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Full Length Article

Effectiveness and safety of anticoagulants among venous thromboembolism cancer patients with and without brain cancer

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ABSTRACT

Introduction: Patients with brain cancer are at a high risk of developing venous thromboembolism (VTE) and are underrepresented in clinical trials. This study compared the risk of recurrent VTE (rVTE), major bleeding (MB), and clinically relevant non-major bleeding (CRNMB) among VTE cancer patients initiating apixaban, low molecular weight heparin (LMWH), or warfarin stratified by patients with brain vs other cancer types.

Materials and methods: Active cancer patients initiating apixaban, LMWH, or warfarin within 30 days after VTE diagnosis were identified from 4 US commercial and the Medicare databases. Inverse probability of treatment weights (IPTW) was used to balance patient characteristics. Cox proportional hazards models were used to evaluate the interaction between brain cancer status and treatment on outcomes (rVTE, MB, and CRNMB), with a p-value <0.1 indicating a significant interaction.

Results: Of 30,586 patients with active cancer (5 % had brain cancer), apixaban (vs. LMWH and warfarin) was associated with lower risk of rVTE, MB, and CRNMB. Generally, no significant interactions ($P > 0.1$) were found between brain cancer status and anticoagulant treatment across outcomes. The exception was MB for apixaban [vs LMWH (p-value for interaction = 0.091)] with a higher reduction among those with brain cancer (HR = 0.32) than those with (HR = 0.72) other cancer.

Conclusions: Among VTE patients with all types of cancer, apixaban (vs LMWH and warfarin) was associated with a lower risk of rVTE, MB, and CRNMB. In general, anticoagulant treatment effects were not significantly different between VTE patients with brain cancer and those with other cancer.

1. Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a leading cause of death in cancer patients [1–3]. An estimated 20 %–30 % of all incident VTE events occur in patients with active cancer, particularly in the first year after a cancer diagnosis [3–8]. VTE is associated with an increased risk of hospitalization and intracranial hemorrhage, as well as delays in cancer treatment, resulting in significant health care utilization and costs [3,9–11]. The likelihood of VTE varies depending on patient age, type of cancer treatment, and cancer stage [12–15]. The type of malignancy is also a factor as those with brain cancer have a considerably higher risk of VTE compared to other cancer patients [5,6,15–18].

Low molecular weight heparin (LMWH) was once the standard of care for VTE among cancer patients [16,19,20]. However, oral anticoagulants such as warfarin have also been used for the treatment of VTE in cancer patients [21]. The last decade has seen the emergence of direct oral anticoagulants (DOACs) including apixaban, dabigatran, edoxaban and rivaroxaban as alternative VTE treatments [16,22–32]. A 2021 guideline released by the American Society of Hematology (ASH) recommended that a DOAC (apixaban or rivaroxaban) or LMWH be used for the initial treatment (within first week) of VTE for patients with cancer

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[33]. In addition, the guideline suggests that DOAC is the preferred treatment over LMWH for the short-term treatment of VTE (3–6 months). The ASH guidelines noted that, compared with LMWH, DOACs have the potential to reduce the risk of recurrent VTE and major bleeding (MB). However, the guideline panel indicated that evidence for their recommendations is uncertain due to the small number of controlled trials that have examined these treatments in cancer patients. Data is also very limited among patients with brain cancer given that these patients are either excluded or represent only a small fraction of the overall sample size (<5 %) among studies examining DOACs [22,25,31].

There is a critical need for more research that evaluates the effects of different anticoagulant treatments, including DOACs, among VTE patients with active brain cancer. The goal of this real-world study was to evaluate the effectiveness (recurrent VTE) and safety (MB and clinically relevant non-major bleeding [CRNMB] events) for apixaban, LMWH, and warfarin among VTE patients with cancer stratified by brain cancer status (i.e., with brain cancer or with other cancer) in a real-world setting.

2. Materials and methods

2.1. Data sources

Medical and pharmacy claims data were pooled from four commercial databases (Optum, Humana, PharMetrics Plus and MarketScan) and the Medicare Fee for Service (FFS) database. The study period ranged from March 1, 2014, through June 30, 2017 (MarketScan), December 31, 2017 (Optum, Humana and Medicare FFS), or March 31, 2018 (PharMetrics). Data were de-identified and data collection complied with the requirements of the Health Insurance Portability and Accountability Act (HIPAA).

2.2. Study design and patient selection

A retrospective longitudinal cohort design analysis was used to examine adults 18 years or older who had been diagnosed with VTE (had any medical claim with an ICD-9-CM or ICD-10-CM diagnosis code for a VTE in any position) with an identification period spanning September 1, 2014, through the end of available data. Patients were included if they had active cancer. Active cancer was defined as having two or more claims at least one day apart for a cancer diagnosis, or one claim for a cancer diagnosis and additional claim for cancer treatment in the 6-months prior to index through 30-days after index. VTE patients with active cancer were also required to be newly treated with an anticoagulant (apixaban, LMWH, or warfarin) within 30 days after index VTE event and have continuous enrollment in medical and pharmacy benefits for the 6-months prior to the index VTE event until the index date. The date of treatment initiation was defined as index date. The final study population excluded patients with prior evidence of atrial fibrillation/flutter, mechanical heart valve, or use of any outpatient anticoagulant in the 6 months prior to the index date and also excluded patients with VTE during 6 months before index VTE event. In addition, patients with evidence of an inferior vena cava filter, pregnancy or antiphospholipid syndrome during the study period were excluded. Additionally among warfarin patients who had LMWH bridging therapy initiated before the warfarin start, those with evidence of MB or recurrent VTE between the LMWH initiation and warfarin start were excluded. The final population also excluded those with a follow-up of 0 days.

2.3. Patient characteristics

Patient characteristics were measured on the index date and included demographics (e.g., age, gender, geographic region), VTE-related factors (e.g., setting of index VTE event), position of VTE diagnosis (primary or secondary), and type of VTE diagnosis (DVT only, PE only, or PE with DVT). Non-cancer provoked factors (i.e., events that were preceded by hormone therapy, fracture/trauma involving lower extremities, pelvic/orthopedic surgery, or hospitalization for any reason for ≥3 days during 3 months prior to index VTE event), comorbidities (National Cancer Institute adaptation of the CCI [NCI Comorbidity Index] and comorbid conditions), selected surgeries, concomitant medications and cancer-related characteristics (e.g., cancer site, evidence of metastasis, hematologic cancer or not, VTE risk level, and cancer-related treatment) were measured in the 6-months prior to index VTE through the index date.

2.4. Outcomes

Study outcomes included recurrent VTE, MB, and CRNMB events which were measured from the index date through the earliest of death, disenrollment, switch to another anticoagulant, discontinuation of treatment (i.e., no evidence of anticoagulant use for at least 30 days after the end of the patient's supply), or 6-months after the index date. A recurrent VTE event was considered an inpatient admission with a diagnosis (ICD-9 or ICD-10) for VTE in the primary or 1st listed position. If the index VTE event was an inpatient admission, any admission within 7 days of the index VTE event was not considered a recurrent VTE. A MB event was an inpatient admission with a diagnosis (ICD-9 or ICD-10) for bleeding in the primary or 1st listed position. A CRNMB event was an inpatient admission for a bleeding event that did not qualify as a MB event (i.e., had a bleed diagnosis in the secondary position and the bleeding was for a non-critical site) or an ambulatory care visit for non-critical bleeding.

