# NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

## Study information

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|---|---|
| **Title** | Evaluation of Anticoagulants among Venous Thromboembolism Patients with Active Cancer: Pooled Analysis from Claims Databases |
| **Protocol number** | B0661123 |
| **Version identifier of the final study report** | 1.0 |
| **Date** | October 16, 2023 |
| **Medicinal product** | Apixaban |
| **Marketing Authorization Holder (MAH)** | Bristol-Myers Squibb Company |
| **Research question and objectives** | **Aim 1:** Compare the demographic and clinical characteristics among venous thromboembolism (VTE) patients with active cancer prescribed apixaban, low molecular weight heparin (LMWH), or warfarin.<br>**Aim 2:** Evaluate treatment patterns among VTE patients with active cancer prescribed apixaban, LMWH, or warfarin.<br>**Aim 3:** Compare the risk of major bleeding, clinically relevant non-major (CRNM) bleeding, and recurrent VTE within 6 months, using all available follow-up periods among VTE patients with active cancer prescribed apixaban, LMWH, or warfarin. |
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Pfizer_Protocol_VTE %20cancer%205%20

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VTE Brain Cancer Final.pdf

Cohen et al-Effectiveness

Effectiveness-safety saf‹-high risk subgroup

# 1. ABSTRACT (STAND-ALONE DOCUMENT)

**Title:** Evaluation of Anticoagulants among Venous Thromboembolism Patients with Active Cancer: Pooled Analysis from Claims Databases

**Rationale and background:** Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) or pulmonary embolism (PE), is the second leading cause of death in cancer patients receiving outpatient chemotherapy. Cancer-associated VTE carries a significantly greater risk of recurrent events and major bleeding (MB) compared to VTE in non-cancer patients. In most cases, VTE is diagnosed after cancer; however, an unprovoked VTE can be the harbinger that leads to a diagnosis of malignancy. The prevalence of VTE in cancer patients was found to be 13 per 1000 person-years. CHEST Guidelines suggest the use of low molecular weight heparin (LMWH) over a vitamin K antagonist (VKA) in patients diagnosed with VTE and cancer. Limited real-world evidence (RWE) is available regarding the safety and effectiveness of anticoagulants among VTE patients with active cancer, even less RWE is available for the effectiveness and safety of anticoagulants in VTE patients with specific cancer type.

This study evaluated the effectiveness and safety of apixaban, warfarin, and LMWH among VTE patients with any types of active cancer and some specific cancer type.

**Objectives**:

**Aim 1:** Compare the demographic and clinical characteristics among VTE patients with active cancer prescribed apixaban, LMWH, or warfarin.

**Aim 2:** Evaluate treatment patterns among VTE patients with active cancer prescribed apixaban, LMWH, or warfarin.

**Aim 3:** Compare the risk of MB, clinically relevant nonmajor (CRNM) bleeding, and recurrent VTE within 6 months and using all available follow-up period among VTE patients with active cancer prescribed apixaban, LMWH, or warfarin.

**Study design:**

This study was a longitudinal retrospective cohort analysis conducted in two phases. During phase 1, four commercial claims databases were used for analysis (Humana,IMS, Optum, and MarketScan). The study period was from March 1, 2014 to the end of the study (MarketScan: 01MAR2014-30JUNE2017; Optum & Humana: 01MAR2014-31DEC2017; PharMetrics: 01MAR2014-31MAR2018). For phase 2, Medicare fee-for-service (FFS) Database (Mar 1 2014 to Jun 30 2017) was added to the analysis

For both phases of the analyses, patients were required to have a VTE diagnosis (index VTE event) and active cancer within 6 months before or 30 days after the VTE diagnosis. Active cancer was defined as either 2 claims with a cancer diagnosis (at least 1 day apart) or a claim with a cancer diagnosis and claim for cancer treatment (chemotherapy, radiation and cancer-

related surgery). Patients were required to have an apixaban, LMWH, or warfarin prescription claim within 30 days of the index VTE event. The first claim date for apixaban, LMWH or warfarin was defined as index date for respective cohort. Patients were followed from the day after the index date until the earliest of treatment discontinuation, treatment switch, death, disenrollment, or end of study. Additional analysis censoring patients at 6 months was also conducted.

**Variables*:*** Demographic and clinical characteristics, clinical treatment patterns, and clinical outcomes including major bleeding, CRNM bleeding, and recurrent VTE.

**Data sources:** The study was conducted using member enrollment as well as medical and pharmacy claims from the Optum, Humana, IMS, MarketScan, and Medicare FFS databases.

**Study size:** All eligible patients available for analysis were included.

**Data analysis:** Means, medians, and standard deviations were provided for continuous variables. Numbers and percentages were provided for dichotomous and polychotomous variables. Bivariate comparisons of baseline characteristics and outcomes measures were provided. Inverse probability treatment weighting (IPTW) was used to balance treatment cohorts. Chi-square and t-tests were used to determine statistically significant differences between cohorts. The cumulative incidence rate for clinical outcomes (major bleeding, CRNM bleeding, and recurrent VTE) was calculated. Cox proportional hazard ratio models were used to evaluate the risk of clinical outcomes (MB, CRNM bleeding, recurrent VTE). Data analysis was executed using statistical software SAS version 9.3/9.4.

**Results:** For the phase 1 analysis, all eligibility criteria were fulfilled by 3,393 apixaban, 6,108 LMWH, and 4,585 warfarin patients. After IPTW, all patient characteristics were balanced. When the follow-up was censored at 6 months, apixaban patients had a lower risk of MB, CRNM bleeding, and recurrent VTE vs. LMWH. Apixaban patients had a lower risk of recurrent VTE and similar risk of MB and CRNM bleeding vs. warfarin. Warfarin patients had a similar risk of MB, CRNM bleeding, and recurrent VTE vs. LMWH. The trends were similar when the entire follow-up was used; however, apixaban patients were also associated with a lower risk of MB vs. warfarin patients. Subgroup analyses by VTE risk level (very high vs. high vs. other), metastatic status (yes vs. no), GI cancer status (yes vs. no) etc showed generally consistent results.

After adding Medicare FFS database to the phase 2 analysis, a total of 30,586 patients met all eligibility criteria. Of them, 7,807 (25.5%) had apixaban, 11,192 (36.6%) had LMWH, and 11,587 (37.9%) had warfarin. After IPTW, all patient characteristics were balanced. Apixaban (vs LMWH) patients had a lower risk of MB , CRNM bleeding, and recurrent VTE during the first 6-months of follow-up. Apixaban patients also had a significantly lower risk of recurrent VTE, MB and CRNM bleeding compared to warfarin patients. Warfarin (vs LMWH) patients had a lower risk of MB, CRNM bleeding, and similar risk of recurrent VTE.

Results were generally consistent when stratified by the presence of tumor of interest (brain, prostate, breast, lung, pancreatic or multiple myeloma) or by prior bleed and renal disease. In

general, no significant interactions were observed between treatment and presence of tumor type or between treatment and prior condition like prior bleed and renal disease.

**Conclusions:** VTE patients with active cancer who initiated apixaban had a significantly lower risk of MB, CRNM bleeding, and recurrent VTE compared to LMWH and warfarin patients. Apixaban treatment effects were generally consistent by tumor types and prior conditions. Further research is needed to fully understand the effectiveness and safety of anticoagulant treatment among VTE patients with active cancer.

## 1. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| AMPLIFY | Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy |
| BMS | Bristol-Myers Squibb |
| COPD | Chronic Obstructive Pulmonary Disease |
| CPT | Current Procedural Terminology |
| CRNM | Clinically Relevant Non-Major |
| DOACs | Direct Oral Anticoagulants |
| DME | Durable Medical Equipment |
| DVT | Deep Vein Thrombosis |
| EDB | Enrollment Database |
| ER | Emergency Room |
| GHP | Group Health Plan |
| GLM | Generalized Linear Models |
| GPP | Good Pharmacoepidemiology Practices |
| HCFA | Health Care Financing Agency |
| HCPCS | Common Procedure Coding System |
| HHA | Home Health Agency |
| HIPAA | Health Insurance Portability and Accountability Act |
| HR | Hazard Ratios |
| ICD-9-CM | International Classification of Disease, 9$^{th}$ Revision, Clinical Modification |
| ICD-10-CM | International Classification of Disease, 10$^{th}$ Revision, Clinical Modification |
| ICH | Intracranial Hemorrhage |
| INR | *International Normalized Ratio* |
| IPTW | Inverse Probability of Treatment Weighting |
| LMWH | Low Molecular Weight Heparin |
| NDC | National Drug Codes |
| OAC | Oral Anticoagulant |
| PAC | Parenteral Anticoagulant |
| PE | Pulmonary Embolism |

| Abbreviation | Definition |
|---|---|
| PPPM | Per Patient Per Month |
| RCT | Randomized Controlled Trial |
| UB | Uniform Bill |
| VKA | Vitamin K antagonist |
| VTE | Venous Thromboembolism |

