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ORIGINAL RESEARCH

Effectiveness and Safety of Apixaban Versus Warfarin Among Older Patients with Venous Thromboembolism with Different Demographics and Socioeconomic Status

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ABSTRACT

Introduction: Impact of demographics and socioeconomic status (SES) on anticoagulant treatment outcomes among patients with venous thromboembolism (VTE) is not well understood. This study evaluated risks of recurrent VTE, major bleeding (MB), and clinically relevant non-major bleeding (CRNMB) among older patients with VTE initiating apixaban or warfarin stratified by demographics and SES.

Methods: Adult patients (≥ 65 years) who initiated apixaban or warfarin after a VTE event were selected from the US CMS Medicare database (September 2014–December 2017). Stabilized inverse probability treatment weighting (IPTW) was used to balance patient characteristics between treatment cohorts. Patients were stratified by age, gender, race, and SES. For each subgroup, Cox proportional hazard models were used to evaluate if there was a significant interaction ($p < 0.10$) between treatment and subgroup for recurrent VTE, MB, and CRNMB.

Results: In total, 22,135 apixaban and 45,840 warfarin patients with VTE were included. Post-IPTW, patient characteristics were balanced between treatment cohorts. In older patients, apixaban treatment was associated with significantly lower risks of recurrent VTE (hazard ratio [HR] 0.64; 95% confidence interval [CI] 0.52–0.79), MB (HR 0.65; 95% CI 0.57–0.75), and CRNMB (HR 0.79; 95% CI 0.75–0.85) versus warfarin. When stratified by demographics and SES, higher incidence rates of recurrent VTE, MB, and CRNMB were observed for black vs white patients and patients with lower vs higher SES. Comparison of apixaban with warfarin by different demographic and SES subgroups showed generally consistent results as the overall analysis. For most subgroups, no significant interaction was observed between

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treatment and subgroup strata for recurrent VTE, MB, and CRNMB.
Conclusion: Among older patients with VTE initiating apixaban or warfarin, higher rates of recurrent VTE and bleeding were observed in black patients and patients with lower SES. Apixaban had a lower risk of recurrent VTE, MB, and CRNMB compared to warfarin. Analyses of demographic and SES subgroups showed consistent findings.

Keywords: Apixaban; Medicare; Race; Socioeconomic status; Venous thromboembolism

Key Summary Points

Why carry out this study?

Venous thromboembolism (VTE) is a common cause of preventable deaths in older hospitalized patients.

There has been a lack of evidence about potential impact of demographics and socioeconomic status on anticoagulant treatment outcomes in patients with VTE.

This study aimed to evaluate the risk of recurrent VTE, major bleeding (MB), and clinically relevant non-MB (CRNMB) among older patients with VTE initiating apixaban or warfarin stratified by demographics and socioeconomic status in routine clinical practice.

What was learned from this study?

Among older patients with VTE, black patients and those with lower socioeconomic status tended to have higher incidence rates of recurrent VTE, MB, and CRNMB compared to their counterparts.

When compared to warfarin, apixaban had a lower risk of recurrent VTE, MB, and CRNMB among patients with VTE. Analyses of the demographics and socioeconomic subgroups showed generally consistent findings.

INTRODUCTION

Venous thromboembolism (VTE) is a common cause of preventable death especially in older hospitalized patients [1, 2]. Acquired risk factors for VTE include age, obesity, smoking, surgery, immobility, hospitalization, pregnancy, hormone therapy, malignancy, and other comorbid medical conditions [3]. There exist racial differences in the incidence of VTE—black patients have a significantly higher rate of VTE and a higher rate of complications such as death, major bleeding (MB), and recurrent VTE compared to white patients [4–6]. Another study showed that black Americans had a 30–60% higher incidence rate of VTE than white Americans despite having lower rates of the two genetic mutations known to increase the risk of VTE [7]. While VTE can occur in all races, gender, and age groups, there is a significantly higher prevalence of VTE among black and older patients [8, 9].

Clinical guidelines recommend the use of direct oral anticoagulants (DOACs; including apixaban, dabigatran, edoxaban, rivaroxaban) and warfarin for the treatment of VTE [10, 11]. However, the effects of demographics and socioeconomic status (SES) on DOAC treatment outcomes are not well understood. Some studies have found associations between SES and the use of DOACs vs vitamin K antagonist in patients with VTE—patients with a lower household income were less likely to use DOACs compared to those with a higher household income [12]. The difference in DOAC treatment rate by SES may lead to disparity in health outcomes such as the risk of developing recurrent VTE. Additionally, patients may respond to anticoagulant treatments differently because of different age, gender, race, and SES.

However, few clinical trials and real-world studies have evaluated the impact of demographics and SES on anticoagulant treatment outcomes among patients with VTE. Minorities and patients with lower SES have been underrepresented in clinical trials [13], and evidence on the effectiveness and safety of anticoagulants in patients with VTE with different

demographics and SES is sparse. Therefore, this study aimed to evaluate the risk of recurrent VTE, MB, and clinically relevant non-major bleeding (CRNMB) among older patients with VTE initiating apixaban or warfarin stratified by demographics and SES in routine clinical practice.

METHODS

Data Source and Patient Selection

This retrospective analysis utilized data from the United States (US) Centers for Medicare and Medicaid Services (CMS) fee-for-service Medicare database. Patients with a VTE diagnosis (based on International Classification of Diseases, 9th and 10th Revision codes) in any position in the inpatient or outpatient setting were identified between September 1, 2014 and December 31, 2017. Patients were required to have at least one pharmacy claim for apixaban or warfarin during the 30-day period following the index VTE event. The first warfarin or apixaban prescription claim was designated as the index date. Patients aged at least 65 years on the index date with continuous health plan enrollment, including medical and pharmacy benefits, for at least 6 months before the index VTE event until the index date were included in the study population. Additional selection criteria are listed in Fig. 1.