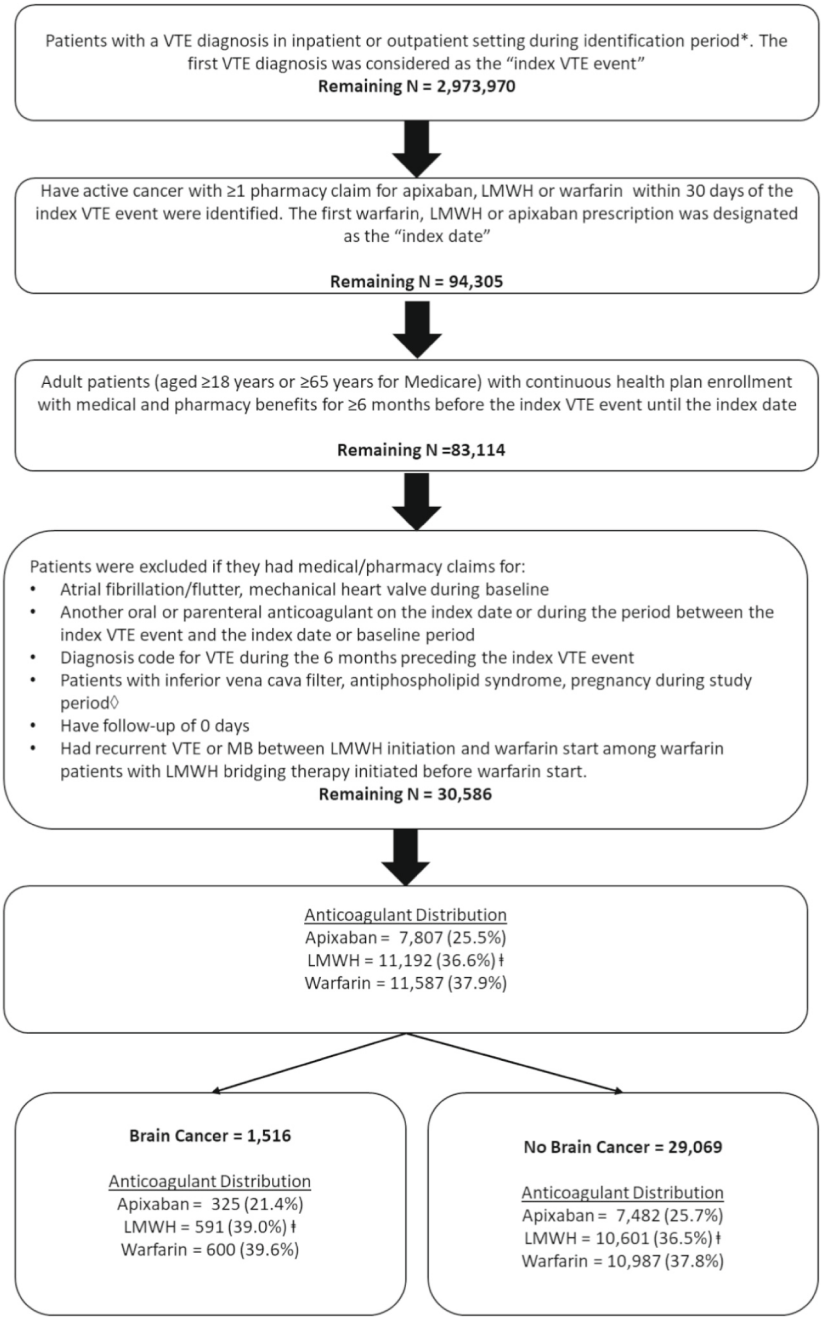
2.5. Analysis

To reduce the potential for confounding, inverse probability of treatment weights (IPTW) using stabilized weights was used to balance patient characteristics across treatment cohorts. Weights were generated as the inverse of the propensity score generated by a multinomial logistic model for the probability of receiving treatment (LMWH, apixaban or warfarin) with LMWH as the reference. Stabilized weights reduce variability in the treatment weights caused by outliers. Patient characteristics with absolute standardized differences (STD) <10 % were considered balanced. After IPTW, Cox proportional hazard models were used to compare the risk of recurrent VTE, MB and CRNMB for apixaban vs. LMWH, warfarin vs. LMWH and apixaban vs. warfarin in patients with all cancer types. Incidence rates (IR) were generated and presented per 100 person-years. Patients were then stratified by the presence of brain cancer or other cancer. Brain cancer was identified by the presence of an ICD-9 or ICD-10 diagnosis code indicating primary brain cancer in the 6-months prior to index through 30-days post index (Supplemental Table 1). The distribution of brain cancer types (not mutually exclusive) is in Supplemental Table 2. Interaction analyses using Cox proportional hazard models were conducted to evaluate whether treatment effects were different for patients with brain vs. other cancer. Models were adjusted for observed unbalanced patient characteristics after IPTW in the overall cancer patients and after stratifying by brain cancer status. Interactions with p-value <0.1 were considered statistically significant.

3. Results

3.1. Patient characteristics and outcomes in overall cancer patients

A total of 30,586 VTE patients with active cancer met all eligibility criteria and were included in this analysis. Among these patients, 25 % were treated with apixaban, 37 % with LMWH, and 38 % with warfarin within 30 days after the index VTE event (Fig. 1). After IPTW, patient characteristics were mostly balanced between treatment cohorts (Table 1). Patient characteristics before IPTW can be found in the



VTE: Venous thromboembolism

LMWH: Low molecular weight heparin

*Identification period across databases were as follows:

MarketScan: September 1, 2014-June 30, 2017

Optum and Humana: September 1, 2014-December 31, 2017

PharMetrics: September 1, 2014-March 31, 2018

Medicare: September 1, 2014-December 31, 2017

◊ Study period across databases were as follows:

MarketScan: March 1, 2014-June 30, 2017

Optum and Humana: March 1, 2014-December 31, 2017

PharMetrics: March 1, 2014-March 31, 2018

Medicare: March 1, 2014-December 31, 2017

ǂ LMWH is generally enoxaparin (98% of cohort)

Fig. 1. Patient selection criteria.