## 2. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site are listed in Appendix 3.1.

### Principal Investigator(s) of the Protocol

| Name, degree(s) | Title | Affiliation | Address |
|---|---|---|---|
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## 3. OTHER RESPONSIBLE PARTIES

Not applicable

# 4. RATIONALE AND BACKGROUND

Cancer is an independent risk factor for VTE, accounting for 18% of the total VTE cases, and it is the strongest predictor for all-cause and PE-related mortality in VTE[2,18]. The risk of VTE depends on patient characteristics such as age, cancer stage, type of malignancy, and cancer treatment[19,20]. Cancer treatments such as cancer surgery and radiation therapy were found to be associated with VTE[21,22]. Breast, lung, colon, and prostate cancers contribute the most to the burden of active cancer associated VTE[23]. Cancer-associated VTE carries a significantly greater risk of recurrent VTE, and major bleeding (MB) compared to VTE in non-cancer patients[24,25]. Given the risk of recurrent VTE following the initial 3 months of anticoagulant therapy, patients with VTE and active cancer usually require ≥6 months of anticoagulation treatment and should be considered for extended treatment until the cancer is cured or quiescent in those who do not have a high bleeding risk[26,27].

Treating VTE patients with cancer is challenging due to an increased risk of bleeding associated with anticoagulant use and potential cancer treatment complications such as drug-drug interactions[26,28]. The recent NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) and ISTH SSC committee recommend the use of apixaban, LMWH, edoxaban, and rivaroxaban for the treatment of cancer associated VTE[29,30]. The American Society of Clinical Oncology suggests the use of LMWH for ≥6 months in VTE cancer patients and recommends the use of indefinite anticoagulation therapy among active cancer patients, such as those with metastatic disease and those receiving chemotherapy[9]. The European Society of Cardiology recommends similar considerations for the treatment of PE in cancer patients[28]. Despite the recommendation to use LMWH and specific DOACs in VTE patients with cancer, real-world data shows that warfarin and a variety of DOACs are being used in routine clinical practice to treat these patients[31].

Clinical trials and real-world studies have assessed DOACs including rivaroxaban and edoxaban vs LMWH for the treatment of cancer-associated VTE[32-34]. However, there is limited evidence for apixaban in VTE cancer patients. CARAVAGGIO, a recently completed multinational prospective, randomized, open-label, blinded end point (PROBE), non-inferiority study found that apixaban was noninferior to dalteparin for the treatment of cancer-associated VTE without an increased risk of major bleeding[16]. The ADAM trial of 300 randomized patients reported that apixaban was associated with low rates of bleeding and VTE recurrence compared to dalteparin in treating cancer associated VTE[13]. Despite these clinical trials, there is a lack of real-world evidence comparing the effectiveness and safety of LMWH with vitamin K antagonists (VKAs) and apixaban among patients with VTE and active cancer. There is even less information about the effectiveness and safety of anticoagulants in various subgroups of patients with VTE and active cancer such as those with different cancer types and different risk for VTE or bleeding. Initially using four US claims databases and later adding Medicare FFS database, this study compared the risk of recurrent VTE, MB, and clinically relevant non-major (CRNM) bleeding among patients with VTE and active cancer who newly initiated apixaban, LMWH, or warfarin in routine clinical practice. Various high-risk subgroups of patients were also evaluated.

# 5. RESEARCH QUESTION AND OBJECTIVES

The following aims were addressed:

**Aim 1:** Compare the demographic and clinical characteristics among VTE patients with active cancer prescribed apixaban, LMWH, or warfarin.

**Aim 2:** Evaluate treatment patterns among VTE patients with active cancer prescribed apixaban, LMWH, or warfarin.

**Aim 3:** Compare the risk of MB, CRNM bleeding, and recurrent VTE within 6 months and using all available follow-up periods among VTE patients with active cancer prescribed apixaban, LMWH, or warfarin.

# 6. RESEARCH METHODS

## 6.1. Study Design

### 6.1.1. Key Index Period Definitions

- **Study period:** The study period ranged from March 1, 2014 through March 31, 2018. The end of study was different for each database based on last available data cut (MarketScan: 30JUN2017; Optum & Humana: 31DEC2017 PharMetrics: 31MAR2018; Medicare: 30JUN2017).

- **Patient identification period:** The identification period ranged from September 1, 2014, through 31MAR2018. Apixaban was approved on March 14, 2014, for VTE. As such, we identified patients from September 2014 to allow for a baseline period of at least 6 months for all patients.

- **Baseline period:** The baseline period was 6 months prior to the index date. See the definition about index date in the next section.

- **Follow-up period:** The follow-up period was from the day after the index date to the earliest of treatment discontinuation, treatment switch, death, health plan disenrollment, or end of study. Additional analysis censoring patients at 6 months was also conducted.

### 6.1.2. Key Index Point Definitions

- **Index VTE event:** The first evidence of a VTE diagnosis in the primary or secondary position in the inpatient or ambulatory setting during the identification period for each patient was designated as the index VTE event.

- **Index therapy:** The apixaban, LMWH, or warfarin treatment prescribed within 30 days from the index VTE event was designated as the index therapy.

- **Index date:** The first prescription claim date for the index therapy was designated as the index date.