The baseline period was defined as 6 months prior to and including the index date; the follow-up period included the day after the index date through the earliest of index therapy discontinuation, switch to another oral anticoagulant or parenteral anticoagulant, health plan disenrollment, death, the end of the study period, or 6-months post-index date. This study employed an on-treatment approach and therefore did not consider events that occurred after a patient switched or discontinued index treatment.

Study Variables

Recurrent VTE and MB were defined by primary diagnosis in the inpatient setting [14–18]. CRNMB was identified by either an inpatient admission with a secondary diagnosis code for non-critical sites of bleeding (excluded if MB occurred before the CRNM bleed or during the same hospitalization) or by a diagnosis code for gastrointestinal bleeding or other selected non-critical site of bleeding in the outpatient setting. This approach aligns with the current recommendation of the International Society on Thrombosis and Haemostasis [14–19].

Demographic variables including age, gender, and race were measured on the index date. Age was categorized as 65–79 years and $\geq$ 80 years. Gender was categorized as male and female. Race was categorized as white, black, and other race (including Asian, Hispanics, North American native, other, and unknown races). Two SES factors were considered—one was Medicare Medicaid dual eligibility or Part D low income subsidy (LIS) anytime during the baseline period. Another was SES status constructed for each US zip code using data on income, education, and occupation from the 2015 US census. This information was then linked to the patient's zip code of residence on the index date to define the SES for the patient [20, 21]. Clinical characteristics (such as the Deyo–Charlson comorbidity index, baseline comorbidities, falls, fracture/trauma involving lower extremities, selected surgeries, and baseline medications) were evaluated during the baseline period. VTE-related variables such as type of index VTE event and index VTE diagnosis were measured during the index VTE event date.

Statistical Methods

Patient characteristics were balanced between the treatment cohorts using stabilized inverse probability treatment weighting (IPTW); baseline demographics, clinical characteristics, and VTE-related variables were covariates included in the model. IPTW weights were stabilized by multiplying the original weights with a

