)	0.016

TABLE 1 (Continued)

Characteristic	Cohort 1		Cohort 2		Cohort 3		Max SMD[a]
	Apixaban (*n* = 2306)	No treatment (*n* = 2325)	Warfarin (*n* = 2761)	No treatment (*n* = 2326)	Apixaban (*n* = 2315)	Warfarin (*n* = 2757)	
Weighted number of patients							
Adherence of initial anticoagulant treatment, mean (SD)							
Mean monthly PDC	0.97 (0.05)	0.97 (0.05)	0.97 (0.05)	0.97 (0.04)	0.97 (0.05)	0.97 (0.05)	0.015
Follow-up period, mean (SD), months	11.9 (10.6)	16.4 (14.7)	22.0 (15.7)	18.6 (16.0)	12.8 (11.3)	21.0 (15.3)	N/A

Abbreviations: ACE, angiotensin-converting enzyme; CCB, calcium channel blocker; DVT, deep vein thrombosis; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke, Bleeding, Labile, Elderly, and Drugs; LIS, low-income subsidy; NSAIDs, non-steroidal anti-inflammatory drugs; PDC, proportion of days covered; PE, pulmonary embolism; PPI, proton pump inhibitor; SD, standard deviation; SMD, standardized mean difference; SSRI, selective serotonin reuptake inhibitor; VTE, venous thromboembolism.

[a]Maximum SMD of the three SMDs calculated for each cohort.

[b]From approximately 17% to 22% of patients with provoked VTE had cancer associated thrombosis.

with a 63% and 61% decreased mortality risk, respectively. There was no difference in mortality rates between the use of warfarin and the use of apixaban (HR, 1.09 [CI, 0.78 to 0.51]).

The results of sensitivity and subgroup analyses (Tables 3, S7, and S8) remained consistent with the main findings except for the subgroup analysis of age in cohort 2 (warfarin vs. no treatment), and the subgroup analysis of the initial presentation of VTE and those with cancer and chronic kidney diseases in cohorts 1 (apixaban vs. no treatment), and in cohort 3 (apixaban vs. warfarin). Warfarin extended users greater than 65 versus less than or equal to 65 years of age showed higher risk of mortality (P-interaction = 0.017) in comparison with those with no extended treatment. Apixaban users with provoked VTE versus unprovoked VTE (both P-interaction <0.001), with vs. without cancer (both P-interaction = 0.001), or with vs. without chronic kidney diseases (both P-interaction <0.001) had increased risk of death in comparison with warfarin users or those with no extended treatment.

Major bleeding

We identified 18, 28, and 38 new major bleeding events and the crude incidence rates of major bleeding events were 2.16, 3.59, and 1.35 per 100 person-years in the apixaban, warfarin, and no-treatment groups, respectively (Table 4). In the Cox proportional hazards model after IPTW, extended apixaban use was not associated with increased risk of a major bleed (HR, 1.29 [CI, 0.68 to 2.45]), whereas compared with no treatment, extended warfarin use was associated with a higher risk of a major bleed (HR, 2.14 [CI, 1.26 to 3.65]). Compared with warfarin use, apixaban use was associated with decreased risk of major bleeding (HR, 0.56 [CI, 0.32 to 0.98]). Results from subgroup and sensitivity analyses remained consistent with the results from the main findings (Tables 4, S9, and S10).

DISCUSSION

To our knowledge, this retrospective cohort study provides the first population-based evidence assessing the effectiveness and safety of extended use of apixaban (up to 10 months) and warfarin (up to 14 months) beyond 6 months of initial treatment. In Medicare beneficiaries with incident VTE who completed a 6-month initial anticoagulant treatment compared with those with no extended treatment, extended anticoagulation apixaban therapy was associated with a decreased recurrent VTE risk without an increased major bleeding risk. By contrast, extended warfarin therapy was associated with

TABLE 2 Risk of recurrent venous thromboembolism during extended treatment in inverse probability treatment weighting adjusted analyses

Analysis	Cohort 1		Cohort 2		Cohort 3	
	Apixaban (*n* = 2306)	No treatment (*n* = 2325)	Warfarin (*n* = 2761)	No treatment (*n* = 2326)	Apixaban (*n* = 2315)	Warfarin (*n* = 2757)
Number of events	[b]	30	15	30	[b]	15
Crude incidence rate per 100 person-years	0.24	1. 44	1.41	1.44	0.24	1.41
Incidence rate[a]	0.17	1.72	1.28	1.72	0.19	1.45
HR (95% CI)	0.08 (0.01–0.41)	Ref	0.62 (0.32–1.21)	Ref	0.13 (0.03–0.63)	Ref

Abbreviations: CI, confidence interval; HR, hazard ratio; *n*, weighted number of patients; Ref, reference.

[a]Incidence rate per 100 person-years after stabilized inverse probability treatment weighting.