Table 1
Patient characteristics for all included VTE cancer patients treated with apixaban, LMWH and warfarin (Post-IPTW).[a]

Characteristic	Apixaban	LMWH	Warfarin	Apixaban vs LMWH	Apixaban vs warfarin	LMWH vs warfarin
	N = 7807	N = 11,192	N = 11,587	STD	STD	STD
Age in years, mean (sd)	71.8 (11.2)	68.5 (12.8)	72.0 (11.1)	27.38	2.33	29.61
18–54	574 (7.4 %)	1402 (12.5 %)	805 (6.9 %)	17.36	1.59	18.92
55–64	1011 (13.0 %)	2190 (19.6 %)	1271 (11.0 %)	18.00	6.12	24.09
65–74	3033 (38.9 %)	3826 (34.2 %)	4649 (40.1 %)	9.71	2.60	12.32
75–79	1390 (17.8 %)	1596 (14.3 %)	2093 (18.1 %)	9.67	0.69	10.36
≥80	1799 (23.0 %)	2178 (19.5 %)	2769 (23.9 %)	8.76	2.03	10.79
Gender						
Male	3541 (45.4 %)	5045 (45.1 %)	5262 (45.4 %)	0.57	0.11	0.68
Female	4266 (54.6 %)	6147 (54.9 %)	6325 (54.6 %)	0.57	0.11	0.68
Geographic region						
Northeast	1567 (20.1 %)	2265 (20.2 %)	2271 (19.6 %)	0.42	1.19	1.60
South	2898 (37.1 %)	4060 (36.3 %)	4247 (36.7 %)	1.73	0.95	0.78
Midwest	2020 (25.9 %)	2914 (26.0 %)	3087 (26.6 %)	0.37	1.75	1.37
West	1315 (16.8 %)	1938 (17.3 %)	1969 (17.0 %)	1.25	0.40	0.85
Other	8 (0.1 %)	15 (0.1 %)	13 (0.1 %)	0.97	0.32	0.65
Setting of index VTE event						
Inpatient	4186 (53.6 %)	5964 (53.3 %)	6328 (54.6 %)	0.66	2.00	2.66
Outpatient[b]	3621 (46.4 %)	5228 (46.7 %)	5259 (45.4 %)	0.66	2.00	2.66
ER	3163 (40.5 %)	4481 (40.0 %)	4591 (39.6 %)	0.96	1.81	0.85
Position of VTE diagnosis						
Primary	5319 (68.1 %)	6897 (61.6 %)	7859 (67.8 %)	13.67	0.65	13.01
Secondary	2488 (31.9 %)	4295 (38.4 %)	3728 (32.2 %)	13.67	0.65	13.01
VTE diagnosis						
DVT only	4314 (55.3 %)	6323 (56.5 %)	6303 (54.4 %)	2.50	1.73	4.23
PE with DVT	946 (12.1 %)	1242 (11.1 %)	1431 (12.4 %)	3.16	0.74	3.90
PE without DVT	2548 (32.6 %)	3627 (32.4 %)	3853 (33.3 %)	0.49	1.32	1.81
Provoked factors[c]	5019 (64.3 %)	7058 (63.1 %)	7419 (64.0 %)	2.55	0.54	2.01
NCI comorbidity index, mean (sd)	3.1 (2.6)	2.9 (2.6)	3.1 (2.7)	6.82	0.59	7.38
Baseline comorbidity						
Anemia	3880 (49.7 %)	5523 (49.4 %)	5761 (49.7 %)	0.69	0.04	0.74
Central venous catheter	1819 (23.3 %)	2812 (25.1 %)	2566 (22.1 %)	4.27	2.74	7.02
Cerebrovascular disease	1078 (13.8 %)	1482 (13.2 %)	1763 (15.2 %)	1.66	4.01	5.67
Hematologic disorders	1266 (16.2 %)	1739 (15.5 %)	1787 (15.4 %)	1.87	2.18	0.30
Thrombocytopenia	990 (12.7 %)	1437 (12.8 %)	1285 (11.1 %)	0.48	4.92	5.40
Ischemic heart/coronary artery disease	2139 (27.4 %)	2765 (24.7 %)	3231 (27.9 %)	6.15	1.08	7.23
Dyspepsia	2767 (35.4 %)	3973 (35.5 %)	3992 (34.4 %)	0.13	2.07	2.20
Hyperlipidemia	4097 (52.5 %)	5303 (47.4 %)	6201 (53.5 %)	10.21	2.07	12.29
Obesity	1418 (18.2 %)	2051 (18.3 %)	2131 (18.4 %)	0.41	0.59	0.18
Pneumonia	1479 (18.9 %)	2081 (18.6 %)	2182 (18.8 %)	0.88	0.27	0.61
Sleep apnea	865 (11.1 %)	1196 (10.7 %)	1298 (11.2 %)	1.27	0.39	1.66
Thrombophilia	477 (6.1 %)	627 (5.6 %)	695 (6.0 %)	2.19	0.51	1.68
Congestive heart failure	1227 (15.7 %)	1489 (13.3 %)	1908 (16.5 %)	6.85	2.03	8.88
Diabetes	2440 (31.2 %)	3395 (30.3 %)	3862 (33.3 %)	1.97	4.45	6.43
Hypertension	5798 (74.3 %)	7772 (69.4 %)	8638 (74.5 %)	10.75	0.63	11.38
Renal disease	2492 (31.9 %)	2800 (25.0 %)	3566 (30.8 %)	15.32	2.46	12.86
Liver disease	1499 (19.2 %)	2817 (25.2 %)	1957 (16.9 %)	14.40	6.03	20.43
COPD	2066 (26.5 %)	2450 (21.9 %)	3134 (27.0 %)	10.70	1.33	12.03
Peripheral vascular disease	1662 (21.3 %)	2202 (19.7 %)	2573 (22.2 %)	4.02	2.22	6.23
Baseline any bleed	2723 (34.9 %)	3934 (35.1 %)	4051 (35.0 %)	0.57	0.18	0.38
Recent history of falls	479 (6.1 %)	664 (5.9 %)	705 (6.1 %)	0.85	0.22	0.64
Fracture/trauma	758 (9.7 %)	1027 (9.2 %)	1112 (9.6 %)	1.84	0.40	1.44
Selected surgeries	3368 (43.1 %)	5055 (45.2 %)	4712 (40.7 %)	4.09	5.00	9.10
Baseline medication use						
Antiarrhythmic	1461 (18.7 %)	2262 (20.2 %)	2070 (17.9 %)	3.78	2.20	5.98
Statins	3067 (39.3 %)	4025 (36.0 %)	4630 (40.0 %)	6.86	1.38	8.24
Anti-platelets	527 (6.8 %)	686 (6.1 %)	815 (7.0 %)	2.55	1.09	3.64
Aromatase inhibitors	440 (5.6 %)	596 (5.3 %)	658 (5.7 %)	1.35	0.16	1.52
Beta blockers	2712 (34.7 %)	3612 (32.3 %)	4112 (35.5 %)	5.22	1.57	6.79
Gastroprotective agents	2825 (36.2 %)	3941 (35.2 %)	4180 (36.1 %)	2.05	0.24	1.81
NSAIDs	1596 (20.4 %)	2406 (21.5 %)	2330 (20.1 %)	2.58	0.84	3.42
Cancer metastasis[d]	3760 (48.2 %)	5637 (50.4 %)	5502 (47.5 %)	4.40	1.36	5.76
Cancer type[d]						
Hematological	1278 (16.4 %)	1924 (17.2 %)	1906 (16.5 %)	2.20	0.22	1.98
Non-hematological	6529 (83.6 %)	9268 (82.8 %)	9681 (83.5 %)	2.20	0.22	1.98
Khorana risk scale						
Very high risk	1091 (14.0 %)	1593 (14.2 %)	1569 (13.5 %)	0.75	1.25	1.99
High risk	3177 (40.7 %)	4695 (41.9 %)	4815 (41.6 %)	2.54	1.73	0.80
Other	3539 (45.3 %)	4904 (43.8 %)	5203 (44.9 %)	3.03	0.85	2.19
Cancer-related treatment[d]						
Cancer related treatment	5020 (64.3 %)	7869 (70.3 %)	7479 (64.6 %)	12.82	0.51	12.31
Chemotherapy	3592 (46.0 %)	5836 (52.1 %)	5205 (44.9 %)	12.30	2.20	14.50
Hormone therapy	493 (6.3 %)	704 (6.3 %)	745 (6.4 %)	0.12	0.44	0.56
Immunotherapy	91 (1.2 %)	169 (1.5 %)	145 (1.2 %)	3.01	0.77	2.24