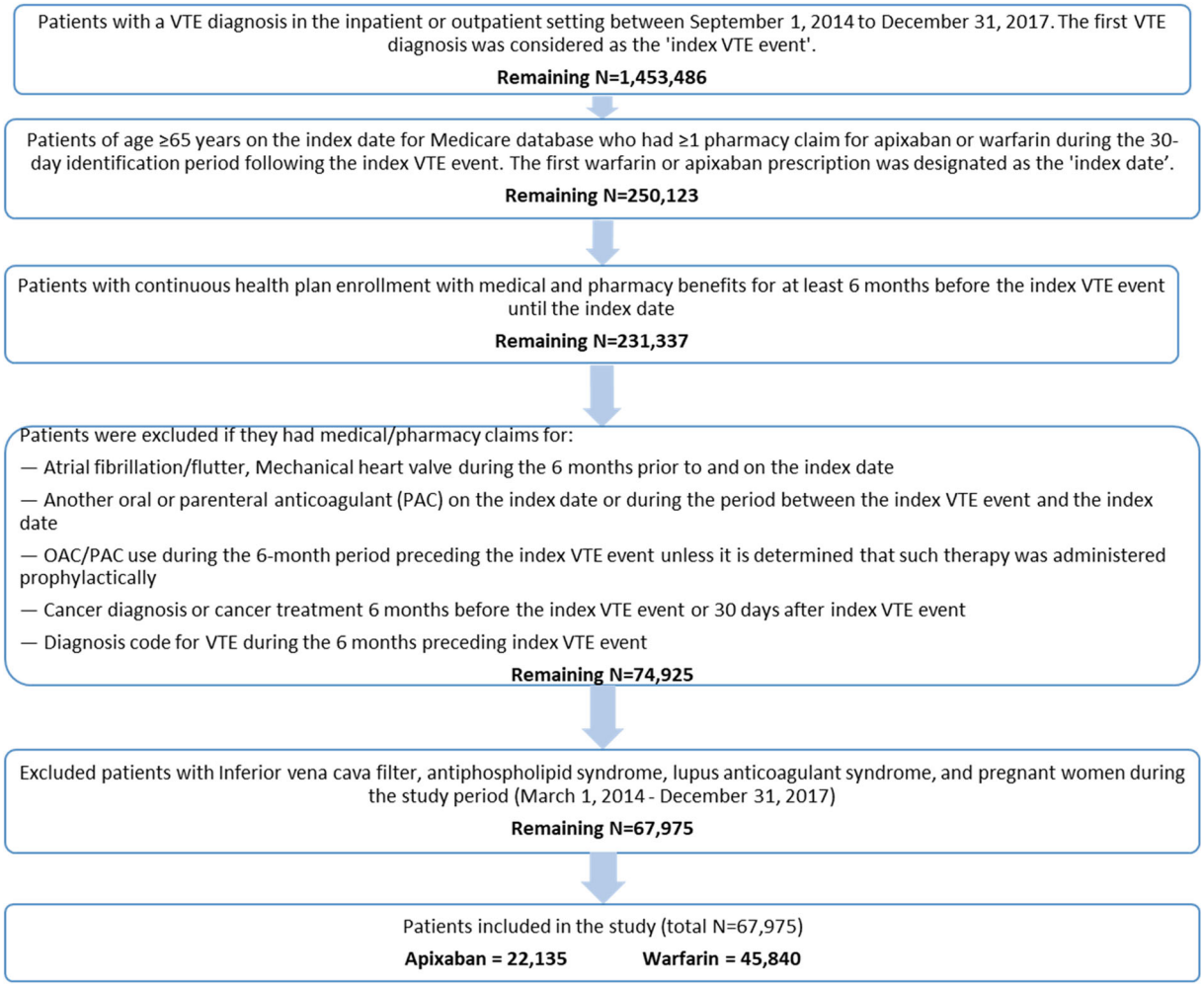

Fig. 1 Patient selection criteria

constant that was equal to the expected value of being in the treatment or comparison cohorts [22–24]. The risk of recurrent VTE, MB, and CRNMB was evaluated by using Cox proportional hazard models. Interaction analyses were conducted using Cox models to evaluate whether treatment effects differ by age (65–79 vs ≥ 80 years), gender (male vs female), race (white vs black), SES (low vs medium vs high), and dual Medicare/Medicaid eligibility or Part-D LIS (yes vs no). For each of the demographic and SES subgroups, a statistical significance ($p < 0.10$) of the interaction between the treatment and subgroup strata on effectiveness and safety was evaluated.

Compliance with Ethics Guidelines

This retrospective database analysis did not involve the collection, use, or transmittal of individual identifiable data. As such, institutional review board (IRB) approval to conduct this study was not required and considered exempt according to 45CFR46.101(b)(4): existing data and specimens—no identifiers. Both the data set itself and the security of the offices where the data are housed meet the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

RESULTS

During the study period, approximately 1.4 million patients had a VTE event in the Medicare database; after application of the selection criteria, 22,135 (32.6%) patients who initiated apixaban and 45,840 (67.4%) patients who initiated warfarin were included in the study (Fig. 1). Table 1 shows demographics, SES, and clinical characteristics for the apixaban and warfarin cohorts before and after IPTW. After IPTW, all patient characteristics were well balanced (Table 1). For both treatment cohorts, most patients were aged 65–79 years (apixaban, 62.6%; warfarin, 62.6%), followed by ≥ 80 years (apixaban, 37.4%; warfarin, 37.4%). The majority of patients were female (apixaban, 62.9%; warfarin, 62.9%) and white (apixaban, 84.2%; warfarin, 83.7%) across the two cohorts. The largest proportion of patients had a high SES (apixaban, 45.2%; warfarin, 42.2%), followed by medium (apixaban, 30.2%; warfarin, 32.6%), and low (apixaban, 22.7%; warfarin, 23.4%). One-third of patients also had Medicare/Medicaid dual-eligibility and/or Part D low income subsidy (apixaban, 28.5%; warfarin, 30.5%) during the baseline period. During the follow-up period, apixaban patients had significantly lower risk of recurrent VTE (hazard ratio [HR] 0.64; 95% confidence interval [CI] 0.52–0.79), MB (HR 0.65; 95% CI 0.57–0.75), and CRNMB (HR 0.79; 95% CI 0.75–0.85) compared to warfarin patients.

The baseline characteristics for older patients with VTE on apixaban vs warfarin stratified by age, gender, race, SES status, and dual eligibility/Part-D LIS are listed in Supplemental Material. For both apixaban and warfarin cohorts, higher mean comorbidity index was observed in patients aged ≥ 80 vs 65–79 years (apixaban, 3.2 vs 2.7; warfarin, 3.2 vs 2.7), low vs high SES (apixaban, 3.5 vs 2.6; warfarin, 3.3 vs 2.7), and dual eligibility/Part-D LIS yes vs no (apixaban, 3.9 vs 2.5; warfarin, 3.8 vs 2.5) and black vs white patients (apixaban, 4.1 vs 2.7; warfarin, 4.1 vs 2.7). Additionally, during the follow-up, the incidence rates per 100 person-years for recurrent VTE were numerically higher for black vs white patients (apixaban, 2.0 vs 1.4; warfarin, 3.3 vs 2.2) and patients with low vs high SES (apixaban, 2.6 vs 1.3; warfarin, 3.2 vs 2.0) and dual eligibility/Part-D LIS yes vs no (apixaban, 2.2 vs 1.3; warfarin, 3.1 vs 2.0) (Fig. 2). Similarly, the incidence rates per 100 person-years for MB were numerically higher for patients aged ≥ 80 vs 65–79 years (apixaban, 5.4 vs 3.1; warfarin, 7.4 vs 5.0), female vs male (apixaban, 4.5 vs 3.1; warfarin, 6.4 vs 5.0), black vs white patients (apixaban, 7.4 vs 3.5; warfarin 10.1 vs 5.3), low vs high SES (apixaban, 5.7 vs 3.2; warfarin, 7.0 vs 5.1), and dual eligibility/Part-D LIS yes vs no (apixaban, 6.3 vs 3.1; warfarin, 8.6 vs 4.8) (Fig. 3).

Figures 2, 3, and 4 show the data of apixaban vs warfarin on risks of recurrent VTE, MB, and CRNMB stratified by demographic and SES factors. No significant interaction was observed between the treatment and the following subgroups on recurrent VTE (Fig. 2) and MB (Fig. 3): age, sex, race, SES, and dual eligibility/LIS. Across all subgroup strata, apixaban patients had a lower incidence rate of recurrent VTE and MB compared to warfarin patients. For CRNMB, no significant interaction was observed between the treatment and the following subgroups: sex, race, and dual eligibility/LIS (Fig. 4). However, there were significant interactions between the treatment and age (interaction p value = 0.001) and between the treatment and SES (interaction p value = 0.012) on CRNMB. Apixaban trended towards a lower risk of CRNMB across both age groups, but the treatment effect on CRNMB was larger for patients aged 65–79 years. Similarly, apixaban trended towards a lower risk of CRNMB across all three SES strata, but the treatment effect was larger for those with medium and high SES (Fig. 4).

