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Effectiveness and Safety of Apixaban versus Warfarin in Venous Thromboembolism Patients with Chronic Kidney Disease

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Abstract

There has been limited evidence reported about the outcomes of oral anticoagulants among patients with venous thromboembolism (VTE) and chronic kidney disease (CKD), especially those with stage V/end-stage renal disease (ESRD). This retrospective cohort analysis of five U.S. claims databases evaluated the risk of recurrent VTE, major bleeding (MB), and clinically relevant nonmajor bleeding (CRNMB) for apixaban versus warfarin among VTE patients diagnosed with CKD, including ESRD. Inverse probability treatment weighting (IPTW) was used to balance patient characteristics between treatment cohorts. Hazard ratios (HRs) were calculated for recurrent VTE, MB, and CRNMB among patients with CKD who experienced an index VTE. An interaction analysis was conducted to evaluate treatment effects across different stages of CKD. A total of 29,790 VTE patients with CKD were selected for analyses, of whom 10,669 (35.8%) initiated apixaban and 19,121 (64.2%) initiated warfarin. Among IPTW-balanced patient cohorts, the apixaban group had significantly lower risk of recurrent VTE (HR: 0.78; 95% confidence interval [CI]: 0.66–0.92), MB (HR: 0.76; 95% CI: 0.65–0.88), and CRNMB (HR: 0.86; 95% CI: 0.80–0.93) than the warfarin group. When stratified by CKD stage (stage I/II: 8.2%; stage III: 49.4%; stage IV: 12.8%; stage V/ESRD: 12.0%; stage unspecified: 17.6%), no significant interaction was observed for effects of apixaban versus warfarin on recurrent VTE or MB. In summary, apixaban was associated with a significantly lower risk of recurrent VTE and MB than warfarin among VTE patients with CKD. CKD stages did not have significant impact on treatment effects for recurrent VTE and MB.

Keywords
- chronic kidney disease
- apixaban
- venous thromboembolism

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Introduction

Epidemiological studies conducted over several decades have found that venous thromboembolism (VTE) is a highly prevalent condition with >100,000 yearly deaths in the United States.[1] Over the last decade, accumulating evidence has suggested that patients with chronic kidney disease (CKD) are at an increased risk of VTE.[2–5] Decreased renal function also increases the risk of bleeding,[6,7] which is associated with platelet dysfunction—particularly in advanced stages of disease.[8,9] Hence, treatments with anticoagulants in VTE patients with CKD need to strike an optimal balance between preventing thrombosis and limiting hemorrhage. The American College of Chest Physicians (CHEST) and American Society of Hematology (ASH) both recommend direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) for most VTE patients due to less bleeding in randomized clinical trials (RCTs) and greater convenience for patients.[10,11] However, CHEST guidelines have recommended VKAs over DOACs if creatinine clearance (CrCl) is <30 mL/min, while the ASH guidelines have noted that the recommendation of DOACs over VKAs is not applicable to patients with CrCl <30 mL/min.[10,11]

There is limited evidence about the effects of DOACs among VTE patients with CKD. The evidence is especially lacking for those with severe CKD, such as end-stage renal disease (ESRD), as pivotal trials of DOACs excluded VTE patients with severe renal impairments (CrCl <25 mL/min for apixaban and <30 mL/min for all other DOACs).[11–15] Real-world data (RWD) (e.g., insurance claims databases) provide an additional data source to evaluate the effectiveness and safety of DOACs among VTE patients with CKD, including those with ESRD. Although several RWD studies have been conducted to evaluate the use of DOACs among VTE patients with CKD, they were limited to a single study center or a single data provider (such as the Medicare supplemental database).[16–18] The aim of this study was to compare the effectiveness and safety outcomes of apixaban versus warfarin among VTE patients with CKD, including those with ESRD, using five U.S. insurance claims databases.

Patients and Methods

Data Source and Patient Selection

This study utilized data from the Centers for Medicare and Medicaid Services (CMS) fee-for-service Medicare database and four U.S. commercial claims databases: IBM MarketScan Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database (MarketScan), IQVIA PharMetrics Plus (PharMetrics), Optum Clinformatics Data Mart (Optum), and the Humana Research Database (Humana).

Patients diagnosed with CKD who had ≥1 medical claim for VTE in any position (index VTE event) in the inpatient or outpatient setting were identified from September 1, 2014 until the end of the study period (MarketScan: September 2018; Optum and Humana: December 2018; PharMetrics: March 2019; CMS Medicare: December 2016). Patients aged ≥18 years on the index date for commercial databases or ≥65 years on the index date for the Medicare database were selected if they had ≥1 pharmacy claim for apixaban or warfarin during the 30-day period following the index VTE event. The date of the first warfarin or apixaban prescription was designated as the index date. International Classification of Diseases (ICD) 9th Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM codes were used to identify VTE (ICD-9: 415.11, 415.13, 415.19, 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; ICD-10: I2692, I2699, I801, I802, I803, I809, I821, I82210, I82220, I82290, I8240, I8241, I8242, I8243, I8244, I8249, I824Y, I824Z, I8260, I8262, I82A1, I82B1, I82C1, I82890, I8290) and CKD (ICD-9: 585; ICD-10: N18). The ICD codes for VTE and CKD have been validated in previously published literature.[19–23] Additional selection criteria are listed in ►**Fig. 1**.

The baseline period was defined as 6 months prior to and including the index date. Patients' follow-up information was collected from the day after the index date through the earliest of the end of the subsequent 6-month period, index therapy discontinuation, switch to another oral anticoagulant or parenteral anticoagulant, health plan disenrollment, death, or the end of the study period. Our study employed an on-treatment approach; thus, we did not include events that occurred after a patient switched or discontinued the index treatment. Patients with each stage of CKD were identified and selected for analysis in this study by using ICD-9-CM or ICD-10-CM codes.[24] Patients with CKD were stratified as stages I/II, III, IV, stage V/ESRD, or stage unspecified.

Outcome Measures

Our analysis evaluated recurrent VTE, major bleeding (MB), and clinically relevant nonmajor bleeding (CRNMB).[25–29] VTE and MB were defined by primary/first-listed diagnosis in the inpatient setting. CRNMB was identified by either an inpatient admission with a secondary diagnosis code for noncritical sites of bleeding (excluded if MB occurred before the CRNMB or during the same hospitalization) or by a diagnosis code for gastrointestinal bleeding or other selected noncritical site of bleeding in the outpatient setting. This approach aligns with the current recommendation of the International Society on Thrombosis and Hemostasis.[30]

Statistical Methods

VTE-related variables were measured on the index VTE event date.[31] To balance patient characteristics between the treatment cohorts of VTE patients with CKD, we used stabilized inverse probability treatment weighting (IPTW).[32] Covariates included in the model were demographics, clinical characteristics, and VTE-related variables. The IPTW weights were stabilized by multiplying the original weights with a constant that was equal to the expected value of being in the treatment or comparison cohorts.[33–35] After IPTW, the baseline characteristics were well balanced across the cohorts and databases. The risk of recurrent VTE, MB, and CRNMB was evaluated with Cox proportional hazard models.