(continued on next page)

Table 1 (*continued*)

Characteristic	Apixaban	LMWH	Warfarin	Apixaban vs LMWH	Apixaban vs warfarin	LMWH vs warfarin
	N = 7807	N = 11,192	N = 11,587	STD	STD	STD
Radiation	2515 (32.2 %)	3875 (34.6 %)	3812 (32.9 %)	5.11	1.46	3.65
Surgery	692 (8.9 %)	1186 (10.6 %)	1051 (9.1 %)	5.88	0.73	5.15

[a] Due to IPTW, totals of subgroups may be higher or lower by 1.
[b] Defined as a VTE that is preceded by hormone therapy, fracture/trauma involving lower extremities, pelvic/orthopedic surgery, or hospitalization for any reason for ≥3 days during 3 months prior to VTE.
[c] Includes ER visits.
[d] Measured in the 6-months prior VTE through 30-days after VTE.

Supplemental Table 3. Compared to LMWH, apixaban was associated with lower risk of recurrent VTE (HR: 0.66; 95 % CI: 0.53–0.83), MB (HR: 0.68; 95 % CI: 0.56–0.83), and CRNMB (HR: 0.74; 95 % CI: 0.66–0.83); (Fig. 2). Compared to warfarin, apixaban was associated with lower risk of recurrent VTE (HR: 0.76; 95 % CI: 0.61–0.94), MB (HR: 0.82; 95 % CI: 0.68–0.99), and CRNMB (HR: 0.85; 95 % CI: 0.77–0.94); (Fig. 3). Warfarin (vs LMWH) had a similar risk of recurrent VTE (HR: 0.95; 95 % CI: 0.77–1.17) and a significantly lower risk of MB (HR: 0.84; 95 % CI: 0.72–0.99) and CRNMB (HR: 0.88; 95 % CI: 0.79–0.98); (Fig. 4).

3.2. Patient characteristics by brain cancer status

Of the 30,586 patients in this analysis, 5 % had brain cancer (21.4 % apixaban, 39.0 % LMWH, 39.6 % warfarin) and 95 % had other cancer type (25.7 % apixaban, 36.5 % LMWH, 37.8 % warfarin) which included multiple myeloma, leukemia and breast cancer (Fig. 1 and Supplemental Table 4). Post IPTW, mean age tended to be lower for brain cancer patients (63–68 years across medication groups) compared to other cancer patients (69–72 years); (Table 2). Patients with brain cancer and other cancer had similar common comorbidities (mean NCI comorbidity index scores ranged from 2.7 to 3.4) and the presence of each comorbidity was generally similar across treatment cohorts by brain cancer status (Table 2). Baseline medication use tended to be lower for brain cancer patients compared to other cancer patients except for gastroprotective agents. In contrast, cancer-related chemotherapy, radiation, and surgery were more common in the brain cancer patient group compared to non-brain cancer.

3.3. Evaluation of outcomes by brain cancer status

3.3.1. Apixaban vs LMWH

As represented in Fig. 2, effects of apixaban vs LMWH were consistent regardless of brain cancer status. Among brain cancer patients, numerically lower incidence rates were observed for apixaban vs. LMWH for recurrent VTE (5.80 vs 19.77; HR: 0.32; 95 % CI: 0.09–1.09), MB (9.76 vs 22.46; HR: 0.32; 95 % CI: 0.13–0.79), and CRNMB (26.62 vs 44.87; HR: 0.58; 95 % CI: 0.33–1.04). Likewise, among other cancer patients, incidence rates were numerically lower for apixaban (vs LMWH) patients for recurrent VTE (7.66 vs 14.76; HR: 0.70; 95 % CI:

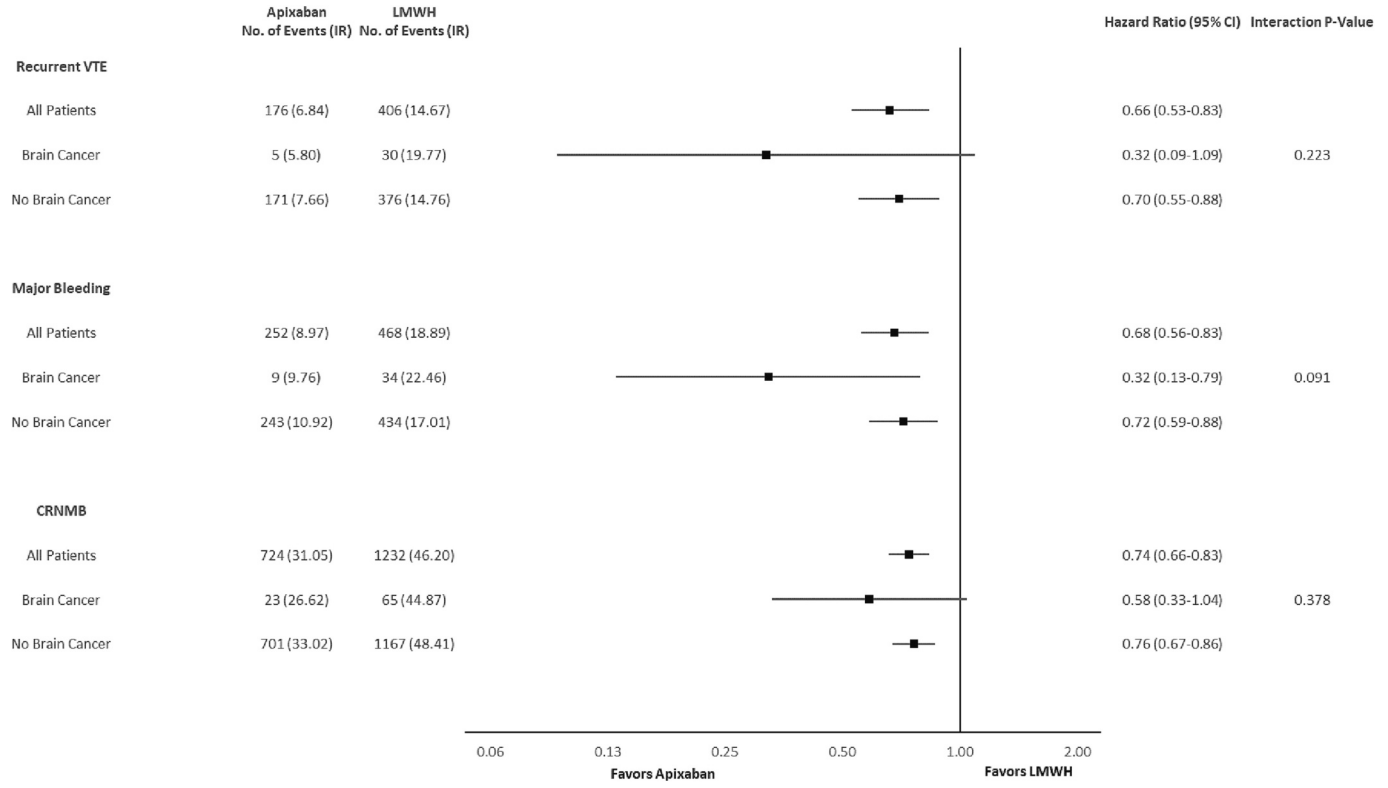


Fig. 2. Apixaban compared to LMWH.*
*Due to IPTW, the sum of events in the brain cancer and non-brain cohorts may be off by a factor of 1 from the reported all patients total. Hazard Ratio was adjusted for unbalanced patient characteristics after IPTW or after stratified by brain cancer status.
Abbreviations: CI, confidence interval; CRNMB, clinically significant non-major bleeding; IR: incidence rate; VTE, venous thromboembolism.