DISCUSSION

There has been a lack of evidence about the potential impact of demographic and SES factors on anticoagulant treatment outcomes in patients with VTE. To help fill in some of the evidence gaps, this study compared the risk of recurrent VTE, MB, and CRNMB among older patients with VTE who initiated apixaban vs warfarin stratified by demographic and SES

Table 1 Baseline and clinical characteristics among older patients with VTE that initiated apixaban vs warfarin pre and post IPTW

	Pre IPTW			Post IPTW**		
	Warfarin cohort	Apixaban cohort	STD*	Warfarin cohort	Apixaban cohort	STD*
Sample size	45,840	22,135		45,840	22,135	
Age (in years), mean (SD)	77.2 (8.1)	77.7 (8.2)	6.01	77.3 (8.1)	77.4 (8.2)	1.57
Age category (in years), *n* (%)						
65–79	29,021 (63.3%)	13,548 (61.2%)	4.34	28,703 (62.6%)	13,848 (62.6%)	0.11
≥ 80	16,819 (36.7%)	8587 (38.8%)	4.34	17,137 (37.4%)	8287 (37.4%)	0.11
Sex, *n* (%)						
Male	16,959 (37.0%)	8300 (37.5%)	1.04	17,019 (37.1%)	8202 (37.1%)	0.15
Female	28,881 (63.0%)	13,835 (62.5%)	1.04	28,821 (62.9%)	13,933 (62.9%)	0.15
Race, *n* (%)						
White	38,487 (84.0%)	18,575 (83.9%)	0.12	38,371 (83.7%)	18,636 (84.2%)	1.33
African American	5239 (11.4%)	2535 (11.5%)	0.07	5404 (11.8%)	2428 (11.0%)	2.58
Other categories	2114 (4.6%)	1025 (4.6%)	0.09	2065 (4.5%)	1070 (4.8%)	1.66
SES status, *n* (%)						
Low	10,374 (22.6%)	5320 (24.0%)	3.32	10,733 (23.4%)	5029 (22.7%)	1.65
Medium	15,083 (32.9%)	6600 (29.8%)	6.66	14,959 (32.6%)	6684 (30.2%)	5.25
High	19,567 (42.7%)	9792 (44.2%)	3.13	19,324 (42.2%)	10,008 (45.2%)	6.17
Missing	816 (1.8%)	423 (1.9%)	0.97	824 (1.8%)	414 (1.9%)	0.52
Medicare/Medicaid dual-eligibility and/or Part D low income subsidy during the baseline period, *n* (%)	13,857 (30.2%)	6385 (28.8%)	3.03	13,990 (30.5%)	6319 (28.5%)	4.32
Type of index VTE event, *n* (%)						

Table 1 continued

	Pre IPTW			Post IPTW**		
	Warfarin cohort	Apixaban cohort	STD*	Warfarin cohort	Apixaban cohort	STD*
Inpatient	29,977 (65.4%)	14,391 (65.0%)	0.80	29,907 (65.2%)	14,418 (65.1%)	0.22
Outpatient	15,863 (34.6%)	7744 (35.0%)	0.80	15,933 (34.8%)	7717 (34.9%)	0.22
Index VTE diagnosis, *n* (%)						
DVT only	24,772 (54.0%)	11,669 (52.7%)	2.65	24,601 (53.7%)	11,913 (53.8%)	0.31
PE with DVT	7091 (15.5%)	3502 (15.8%)	0.97	7145 (15.6%)	3448 (15.6%)	0.02
PE without DVT	13,977 (30.5%)	6964 (31.5%)	2.10	14,094 (30.7%)	6773 (30.6%)	0.32
Deyo–Charlson comorbidity index, mean (SD)	2.9 (2.5)	2.9 (2.5)	1.40	2.9 (2.5)	2.9 (2.5)	0.37
Baseline comorbidity, *n* (%)						
AIDS	128 (0.3%)	46 (0.2%)	1.45	130 (0.3%)	48 (0.2%)	1.29
Alcohol abuse	1178 (2.6%)	525 (2.4%)	1.28	1152 (2.5%)	561 (2.5%)	0.13
Anemia	17,520 (38.2%)	8026 (36.3%)	4.06	17,246 (37.6%)	8340 (37.7%)	0.11
Central venous catheter	4047 (8.8%)	1597 (7.2%)	5.94	3810 (8.3%)	1835 (8.3%)	0.08
Cerebrovascular disease	7918 (17.3%)	3786 (17.1%)	0.45	8006 (17.5%)	3724 (16.8%)	1.70
Coagulation defects	4429 (9.7%)	1870 (8.4%)	4.23	4254 (9.3%)	2064 (9.3%)	0.15
Ischemic heart/coronary artery disease	15,724 (34.3%)	8111 (36.6%)	4.90	16,071 (35.1%)	7757 (35.0%)	0.03
Dementia	4868 (10.6%)	3041 (13.7%)	9.55	4934 (10.8%)	2996 (13.5%)	8.48
Dyspepsia or stomach discomfort	11,168 (24.4%)	5336 (24.1%)	0.60	11,150 (24.3%)	5413 (24.5%)	0.31
Hemiplegia or paraplegia	1157 (2.5%)	542 (2.4%)	0.48	1157 (2.5%)	562 (2.5%)	0.11