[b]Numbers <11 are not reported owing to the cell size suppression policy of the Centers for Medicare & Medicaid Services.

TABLE 3 Risk of all-cause mortality during extended treatment in inverse probability treatment weighting adjusted analyses

Analysis	Cohort 1		Cohort 2		Cohort 3	
	Apixaban (*n* = 2306)	No treatment (*n* = 2325)	Warfarin (*n* = 2761)	No treatment (*n* = 2326)	Apixaban (*n* = 2315)	Warfarin (*n* = 2757)
Number of events	50	231	76	231	50	76
Crude incidence rate per 100 person-years	5.97	11.02	7.14	11.02	5.97	7.14
Incidence rate[a]	6.27	12.20	6.70	12.06	7.81	7.07
HR (95% CI)	0.37 (0.27–0.51)	Ref	0.39 (0.29–0.51)	Ref	1.09 (0.78–1.51)	Ref

Abbreviations: CI, confidence interval; HR, hazard ratio; *n*, weighted number of patients; Ref, reference.

[a]Incidence rate per 100 person-years after stabilized inverse probability treatment weighting.

TABLE 4 Risk of major bleeding events during extended treatment in inverse probability treatment weighting adjusted analyses

Analysis	Cohort 1		Cohort 2		Cohort 3	
	Apixaban (*n* = 2306)	No treatment (*n* = 2325)	Warfarin (*n* = 2761)	No treatment (*n* = 2326)	Apixaban (*n* = 2315)	Warfarin (*n* = 2757)
Number of events	18	38	28	38	18	28
Crude incidence rate per 100 person-years	2.16	1.35	3.59	1.35	2.16	3.59
Incidence rate[a]	2.14	1.35	3.58	1.32	2.07	3.69
HR (95% CI)	1.29 (0.68–2.45)	Ref	2.14 (1.26–3.65)	Ref	0.56 (0.32–0.98)	Ref

Abbreviations: CI, confidence interval; HR, hazard ratio; *n*, weighted number of patients; Ref, reference.

[a]Incidence rate per 100 person-years after stabilized inverse probability treatment weighting.

increased risk of major bleeding without decreased risk of recurrent VTE. In the head-to-head comparison of warfarin and apixaban, apixaban use was associated with a lower risk of recurrent VTE and major bleeding compared with warfarin use. There was decreased risk of mortality with extended therapy using either apixaban or warfarin. These findings were robust in several sensitivity analyses, including an ITT analysis and across different subgroups of patients by VTE type (provoked vs. unprovoked) and with or without a history of cancer, chronic kidney disease, hypercoagulable state, or obesity.

This study has important clinical implications. Our results suggest a potential beneficial effect of extended anticoagulation therapy (up to 10 months in addition to 6 months of initial treatment) with apixaban for Medicare beneficiaries with VTE regardless of the type of VTE or comorbidities in routine care similar to what was reported in the AMPLIFY-EXT trial.[9] Whereas the AMPLIFY-EXT trial showed reduced recurrent VTE risk without increasing the major bleeding risk with extended apixaban therapy compared with placebo during 12 months' follow-up after 6–12 months of initial treatment, the present study

extends these findings by comparing apixaban to another commonly used anticoagulant, warfarin. In a recent study by a member of our team comparing extended apixaban therapy versus extended warfarin therapy in commercially insured patients, use of apixaban was associated with a decreased risk of a major bleed, but no differences in recurrent VTE risk was observed, whereas the present study found that extended-apixaban use was associated with reduced recurrent VTE risk without an increased risk of a major bleed.[31] We also showed that mortality was higher among individuals with provoked versus unprovoked VTE, with versus without cancer, and with versus without chronic kidney disease for extended apixaban therapy compared with warfarin or with no extended therapy, an observation that may be partially explained by the older adults included in our study (mean age of 72–73 years vs. 58 years in AMPLIFY-EXT).[32,33] In addition, a sensitivity analysis in which we conducted ITT analyses and an analysis with extended exposure effect windows from 7 days to 60 days after patients discontinued therapy provided results that were generally consistent with these findings. In contrast to clinical trial settings with strict inclusion and exclusion criteria, our study results are more generalizable to routine clinical care. Notably, our study included 27%–30% of patients with provoked VTE (8.3% in AMPLIFY-EXT) and 83%–89% of patients with PE (35% in AMPLIFY-EXT) as well as patients having a higher comorbidity burden (e.g., active cancer). Thus, our study provides confirmatory evidence on the effectiveness and safety of apixaban as extended therapy in routine care.