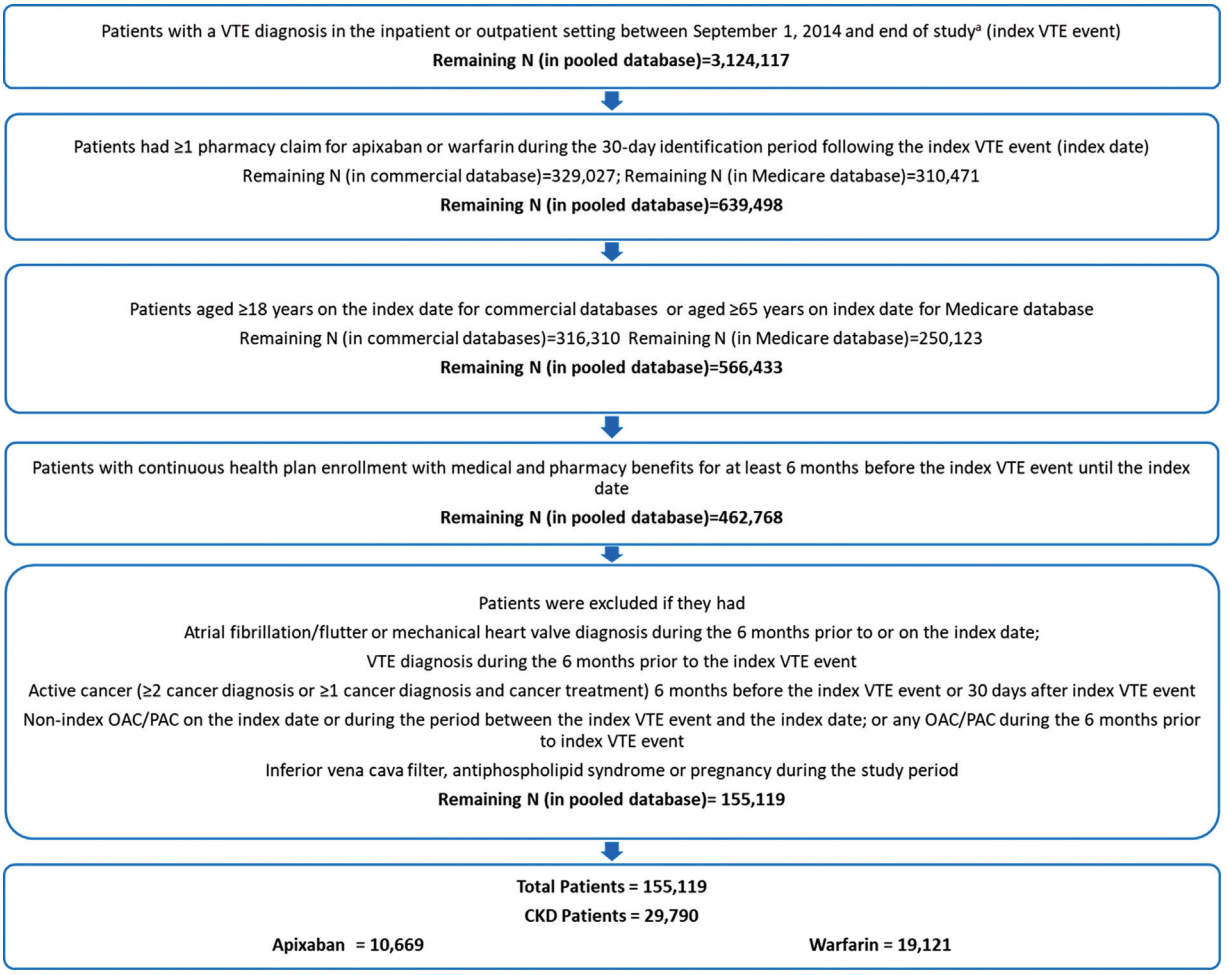

Fig. 1 Patient selection criteria. The figure illustrates the process and selection criteria used to identify patient records from the databases used in this study. Patient records were included if the patient had both CKD (defined by ICD-9-CM codes 585.1–585.9 or ICD-10-CM codes N18.1–N18.9) and a diagnosis of VTE, and was treated with either apixaban or warfarin within 30 days after the index VTE. Patients were excluded on the basis of the following criteria: age (Medicare only), health insurance continuous enrollment status, medical history, and medication use. CKD, chronic kidney disease; CM, clinical modification; ICD, International Classification of Diseases; OAC, oral anticoagulant; PAC, parenteral anticoagulant; VTE, venous thromboembolism. [a]MarketScan: September 2018; Optum and Humana: December 2018; PharMetrics: March 2019; CMS Medicare: December 2016.

Analysis of Patients Stratified by Stage of CKD

An interaction analysis was conducted to evaluate the treatment effect across different stages of CKD: stages I/II, III, IV, V/ESRD. Patients with stage-unspecified CKD were not included in the interaction analysis due to the lack of clinical information regarding the stage/severity of their disease. We determined the statistical significance ($p < 0.10$) of the interaction between CKD stages and treatment effects of apixaban versus warfarin and evaluated the impact of any interaction on effectiveness and safety.

Results

A total of 29,790 VTE patients with CKD were identified after application of the selection criteria, of whom 10,669 (35.8%) initiated apixaban and 19,121 (64.2%) initiated warfarin (►**Fig. 1**). The pre- and post-IPTW baseline characteristics among VTE patients with CKD who initiated apixaban or warfarin are shown in ►**Table 1**. Before IPTW, the average Charlson comorbidity index (CCI) score was 5.2 to 5.3, the average age was approximately 75 years, and 43.2 to 45.0% of patients were male. During the baseline period, patients initiating apixaban had a lower proportion with stage V/ESRD (8.5 vs. 13.9%) compared with warfarin patients. After applying IPTW, baseline characteristics were well balanced among VTE patients with CKD across the apixaban and warfarin cohorts. The primary effectiveness and safety outcomes of the VTE patients with CKD are shown in ►**Fig. 2**. VTE patients with CKD who initiated apixaban had a significantly lower risk of recurrent VTE (hazard ratio [HR]: 0.78; 95% confidence interval [CI]: 0.66–0.92), MB (HR: 0.76; 95% CI: 0.65–0.88), and CRNMB (HR: 0.86; 95% CI: 0.80–0.93) compared with warfarin patients.

To gain a better understanding of the impact of CKD stage on clinical outcomes, patients were stratified by stage. ►**Table 2** shows the demographic and clinical characteristics of patients stratified by different stages of CKD. Among the 29,790 VTE patients with CKD in both the apixaban and warfarin cohorts, the largest proportion of patients had CKD stage III (49.4%) followed by stage

Table 1 Descriptive pre- and post-IPTW baseline characteristics among VTE patients with CKD that initiated apixaban versus warfarin