Table 1 continued

	Pre IPTW			Post IPTW**		
	Warfarin cohort	Apixaban cohort	STD*	Warfarin cohort	Apixaban cohort	STD*
Hyperlipidemia	27,678 (60.4%)	14,048 (63.5%)	6.36	28,129 (61.4%)	13,563 (61.3%)	0.19
Obesity	11,558 (25.2%)	5794 (26.2%)	2.20	11,689 (25.5%)	5631 (25.4%)	0.14
Pneumonia	7893 (17.2%)	3912 (17.7%)	1.20	7980 (17.4%)	3868 (17.5%)	0.17
Rheumatologic disease	3060 (6.7%)	1455 (6.6%)	0.41	3044 (6.6%)	1465 (6.6%)	0.08
Sleep apnea	6394 (13.9%)	3086 (13.9%)	0.02	6375 (13.9%)	3054 (13.8%)	0.32
Spinal cord injury	130 (0.3%)	46 (0.2%)	1.53	119 (0.3%)	59 (0.3%)	0.10
Thrombophilia	1450 (3.2%)	627 (2.8%)	1.94	1397 (3.0%)	670 (3.0%)	0.11
Varicose veins	1999 (4.4%)	1059 (4.8%)	2.03	2065 (4.5%)	996 (4.5%)	0.02
Congestive heart failure	10,648 (23.2%)	5233 (23.6%)	0.97	10,731 (23.4%)	5221 (23.6%)	0.42
Diabetes	17,825 (38.9%)	8031 (36.3%)	5.38	17,978 (39.2%)	7900 (35.7%)	7.29
Hypertension	38,312 (83.6%)	18,691 (84.4%)	2.36	38,446 (83.9%)	18,571 (83.9%)	0.08
Non-ESRD renal disease	9408 (20.5%)	4615 (20.8%)	0.80	9466 (20.6%)	4585 (20.7%)	0.16
End stage renal disease	1588 (3.5%)	449 (2.0%)	8.79	1375 (3.0%)	675 (3.0%)	0.28
Chronic liver disease	2861 (6.2%)	1570 (7.1%)	3.41	2807 (6.1%)	1610 (7.3%)	4.59
COPD	11,754 (25.6%)	5814 (26.3%)	1.43	11,858 (25.9%)	5800 (26.2%)	0.76
Peptic ulcer disease	1296 (2.8%)	533 (2.4%)	2.63	1267 (2.8%)	564 (2.5%)	1.35
Inflammatory bowel disease	853 (1.9%)	378 (1.7%)	1.16	829 (1.8%)	395 (1.8%)	0.19

Table 1 continued

	Pre IPTW			Post IPTW**		
	Warfarin cohort	Apixaban cohort	STD*	Warfarin cohort	Apixaban cohort	STD*
Peripheral vascular disease	11,958 (26.1%)	5840 (26.4%)	0.68	12,052 (26.3%)	5760 (26.0%)	0.61
Baseline bleed	11,159 (24.3%)	4544 (20.5%)	9.15	10,590 (23.1%)	5112 (23.1%)	0.02
Recent history of falls, *n* (%)	4488 (9.8%)	2198 (9.9%)	0.47	4522 (9.9%)	2184 (9.9%)	0.01
Fracture/trauma involving lower extremities, *n* (%)	7075 (15.4%)	3636 (16.4%)	2.71	7245 (15.8%)	3523 (15.9%)	0.30
Selected surgeries, *n* (%)	12,264 (26.8%)	5844 (26.4%)	0.80	12,210 (26.6%)	5885 (26.6%)	0.11
Baseline medication use, *n* (%)						
Antiarrhythmic	4804 (10.5%)	2354 (10.6%)	0.50	4829 (10.5%)	2333 (10.5%)	0.03
Statins	21,848 (47.7%)	11,057 (50.0%)	4.58	22,189 (48.4%)	10,706 (48.4%)	0.07
Anti-platelets	4649 (10.1%)	2562 (11.6%)	4.61	4859 (10.6%)	2337 (10.6%)	0.14
Aromatase inhibitors	103 (0.2%)	53 (0.2%)	0.31	105 (0.2%)	50 (0.2%)	0.07
Beta blockers	19,886 (43.4%)	9739 (44.0%)	1.24	19,978 (43.6%)	9652 (43.6%)	0.04
Gastroprotective agents	15,790 (34.4%)	7643 (34.5%)	0.17	15,811 (34.5%)	7646 (34.5%)	0.11
SERMS	378 (0.8%)	233 (1.1%)	2.36	410 (0.9%)	197 (0.9%)	0.04
NSAIDs	10,052 (21.9%)	5433 (24.5%)	6.20	10,438 (22.8%)	5031 (22.7%)	0.10
Hormone therapy	1138 (2.5%)	578 (2.6%)	0.82	1164 (2.5%)	573 (2.6%)	0.31

AIDS acquired immunodeficiency syndrome, *COPD* chronic obstructive pulmonary disorder, *DVT* deep vein thrombosis, *ESRD* end stage renal disease, *IPTW* inverse probability of treatment weighting, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PE* pulmonary embolism, *SERMS* selective estrogen receptor modulators, *SES* socioeconomic status, *SD* standard deviation, *STD* standardized differences, *VTE* venous thromboembolism

*STD = 100 × |actual standardized difference|. Standardized difference (STD) greater than 10 was considered significant

**After weightings were applied, the values for the baseline variables were not whole numbers; therefore, as a result of rounding the sum of patients may not equal 100%