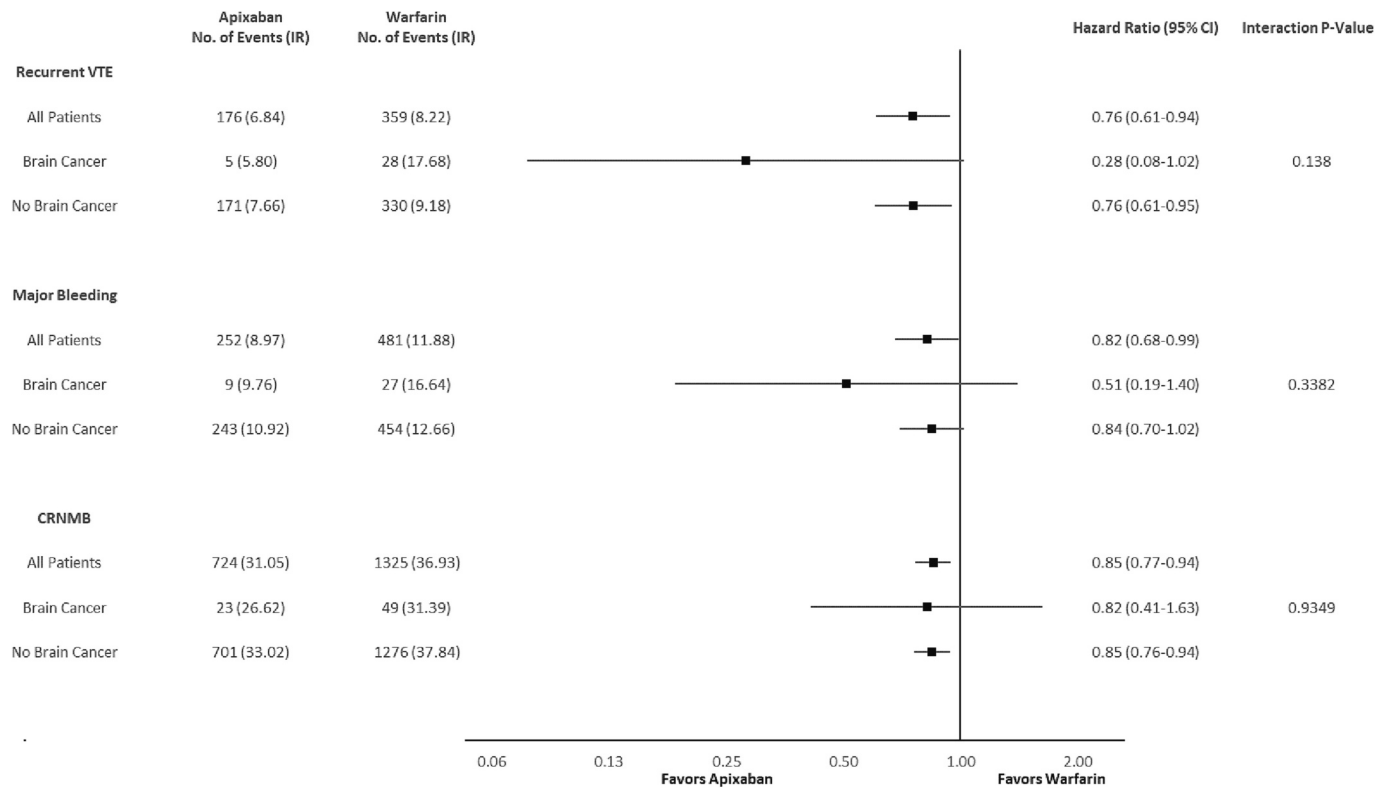


Fig. 3. Apixaban compared to warfarin.*
*Due to IPTW, the sum of events in the brain cancer and non-brain cohorts may be off by a factor of 1 from the reported all patients total. Hazard Ratio was adjusted for unbalanced patient characteristics after IPTW or after stratified by brain cancer status. Abbreviations: CI, confidence interval; CRNMB, clinically significant non-major bleeding; VTE, venous thromboembolism.