	Pre-IPTW			Post-IPTW[a]		
	Warfarin cohort	Apixaban cohort	STD[b]	Warfarin cohort	Apixaban cohort	STD[b]
Sample size	19,121	10,669		19,121	10,669	
Age, mean (SD)	75.1 (12.1)	75.2 (12.2)	0.79	75.1 (12.1)	75.3 (12.2)	1.54
18–54	1,092 (5.7%)	608 (5.7%)	0.05	1,085 (5.7%)	603 (5.7%)	0.11
55–64	1,536 (8.0%)	1,013 (9.5%)	5.17	1,626 (8.5%)	907 (8.5%)	0.01
65–74	6,057 (31.7%)	3,201 (30.0%)	3.63	5,942 (31.1%)	3,311 (31.0%)	0.08
75–79	3,356 (17.6%)	1,879 (17.6%)	0.16	3,369 (17.6%)	1,889 (17.7%)	0.23
≥80	7,080 (37.0%)	3,968 (37.2%)	0.34	7,099 (37.1%)	3,959 (37.1%)	0.04
Gender, *n* (%)						
Male	8,267 (43.2%)	4,804 (45.0%)	3.61	8,393 (43.9%)	4,686 (43.9%)	0.06
Female	10,854 (56.8%)	5,865 (55.0%)	3.61	10,728 (56.1%)	5,983 (56.1%)	0.06
Geographic region, *n* (%)						
Northeast	2,897 (15.2%)	1,337 (12.5%)	7.59	2,714 (14.2%)	1,496 (14.0%)	0.48
Midwest	5,596 (29.3%)	2,168 (20.3%)	20.83	4,986 (26.1%)	2,779 (26.0%)	0.07
South	7,227 (37.8%)	5,636 (52.8%)	30.54	8,245 (43.1%)	4,595 (43.1%)	0.11
West	3,371 (17.6%)	1,516 (14.2%)	9.36	3,149 (16.5%)	1,783 (16.7%)	0.66
Other	30 (0.2%)	12 (0.1%)	1.21	27 (0.1%)	16 (0.2%)	0.21
Type of index encounter, *n* (%)						
Inpatient	13,805 (72.2%)	7,044 (66.0%)	13.39	13,367 (69.9%)	7,433 (69.7%)	0.52
Outpatient	5,316 (27.8%)	3,625 (34.0%)	13.39	5,754 (30.1%)	3,236 (30.3%)	0.52
VTE diagnosis, *n* (%)						
DVT only	11,405 (59.6%)	6,144 (57.6%)	4.18	11,264 (58.9%)	6,292 (59.0%)	0.13
PE with or without DVT	7,716 (40.4%)	4,525 (42.4%)	4.18	7,857 (41.1%)	4,377 (41.0%)	0.13
VTE etiology						
Provoked	13,955 (73.0%)	7,038 (66.0%)	15.28	13,467 (70.4%)	7,501 (70.3%)	0.27
Unprovoked	5,166 (27.0%)	3,631 (34.0%)	15.28	5,654 (29.6%)	3,168 (29.7%)	0.27
Deyo–Charlson comorbidity index, mean (SD)	5.3 (2.3)	5.2 (2.3)	1.70	5.3 (2.3)	5.3 (2.3)	0.11
Baseline comorbidity, *n* (%)						
AIDS	114 (0.6%)	62 (0.6%)	0.20	120 (0.6%)	57 (0.5%)	1.22
Alcohol abuse	505 (2.6%)	269 (2.5%)	0.76	499 (2.6%)	278 (2.6%)	0.01
Anemia	10,497 (54.9%)	5,250 (49.2%)	11.41	10,106 (52.9%)	5,630 (52.8%)	0.17

(*Continued*)

Table 1 (*Continued*)

	Pre-IPTW			Post-IPTW[a]		
	Warfarin cohort	Apixaban cohort	STD[b]	Warfarin cohort	Apixaban cohort	STD[b]
Central venous catheter	3,214 (16.8%)	1,353 (12.7%)	11.66	2,931 (15.3%)	1,627 (15.2%)	0.22
Cerebrovascular disease	3,965 (20.7%)	2,111 (19.8%)	2.36	3,927 (20.5%)	2,142 (20.1%)	1.15
Coagulation defects	2,594 (13.6%)	1,179 (11.1%)	7.66	2,431 (12.7%)	1,370 (12.8%)	0.38
Ischemic heart/coronary artery disease	8,457 (44.2%)	4,781 (44.8%)	1.17	8,493 (44.4%)	4,727 (44.3%)	0.23
Dementia	2,024 (10.6%)	1,402 (13.1%)	7.91	2,021 (10.6%)	1,434 (13.4%)	8.83
Dyspepsia or stomach discomfort	5,323 (27.8%)	2,860 (26.8%)	2.32	5,261 (27.5%)	2,947 (27.6%)	0.24
Hemiplegia or paraplegia	543 (2.8%)	303 (2.8%)	0.00	534 (2.8%)	313 (2.9%)	0.84
Hyperlipidemia	13,055 (68.3%)	7,457 (69.9%)	3.50	13,169 (68.9%)	7,338 (68.8%)	0.20
Obesity	6,371 (33.3%)	3,818 (35.8%)	5.19	6,534 (34.2%)	3,641 (34.1%)	0.10
Pneumonia	4,077 (21.3%)	2,219 (20.8%)	1.28	4,033 (21.1%)	2,238 (21.0%)	0.29
Rheumatologic disease	1,244 (6.5%)	683 (6.4%)	0.42	1,232 (6.4%)	677 (6.3%)	0.40
Sleep apnea	3,303 (17.3%)	1,854 (17.4%)	0.27	3,306 (17.3%)	1,843 (17.3%)	0.04
Spinal cord injury	49 (0.3%)	31 (0.3%)	0.66	51 (0.3%)	28 (0.3%)	0.09
Thrombophilia	647 (3.4%)	354 (3.3%)	0.37	641 (3.4%)	354 (3.3%)	0.19
Varicose veins	749 (3.9%)	486 (4.6%)	3.17	788 (4.1%)	437 (4.1%)	0.12
Congestive heart failure	7,242 (37.9%)	3,754 (35.2%)	5.59	7,156 (37.4%)	3,851 (36.1%)	2.75
Diabetes	10,544 (55.1%)	5,564 (52.2%)	6.00	10,560 (55.2%)	5,563 (52.1%)	6.20
Hypertension	18,098 (94.6%)	10,051 (94.2%)	1.93	18,068 (94.5%)	10,077 (94.5%)	0.16
Stage I & II CKD	1,401 (7.3%)	1,031 (9.7%)	8.39	1,569 (8.2%)	879 (8.2%)	0.09
Stage III CKD	9,059 (47.4%)	5,659 (53.0%)	11.35	9,445 (49.4%)	5,267 (49.4%)	0.05
Stage IV CKD	2,604 (13.6%)	1,208 (11.3%)	6.95	2,445 (12.8%)	1,363 (12.8%)	0.02
Stage V/ESRD CKD	2,666 (13.9%)	904 (8.5%)	17.40	2,291 (12.0%)	1,277 (12.0%)	0.04
CKD unspecified stage	3,391 (17.7%)	1,867 (17.5%)	0.62	3,371 (17.6%)	1,883 (17.6%)	0.04
Chronic liver disease	1,574 (8.2%)	920 (8.6%)	1.41	1,531 (8.0%)	958 (9.0%)	3.50
COPD	5,495 (28.7%)	3,023 (28.3%)	0.89	5,496 (28.7%)	3,056 (28.6%)	0.21
Peptic ulcer disease	645 (3.4%)	287 (2.7%)	3.99	615 (3.2%)	314 (2.9%)	1.57
Inflammatory bowel disease	387 (2.0%)	188 (1.8%)	1.92	369 (1.9%)	204 (1.9%)	0.13
Peripheral vascular disease	6,192 (32.4%)	3,366 (31.5%)	1.79	6,183 (32.3%)	3,380 (31.7%)	1.40
Baseline bleed	5,594 (29.3%)	2,583 (24.2%)	11.42	5,247 (27.4%)	2,925 (27.4%)	0.06

Table 1 (*Continued*)

	Pre-IPTW			Post-IPTW[a]		
	Warfarin cohort	Apixaban cohort	STD[b]	Warfarin cohort	Apixaban cohort	STD[b]
Recent history of falls, *n* (%)	1,855 (9.7%)	1,076 (10.1%)	1.29	1,875 (9.8%)	1,036 (9.7%)	0.32
Fracture/trauma involving lower extremities, *n* (%)	3,057 (16.0%)	1,773 (16.6%)	1.71	3,105 (16.2%)	1,732 (16.2%)	0.01
Selected surgeries, *n* (%)	6,684 (35.0%)	3,343 (31.3%)	7.70	6,441 (33.7%)	3,588 (33.6%)	0.11
Baseline medication use, *n* (%)						
Antiarrhythmic	2,448 (12.8%)	1,355 (12.7%)	0.31	2,435 (12.7%)	1,351 (12.7%)	0.21
Statins	10,770 (56.3%)	6,101 (57.2%)	1.73	10,829 (56.6%)	6,042 (56.6%)	0.00
Antiplatelets	2,742 (14.3%)	1,578 (14.8%)	1.28	2,765 (14.5%)	1,529 (14.3%)	0.37
Aromatase Inhibitors	38 (0.2%)	24 (0.2%)	0.57	39 (0.2%)	22 (0.2%)	0.08
Beta blockers	10,968 (57.4%)	5,916 (55.5%)	3.85	10,830 (56.6%)	6,043 (56.6%)	0.00
Gastroprotective agents	7,340 (38.4%)	3,996 (37.5%)	1.92	7,282 (38.1%)	4,062 (38.1%)	0.02
SERMS	102 (0.5%)	62 (0.6%)	0.64	106 (0.6%)	60 (0.6%)	0.13
NSAIDs	3,680 (19.2%)	2,458 (23.0%)	9.30	3,940 (20.6%)	2,198 (20.6%)	0.01
Hormone therapy (estrogen)	362 (1.9%)	193 (1.8%)	0.62	353 (1.8%)	195 (1.8%)	0.15
Apixaban index dose, *n* (%)						
On standard dose (apixaban 5 mg)		9,109 (85.4%)			8,997 (84.3%)	
Lower dose (2.5 mg apixaban)		1,560 (14.6%)			1,672 (15.7%)	