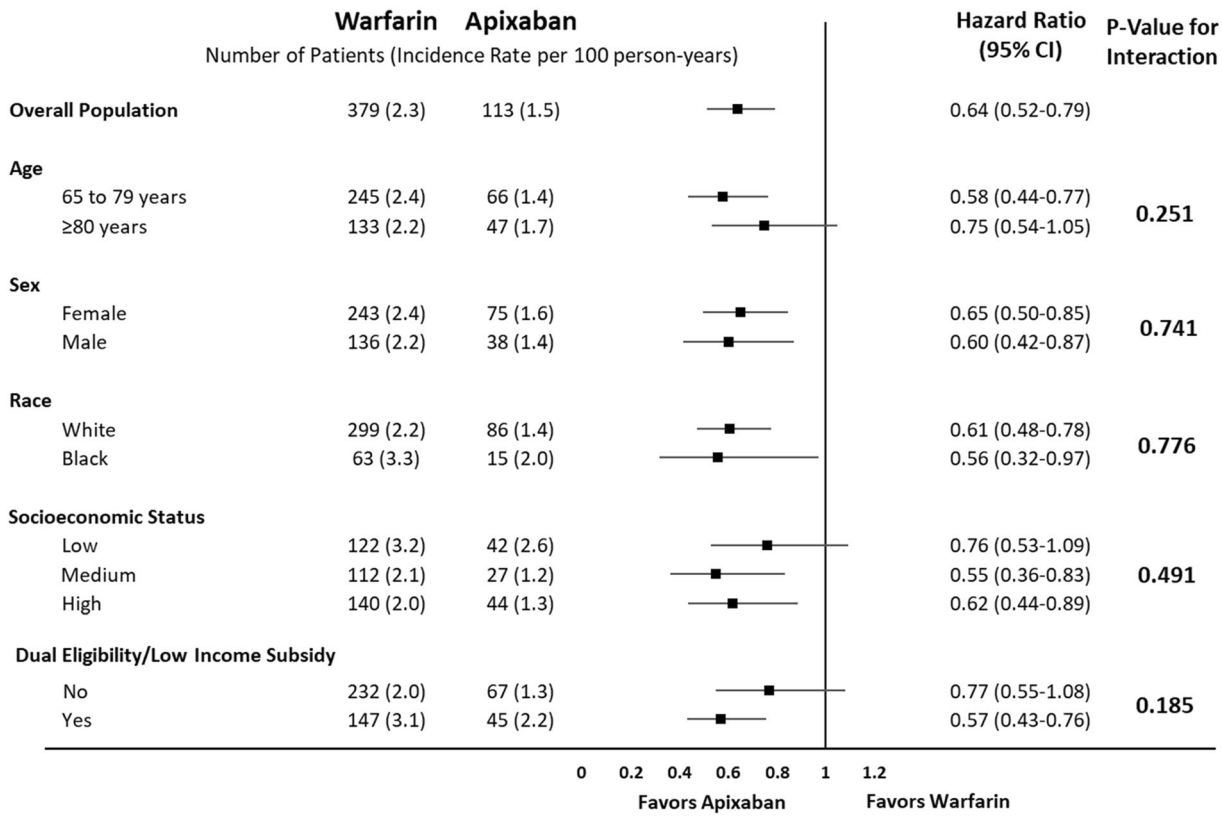

Fig. 2 Risk of recurrent VTE among older patients with VTE stratified by demographic and socioeconomic factors. CI: confidence interval

factors including age, sex, race, SES, and dual eligibility/Part-D LIS. In patients with VTE aged $\geq$ 65 years, apixaban was associated with significantly lower risk of recurrent VTE, MB, and CRNMB compared to warfarin. When stratified by the demographic and socioeconomic factors, black patients and patients with lower SES tended to have higher incidence rates of recurrent VTE, MB, and CRNMB than their respective counterparts for both apixaban and warfarin cohorts. Comparisons of apixaban with warfarin on recurrent VTE and MB by the demographic and socioeconomic factors show no significant interaction between the treatment and the following subgroups: age, sex, race, SES, and dual eligibility/Part-D LIS. Two significant interactions were observed for CRNMB, but apixaban patients trended towards a lower risk of CRNMB across all subgroup strata.

Our findings are generally consistent with the age and gender subgroup analysis of the AMPLIFY clinical trial. AMPLIFY demonstrated that apixaban was noninferior to enoxaparin followed by warfarin for the treatment of VTE and was associated with significantly less bleeding among patients with VTE [13]. For AMPLIFY, approximately 58% of patients were male with an average age of 57 years [13]. In the subgroup analysis of AMPLIFY, there was no significant interaction between treatment and age subgroups (aged $<$ 65 years, 65–74 years, and $\geq$ 75 years, interaction $p = 0.3427$) as well as between treatment and gender (interaction $p = 0.4514$) with regards to recurrent VTE or VTE-related death [13]. There was also no significant interaction between treatment and age (interaction $p = 0.8174$) or between treatment and gender (interaction $p = 0.4168$) with regards to MB [13]. Consistently, our study did not observe significant interactions between the