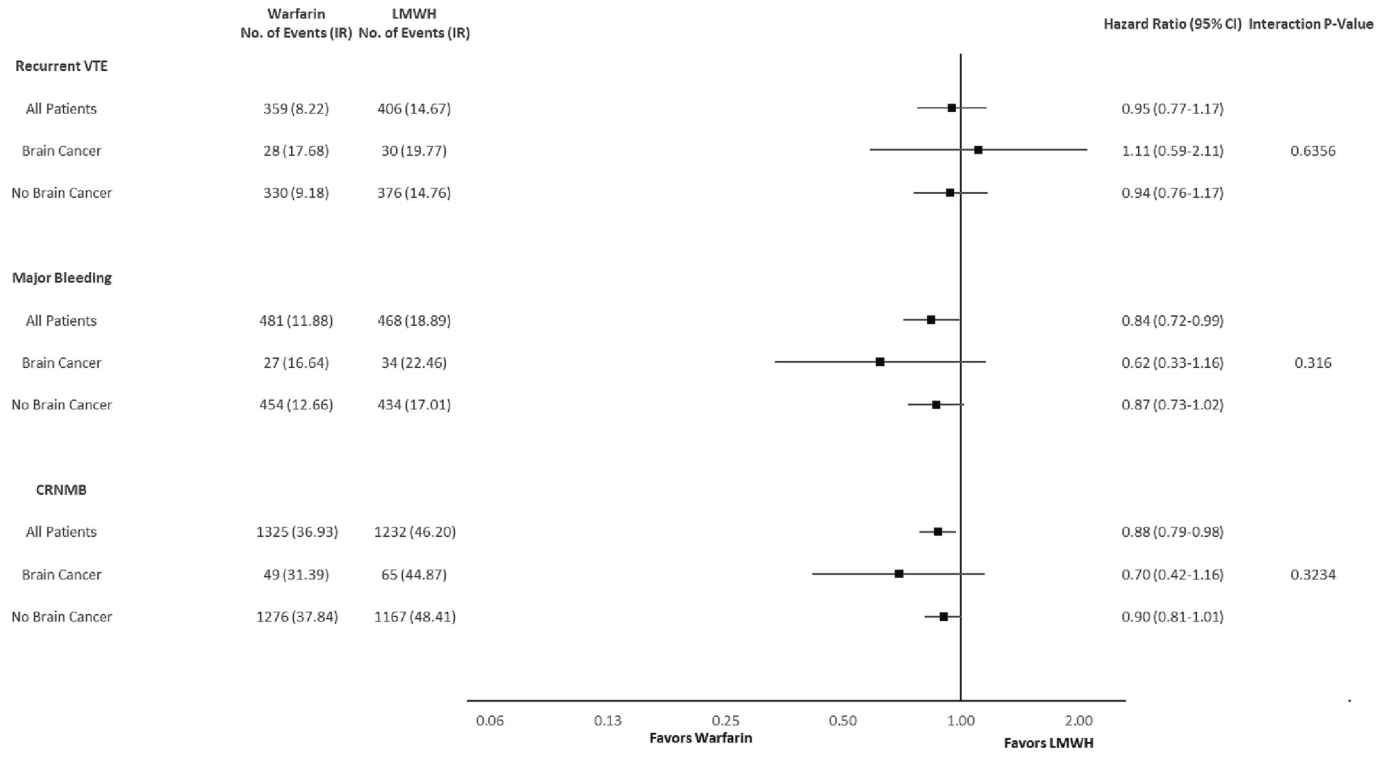


Fig. 4. Warfarin compared to LMWH.*
*Due to IPTW, the sum of events in the brain cancer and non-brain cohorts may be off by a factor of 1 from the reported all patients total. Hazard Ratio was adjusted for unbalanced patients characteristics after IPTW or after stratified by brain cancer status.

Table 2
Post-IPTW patient characteristics by brain cancer status.[a]

Characteristic	Brain cancer (N = 1516)			No brain cancer (N = 29,069)		
	Apixaban	LMWH	Warfarin	Apixaban	LMWH	Warfarin
	N = 325	N = 591	N = 600	N = 7482	N = 10,601	N = 10,987
Age (years), mean (sd)	67.8 (12.3)	62.9 (11.3)	66.2 (16.1)	71.9 (11.1)	68.8 (12.8)	72.3 (10.8)
18–54	31 (9.6 %)	139 (23.6 %)	103 (17.2 %)	543 (7.3 %)	1263 (11.9 %)	701 (6.4 %)
55–64	76 (23.2 %)	162 (27.4 %)	103 (17.1 %)	936 (12.5 %)	2029 (19.1 %)	1168 (10.6 %)
65–74	138 (42.6 %)	183 (30.9 %)	241 (40.1 %)	2895 (38.7 %)	3643 (34.4 %)	4408 (40.1 %)
75–79	58 (17.8 %)	53 (9.0 %)	93 (15.6 %)	1332 (17.8 %)	1543 (14.6 %)	2000 (18.2 %)
≥80	22 (6.9 %)	54 (9.2 %)	60 (10.0 %)	1776 (23.7 %)	2124 (20.0 %)	2709 (24.7 %)
Gender						
Male	138 (42.4 %)	330 (55.9 %)	274 (45.7 %)	3404 (45.5 %)	4715 (44.5 %)	4988 (45.4 %)
Female	188 (57.6 %)	260 (44.1 %)	326 (54.3 %)	4078 (54.5 %)	5886 (55.5 %)	5999 (54.6 %)
Geographic region						
Northeast	68 (20.8 %)	131 (22.1 %)	102 (17.1 %)	1500 (20.0 %)	2135 (20.1 %)	2169 (19.7 %)
South	98 (30.1 %)	209 (35.3 %)	231 (38.4 %)	2800 (37.4 %)	3852 (36.3 %)	4017 (36.6 %)
Midwest	76 (23.3 %)	152 (25.7 %)	172 (28.7 %)	1944 (26.0 %)	2762 (26.1 %)	2915 (26.5 %)
West	84 (25.9 %)	98 (16.6 %)	94 (15.7 %)	1231 (16.4 %)	1839 (17.4 %)	1875 (17.1 %)
Other	0 (0.0 %)	1 (0.2 %)	1 (0.2 %)	8 (0.1 %)	13 (0.1 %)	12 (0.1 %)
Index VTE setting						
Inpatient	155 (47.7 %)	284 (48.1 %)	306 (50.9 %)	4030 (53.9 %)	5679 (53.6 %)	6022 (54.8 %)
Outpatient	170 (52.3 %)	306 (51.9 %)	294 (49.1 %)	3451 (46.1 %)	4922 (46.4 %)	4965 (45.2 %)
ER	159 (48.7 %)	287 (48.6 %)	278 (46.4 %)	3004 (40.2 %)	4194 (39.6 %)	4313 (39.3 %)
Position of VTE diagnosis						
Primary	212 (65.2 %)	418 (70.8 %)	418 (69.7 %)	5107 (68.3 %)	6479 (61.1 %)	7441 (67.7 %)
Secondary	113 (34.8 %)	173 (29.2 %)	182 (30.3 %)	2375 (31.7 %)	4123 (38.9 %)	3546 (32.3 %)
VTE diagnosis						
DVT only	199 (61.0 %)	328 (55.6 %)	322 (53.6 %)	4115 (55.0 %)	5995 (56.6 %)	5981 (54.4 %)
PE with DVT	29 (8.8 %)	81 (13.7 %)	80 (13.3 %)	917 (12.3 %)	1161 (11.0 %)	1352 (12.3 %)
PE without DVT	98 (30.1 %)	182 (30.8 %)	199 (33.1 %)	2450 (32.7 %)	3445 (32.5 %)	3654 (33.3 %)
Provoked factors[b]	261 (80.2 %)	433 (73.3 %)	458 (76.4 %)	4758 (63.6 %)	6624 (62.5 %)	6961 (63.4 %)
NCI comorbidity index	3.4 (3.3)	2.7 (2.0)	3.1 (3.0)	3.1 (2.6)	3.0 (2.7)	3.1 (2.6)
Baseline comorbidity						
Anemia	165 (50.8 %)	200 (33.8 %)	259 (43.1 %)	3715 (49.7 %)	5324 (50.2 %)	5502 (50.1 %)
Central venous catheter	80 (24.5 %)	97 (16.4 %)	142 (23.7 %)	1739 (23.2 %)	2716 (25.6 %)	2424 (22.1 %)
Cerebrovascular disease	156 (48.0 %)	241 (40.8 %)	270 (45.1 %)	922 (12.3 %)	1241 (11.7 %)	1493 (13.6 %)
Hematologic disorders	99 (30.4 %)	119 (20.2 %)	105 (17.5 %)	1167 (15.6 %)	1619 (15.3 %)	1683 (15.3 %)
Thrombocytopenia	81 (24.9 %)	110 (18.6 %)	86 (14.3 %)	909 (12.2 %)	1328 (12.5 %)	1199 (10.9 %)
Ischemic heart/coronary artery disease	57 (17.7 %)	96 (16.3 %)	108 (18.0 %)	2082 (27.8 %)	2669 (25.2 %)	3123 (28.4 %)
Dyspepsia	87 (26.9 %)	130 (22.0 %)	164 (27.3 %)	2679 (35.8 %)	3843 (36.2 %)	3828 (34.8 %)
Hemiplegia or paraplegia	81 (24.7 %)	139 (23.5 %)	119 (19.8 %)	111 (1.5 %)	148 (1.4 %)	213 (1.9 %)
Hyperlipidemia	153 (47.1 %)	246 (41.6 %)	302 (50.3 %)	3944 (52.7 %)	5057 (47.7 %)	5899 (53.7 %)
Obesity	39 (11.9 %)	102 (17.2 %)	110 (18.3 %)	1379 (18.4 %)	1949 (18.4 %)	2022 (18.4 %)
Pneumonia	81 (24.9 %)	99 (16.8 %)	112 (18.6 %)	1398 (18.7 %)	1982 (18.7 %)	2070 (18.8 %)
Sleep apnea	37 (11.4 %)	52 (8.8 %)	61 (10.2 %)	828 (11.1 %)	1143 (10.8 %)	1236 (11.3 %)
Thrombophilia	23 (7.0 %)	39 (6.6 %)	22 (3.6 %)	455 (6.1 %)	588 (5.5 %)	673 (6.1 %)
Congestive heart failure	20 (6.1 %)	65 (11.0 %)	57 (9.5 %)	1207 (16.1 %)	1425 (13.4 %)	1851 (16.8 %)
Diabetes	77 (23.6 %)	122 (20.7 %)	165 (27.5 %)	2363 (31.6 %)	3273 (30.9 %)	3697 (33.6 %)
Hypertension	236 (72.5 %)	375 (63.6 %)	427 (71.2 %)	5563 (74.3 %)	7397 (69.8 %)	8210 (74.7 %)
Renal disease	72 (22.2 %)	91 (15.4 %)	103 (17.1 %)	2419 (32.3 %)	2709 (25.6 %)	3463 (31.5 %)
Liver disease	72 (22.3 %)	92 (15.5 %)	126 (21.1 %)	1427 (19.1 %)	2725 (25.7 %)	1830 (16.7 %)
COPD	91 (28.0 %)	98 (16.5 %)	142 (23.6 %)	1975 (26.4 %)	2352 (22.2 %)	2992 (27.2 %)
Peripheral vascular disease	65 (19.9 %)	71 (12.1 %)	90 (15.0 %)	1598 (21.4 %)	2130 (20.1 %)	2483 (22.6 %)
Baseline any bleed	151 (46.4 %)	209 (35.4 %)	290 (48.3 %)	2572 (34.4 %)	3725 (35.1 %)	3761 (34.2 %)
Recent history of falls	26 (8.1 %)	50 (8.5 %)	52 (8.7 %)	453 (6.1 %)	614 (5.8 %)	653 (5.9 %)
Fracture/trauma	25 (7.7 %)	51 (8.6 %)	31 (5.2 %)	734 (9.8 %)	976 (9.2 %)	1081 (9.8 %)
Selected surgeries	240 (73.9 %)	377 (63.7 %)	432 (72.0 %)	3127 (41.8 %)	4679 (44.1 %)	4280 (39.0 %)
Baseline medication use						
Antiarrhythmic	62 (18.9 %)	81 (13.8 %)	81 (13.6 %)	1400 (18.7 %)	2181 (20.6 %)	1989 (18.1 %)
Statins	118 (36.2 %)	177 (29.9 %)	206 (34.4 %)	2949 (39.4 %)	3848 (36.3 %)	4423 (40.3 %)
Beta blockers	89 (27.3 %)	129 (21.9 %)	155 (25.8 %)	2623 (35.1 %)	3482 (32.8 %)	3956 (36.0 %)
Gastroprotective agents	137 (42.1 %)	254 (43.0 %)	289 (48.2 %)	2689 (35.9 %)	3687 (34.8 %)	3891 (35.4 %)
NSAIDs	56 (17.3 %)	115 (19.5 %)	79 (13.2 %)	1540 (20.6 %)	2290 (21.6 %)	2251 (20.5 %)
Cancer metastasis[c]	217 (66.7 %)	270 (45.7 %)	405 (67.6 %)	3543 (47.4 %)	5367 (50.6 %)	5097 (46.4 %)
Cancer type[c]						
Hematological	41 (12.7 %)	45 (7.6 %)	64 (10.7 %)	1237 (16.5 %)	1879 (17.7 %)	1842 (16.8 %)
Non-hematological	284 (87.3 %)	546 (92.4 %)	536 (89.3 %)	6245 (83.5 %)	8722 (82.3 %)	9145 (83.2 %)
Khorana risk scale						
Very high risk	289 (88.9 %)	535 (90.6 %)	542 (90.3 %)	802 (10.7 %)	1058 (10.0 %)	1027 (9.4 %)
High risk	20 (6.1 %)	46 (7.7 %)	34 (5.7 %)	3158 (42.2 %)	4649 (43.9 %)	4780 (43.5 %)
Other	16 (5.0 %)	10 (1.7 %)	24 (3.9 %)	3522 (47.1 %)	4894 (46.2 %)	5179 (47.1 %)
Cancer-related treatment[c]						
Cancer treatment	307 (94.3 %)	543 (91.9 %)	539 (89.8 %)	4714 (63.0 %)	7326 (69.1 %)	6941 (63.2 %)
Chemotherapy	198 (60.9 %)	363 (61.4 %)	317 (52.9 %)	3394 (45.4 %)	5473 (51.6 %)	4887 (44.5 %)
Hormone therapy	9 (2.8 %)	9 (1.5 %)	14 (2.4 %)	484 (6.5 %)	695 (6.6 %)	730 (6.6 %)