Abbreviations: AIDS, acquired immunodeficiency syndrome; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRNM, clinically relevant nonmajor; DVT, deep-vein thrombosis; ESRD, end-stage renal disease; IPTW, inverse probability treatment weighting; NSAID, nonsteroidal anti-inflammatory drug; PE, pulmonary embolism; SERM, selective estrogen receptor modulator; STD, standardized difference; VTE, venous thromboembolism.

[a]After applying weights, the values for categorical variables were not whole numbers; therefore, due to rounding the sum of patients may not equal 100%.

[b]Standardized difference = 100*|actual std. diff.|. Standardized difference greater than 10 was considered significant.

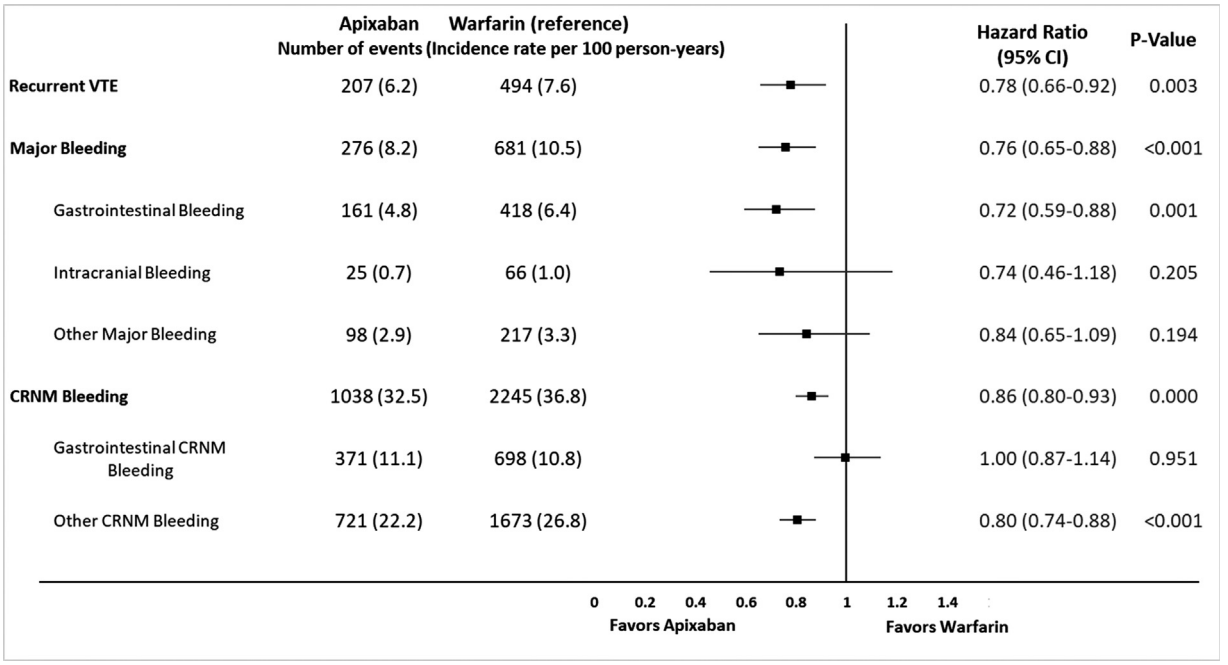

Fig. 2 Risk of recurrent venous thromboembolism (VTE), major bleeding, and clinically relevant nonmajor bleeding among patients with chronic kidney disease prescribed apixaban or warfarin to treat VTE. The figure shows a forest plot of the risks of recurrent VTE, major bleeding, and CRNMB. The patient population consisted of patients with CKD being treated for VTE with apixaban or warfarin during the study period. The number of events and the incidence per 100 person-years are listed for each outcome and treatment. Risk is indicated by an HR and 95% CI. The degree of risk is indicated along the *x*-axis. *Black squares* indicate the hazard ratio; *solid black lines* indicate the 95% CI. CI, confidence interval; CKD, chronic kidney disease; CRNMB, clinically relevant nonmajor bleeding; HR, hazard ratio; VTE, venous thromboembolism.

unspecified (17.6%), stage IV (12.8%), stage V/ESRD (12.0%), and stage I/II (8.2%). Patients with CKD stage IV were oldest (77.1–78.5 years), followed by stage III (76.4–76.5 years), stage unspecified (75.1–75.5 years), stage I/II (72.4–73.3 years), and stage V/ESRD (68.9 years); in contrast, the mean CCI score was the highest for stages V/ESRD (6.1–6.2) and generally decreased with the following stages (stage IV: 5.6–5.7; stage III: 5.1; stage unspecified: 5.0; stage I/II: 4.9). For type of index VTE event, the proportion of patients that had an index deep-vein thrombosis (DVT) event or provoked event was highest for stage V/ESRD patients (DVT: 76.0–77.2%; provoked: 76.0–78.3%) followed by stage IV (DVT: 64.5–67.4%; provoked: 70.4–74.0%), stage unspecified (DVT: 54.7–55.8%; provoked: 72.2–72.6%), stage III (DVT: 55.2%; provoked: 68.1–68.7%), and stage I/II (DVT: 51.5–54.2%; provoked: 63.5–66.8%). Other demographic characteristics with notable differences between patients with stage V/ESRD CKD and those with stage I/II CKD were a substantially greater proportion of selected surgeries (58.9–62.5 vs. 28.6–31.1%, respectively) and a twofold increase in the rates of anemia (84.2–87.1 vs. 38.2–43.9%, respectively).

►**Fig. 3** shows the incidence rates and HRs of recurrent VTE, MB, and CRNMB for apixaban compared with warfarin across different stages of CKD. During the follow-up, patients with stage V/ESRD had the highest incidence rate of recurrent VTE, MB, and CRNMB (►**Fig. 3**). Across all stages of CKD, patients who received apixaban had a numerically lower incidence of recurrent VTE (stage V/ESRD [7.7 vs. 11.6], stage IV [5.8 vs. 7.8], stage III [6.2 vs. 6.9], stage I/II [5.2 vs. 7.6]) and MB (stage V/ESRD [16.9 vs. 18.0], stage IV [12.6 vs. 12.8], stage III [7.3 vs. 9.6], and stage I/II [2.9 vs. 6.6]) compared with patients who received warfarin. The apixaban group also experienced numerically lower incidences of CRNMB for patients with CKD (stage V/ESRD [38.0 vs. 52.0], stage IV [31.1 vs. 40.9], stage III [33.2 vs. 33.9], and stage I/II [28.0 vs. 33.0]).

When stratified by CKD stage, no significant interaction was observed between CKD stage and the treatment effects of apixaban versus warfarin on recurrent VTE (interaction $p = 0.570$) or MB (interaction $p = 0.124$). However, there was a significant interaction between CKD stage and treatment effects on CRNMB: while patients treated with apixaban trended toward a lower risk of CRNMB compared with patients treated with warfarin across all CKD stages, the magnitude of difference was greater for those with CKD stage IV or V/ESRD than for those with CKD stage I/II or III (►**Fig. 3**).