**Figure 1. Study Design Figure for LMWH Only**

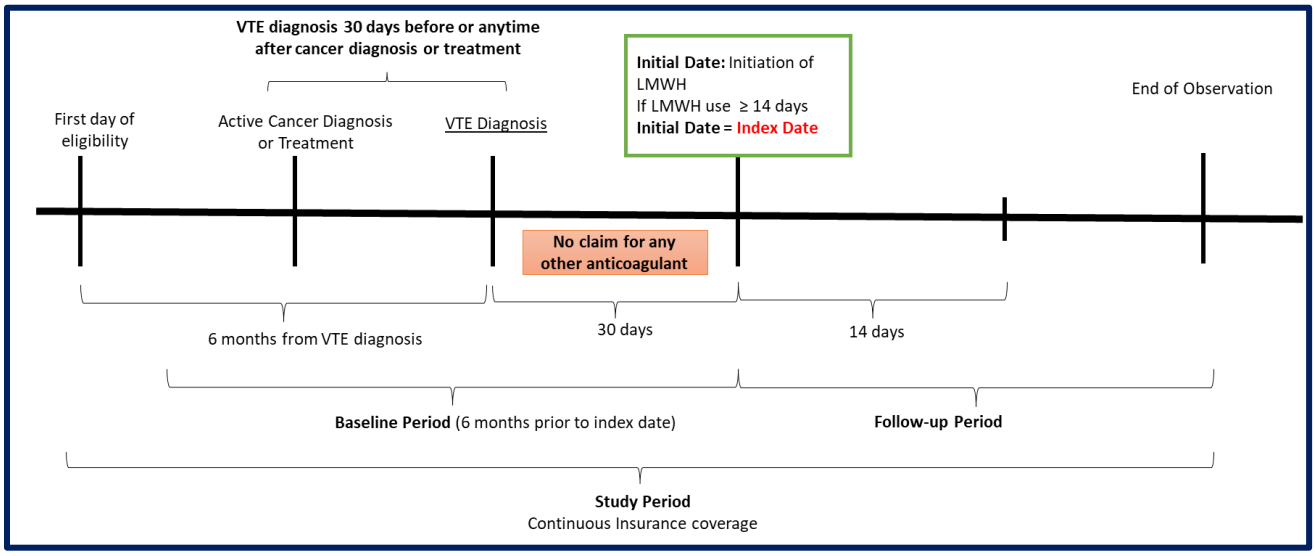



**Figure 2. Study Design Figure for Warfarin Only**

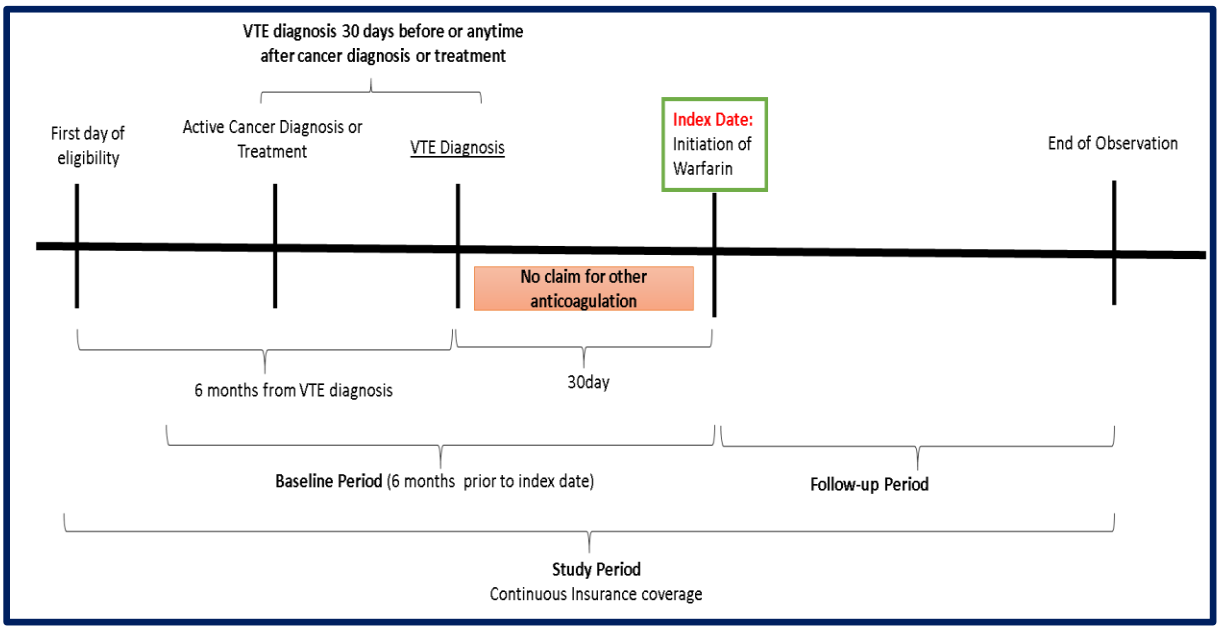


**Figure 3. Study Design Figure for Warfarin LMWH Bridging Therapy**

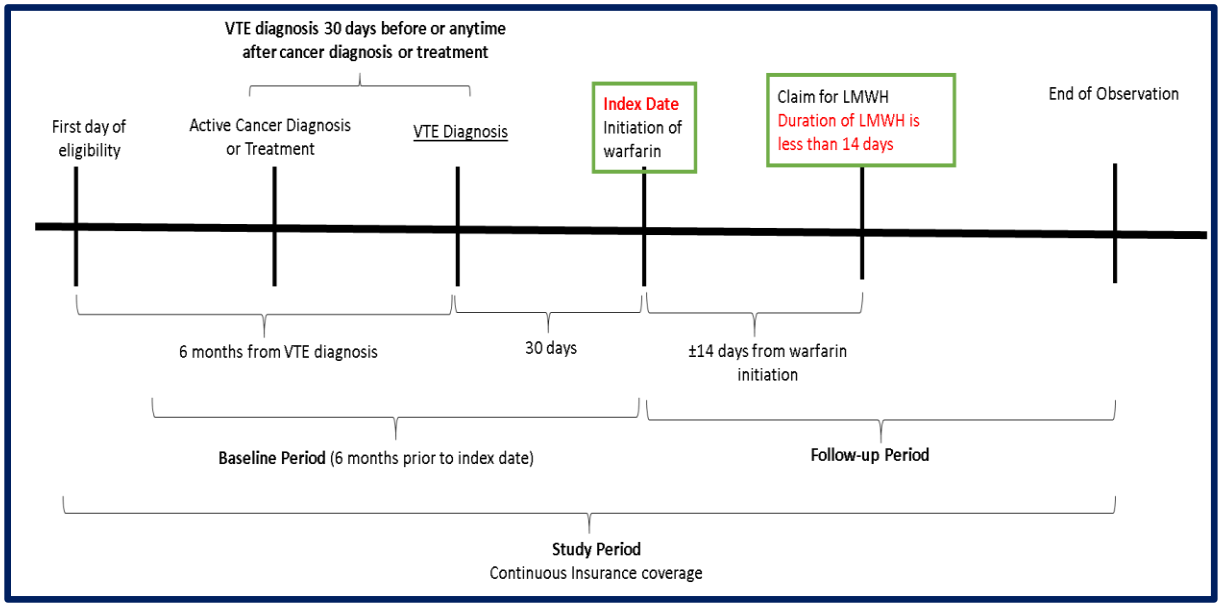
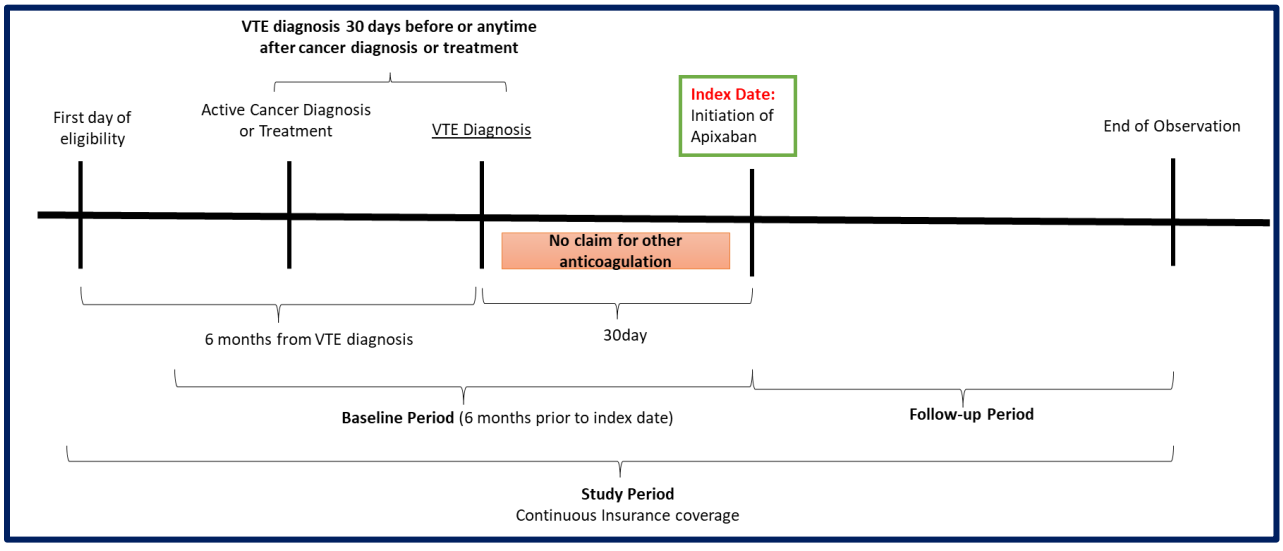



**Figure 4. Study Design Figure for Apixaban Only**



## 6.2. Setting

Adult patients prescribed apixaban, LMWH, or warfarin were selected between September 1, 2014, and July 31, 2017. Patients were required to have a VTE diagnosis in the primary or secondary position (index VTE event) and active cancer. Active cancer was defined as having a cancer diagnosis or cancer treatment (chemotherapy [IV and oral], radiation, or cancer-related surgery) from 6 months prior through 30 days after the index VTE event. Patients were also required to have an anticoagulant (apixaban, LMWH, or warfarin) prescription claim within 30 days of the index VTE event. The final population included adults (age ≥18 on index date) with health plan enrollment for 6 months prior to the index VTE event.

***Follow-up Period:***

The follow-up period was defined as the period from the day after the index date through the earliest of the health plan disenrollment, death, index therapy discontinuation, switch to another OAC, initiation of (new) parenteral anticoagulant (PAC) treatment, or end of study period. Additional analysis censoring patients at 6 months was conducted.

Discontinuation was defined as no evidence of index apixaban, LMWH, or warfarin use for 30 days from the last day of days' supply of the last filled prescription. The discontinuation date was the last day of days' supply of the last filled prescription. The follow-up period was censored at 30 days after the index drug discontinuation date.

Switch was defined as receiving a prescription for an OAC other than the index therapy within ±30 days of the last days' supply of the index therapy. For the Warfarin-LMWH Bridging cohort, a LMWH claim was allowed within 14 days before or after the first warfarin claim if the days of supply was <14 days.