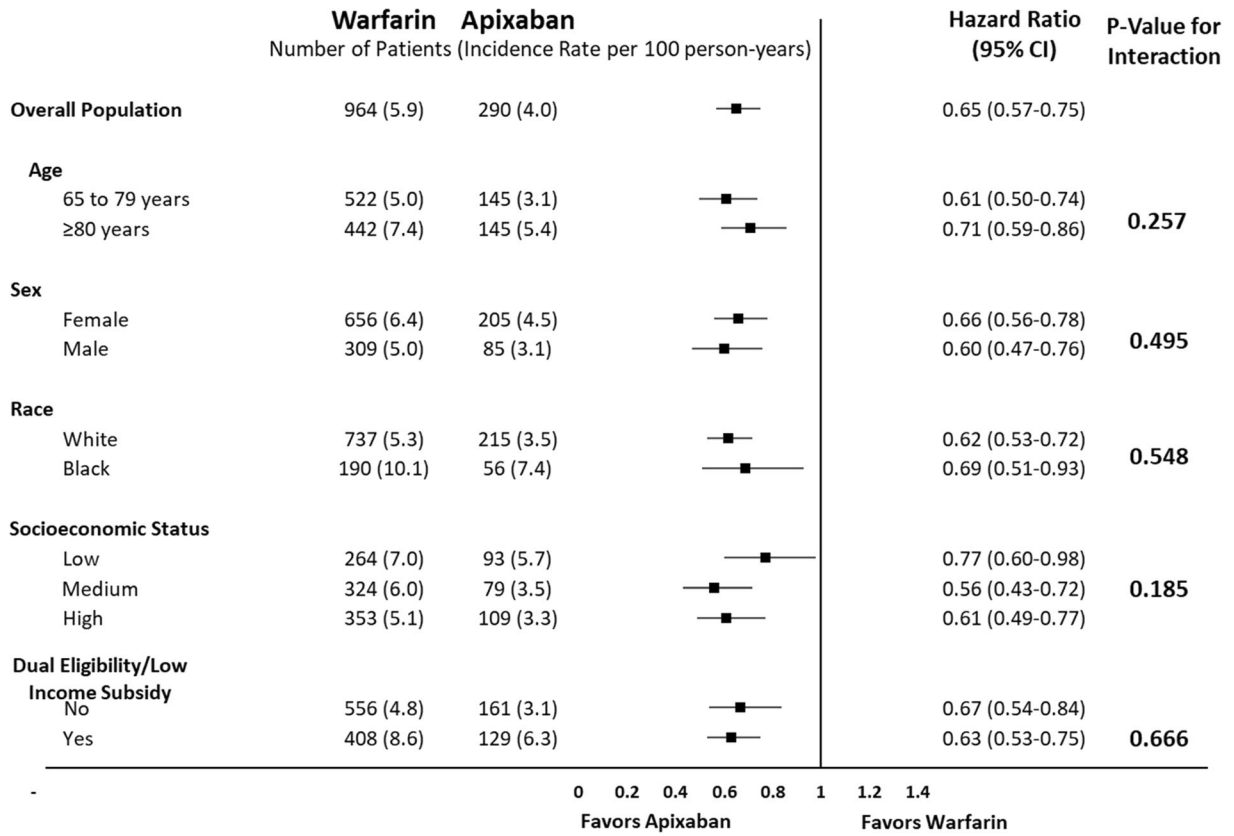

Fig. 3 Risk of major bleeding among older patients with VTE stratified by demographic and socioeconomic factors. CI: confidence interval

treatment and age or gender for recurrent VTE or MB.

Race has been found to be a risk factor for VTE and racial disparity in VTE event rates has been well documented in the literature [25–27]. In general, black patients were found to have a higher incidence and risk of VTE compared to white patients [25–27] possibly due to underlying risk factors for VTE compared to white patients as well as low adherence to treatment [28]. Consistent with this, the current study found that black patients had a higher incidence rate per 100 person-years for recurrent VTE compared to white patients. Additionally, we found a higher incidence rate of MB and CRNMB for black vs white patients. A previously published single-center study also showed that among DVT patients, race (non-white race—relative hazard 1.6; 95% CI 1.2–2.1) was a risk factor for bleeding during hospitalization [29]. Despite the higher risk of VTE among black patients, a retrospective study found that black patients with VTE were significantly less likely to receive a DOAC treatment compared to white patients (odds ratio [OR] 0.86; 95% CI 0.77–0.97) [12]. In this study of apixaban vs warfarin, we did not observe any significant interaction between treatment and race for recurrent VTE, MB, or CRNMB. The treatment effects of apixaban vs warfarin were consistently observed between black and white patients. Similarly, most of the subgroup analyses of the DOAC pivotal trials in patients with VTE did not find significant differences in treatment outcomes by race [6]. More studies are needed to understand the reasons for the racial disparity in VTE treatments.

Disparities in VTE treatments also exist among patients with different SES. A retrospective analysis of patients with VTE reported that patients with an income of greater than US$100,000/year were more likely to receive