Discussion

In this retrospective analysis, which used data from five U.S. claims databases to compare the outcomes of apixaban versus warfarin among VTE patients with CKD, we found that risks of recurrent VTE, MB, and CRNMB were lower for apixaban than for warfarin. In analysis that stratified patients by different stages of CKD, no significant interaction was observed between CKD stage and the treatment

Table 2 Descriptive baseline characteristics among VTE with CKD patients that initiated apixaban versus warfarin stratified by CKD staging

	Stage I & II CKD[a]			Stage III CKD[a]			Stage IV CKD[a]			Stage V/ESRD CKD[a]			Stage unspecified CKD[a]		
	Warfarin cohort (reference)	Apixaban cohort	STD[b]	Warfarin cohort (reference)	Apixaban cohort	STD[b]	Warfarin cohort (reference)	Apixaban cohort	STD[b]	Warfarin cohort (reference)	Apixaban cohort	STD[b]	Warfarin cohort (reference)	Apixaban cohort	STD[b]
Sample size	1,569	879	0	9,445	5,267	0	2,445	1,363	0	2,291	1,277	0	3,371	1,883	0
Age	73.3 (13.2)	72.4 (12.2)	7.46	76.4 (11.4)	76.5 (10.6)	0.43	77.1 (11.3)	78.5 (12.4)	11.38	68.9 (12.2)	68.9 (16.2)	0.23	75.1 (12.4)	75.5 (12.4)	2.99
18–54	115 (7.4%)	84 (9.6%)	8.10	344 (3.6%)	173 (3.3%)	1.94	102 (4.2%)	42 (3.0%)	6.04	302 (13.2%)	189 (14.8%)	4.32	221 (6.6%)	115 (6.1%)	1.88
55–64	173 (11.0%)	103 (11.7%)	2.25	694 (7.4%)	405 (7.7%)	1.31	168 (6.9%)	89 (6.5%)	1.23	316 (13.8%)	162 (12.7%)	2.98	275 (8.2%)	147 (7.8%)	1.32
65–74	531 (33.8%)	286 (32.6%)	2.72	2,831 (30.0%)	1,610 (30.6%)	1.27	641 (26.2%)	350 (25.7%)	1.23	932 (40.7%)	495 (38.7%)	3.71	1,006 (29.9%)	571 (30.3%)	1.00
75–79	269 (17.1%)	150 (17.1%)	0.22	1,786 (18.9%)	1,000 (19.0%)	0.19	426 (17.4%)	246 (18.1%)	1.68	320 (14.0%)	183 (14.3%)	0.99	568 (16.9%)	310 (16.5%)	1.07
≥ 80	481 (30.6%)	255 (29.1%)	3.46	3,789 (40.1%)	2,079 (39.5%)	1.32	1,108 (45.3%)	636 (46.6%)	2.65	421 (18.4%)	248 (19.4%)	2.46	1,300 (38.6%)	740 (39.3%)	1.56
Gender															
Male	799 (50.9%)	419 (47.6%)	6.55	4,061 (43.0%)	2,292 (43.5%)	1.04	954 (39.0%)	495 (36.3%)	5.46	1,074 (46.9%)	631 (49.4%)	4.85	1,505 (44.7%)	849 (45.1%)	0.88
Female	771 (49.1%)	460 (52.4%)	6.55	5,383 (57.0%)	2,975 (56.5%)	1.04	1,491 (61.0%)	868 (63.7%)	5.46	1,218 (53.1%)	646 (50.6%)	4.85	1,865 (55.3%)	1,034 (54.9%)	0.88
Geographic region															
Northeast	216 (13.8%)	118 (13.5%)	0.85	1,262 (13.4%)	702 (13.3%)	0.07	370 (15.2%)	186 (13.6%)	4.33	350 (15.3%)	175 (13.7%)	4.25	516 (15.3%)	315 (16.7%)	3.95
Midwest	336 (21.4%)	202 (23.0%)	3.76	2,680 (28.4%)	1,454 (27.6%)	1.70	610 (24.9%)	369 (27.1%)	4.74	474 (20.7%)	257 (20.2%)	1.29	885 (26.3%)	496 (26.3%)	0.17
South	742 (47.2%)	406 (46.2%)	2.13	3,890 (41.2%)	2,189 (41.6%)	0.76	1,087 (44.5%)	609 (44.7%)	0.44	1,112 (48.5%)	617 (48.3%)	0.42	1,415 (42.0%)	774 (41.1%)	1.77
West	274 (17.4%)	153 (17.4%)	0.22	1,600 (16.9%)	914 (17.4%)	1.12	374 (15.3%)	196 (14.4%)	2.45	353 (15.4%)	226 (17.7%)	5.77	549 (16.3%)	294 (15.6%)	1.84
Other	<11	<11	4.61	13 (0.1%)	<11	0.27	<11	<11	2.00	<11	<11	1.63	<11	<11	0.45
Type of index encounter															
Inpatient	1,026 (65.4%)	605 (68.8%)	7.43	6,407 (67.8%)	3,626 (68.8%)	2.18	1,775 (72.6%)	943 (69.2%)	7.36	1,784 (77.9%)	896 (70.1%)	16.41	2,375 (70.5%)	1,363 (72.4%)	4.25
Outpatient	544 (34.6%)	274 (31.2%)	7.43	3,037 (32.2%)	1,641 (31.2%)	2.18	670 (27.4%)	420 (30.8%)	7.36	507 (22.1%)	382 (29.9%)	16.41	996 (29.5%)	520 (27.6%)	4.25
VTE diagnosis															
DVT only	851 (54.2%)	452 (51.5%)	5.51	5,212 (55.2%)	2,905 (55.2%)	0.05	1,578 (64.5%)	918 (67.4%)	5.84	1,741 (76.0%)	986 (77.2%)	2.63	1,883 (55.8%)	1,030 (54.7%)	2.24
PE with or without DVT	719 (45.8%)	426 (48.5%)	5.51	4,233 (44.8%)	2,362 (44.8%)	0.05	867 (35.5%)	445 (32.6%)	5.84	550 (24.0%)	292 (22.8%)	2.63	1,488 (44.2%)	852 (45.3%)	2.24
VTE etiology															
Provoked	996 (63.5%)	587 (66.8%)	7.11	6,435 (68.1%)	3,617 (68.7%)	1.17	1,808 (74.0%)	960 (70.4%)	7.69	1,793 (78.3%)	970 (76.0%)	5.14	2,434 (72.2%)	1,366 (72.6%)	0.77
Unprovoked	573 (36.5%)	291 (33.2%)	7.11	3,010 (31.9%)	1,650 (31.3%)	1.17	637 (26.0%)	403 (29.6%)	7.69	498 (21.7%)	307 (24.0%)	5.14	936 (27.8%)	516 (27.4%)	0.77
Baseline comorbidity	4.9 (2.4)	4.9 (2.0)	0.89	5.1 (2.3)	5.1 (2.1)	0.16	5.6 (2.2)	5.7 (2.5)	6.14	6.2 (2.3)	6.1 (3.0)	4.35	5.0 (2.2)	5.0 (2.2)	0.42
Deyo–Charlson comorbidity index															
AIDS	18 (1.1%)	<11	7.72	47 (0.5%)	21 (0.4%)	1.52	13 (0.5%)	<11	0.38	25 (1.1%)	13 (1.0%)	0.51	17 (0.5%)	11 (0.6%)	1.40
Alcohol abuse	47 (3.0%)	22 (2.5%)	3.01	222 (2.3%)	125 (2.4%)	0.15	47 (1.9%)	32 (2.3%)	2.73	76 (3.3%)	35 (2.8%)	2.96	108 (3.2%)	65 (3.4%)	1.30
Anemia	600 (38.2%)	386 (43.9%)	11.79	4,426 (46.9%)	2,440 (46.3%)	1.10	1,589 (65.0%)	894 (65.6%)	1.17	1,995 (87.1%)	1,075 (84.2%)	7.66	1,497 (44.4%)	835 (44.4%)	0.09
Central venous catheter	146 (9.3%)	80 (9.1%)	0.88	963 (10.2%)	541 (10.3%)	0.25	310 (12.7%)	190 (13.9%)	3.67	1,051 (45.9%)	564 (44.2%)	3.23	461 (13.7%)	252 (13.4%)	0.80
Cerebrovascular disease	307 (19.5%)	171 (19.5%)	0.06	1,780 (18.8%)	987 (18.7%)	0.29	523 (21.4%)	311 (22.8%)	3.35	616 (26.9%)	296 (23.1%)	8.13	702 (20.8%)	377 (20.0%)	1.95
Coagulation defects	170 (10.8%)	84 (9.6%)	4.12	1,099 (11.6%)	612 (11.6%)	0.03	285 (11.7%)	191 (14.0%)	6.77	468 (20.4%)	282 (22.1%)	3.76	409 (12.1%)	201 (10.7%)	4.59
Ischemic heart/coronary artery disease	589 (37.5%)	350 (39.9%)	4.86	4,057 (43.0%)	2,255 (42.8%)	0.30	1,220 (49.9%)	672 (49.3%)	1.17	1,174 (51.3%)	638 (49.9%)	2.50	1,452 (43.1%)	811 (43.1%)	0.04