## 6.3. Subjects

### 6.3.1. Inclusion Criteria

Patients were included in the study if they:

a) had a medical claim with a primary or secondary VTE diagnosis (index VTE event) in the inpatient or ambulatory setting during the identification period (01SEP2014-31JULY2017). If occurring in the outpatient setting, the index VTE event date was defined as the service date; if in the inpatient setting, the discharge date was designated as the index VTE event date. Qualifying outpatient encounters followed by qualifying inpatient encounters within 7 days was considered an inpatient episode (unless LMWH, warfarin or apixaban was initiated between encounters, in which case it would be classified as an outpatient VTE event);

b) had active cancer. Active cancer was defined as having ≥2 medical claims for cancer diagnosis on different days or 1 claim for cancer diagnosis plus ≥1 claim for cancer treatment (eg, chemotherapy, radiation, cancer-related surgery) within the time period 6 months before or 30 days after the index VTE event. The reason to include patients with active cancer

30 days after the index VTE event is that some patients may present with VTE even before the cancer diagnosis was made. Whether the 30-day period from index VTE to active cancer should be extended to a longer time period (eg, 60 days or 90 days) was finalized after conducting a feasibility analysis;

c) had ≥1 pharmacy claim for apixaban, LMWH, or warfarin during the 30-day period following the index VTE event;

   1. **LMWH Cohort:** If patients had LMWH for ≥14 days after the index VTE event and did not have another anticoagulant (Table 1 except LMWH) during the period between index VTE event and 14 days after LMWH initiation, then the first LMWH prescription date was designated as the index date. The reason to have LMWH treatment for ≥14 days for this cohort is to ensure that the LMWH used here was not intended for short-term bridging therapy;
   2. **Warfarin Only Cohort:** If patients who initiated warfarin within 30 days after index VTE event and did not have a claim for any other anticoagulant (Table 1 except warfarin) between the index VTE event and the warfarin prescription date or a LMWH claim 14 days after warfarin initiation, then their first warfarin prescription date was designated as the index date;
   3. **Warfarin LMWH Bridging Cohort:** If patients used warfarin and had a claim for LMWH (LMWH cannot be used for ≥14 days) within 14 days before or after warfarin initiation, then their first warfarin prescription date was designated as the index date. There should be no other anticoagulant (Table 1 except warfarin or LMWH) during the following time periods:

      (a) between index VTE event and initiation of warfarin

      (b) for the duration of LMWH treatment if it occurs within 14 days after warfarin initiation.

      Feasibility analysis was conducted to calculate the number of patients in the Warfarin LMWH Bridging cohort that had an event between the LMWH claim and the warfarin claim. Based on the sample size, the team decided to include the patients in the warfarin bridging cohort
   4. **Apixaban Only Cohort:** If patients who initiated apixaban within 30 days after index VTE event and did not have a claim for any other anticoagulant (Table 1 except apixaban) between the index VTE event and the initiation of apixaban, the first apixaban prescription date was designated as the index date;

d) were aged ≥18 years (≥65 years for Medicare only) as of the index date; and

e) had continuous health plan enrollment for ≥6 months prior to the index VTE event until the index date.

**Table 1. Oral and Parenteral Anticoagulants**

| Drug | Anticoagulant Type | HCPCS Codes |
|---|---|---|
| Low Molecular Weight Heparin | PAC | |

| Drug | Anticoagulant Type | HCPCS Codes |
|---|---|---|
| Dalteparin | PAC | J1645 |
| Enoxaparin | PAC | J1650 |
| Tinzaparin | PAC | J1655 |
| Heparin | PAC | J1642, J1644 |
| Fondaparinux | PAC | J1652 |
| Warfarin | OAC | - |
| Apixaban | OAC | - |
| Dabigatran etexilate mesylate | OAC | - |
| Rivaroxaban | OAC | - |
| Edoxaban | OAC | - |

### 6.3.2. Exclusion Criteria

Patients were excluded from the study if they:

a) had evidence of atrial fibrillation/flutter during the 6-month period preceding the index date (to ensure that OAC use is associated with VTE diagnosis only);

b) had evidence of mechanical heart valve during the 6-month period preceding the index date;

c) had evidence of receiving another OAC or PAC on the index date (or during the period between the index VTE event and the index date). LMWH is allowed between the index VTE event and index date for the Warfarin-LMWH Bridging cohort;

d) had evidence of VTE during the 6-month period preceding the index VTE event since the study aims to capture new VTE patients;

e) had evidence of any OAC/PAC use during the 6-month period preceding the index VTE event unless it is determined that such therapy was administered prophylactically (See Appendix 2);

**NOTE:** Prophylactic use of OAC/PAC was determined based on the duration of use and timing of use (eg, relative to knee/hip replacement surgery or medical inpatient admission); the operational algorithm to be employed to differentiate between prophylactic and therapeutic OAC/PAC use is set forth in Appendix 2.

f) had evidence of inferior vena cava filter at any time during the study period; or

g) had evidence of pregnancy at any time during the study period;

h) had medical claims indicating antiphospholipid syndrome (APS) during the study period.

All codes for the selection criteria are detailed in Table 1 of Appendix 1.

### 6.3.3. Cohorts

After applying the inclusion and exclusion criteria, eligible patients were assigned to the following cohorts based on index treatment:

- **LMWH only:** Patients that had a LMWH claim within 30 days of the index VTE events, were treated for ≥14 days after the index VTE event and did not have another anticoagulant (Table 1 except LMWH) during the period between index VTE event and 14 days after LMWH initiation. These patients were identified first.

- **Warfarin only:** Patients who initiated warfarin within 30 days after the index VTE event and did not have a claim for any other anticoagulant (Table 1 except warfarin) during the period between the index VTE event and the initiation of warfarin or a LMWH within 14 days after warfarin initiation

- **Warfarin LMWH bridging cohort:** Patients that used warfarin within 30 days after the index VTE event and had a claim for LMWH within 14 days before or after warfarin initiation. LMWH cannot be used for ≥14 days. There should be no other anticoagulant (Table 2 except warfarin and LMWH) during the period between index VTE event and initiation of warfarin as well as for the duration of LMWH if it occurs within 14 days after warfarin initiation. Feasibility analysis was conducted to calculate the number of patients in the Warfarin LMWH bridging cohort that had an event between the LMWH claim and the warfarin claim. Warfarin LMWH bridging cohort was combined with the warfarin only cohort.

- **Apixaban only:** Patients who initiated apixaban within 30 days after the index VTE event and did not have a claim for any other anticoagulant (Table 1 except apixaban) during the period between the index VTE event and the initiation of apixaban.

## 6.4. Variables

Baseline variables during the 6 months prior to and on the index date were measured. Baseline variables were evaluated using codes in any position (primary or secondary) unless noted otherwise.

**Table 2. Baseline Demographic and Clinical Characteristic Variables**

| Variable | Operational Definition |
|---|---|
| **Variables were measured during baseline period (6 months prior to and on the index date)** | |
| **Age** | Age was defined as of the index date and used to assign patients to the following age groups: 18-54, 55-64, 65-74, 75-79, and ≥80 years. |
| **Sex** | A flag was created for female beneficiaries and reported as a percentage. |
| **US Geographic Region** | The United States was divided into five regions: Northeast, South, Midwest, West, and Other. Geographic region was captured from enrollment data. |

| Variable | Operational Definition |
|---|---|
| **Medicare/Medicaid dual eligibility** | A flag was created for patients who had Medicare/Medicaid dual eligibility with results reported as a percentage (for Medicare database only). |
| **Part D low-income subsidy** | A flag was created for patients who had a Part D low-income subsidy with results reported as a percentage (for Medicare database only). |
| **Race** | Race was identified and categorized as: White, Black, and Other (for Medicare and Humana only) |
| **Index Year** | A flag was created for proportion of unique patients identified in 2014, 2015, 2016, 2017, 2018, 2019, and 2020 (up to 2017 for Medicare database). |
| **Setting of Index VTE Event** | Flags were created for patients with index VTE event in inpatient or ambulatory settings. Qualifying outpatient encounters followed by qualifying inpatient encounters within 7 days were considered an inpatient episode (unless warfarin, LMWH, or apixaban were initiated between encounters, in which case it was classified as an outpatient encounter). |
| **Position of VTE Diagnosis** | Flags were created for the position of VTE diagnosis including primary (principle diagnosis or first listed) or secondary position. |
| **VTE Diagnosis** | Flags were created for the type of VTE diagnosis including DVT only, PE with DVT, or PE without DVT. |
| **VTE Etiology** | Flags were created for VTE etiology, including provoked or unprovoked VTE. Provoked VTE was defined as events that are preceded by hormone therapy, fracture/trauma involving lower extremities, pelvic/orthopedic surgery, or hospitalization for any reason for ≥3 days during 3 months prior to index VTE event; unprovoked VTE was defined as all events not classified as provoked. |
| **AIDS** | A flag was created for patients with claims for AIDS. |
| **Alcohol abuse** | A flag was created for patients with claims for alcohol abuse. |
| **Anemia** | A flag was created for patients with claims for anemia. |
| **Central venous Catheter** | A flag was created for patients with claims for central venous catheter. |
| **Cerebrovascular disease** | A flag was created for patients with claims for cerebrovascular disease. |
| **Hematologic disorders associated with bleeding** | A flag was created for patients with claims for hematologic disorders associated with bleeding.<br>* A separate flag was created for patients with claims for thrombocytopenia. |
| **Ischemic heart/ coronary artery disease** | A flag was created for patients with claims for ischemic heart/coronary artery disease. |
| **Dementia** | A flag was created for patients with claims for dementia. |
| **Dyspepsia or stomach discomfort** | A flag was created for patients with claims for dyspepsia or stomach discomfort. |
| **Hemiplegia or Paraplegia** | A flag was created for patients with claims for hemiplegia or paraplegia |
| **Hyperlipidemia** | A flag was created for patients with claims for hyperlipidemia. |