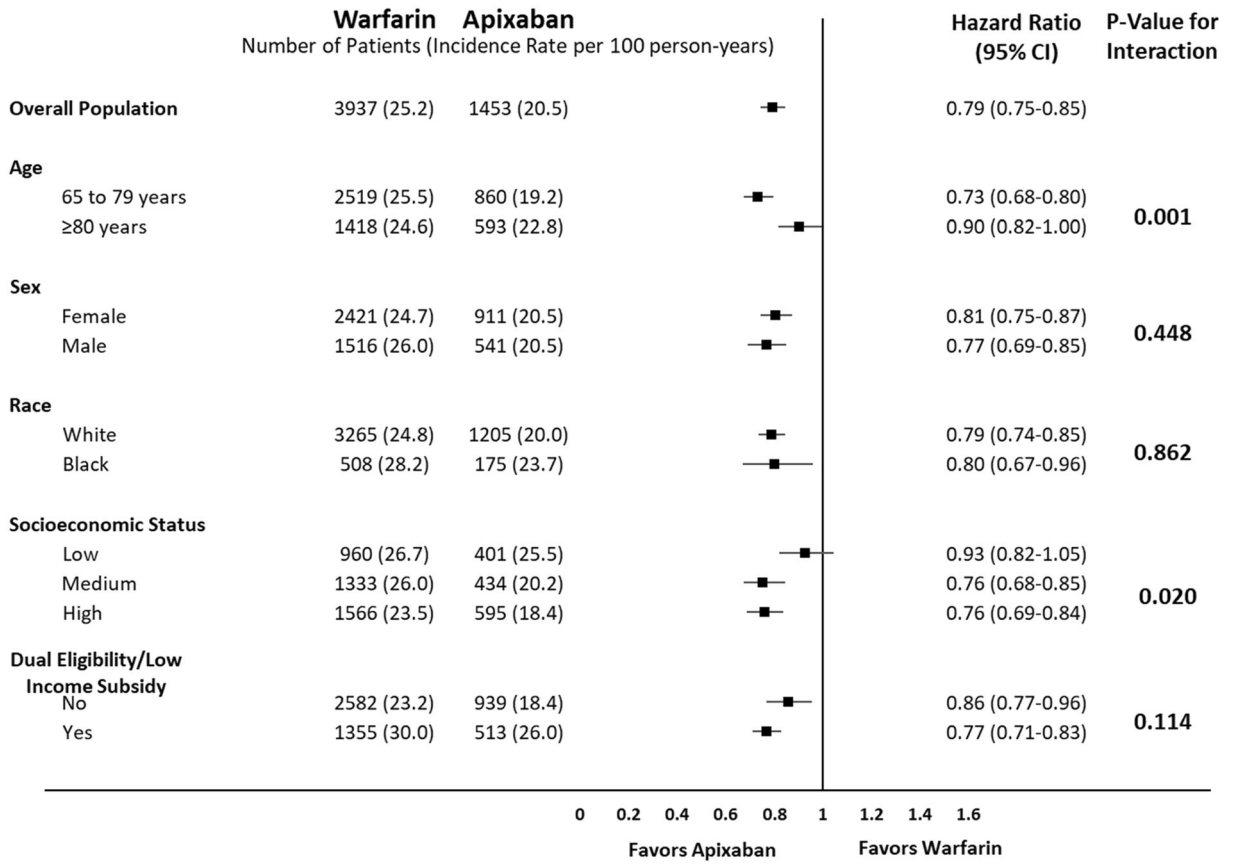

Fig. 4 Risk of clinically relevant non-major bleeding among older patients with VTE stratified by demographic and socioeconomic factors. CI: confidence interval

DOAC therapy compared with patients with an income of less than US$40,000 per year (OR 1.50; 95% CI 1.33–1.69) after controlling for other factors [12]. To address the treatment disparity, it is important to understand whether DOAC treatment effects differ by different SES. In the current study, we compared apixaban with warfarin for recurrent VTE, MB, and CRNMB stratified by SES and by Medicare Medicaid dual eligibility or LIS which is a group of vulnerable patients with low income and complex medical needs. No significant interaction was found between the treatment and SES or between the treatment and dual eligibility/LIS for recurrent VTE and MB. The treatment effects of apixaban vs warfarin on recurrent VTE and MB were consistently observed regardless of SES and dual eligibility/LIS. Although a significant interaction was found between the treatment and SES on CRNMB, apixaban patients trended towards a lower risk of CRNMB across all strata of SES. Additional efforts are needed to optimize VTE treatments for patients with low SES.

As with any retrospective claims analysis, the current study has several limitations. First, the definitions of recurrent VTE and MB were based on inpatient claims with primary diagnosis code for VTE and MB, respectively. While the use of inpatient primary diagnosis would ensure that the recurrent VTE and MB events being captured are indeed major acute events, such definitions may be too strict to cause underestimates of the events. Moreover, the definition for CRNMB has not been validated in the literature, although it attempts to align with the

definition suggested by the International Society on Thrombosis and Haemostasis [19]. Second, the race categories used in the study were based on what have been defined in the Medicare database and a small percentage of patients in the database had unknown race. It is also possible that there could be some misclassification of race in the database. Third, the SES was based on zip codes rather than the income of the patients. However, studies have shown that zip code level classification of SES is a more conservative proxy and is often used [30–32]. Fourth, only association rather than causation could be inferred and hence the results should be interpreted with caution. Fifth, the baseline medications included in this study were mostly limited to those that were likely to increase the risk of bleeding or clots. This list may not be comprehensive, and some other important medications may be missed. Sixth, polypharmacy was not adjusted for in the model and could have an impact on risk of recurrent VTE and bleeding. Lastly, the results of this study cannot be generalized to older patients with other insurances such as Medicare Advantage, Veterans Affairs, or those who are uninsured.

CONCLUSIONS

In this study of patients with VTE aged $\geq$ 65 years, higher incidence rates of recurrent VTE, MB, and CRNMB were observed in black vs white patients and patients with lower vs higher SES. Apixaban had a lower risk of recurrent VTE, MB, and CRNMB compared to warfarin. The treatment effects of apixaban vs warfarin were generally consistent across the demographic and socioeconomic subgroups. More studies are needed to identify optimal VTE management strategies for black patients and patients with lower SES.

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Compliance with Ethics Guidelines. This retrospective database analysis did not involve the collection, use, or transmittal of individual identifiable data. As such, IRB approval to conduct this study was not required and considered exempt according to 45CFR46.101(b)(4):

Existing Data & Specimens - No Identifiers. Both the data set itself and the security of the offices where the data are housed meet the HIPAA requirements of 1996.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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