(*Continued*)

Table 2 (*Continued*)

	Stage I & II CKD[a]			Stage III CKD[a]			Stage IV CKD[a]			Stage V/ESRD CKD[a]			Stage unspecified CKD[a]		
	Warfarin cohort (reference)	Apixaban cohort	STD[b]	Warfarin cohort (reference)	Apixaban cohort	STD[b]	Warfarin cohort (reference)	Apixaban cohort	STD[b]	Warfarin cohort (reference)	Apixaban cohort	STD[b]	Warfarin cohort (reference)	Apixaban cohort	STD[b]
Dementia	150 (9.6%)	96 (11.0%)	4.67	1,008 (10.7%)	683 (13.0%)	7.18	254 (10.4%)	236 (17.3%)	19.54	181 (7.9%)	135 (10.6%)	8.52	428 (12.7%)	284 (15.1%)	6.84
Dyspepsia or stomach discomfort	395 (25.2%)	234 (26.6%)	3.27	2,471 (26.2%)	1,336 (25.4%)	1.86	640 (26.2%)	384 (28.1%)	4.31	779 (34.0%)	445 (34.9%)	1.76	976 (29.0%)	549 (29.2%)	0.44
Hemiplegia or paraplegia	44 (2.8%)	29 (3.3%)	3.07	218 (2.3%)	128 (2.4%)	0.86	60 (2.4%)	24 (1.8%)	4.65	87 (3.8%)	53 (4.2%)	1.86	126 (3.7%)	78 (4.1%)	2.09
Hyperlipidemia	1,047 (66.7%)	596 (67.8%)	2.40	6,678 (70.7%)	3,689 (70.0%)	1.47	1,744 (71.3%)	993 (72.8%)	3.23	1,566 (68.3%)	842 (65.9%)	4.81	2,134 (63.3%)	1,218 (64.7%)	2.90
Obesity	577 (36.8%)	314 (35.8%)	2.12	3,300 (34.9%)	1,879 (35.7%)	1.53	859 (35.1%)	467 (34.3%)	1.78	738 (32.2%)	388 (30.4%)	3.72	1,060 (31.4%)	593 (31.5%)	0.09
Pneumonia	278 (17.7%)	154 (17.5%)	0.54	1,823 (19.3%)	1,053 (20.0%)	1.74	527 (21.6%)	290 (21.3%)	0.73	663 (28.9%)	318 (24.9%)	8.60	742 (22.0%)	424 (22.5%)	1.16
Rheumatologic disease	92 (5.9%)	54 (6.2%)	1.41	621 (6.6%)	346 (6.6%)	0.02	181 (7.4%)	96 (7.0%)	1.34	100 (4.4%)	54 (4.2%)	0.85	238 (7.1%)	126 (6.7%)	1.38
Sleep apnea	249 (15.8%)	154 (17.5%)	4.51	1,689 (17.9%)	936 (17.8%)	0.29	428 (17.5%)	242 (17.7%)	0.51	365 (15.9%)	209 (16.4%)	1.20	575 (17.0%)	302 (16.0%)	2.73
Spinal cord injury	<11 (0.2%)	<11 (0.4%)	2.43	21 (0.2%)	11 (0.2%)	0.42	<11	<11	3.54	11 (0.5%)	<11	3.50	13 (0.4%)	<11	0.04
Thrombophilia	59 (3.8%)	41 (4.6%)	4.28	328 (3.5%)	170 (3.2%)	1.43	70 (2.9%)	33 (2.4%)	2.84	81 (3.5%)	53 (4.2%)	3.04	102 (3.0%)	57 (3.0%)	0.17
Varicose veins	70 (4.5%)	37 (4.2%)	1.36	406 (4.3%)	229 (4.4%)	0.27	113 (4.6%)	59 (4.3%)	1.31	60 (2.6%)	30 (2.3%)	1.69	139 (4.1%)	82 (4.3%)	1.12
Congestive heart failure	420 (26.8%)	228 (25.9%)	1.94	3,244 (34.4%)	1,757 (33.4%)	2.12	1,146 (46.9%)	639 (46.9%)	0.03	1,171 (51.1%)	593 (46.4%)	8.83	1,174 (34.8%)	635 (33.7%)	2.33
Diabetes	810 (51.6%)	428 (48.7%)	5.79	5,017 (53.1%)	2,637 (50.1%)	6.16	1,493 (61.1%)	815 (59.8%)	2.63	1,579 (68.9%)	823 (64.4%)	8.93	1,661 (49.3%)	860 (45.7%)	7.20
Hypertension	1,424 (90.7%)	788 (89.7%)	3.40	8,923 (94.5%)	5,004 (95.0%)	2.32	2,384 (97.5%)	1,326 (97.3%)	1.35	2,234 (97.5%)	1,232 (96.5%)	5.53	3,104 (92.1%)	1,727 (91.8%)	1.16
Chronic liver disease	125 (8.0%)	86 (9.7%)	6.34	672 (7.1%)	414 (7.9%)	2.88	164 (6.7%)	109 (8.0%)	4.86	311 (13.6%)	183 (14.4%)	2.08	259 (7.7%)	166 (8.8%)	4.16
COPD	398 (25.4%)	225 (25.6%)	0.60	2,663 (28.2%)	1,416 (26.9%)	2.97	754 (30.8%)	457 (33.5%)	5.61	665 (29.0%)	371 (29.0%)	0.03	1,015 (30.1%)	588 (31.2%)	2.36
Peptic ulcer disease	40 (2.6%)	17 (1.9%)	4.21	274 (2.9%)	138 (2.6%)	1.73	83 (3.4%)	29 (2.1%)	7.81	107 (4.7%)	61 (4.8%)	0.37	111 (3.3%)	70 (3.7%)	2.30
Inflammatory bowel disease	21 (1.4%)	14 (1.6%)	1.78	180 (1.9%)	83 (1.6%)	2.58	49 (2.0%)	36 (2.6%)	4.24	55 (2.4%)	24 (1.9%)	3.21	63 (1.9%)	47 (2.5%)	4.10
Peripheral vascular disease	492 (31.4%)	266 (30.2%)	2.50	2,901 (30.7%)	1,611 (30.6%)	0.26	844 (34.5%)	466 (34.2%)	0.74	894 (39.0%)	502 (39.3%)	0.62	1,052 (31.2%)	535 (28.4%)	6.08
Baseline bleed	372 (23.7%)	231 (26.3%)	6.17	2,343 (24.8%)	1,300 (24.7%)	0.27	649 (26.6%)	372 (27.3%)	1.65	921 (40.2%)	519 (40.6%)	0.81	963 (28.6%)	502 (26.7%)	4.22
Recent history of falls	137 (8.7%)	80 (9.1%)	1.41	912 (9.7%)	507 (9.6%)	0.08	270 (11.1%)	143 (10.5%)	1.71	198 (8.6%)	90 (7.0%)	5.73	358 (10.6%)	216 (11.5%)	2.68
Fracture/trauma involving lower extremities	227 (14.5%)	133 (15.1%)	1.92	1,494 (15.8%)	854 (16.2%)	1.07	434 (17.8%)	245 (17.9%)	0.47	425 (18.5%)	190 (14.9%)	9.35	525 (15.6%)	311 (16.5%)	2.54
Selected surgeries	488 (31.1%)	251 (28.6%)	5.45	2,718 (28.8%)	1,530 (29.1%)	0.61	728 (29.8%)	448 (32.9%)	6.54	1,433 (62.5%)	753 (58.9%)	6.90	1,073 (31.8%)	605 (32.1%)	0.66
Baseline medication use															
Antiarrhythmic	177 (11.3%)	106 (12.1%)	2.52	1,156 (12.2%)	648 (12.3%)	0.21	337 (13.8%)	178 (13.1%)	2.09	346 (15.1%)	166 (13.0%)	5.62	419 (12.4%)	252 (13.4%)	2.87
Statins	846 (53.9%)	485 (55.2%)	2.60	5,505 (58.3%)	3,029 (57.5%)	1.59	1,471 (60.2%)	835 (61.2%)	2.06	1,258 (54.9%)	710 (55.6%)	1.23	1,747 (51.8%)	983 (52.2%)	0.79
Antiplatelets	185 (11.8%)	96 (10.9%)	2.84	1,296 (13.7%)	729 (13.8%)	0.38	411 (16.8%)	238 (17.4%)	1.66	419 (18.3%)	211 (16.6%)	4.34	454 (13.5%)	254 (13.5%)	0.15
Aromatase inhibitors	<11	<11	8.66	20 (0.2%)	<11	1.61	<11	<11	0.76	<11	<11	5.95	<11	<11	7.57
Beta blockers	725 (46.2%)	409 (46.5%)	0.65	5,199 (55.0%)	2,879 (54.7%)	0.79	1,586 (64.9%)	873 (64.0%)	1.67	1,577 (68.8%)	877 (68.7%)	0.32	1,743 (51.7%)	1,005 (53.4%)	3.34
Gastroprotective agents	544 (34.6%)	317 (36.0%)	2.96	3,502 (37.1%)	1,932 (36.7%)	0.86	967 (39.6%)	586 (43.0%)	6.82	972 (42.4%)	536 (41.9%)	0.96	1,296 (38.4%)	692 (36.8%)	3.46
SERMS	<11	<11	0.97	57 (0.6%)	32 (0.6%)	0.11	16 (0.7%)	<11	1.74	<11	<11	1.49	<11	<11	1.67
NSAIDs	425 (27.1%)	239 (27.2%)	0.42	1,934 (20.5%)	1,112 (21.1%)	1.57	401 (16.4%)	207 (15.2%)	3.27	370 (16.2%)	172 (13.5%)	7.12	809 (24.0%)	467 (24.8%)	1.82
Hormone therapy (estrogen)	32 (2.0%)	20 (2.3%)	1.76	175 (1.9%)	94 (1.8%)	0.61	42 (1.7%)	19 (1.4%)	2.49	33 (1.4%)	25 (1.9%)	3.54	70 (2.1%)	37 (2.0%)	0.79