(*continued on next page*)

Table 2 (*continued*)

Characteristic	Brain cancer ($N = 1516$)			No brain cancer ($N = 29,069$)		
	Apixaban	LMWH	Warfarin	Apixaban	LMWH	Warfarin
	$N = 325$	$N = 591$	$N = 600$	$N = 7482$	$N = 10,601$	N = 10,987
Immunotherapy	15 (4.7 %)	14 (2.4 %)	24 (3.9 %)	76 (1.0 %)	155 (1.5 %)	121 (1.1 %)
Radiation	269 (82.8 %)	464 (78.5 %)	490 (81.7 %)	2245 (30.0 %)	3411 (32.2 %)	3322 (30.2 %)
Cancer-related surgery	148 (45.5 %)	236 (39.9 %)	281 (46.9 %)	544 (7.3 %)	951 (9.0 %)	769 (7.0 %)

[a] Due to rounding from IPTW, patient counts and proportions may be off slightly.
[b] Defined as a VTE that is preceded by hormone therapy, fracture/trauma involving lower extremities, pelvic/orthopedic surgery, or hospitalization for any reason for ≥3 days during 3 months prior to VTE.
[c] Measured in the 6-months prior VTE through 30-days after VTE.

0.55–0.88), MB (10.92 vs 17.01; HR: 0.72; 95 % CI: 0.59–0.88), and CRNMB (33.02 vs 48.41; HR: 0.76; 95 % CI: 0.67–0.86). There were no significant interactions between treatment (apixaban vs. LMWH) and brain cancer status on recurrent VTE and CRNMB (Fig. 2, *p*-value for interactions >0.1). A significant interaction was observed for MB (Fig. 2, p's value for interaction = 0.091). Although apixaban was consistently associated with a lower risk of MB vs. LMWH for all patients regardless of brain cancer status, a higher reduction was observed among those with brain cancer (HR = 0.32) than those with (HR = 0.72) other cancer.