| Variable | Operational Definition |
|---|---|
| **Obesity** | A flag was created for patients with claims for obesity |
| **Pneumonia** | A flag was created for patients with claims for pneumonia. |
| **Rheumatologic disease** | A flag was created for patients with claims for rheumatologic disease. |
| **Sleep apnea** | A flag was created for patients with claims for sleep apnea. |
| **Spinal cord injury** | A flag was created for patients with claims for spinal cord injury. |
| **Thrombophilia** | A flag was created for patients with claims for thrombophilia. |
| **Varicose Veins** | A flag was created for patients with claims for varicose veins. |
| **Congestive Heart Failure** | A flag was created for patients with claims for congestive heart failure. |
| **Diabetes** | A flag was created for patients with claims for diabetes. |
| **Hypertension** | A flag was created for patients with claims for hypertension. |
| **Renal Disease** | A flag was created for patients with claims for renal disease.<br>A flag for chronic kidney disease stage V, end-stage renal disease, or dialysis was created. |
| **Liver Disease** | A flag was created for patients with claims for liver disease. |
| **COPD** | A flag was created for patients with claims for chronic obstructive pulmonary disease. |
| **Peptic Ulcer Disease** | A flag was created for patients with claims for ulcer disease. |
| **Inflammatory bowel disease** | A flag was created for patients with claims for inflammatory bowel disease. |
| **Peripheral vascular disease** | A flag was created for patients with claims for peripheral vascular disease. |
| **Baseline Bleed** | A flag was created for patients with claims for bleeding. |
| **Recent history of falls** | A flag was created for patients having a fall and reported as a percentage. |
| **Fracture/trauma involving the lower extremities** | A flag was created for patients having a fracture or a trauma and reported as a percentage. |
| **Selected surgeries** | A flag was created for patients having a surgery and reported as a percentage. |
| **Deyo-Charlson Comorbidity Index** | The Deyo-Charlson Comorbidity Index was created. |
| **Other Baseline Medications** | Flags were created for patients with prescription fills for antiarrhythmic, statin, antiplatelet, aromatase inhibitors, beta blockers, gastroprotective agents, SERMs, NSAIDs, and hormone therapy. |
| **Apixaban Index dose** | Standard dose (apixaban 5 mg) and lower dose (apixaban 2.5 mg) based on dose of the initial prescription of apixaban. |
| **Cancer-related variables were measured 6 months prior to index date until 30 days after index date** | |
| **Cancer Site** | Flags were created for site of the cancer in the body. |

| Variable | Operational Definition |
|---|---|
| **Cancer Type** | A flag was created for hematologic cancer and reported as a percentage. |
| **Cancer-related Treatment** | Flags were created for patients with claims for chemotherapy, immunotherapy, radiation, or cancer-related surgery. |
| **VTE Risk Scale** | Flags were created for patients that had very high risk of cancer (stomach, pancreas, and brain), high risk (lung, lymphoma, gynecologic, bladder, testicular, renal cell carcinoma), and other cancers[37,61]. |
| **Cancer Metastasis** | A flag was created for patients that had a metastatic diagnosis. |

## Table 3. Clinical and Outcome Variables

| Variable | Operational Definition |
|---|---|
| **Major Bleeding** | A major bleeding event observed during follow-up was identified using hospital records which had a major bleeding diagnosis as the first listed diagnosis (commercial datasets) or primary diagnosis (Medicare) as listed by ICD-9-CM or ICD-10 diagnosis or procedure code. Major bleeding event was a dichotomous variable that equals 1 if there was ≥1 bleeding event during the follow-up period. Time to the first major bleeding event was calculated.<br><br>Major bleeding was further reported as GI bleeding, ICH, and other bleeding. |

| Variable | Operational Definition |
|---|---|
| **CRNM Bleeding** | A CRNM bleeding event was defined as a bleeding event not considered to be major bleeding (without a principal diagnosis code for GI/ICH/other bleeding or a procedure code for bleeding treatment). This includes:<br>• an acute-care inpatient admission with a secondary diagnosis for "non-critical site" bleeding such as GI bleeding, or other selected non-critical types/sites of bleeding; or<br>• an ambulatory-care encounter with a diagnosis code for GI bleeding, and other selected non-critical types/sites of bleeding (without a diagnosis code for ICH bleeding). |
| **Recurrent VTE** | A recurrent VTE event was identified as an acute-care inpatient admission with a corresponding first listed diagnosis (commercial datasets) or primary diagnosis (Medicare); admissions occurring within 7 days of the qualifying VTE event-irrespective of care setting were not considered as a recurrent VTE event. |
| **Discontinuation** | Discontinuation was defined as no evidence of index prescription for 30 days from the last day of days' supply of last filled prescription. The date of discontinuation was the last day of days' supply of last filled prescription. |
| **Time-to-Discontinuation** | Time from the index date to discontinuation date was evaluated among patients that discontinued index therapy. |
| **Switch among Anticoagulants** | Switch was defined as receiving a prescription for an anticoagulant other than the index drug prescription within ±30 days of last days' supply of the index drug and was further categorized into the drug they switched to: Apixaban, dabigatran, edoxaban, rivaroxaban, warfarin, LMWH, unfractionated heparin (UFH), and fondaparinux. |
| **Persistence** | Persistence (in days) was defined as the number of days the patient remained on the index drug with a gap of ≤30 days between the run-out date of the previous prescription and the following prescription. Percentage of patients that continued treatment during the follow-up period were also evaluated. |

## 6.5. Data Sources and Measurement

### *MarketScan*

The Truven MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits database were used for this study. The MarketScan Commercial Claims and Encounters database is a high-quality resource with the combined claims of employer-and health plan-sourced data containing medical and drug data for several million individuals annually. The database offers the largest convenience sample, with >94 million unique patients since 1996. All census regions are represented, predominantly the South and North Central (Midwest) regions. The database includes enrollment history and claims for medical (provider and institutional) and pharmacy services. Inpatient services are at both the claim and summarized stay level. The Medicare Supplemental and Coordination of Benefits database only includes a subset of the Medicare population that are Medicare-eligible retirees with employer-sponsored Medicare

Supplemental plans. This database contains predominantly fee-for-service plan data. The Medicare Supplemental and Coordination of Benefits database may not accurately represent the US Medicare population.

***Optum***

Optum Insight has access to a proprietary research database containing claims and enrollment data dating back to 1993. For 2013, data relating to ~57 million individuals with both medical and pharmacy benefit coverage are available. An additional 39 million enrollees with medical benefits only are also available. The underlying information is geographically diverse across the United States and is updated frequently. The research activities utilize de-identified data from the research database except in limited instances where applicable law allows the use of patient identifiable data.

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. The claims history is a profile of all outpatient prescription pharmacy services provided and covered by the health plan. Pharmacy claims data include drug name, dosage form, drug strength, fill date, days of supply, financial information, and de-identified patient and prescriber codes, allowing for longitudinal tracking of medication refill patterns and changes in medications. Pharmacy claims are typically added to the research database within 6 weeks of dispensing.

Medical claims or encounter data are collected from all available health care sites (inpatient hospital, outpatient hospital, emergency room [ER], physician's office, surgery center, etc) for virtually all types of provided services, including specialty, preventive, and office-based treatments. Medical claims and coding conform to insurance industry standards. Claims for ambulatory services submitted by individual providers (eg, physicians) use the Health Care Financing Agency (HCFA)-1500 format. Claims for facility services submitted by institutions, (eg, hospitals) use the uniform bill (UB)-82 or UB-92 format. Medical claims include multiple diagnosis codes recorded with the ICD-9-CM diagnosis codes; procedures recorded with ICD-9-CM procedure codes, Current Procedural Terminology (CPT), or HCFA Common Procedure Coding System (HCPCS) codes; site of service codes; provider specialty codes; revenue codes (for facilities); paid amounts; and other information. Typically, facility claims do not include any drugs administered in hospital. Approximately 6 months following the delivery of services is required for complete medical data. Medical claims identify patients that used United Health Group for their healthcare services.

***IMS PharMetrics Plus***

The IMS PharMetrics Plus claims database includes claims for medical (provider and institutional) and pharmacy services in the United States, with claim paid and allowed amounts as well as all-patient payment amounts. The database reflects ~40 million lives in any given recent year. IMS PharMetrics Plus is the product of a strategic partnership between IMS and Blue Health Intelligence (BHI) and incorporates a number of Blue Cross Blue Shield plans. Complete data

from a large number of commercial health plans covering all 50 states are available. The population aged >65 years consists of enrollees in managed care plans for seniors, the working elderly, and others in commercial plans; BHI Medicare Advantage members are not included.