Table 2 (*Continued*)

	Stage I & II CKD[a]			Stage III CKD[a]			Stage IV CKD[a]			Stage V/ESRD CKD[a]			Stage unspecified CKD[a]		
	Warfarin cohort (reference)	Apixaban cohort	STD[b]	Warfarin cohort (reference)	Apixaban cohort	STD[b]	Warfarin cohort (reference)	Apixaban cohort	STD[b]	Warfarin cohort (reference)	Apixaban cohort	STD[b]	Warfarin cohort (reference)	Apixaban cohort	STD[b]
Apixaban index dose															
On standard dose (apixaban 5 mg)		805 (91.6%)			4,644 (88.2%)			992 (72.8%)			906 (70.9%)			1,650 (87.7%)	
Lower dose (2.5 mg apixaban)		74 (8.4%)			624 (11.8%)			371 (27.2%)			371 (29.1%)			232 (12.3%)	

Abbreviations: AIDS, acquired immunodeficiency syndrome; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRNM, clinically relevant nonmajor; DVT, deep-vein thrombosis; ESRD, end-stage renal disease; IPTW, inverse probability treatment weighting; NSAID, nonsteroidal anti-inflammatory drug; PE, pulmonary embolism; SERM, selective estrogen receptor modulator; STD, standardized difference; VTE, venous thromboembolism.

[a]After applying weights, the values for categorical variables were not whole numbers; therefore, due to rounding the sum of patients may not equal 100%.

[b]Standardized difference = 100*|actual std. diff|. Standardized difference greater than 10 was considered significant.

effects of apixaban versus warfarin on recurrent VTE and MB. The lack of interaction suggests that the effects associated with use of apixaban or warfarin were consistent across different stages of CKD, including ESRD.

The findings of this RWD analysis provide complementary information to that of the AMPLIFY RCT.[12] The AMPLIFY trial found that apixaban was noninferior to conventional therapy for the prevention of recurrent VTE and was associated with less bleeding.[12] Moreover, included subgroup analysis showed no significant interaction between the level of renal function and treatment effects of apixaban versus warfarin on recurrent VTE (interaction $p = 0.8757$) or MB (interaction $p = 0.3606$), suggesting that the efficacy and safety of apixaban were consistent across the different levels of renal function. Our study expanded upon this renal subgroup analysis with additional data on effectiveness and safety of apixaban versus warfarin among VTE patients with CKD in routine clinical practice, including those with stage V/ESRD. We found apixaban to be associated with both lower risk of recurrent VTE and MB than for warfarin and consistent findings across different stages of CKD, including stage V/ESRD.

Several RWD studies have evaluated apixaban use among patients with CKD.[16–18] Dawwas et al reported that recurrent VTE (8.0 vs. 13.0 per 100 person-years) and MB (7.0 vs. 15.0 per 100 person-years) were significantly lower in apixaban patients compared with warfarin patients among VTE patients with CKD.[16] No significant interaction was observed between CKD status and treatment effects on recurrent VTE (interaction $p = 0.90$); however, a significant interaction was observed for MB (interaction $p = 0.09$); apixaban patients trended toward a lower risk of MB across both CKD and non-CKD cohorts.[16] In a similar study of patients with CrCl <25 mL/min, Hanni et al found lower risk of thrombotic or bleeding events with apixaban (HR: 0.47; 95% CI: 0.25–0.92) compared with warfarin.[17] In addition, a systematic literature review by Cheung et al found no significant difference between apixaban and warfarin in reducing recurrent VTE or bleeding events in patients with moderate CKD as well as no difference on VTE outcomes among patients with severe CKD who were on dialysis.[18] Our study extends these findings and includes a much larger sample size and more comprehensive analyses of the effectiveness and safety of apixaban versus warfarin among VTE patients with CKD. An additional strength of our study is that we evaluated not only the population of patients with CKD as a whole but also stratified them by the severity of CKD. This level of analysis can help address some of the data gaps regarding the use of anticoagulants by patients with ESRD.