In contrast to the findings for apixaban, we found no benefit for preventing recurrent VTE associated with extended warfarin use, but we found two-fold higher risk of major bleeding. Despite those results, we also found that use of warfarin was associated with decreased mortality on par with apixaban. Although our results appear to contradict the PADIS-PE finding that patients with PE having an additional 12 months of warfarin treatment after 6 months of initial treatment had decreased rates of recurrent VTE without increased major bleeding risk, much of the differences in these findings is likely explained by the close monitoring and adjustment of warfarin dose based on the laboratory results assessing the anticoagulation state in PADIS-PE. Such close monitoring and adjustment of warfarin dose is a main hinderance for using warfarin in clinical practice.[8] In addition, although exact warfarin dosing information or international normalized ratio (INR) was not available in our study, we believe that low-dose warfarin may have been prescribed to reduce the risk of major bleeding in routine care, and providers may tolerate a slightly lower INR for long-term anticoagulation, which may result in no difference in the effectiveness of preventing recurrent VTE compared with no treatment.[34,35]

We also suspect that the differences in findings may be due to our broader inclusion criteria, our heterogeneous population (such as patients with provoked VTE, DVT, and cancer, which the PADIS-PE study excluded), and our study's large sample size ($n = 7399$) compared with PADIS-PE ($n = 371$). Our subgroup analyses found that among those with extended warfarin therapy compared with those with no extended treatment, higher recurrent VTE risk was observed for patients with versus without obesity and for patients with versus without anticoagulable states, both well-known risk factors for recurrent VTE.[36–39] Overall, our study findings were more in line with the results of a recent meta-analysis comparing 3, 6, and 12 months of warfarin therapy, in which the extended warfarin use did not lower the recurrent VTE risk of but did increase the bleeding risk.[15,16] Several other studies have also reported a higher risk of bleeding for long-term warfarin use in real-world settings than the risks reported in randomized clinical trials.[40,41]

Our study also provides evidence based on direct comparisons of apixaban and warfarin as extended phase therapy. To our knowledge, this study is the first real-world assessment using data from routine clinical practice to report a reduced risk of developing recurrent VTE and major bleeding events with extended therapy apixaban compared with warfarin. Evidence based on direct comparisons, such as the present study, is needed to enhance treatment decision making. Our findings suggest that apixaban may be an effective and safer option having fewer events of a major bleed compared to warfarin for those continuing anticoagulation therapy for secondary prophylaxis beyond the initial 6-month treatment. These findings support the recent update to the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, which suggest using extended phase anticoagulation therapy with DOACs for patients with VTE and an absence of transient provocation.[10]

Our study has several strengths. First, we obtained our data using the Medicare database, a national representative database of adults greater than or equal to 65 years of age who reside in the United States and of individuals with specific medical conditions regardless of age who qualify for Medicare, which enabled longitudinal follow-up and sufficient statistical power. Second, we used IPTW for adjustment of differences in baseline demographic and clinical characteristics in the two treatment and one no-treatment groups. We also used a competing risk model to address competing risk of death. Third, our results remained consistent across several sensitivity and subgroup analyses, which provides re-assurance that our findings are robust.

This study has several limitations. First, our study relied on ICD codes recorded in claims data to measure

outcome events. Although prior validation studies found the positive predictive value of major bleeding events to be 89%–99% and that of VTE to be 73%–83%,[19,20] miscoded, missing, or incomplete claims could have impacted our study's findings. Any existing coding errors most likely would have been evenly distributed among the groups. Second, we adjusted for many confounders known to be associated with recurrent VTE or major bleeding although, because we were dependent on administrative data, there may be some unmeasured confounders (e.g., INR). It is also possible that some unmeasured confounding may be related to prescribing choices, which may result in selection bias; however, by using IPTW, we tried to minimize such bias. Third, the small sample size made stratifying the results by the dose of apixaban (2.5 mg vs. 5.0 mg) infeasible. Therefore, we could not determine whether different doses had similar safety and effectiveness when administered as an extended anticoagulation therapy. A previous study did not find that the clinical outcomes differenced when comparing patients prescribed low-dose apixaban versus those prescribed the full-dose of apixaban during extended treatment.[42] Fourth, we had a relatively short follow-up period, which did not enable full exploration of the long-term effects of extended phase anticoagulant therapy. Last, this study is generalizable only to Medicare beneficiaries, who are older or have more comorbidities compared to an average adult population.

CONCLUSION

This analysis of a large population-based cohort of patients with VTE suggests that using extended apixaban therapy is effective and safe as an alternative to warfarin or to no extended therapy extended therapy. The use of apixaban as extended treatment compared with no extended treatment was associated with decreased recurrent VTE and mortality risks without an increased risk of a major bleed and when compared with warfarin had significantly fewer recurrent VTEs and a better safety profile.

AUTHOR CONTRIBUTIONS
H.P., H.-R.K., P.-L.H., W.-H.L.-C., C.D., D.W., and E.D. wrote the manuscript. H.P., H.-R.K., P.-L.H., W.-H.L.-C., C.D., D.W., and E.D. designed the research. H.P., H.-R.K., P.-L.H., W.-H.L.-C., C.D., D.W., and E.D. performed the research. H.P., H.-R.K., P.-L.H., and W.-H.L.-C. analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.