***Humana***

The Humana database includes over 18 million lives of commercial and Medicare members and covers all census regions in the United States. The database contains information on patient demographics; enrollment history; and claims for inpatient, outpatient, ER, and other medical services. In addition, the Humana database contains information on pharmacy and laboratory claims. Most of the members in Humana reside in Midwestern and southern regions of the country. More than 9 million people in Humana have both medical and pharmacy coverage. Medical claims include information regarding physician visits, outpatient visits and hospital inpatient stay. Pharmacy data includes information on prescription fills for each member, days of supply, payment amounts per insurers and beneficiaries and dates of services.

***Medicare***

Medicare is the federal health insurance program for people aged ≥65 years, certain younger people with disabilities, and people with end stage renal disease (permanent kidney failure requiring dialysis or a transplant); this comprises ~38 million fee-for-service (FFS) beneficiaries. The database contains medical, and pharmacy claims from 100% national Medicare data, which includes hospital inpatient, outpatient, Medicare carrier, Part D, skilled nursing facility, home health agency, and durable medical equipment claims.

Medicare Inpatient Data

The inpatient claim file contains final action claims data submitted by inpatient hospital providers for the reimbursement of facility costs. Some information contained in this file includes diagnosis (ICD-9-CM and procedure [ICD-9]) codes, diagnosis-related groups, dates of service, reimbursement amounts, hospital providers, and beneficiary demographic information. Each observation in this file is at the claim level.

Medicare Outpatient Data

The outpatient claim file contains final action claims data submitted by institutional outpatient providers. Examples of institutional outpatient providers include hospital outpatient departments, rural health clinics, renal dialysis facilities, outpatient rehabilitation facilities, comprehensive outpatient rehabilitation facilities, and community mental health centers. Some information contained in this file includes diagnosis and procedure codes (ICD-9-CM diagnosis and ICD-9 procedure codes, CMS Healthcare Common Procedure Coding System [HCPCS] codes), dates of service, reimbursement amounts, outpatient provider numbers, revenue center codes, and beneficiary demographic information. Each observation in this file is at the claim level.

Medicare Carrier File

The Carrier file (also known as the Physician/Supplier Part B claims file) contains final action, FFS claims submitted on a CMS-1500 claim form. Most of the claims are from non-institutional providers such as physicians, physician assistants, clinical social workers, and nurse practitioners. Claims for other providers, such as free-standing facilities, are also found in the Carrier file. Examples include independent clinical laboratories, ambulance providers, and free-standing ambulatory surgical centers. This file includes diagnosis and procedure codes, dates of service, reimbursement amounts, provider numbers, and patient demographic information.

Medicare Part D Drug Events Data

The Medicare Part D Drug Events (PDE) data contains prescription drug costs and payment data that enable CMS to make payments to the plans and otherwise administer Part D benefits. When a beneficiary fills a prescription under Medicare Part D, a prescription drug plan sponsor must submit a summary record to CMS. The PDE data are not the same as individual drug claim transactions: they are summary extracts using CMS-defined standard fields.

Skilled Nursing Facility

The skilled nursing facility (SNF) file contains final action, FFS claims data submitted by SNF providers. This file includes ICD-9-CM diagnosis and procedure codes, dates of service, reimbursement amount, SNF provider number, and beneficiary demographic information.

Home Health Agency

The home health agency (HHA) file contains final action, FFS claims submitted by HHA providers. This file includes number of visits, type of visit (skilled nursing care, home health aides, physical therapy, speech therapy, occupational therapy, and medical social services), diagnosis (ICD-9-CM diagnosis), date of visits, reimbursement amount, HHA provider number, and beneficiary demographic information.

Hospice

The hospice file contains final action claims submitted by hospice providers. Once a beneficiary elects a hospice, all hospice-related claims were found in this file, regardless of whether the beneficiary is in Medicare FFS or a Medicare managed care plan. This file includes the level of hospice care received (e.g., routine home care, inpatient respite care), terminal diagnosis (ICD-9-CM diagnosis), dates of service, reimbursement amounts, hospice provider number, and beneficiary demographic information.

Durable Medical Equipment

The durable medical equipment (DME) file contains final action, FFS claims submitted by DME suppliers. This file includes diagnosis (ICD-9-CM diagnosis), services provided (CMS HCPCS codes), dates of service, reimbursement amounts, DME provider numbers, and beneficiary demographic information.

Medicare Denominator File

The denominator file contains demographic and enrollment information for enrolled and/or entitled Medicare beneficiaries in a given year. It combines Medicare beneficiary entitlement status information from administrative enrollment records with third-party payer information and group health plan enrollment information. It is an abbreviated version of the enrollment database selected data elements.

Some information contained in this file includes the beneficiary's unique identifiers, state and county codes, ZIP codes, dates of birth, dates of death, gender, race, age, monthly entitlement indicators (A/B/Both), reasons for entitlement, state buy-in indicators, and monthly managed care indicators (Yes/No).

Data are collected on an ongoing basis, with the files constructed on an annual basis. The file does not contain data for all beneficiaries ever entitled to Medicare: the file only contains data for beneficiaries who were entitled during the year of the data. These data are available annually in May of the current year for the previous year.

All patient identifiers in the database have been fully encrypted, and the database is fully compliant with the Health Insurance Portability and Accountability Act of 1996.

### 6.6. Study Size

All eligible patients available for analysis were included. For the phase 1 analysis, the four commercial databases described were pooled together to create a master pooled dataset. For the phase 2 analysis, the four commercial databases and Medicare database described were pooled together to create a master pooled dataset. The advantages of using the pooled dataset include large study sample, diverse patient population and generalizability of the data.

### 6.7. Data Transformation

This study used secondary data collected in the MarketScan, Optum, PharMetrics, Humana, and Medicare Database, which is de-identified and HIPAA compliant. All data analysis were executed using statistical software STATA and SAS version 9.3/9.4.

### 6.8. Statistical Methods

#### 6.8.1. Main Summary Measures

Baseline demographic and clinical factors such as age, gender, geographic region, type of index VTE event, position of VTE diagnosis, VTE diagnosis, VTE etiology, baseline medications and co-morbidities among VTE patients newly initiated with apixaban, LMWH, or warfarin were summarized. Descriptive statistics, i.e., mean, standard deviation, median and inter-quartile range for continuous variables and differences across treatments were compared using the Student's t-test. Percentages for categorical and binary variables were presented for all baseline patient characteristics and were compared using the chi-square test.

### 6.8.2. Main Statistical Methods

Treatment patterns included medication discontinuation, switching and persistence. Patients that received a prescription for an anticoagulant other than the index drug prescription during the follow-up period were considered switchers if this prescription was within ±30 days of last days' supply. Among patients that did not switch, percentage of patients that discontinued their index treatment were evaluated. Discontinuation was defined as no evidence of index prescription for 30 days from the last day of days' supply of last filled prescription. The date of discontinuation was the last day of days' supply of last filled prescription. Time from the index date to discontinuation date was evaluated among patients that discontinued index therapy. Numbers and percentages were provided for dichotomous and polychotomous variables for the descriptive analysis of categorical data. Discontinuation and switch were further evaluated among patients that had at least 6 months of continuous enrollment (including patients that died during this period).

Persistence (in days) was defined as the number of days the patient remained on the index drug with a gap of ≤30 days between the run-out date of the previous prescription and the following prescription. Percentage of patients that continued treatment during the follow-up period were also evaluated.

Additional analysis was conducted using IPTW (see below) to balance patient characteristics.

The cumulative incidence rates for clinical outcomes (major bleeding, CRNM bleeding, recurrent VTE) were calculated. Major bleeding was further identified as GI bleeding, ICH, and other bleeding; CRNM bleeding was further identified as GI bleeding and other bleeding. The incidence rate was calculated as the number of patients who experience the event divided by the observed time at risk. The incidence rate was calculated per 100 person-years.

Inverse probability treatment weighting (IPTW) was used to balance patient characteristics among different cohorts. IPTW used propensity scores to obtain estimates of the average treatment effect. The propensity score was calculated using a multinomial logistic model with three treatment cohorts (apixaban, warfarin, and LMWH) included in the model, using LMWH patients as the reference (i.e., control cohort). The propensity score was defined as the probability of a patient receiving a certain treatment or not conditional on their observed baseline covariates (e.g., age, gender, comorbidities, medications, etc.). The list of variables included in the logistic model was based on clinical rationale. The propensity score acted as a balancing score between the cohorts. Each patient was weighted by the inverse of the probability of their treatment option (weight=1/propensity score).