3.3.2. Apixaban vs warfarin

Similarly, as represented in Fig. 3, effects of apixaban vs. warfarin on recurrent VTE, MB and CRNMB were not significantly different between patients with brain cancer and patients with other cancer (*p*-value for interactions >0.1). Incidence rates were numerically lower for apixaban patients (vs warfarin) among those with brain cancer for recurrent VTE (5.80 vs 17.68; HR: 0.28; 95 % CI: 0.08–1.02), MB (9.76 vs 16.64; HR: 0.51; 95 % CI: 0.19–1.40), and CRNMB (26.62 vs 31.39; HR: 0.82; 95 % CI: 0.41–1.63). Likewise, the incidence rates were numerically lower for apixaban patients (vs warfarin) among those with other cancer for recurrent VTE (7.66 vs 9.18; HR: 0.76; 95 % CI: 0.61–0.95), MB (10.92 vs 12.66; HR: 0.84; 95 % CI: 0.70–1.02), and CRNMB (33.02 vs 37.84; HR: 0.85; 95 % CI: 0.76–0.94).

3.3.3. Warfarin vs LMWH

As represented in Fig. 4, effects of warfarin vs. LMWH on recurrent VTE, MB and CRNMB were not significantly different between patients with brain cancer and patients with other cancer (*p*-value for interactions >0.1). For recurrent VTE, the HR for warfarin vs. LMWH after adjustment for unbalanced observed patient characteristics was close to 1 for patients with brain cancer (17.68 vs 19.77; HR: 1.11; 95%CI: 0.59–2.11) and patients without brain cancer (9.18 vs 14.76; HR: 0.94; 95 % CI: 0.76–1.17). For MB and CRNMB, incidence rates were numerically lower for warfarin vs. LMWH for patients with brain cancer: MB (16.64 vs 22.46; HR: 0.62; 95 % CI: 0.33–1.16), and CRNMB (31.39 vs 44.87; HR: 0.70; 95 % CI: 0.42–1.16). Likewise, the incidence rates were numerically lower for warfarin patients (vs LMWH) among those with other cancer for MB (12.66 vs 17.01; HR: 0.87; 95 % CI: 0.73–1.02), and CRNMB (37.84 vs 48.41; HR: 0.90; 95 % CI: 0.81–1.01).

4. Discussion

The present study evaluated the risk of recurrent VTE, MB, and CRNMB among VTE patients with active cancer who initiated apixaban, LMWH, or warfarin stratified by the presence of brain vs. other cancer. In VTE patients with all types of cancer, apixaban was associated with lower risk of recurrent VTE, MB, and CRNMB compared to LMWH and warfarin, and warfarin had similar risk of recurrent VTE and a lower risk of MB and CRNMB than LMWH. When stratified by brain cancer status, treatment effects were generally consistent between patients with brain cancer and patients with other cancer and consistent with the overall population.

The findings from this study add to a growing body of research demonstrating the efficacy/effectiveness and safety of DOACs such as apixaban in VTE patients with cancer [25,31,34]. By using four commercial and Medicare databases, this study included a larger starting sample size and allowed for opportunities to evaluate specific tumor types such as brain cancer [34]. The study results related to the comparison of apixaban to LMWH for overall cancer patients were generally consistent with previous studies [25,31,34].

There has historically been a lack of evidence regarding the efficacy/effectiveness and safety of apixaban in VTE patients with brain cancer. For example, CARAVAGGIO, the largest randomized clinical trial that has examined the efficacy and safety of apixaban relative to dalteparin (LMWH) in VTE patients with cancer excluded individuals with brain cancer [31]. The current study helps to address this evidence gap. When stratified by brain vs. other cancer, in general no significant interactions were observed between treatments (apixaban vs. LMWH, warfarin vs. LMWH, and warfarin vs. LMWH) and brain cancer status on the outcomes of recurrent VTE, MB, and CRNMB. These findings suggest that the treatment effects of apixaban, LMWH, and warfarin in VTE patients with brain cancer were generally consistent with the treatment effects in those with other cancer types. These data provide some initial evidence to inform the effectiveness and safety of apixaban in VTE patients with brain cancer.

4.1. Limitations

The present analysis should be reviewed within the context of several limitations associated with retrospective claims analyses. First, only associations and not causation can be inferred from this study. Second, residual confounding may be present, even though IPTW was used to balance patient characteristics between treatment cohorts in overall cancer patients and further adjusted for variables that became unbalanced after stratifying by brain cancer status. Third, there may be unmeasured confounding as we do not have information on some factors that may impact treatment outcomes such as cancer stage, whether the tumor was primary resected, over-the-counter medication use, and lab values. Fourth, the commercial databases do not have complete death information for the patients, and consequently, mortality and fatal recurrent VTE in patients with brain or other cancer were not assessed. Mortality may be a competing risk in both patient populations. Fifth, there were differences between cancer cohorts that could have impacted study findings, including a small sample size for the brain cancer cohort and variable types of cancer represented in the other cancer cohort. Sixth, our algorithm to identify active cancer was based on diagnosis codes and prescription claims, not clinical assessment. Although we have tried to ensure that the diagnosis and cancer treatment were close to index VTE event (≤6 months) and included two diagnoses at least 1 month apart to avoid regular follow-up, there may be misclassification of active cancer vs. history of cancer. Seventh, misclassifications of exposures and outcomes may also be possible as the databases in this analysis are designed for billing rather than diagnostic purposes. Coding errors and missing data may exist, which could contribute to underreporting of outcomes. Specifically, the algorithm used to determine CRNMB events (including ICD-9 and ICD-10 diagnosis codes) has not

been validated; however, this algorithm does follow the suggested definition by the International Society on Thrombosis and Hematology (ISTH) as closely as possible [35]. Moreover, the presence of a diagnosis code on a medical claim may not indicate a positive presence of recurrent VTE or any disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. Eighth, this study used data from 2014 to 2018 when main international clinical guidelines recommended LMWH as the treatment of choice in cancer-associated thrombosis. Patients receiving warfarin during that time were against clinical guidelines [36,37]. They constituted a special group of patients and findings related to warfarin comparison should be interpreted with caution. Finally, the results reported here may not apply to the entire US VTE population with brain cancer as uninsured patients, Medicaid enrollees, and patients within the Veterans Affairs health system were not included. Additionally, the data were from US databases and may not generalize to non-US populations.

5. Conclusions

Among VTE patients with active cancer, apixaban (vs LMWH and warfarin) was associated with a lower risk of recurrent VTE, MB, and CRNMB. Warfarin (vs LMWH) was associated with similar risk of recurrent VTE and a lower risk of MB and CRNMB. Analyses stratified by brain vs. other cancer generally showed no significant difference in the treatment effects between those with brain cancer and those with other cancer. More research is needed to discern the most effective and safe anticoagulant treatment in VTE patients with brain cancer.

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Declaration of competing interest

AC received research support from Pfizer Inc. and Bristol-Myers Squibb Company. VN, RB and SS were paid employees of STATinMED at the time of the study; STATinMED is a paid consultant to Pfizer, Inc. and Bristol-Myers Squibb Company in connection with the development of this manuscript. AD is a paid employee of Bristol-Myers Squibb Company. DMH, TA, and XL are paid employees of Pfizer, Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2023.04.009.

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