This study has some limitations that are inherent to analyses using claims data. While associations can be inferred from this type of analysis, causal relationships cannot. Although IPTW has been used to balance patient characteristics between treatment cohorts, residual confounding may persist. The databases lacked information regarding inpatient bridging therapy and international normalized ratio values for the warfarin cohort, thus we could not observe

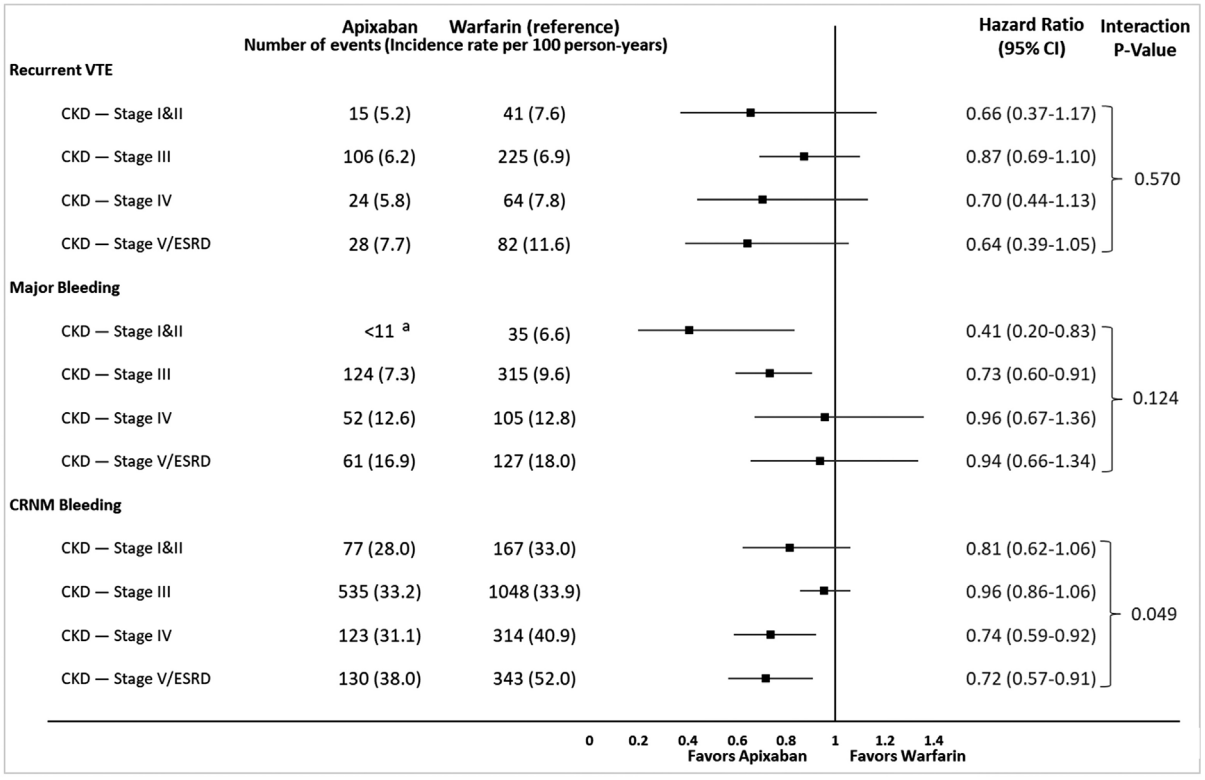

Fig. 3 Risk of recurrent venous thromboembolism (VTE), major bleeding, and clinically relevant nonmajor bleeding among patients with chronic kidney disease prescribed apixaban or warfarin to treat VTE, stratified by CKD stages. The figure shows a forest plot of the risks of recurrent VTE, major bleeding, and CRNMB. The patient population consisted of patients with CKD being treated for VTE with apixaban or warfarin during the study period, stratified by the stage of CKD (stage I/II, stage III, stage IV, stage V/ESRD). The number of events and the incidence per 100 person-years are listed for each outcome, stage, and treatment. Risk is indicated by an HR and 95% CI. The degree of risk is indicated along the *x*-axis. The *p*-value for interaction indicates the association between CKD stages and treatment effects on a specific outcome. *Black squares* indicate the hazard ratio; *solid black lines* indicate the 95% CI. CI, confidence interval; CKD, chronic kidney disease; CRNMB, clinically relevant nonmajor bleeding; ESRD, end-stage renal disease; HR, hazard ratio; VTE, venous thromboembolism. [a] < 11 used due to agreements with commercial providers to assure privacy for very small number of events; interaction is significant if $p < 0.10$.

certain clinical treatment decisions. We identified CKD based on diagnosis codes only, without any laboratory data for renal function, and 17 to 18% of the patients had stage-unspecified CKD. In addition, patients with less severe disease, such as stage 1/II, may be underreported. Although previous studies that validated ICD codes to identify CKD have found reasonably high positive predictive values (range: 63–97%),[23,36] results on patients stratified by CKD stages should be interpreted with caution. Both ICD-9 and ICD-10 codes were used to identify recurrent VTE and MB, yet the conversion from ICD-9 to ICD-10 may not be perfect and the presence of a code may not always be associated with adverse events (e.g., coding error or rule out criteria). The MB and recurrent VTE events were defined based on primary or first listed ICD 9/10 diagnosis codes. These events were not adjudicated based on strict clinical criteria or validated against patients' medical records. Moreover, our CRNMB definition was based on diagnosis codes without consideration of laboratory values and has not been validated through clinical confirmation. Hence, the incidence of recurrent VTE and bleeding events may be over- or underestimated. Further, we did not include death as a competing risk, as mortality data were not available for all utilized databases. Nonetheless, we expect the impact of mortality on clinical outcomes is likely to be minimal, given that our analysis of a database with available mortality data showed a low mortality rate for the study population (~5%). Finally, our patient population did not include those who were uninsured or those with other insurance types not included in our study. Thus, our results may not be generalizable to the entire population of patients with CKD and VTE.

Conclusion

Our study showed that the use of apixaban was associated with significantly lower risks of recurrent VTE, MB, and CRNMB when compared with warfarin among VTE patients with CKD. Additionally, CKD stages, including stage V/ESRD, did not have significant impacts on treatment effects for recurrent VTE and MB. While this study provides additional evidence to support the use of apixaban by VTE patients with CKD, more studies are needed to confirm our findings.

What is known about this topic?

- Patients with chronic kidney disease (CKD) are at increased risk of venous thromboembolism (VTE) and bleeding.
- VTE patients with CKD, especially those with end-stage renal disease (ESRD), were underrepresented or excluded from pivotal trials of oral anticoagulants.
- Limited studies based on a single data source showed that apixaban may be associated with a lower risk of recurrent VTE and major bleeding (MB) among patients with CKD.

What does this paper add?

- This study used five U.S. claims databases and included the largest sample to date of VTE patients with CKD being treated with apixaban versus warfarin.
- The findings of this study provide additional evidence to suggest that apixaban was associated with a reduced risk of recurrent VTE and MB among VTE patients diagnosed with CKD.
- Analysis of VTE patients with stages I to V/ESRD of CKD showed that the results on recurrent VTE and MB were consistent across different stages of CKD, including ESRD.

Author Contributions

All authors were involved in conceptualization, methodology, and writing and review of the manuscript. The statistical analysis was performed by J. Sah and R. Delinger, employees of STATinMED Research, a paid consultant to Pfizer and Bristol Myers Squibb Company.

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Conflict of Interest

A.T.C. received research support from Pfizer and Bristol Myers Squibb Company. J.S. and R.D. are employed by SIMR, LLC—a paid consultant to Pfizer and Bristol Myers Squibb Company, in connection with the development of the manuscript. T.L., P.H., B.E., and X.L. are employees of Pfizer, a study sponsor. A.D.D. and L.R. are employees of Bristol Myers Squibb Company, a study sponsor. H.Y. has no financial relationships or other potential conflicts of interest to declare.

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