If a treated patient had a very low propensity score, a very large weight was generated. Large weights can increase the variability of estimated treatment effect. In order to address this, the weights were stabilized. In order to stabilize the weights, the treatment option and control weights was multiplied by a constant, equal to the expected value of being in the treatment or comparison cohorts, respectively. This reduced the variability of the weights and reduced the variance of the treatment effect estimates.

$$\frac{\sum_{i=1}^{N_T} PS_i}{N_T} * \frac{1}{PS_i}$$

The distribution of the stabilized weight was reviewed. In the case of extreme outliers, the large weights were set to a less extreme value (e.g. recoding all weights that are outside 5$^{th}$ and 95$^{th}$ percentile to the 5$^{th}$ and 95$^{th}$ value, respectively). If needed, truncation was also done after stabilizing the weights.

After the weights are applied, the balance of the baseline covariates were assessed. First, the means and proportions of baseline variables were compared. The standardized difference compared the difference in means in units of the standard deviation. If the standardized difference was less than 10%, the covariates were considered balanced. For continuous variables, the balance of the distribution was also assessed. The high-order movements and interactions between variables were similar between cohorts. The standardized difference were used to compare the mean of the square of continuous variables.

Cox proportional hazards models were used to compare the time to MB, CRNM bleeding, and recurrent VTE between apixaban, warfarin, and LMWH cohorts after inverse probability treatment weighting. Thereby, proportional hazards on survival (or time-to-event) data were tested via maximum likelihood, with consideration of exponential Weibull and Gompertz distributions.

The proportional hazards proportionality assumption was evaluated by visually inspecting the Kaplan-Meier plot within the matched cohort and confirmed by testing the significance of interactions between treatment and the log of time. If this assumption was invalidated, an interaction term of time or time-dependent covariate was added.

### 6.8.3. Missing Values

None

### 6.8.4. Phase 1 Subgroup Analyses

Subgroup analyses were conducted to evaluate whether study findings are consistent across different strata for each of the subgroups. Statistical significance (P<0.10) of the interaction between treatments and each of the subgroup on safety and effectiveness outcomes were evaluated. The subgroup analyses were conducted based on a maximum 6 months of follow-up. The following subgroups were evaluated in the phase 1 analysis by using four commercial databases describe above:

1. VTE risk scale (very high risk, high risk, low risk)
2. Cancer treatment vs. no cancer treatment
3. Chemotherapy vs. no chemotherapy
4. Metastasis vs. no metastasis
5. GI cancer vs. no GI cancer

6. Index DVT only vs. Index PE with or without DVT
7. GI + bladder cancer vs. no GI + bladder cancer

### 6.8.5. Phase 2 Subgroup Analyses

The following subgroups were evaluated in the phase 2 analysis by using four commercial databases plus Medicare database:

1. Brain cancer
2. Pancreatic cancer
3. Lung cancer
4. Breast cancer
5. Prostate cancer
6. Multiple myeloma
7. Renal disease
8. Prior bleeding

The following feasibility analysis was conducted before finalizing the selection criteria:

1. The number of patients that had a cancer diagnosis during 30, 60, or 90 days after index VTE events—this was evaluated to determine which time period (30 vs. 60 vs. 90) was used in final protocol.

2. The number of patients that had ≥2 medical claims for cancer diagnosis or ≥1 claim for cancer diagnosis and ≥1 claim for cancer treatment (eg, chemotherapy, radiation, cancer-related surgery)—this analysis was conducted to finalize the definition for "active cancer" patients.

3. The number of patients in the Warfarin LMWH Bridging cohort that had an event between the LMWH claim and the warfarin claim was calculated. Depending on the sample size, the team decided whether to exclude them or include them in the warfarin bridging cohort.

### 6.8.6. Amendments to the Statistical Analysis Plan

None

## 6.9. Quality Control

STATinMED Research's approach combines scientific rigor with accurate results. The company focuses on quality at each step of the process, including, but not limited to the following:

1. Sound scientific design and clinically rigorous review. Detailed study protocol, that includes definitions, codes, analyses, and table shells. A member of the STATinMED clinical team reviewed the appropriateness and validity of the coding strategy and identify relevant issues.

2. The protocol further provides STATinMED Research and Pfizer the opportunity to solidify research questions and to address any potential gaps in information.
3. Rigorous quality assurance checks were performed during the construction of the dataset. Several checks are used, including record-level verification of all data elements, double programming of certain portions of the dataset, programming data edit checks, visual review of raw data against the constructed data elements, and review of analysis to assess validity of results.
4. STATinMED Research's analysis were performed by an analyst under the supervision of the project manager, lead analyst, and/or vice president. These team members review programs and output for consistency with the analysis plan, quality, and accuracy. Further, results were reviewed with Pfizer to establish that the results meet Pfizer's expectations.

### 6.10. Protection of Human Subjects

Subject information and consent

As a secondary data collection study using fully anonymized data, informed consent is not required.

Independent ethics committee (IEC)/institutional review board (IRB)

IRB/IEC review was not required.

Ethical conduct of the study

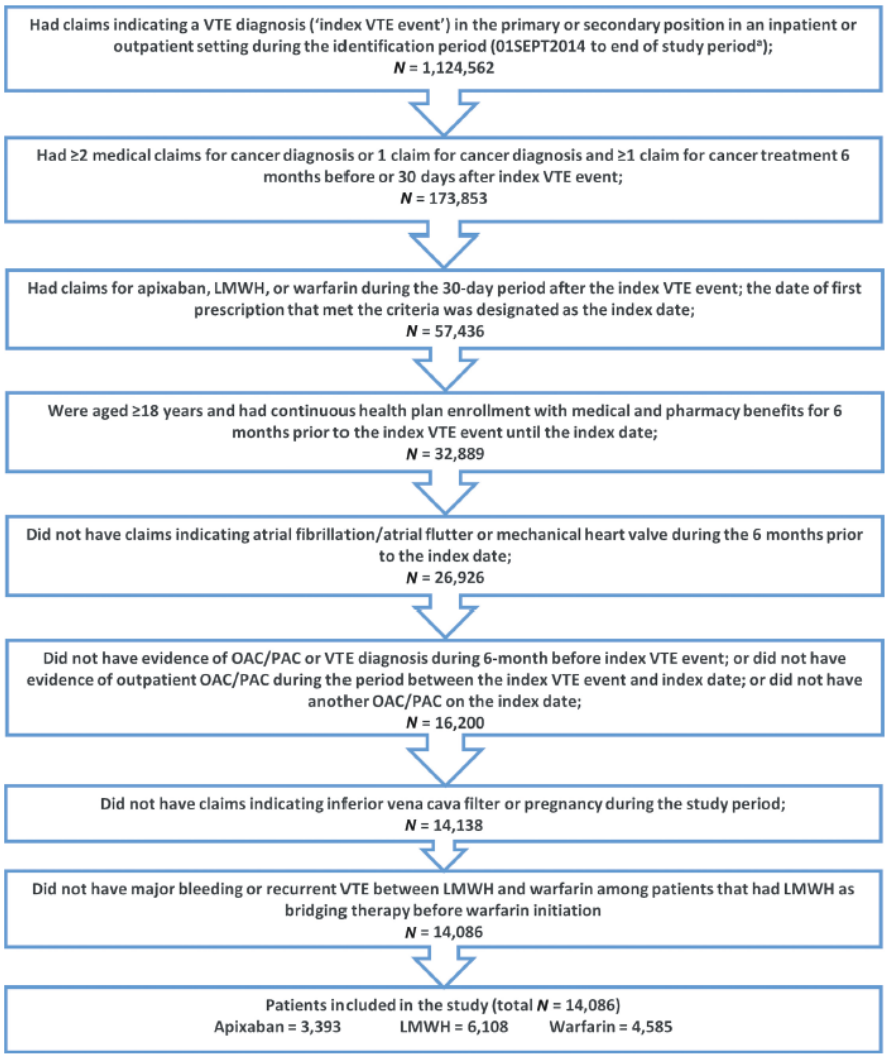
The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and followed generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE).

## 7. PHASE 1 RESULTS

### 7.1. Participants

Figure 5 shows the patient selection process. A total of 14,086 patients met all eligibility criteria, 6,108 (43.4%) were prescribed LMWH, 4,585 (32.6%) were prescribed warfarin, and 3,393 (24.1%) were prescribed apixaban.

**Figure 5: Patient selection process (Phase 1)**




## 7.2. Descriptive Data

Pre-IPTW baseline characteristics for each treatment cohort among VTE cancer patients are described in Table 4. Before IPTW, warfarin patients were older and had the highest baseline CCI followed by apixaban and LMWH. Across the 3 treatment cohorts, about 55%-58% patients had the index VTE as DVT only and 58%-66% patients had the index VTE as a provoked VTE event. The mean CCI was 2.1, 1.6, and 2.3 for apixaban, LMWH, and warfarin respectively. About 27% of apixaban patients, 35% of LMWH patients, and 35% of warfarin patients had evidence of baseline bleeding prior to initiation of anticoagulation. A total of 9.5%, 20.6%, and 9.6% of apixaban, LMWH, and warfarin patients, respectively, were categorized as having very high-risk cancer types. Most LMWH (88.7%), warfarin (63.6%) and apixaban (68.4%) patients received cancer-related treatment.

## Table 4: Phase 1 Pre-IPTW patient characteristics

| | Pre-IPTW | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | LMWH cohort (reference) | | Warfarin cohort | | | Apixaban cohort | | |
| | N/mean | %/SD | N/mean | %/SD | STD[a] | N/mean | %/SD | STD[a] |
| Sample size | *6,108* | | *4,585* | | | 3,393 | | |
| Age[b,c] | 60.3 | 12.5 | 67.1 | 12.9 | 53.5 | 66.8 | 12.9 | 51.3 |
| 18–54 | 1,650 | 27.0% | 701 | 15.3% | 29.0 | 544 | 16.0% | 27.0 |
| 55–64 | 2,357 | 38.6% | 1,219 | 26.6% | 25.8 | 951 | 28.0% | 22.5 |
| 65–74 | 1,377 | 22.5% | 1,285 | 28.0% | 12.6 | 905 | 26.7% | 9.6 |
| 75–79 | 375 | 6.1% | 629 | 13.7% | 25.5 | 421 | 12.4% | 21.7 |
| ≥ 80 | 349 | 5.7% | 751 | 16.4% | 34.5 | 572 | 16.9% | 35.8 |
| Gender[b,d] | | | | | | | | |
| Male | 2,861 | 46.8% | 2,285 | 49.8% | 6.0 | 1,635 | 48.2% | 2.7 |
| Female | 3,245 | 53.1% | 2,298 | 50.1% | 6.0 | 1,757 | 51.8% | 2.7 |
| Geographic region[b,c] | | | | | | | | |
| Northeast | 1,460 | 23.9% | 642 | 14.0% | 25.5 | 421 | 12.4% | 30.2 |
| South | 2,137 | 35.0% | 1,657 | 36.1% | 2.4 | 1,797 | 53.0% | 36.8 |
| Midwest | 1,528 | 25.0% | 1,337 | 29.2% | 9.3 | 682 | 20.1% | 11.8 |
| West | 972 | 15.9% | 945 | 20.6% | 12.2 | 491 | 14.5% | 4.0 |
| Other | 11 | 0.2% | 4 | 0.1% | 2.5 | 2 | 0.1% | 3.5 |
| Setting of index VTE event[b] | | | | | | | | |
| Inpatient | 2,676 | 43.8% | 2,639 | 57.6% | 27.8 | 1,771 | 52.2% | 16.8 |
| Outpatient | 3,432 | 56.2% | 1,946 | 42.4% | 27.8 | 1,622 | 47.8% | 16.8 |
| Position of VTE diagnosis | | | | | | | | |
| Primary (principle or first listed) | 3,985 | 65.2% | 3,328 | 72.6% | 15.9 | 2,482 | 73.2% | 17.2 |
| Secondary | 2,123 | 34.8% | 1,257 | 27.4% | 15.9 | 911 | 26.8% | 17.2 |
| VTE diagnosis[b] | | | | | | | | |
| DVT only | 3,399 | 55.6% | 2,662 | 58.1% | 4.9 | 1,934 | 57.0% | 2.7 |
| PE with or without DVT | 2,709 | 44.4% | 1,923 | 41.9% | 4.9 | 1,459 | 43.0% | 2.7 |
| Baseline comorbidity[b] | | | | | | | | |
| Deyo–Charlson comorbidity index[e] | 1.6 | 1.8 | 2.3 | 2.2 | 34.0 | 2.1 | 2.1 | 23.6 |
| Acquired immunodeficiency syndrome | 44 | 0.7% | 25 | 0.5% | 2.2 | 9 | 0.3% | 6.5 |
| Alcohol abuse | 153 | 2.5% | 135 | 2.9% | 2.7 | 84 | 2.5% | 0.2 |
| Anemia | 2,790 | 45.7% | 2,025 | 44.2% | 3.0 | 1,397 | 41.2% | 9.1 |
| Central venous catheter | 2,078 | 34.0% | 1,067 | 23.3% | 23.9 | 785 | 23.1% | 24.3 |
| Cerebrovascular disease | 624 | 10.2% | 612 | 13.3% | 9.7 | 354 | 10.4% | 0.7 |
| Coagulation defects | 922 | 15.1% | 709 | 15.5% | 1.0 | 363 | 10.7% | 13.1 |
| Ischemic heart/coronary artery disease | 913 | 14.9% | 1,085 | 23.7% | 22.2 | 747 | 22.0% | 18.3 |
| Dementia | 49 | 0.8% | 137 | 3.0% | 16.1 | 114 | 3.4% | 18.0 |
| Dyspepsia or stomach discomfort | 2,383 | 39.0% | 1,534 | 33.5% | 11.6 | 1,043 | 30.7% | 17.4 |
| Hemiplegia or paraplegia | 182 | 3.0% | 121 | 2.6% | 2.1 | 74 | 2.2% | 5.0 |
| Hyperlipidemia | 2,081 | 34.1% | 2,129 | 46.4% | 25.4 | 1,544 | 45.5% | 23.5 |
| Obesity | 956 | 15.7% | 966 | 21.1% | 14.0 | 658 | 19.4% | 9.9 |
| Pneumonia | 1,001 | 16.4% | 855 | 18.6% | 5.9 | 564 | 16.6% | 0.6 |

| | Pre-IPTW | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | LMWH cohort (reference) | | Warfarin cohort | | | Apixaban cohort | | |
| | *N*/mean | %/SD | *N*/mean | %/SD | STD[a] | *N*/mean | %/SD | STD[a] |
| Rheumatologic disease | 120 | 2.0% | 166 | 3.6% | 10.1 | 145 | 4.3% | 13.3 |
| Sleep apnea | 531 | 8.7% | 552 | 12.0% | 11.0 | 389 | 11.5% | 9.2 |
| Spinal cord injury | 16 | 0.3% | 5 | 0.1% | 3.6 | 10 | 0.3% | 0.6 |
| Thrombophilia | 326 | 5.3% | 358 | 7.8% | 10.0 | 184 | 5.4% | 0.4 |
| Varicose veins | 75 | 1.2% | 115 | 2.5% | 9.5 | 95 | 2.8% | 11.2 |
| Congestive heart failure | 441 | 7.2% | 681 | 14.9% | 24.5 | 447 | 13.2% | 19.8 |
| Diabetes | 1,335 | 21.9% | 1,460 | 31.8% | 22.7 | 950 | 28.0% | 14.2 |
| Hypertension | 3,285 | 53.8% | 3,269 | 71.3% | 36.8 | 2,345 | 69.1% | 31.9 |
| Renal disease | 1,106 | 18.1% | 1,409 | 30.7% | 29.7 | 964 | 28.4% | 24.6 |
| Liver disease | 1,641 | 26.9% | 756 | 16.5% | 25.4 | 561 | 16.5% | 25.3 |
| Chronic obstructive pulmonary disease | 956 | 15.7% | 1,060 | 23.1% | 19.0 | 734 | 21.6% | 15.4 |
| Peptic ulcer disease | 170 | 2.8% | 135 | 2.9% | 1.0 | 69 | 2.0% | 4.9 |
| Inflammatory bowel disease | 91 | 1.5% | 81 | 1.8% | 2.2 | 65 | 1.9% | 3.3 |
| Peripheral vascular disease | 700 | 11.5% | 867 | 18.9% | 20.9 | 566 | 16.7% | 15.1 |
| Baseline any bleed | 2,145 | 35.1% | 1,596 | 34.8% | 0.6 | 939 | 27.7% | 16.1 |
| Recent history of falls[b] | 158 | 2.6% | 255 | 5.6% | 15.1 | 160 | 4.7% | 11.4 |
| Fracture/trauma involving lower extremities[b] | 365 | 6.0% | 445 | 9.7% | 13.9 | 326 | 9.6% | 13.6 |
| Selected surgeries | 2,933 | 48.0% | 2,090 | 45.6% | 4.9 | 1,464 | 43.1% | 9.8 |
| Baseline medication use[b] | | | | | | | | |
| Antiarrhythmic | 1,687 | 27.6% | 795 | 17.3% | 24.8 | 700 | 20.6% | 16.4 |
| Statins | 1,558 | 25.5% | 1,722 | 37.6% | 26.2 | 1,202 | 35.4% | 21.7 |
| Antiplatelets | 155 | 2.5% | 282 | 6.2% | 17.8 | 206 | 6.1% | 17.5 |
| Aromatase inhibitors | 208 | 3.4% | 246 | 5.4% | 9.6 | 244 | 7.2% | 17.0 |
| Beta blockers | 1,335 | 21.9% | 1,566 | 34.2% | 27.6 | 1,067 | 31.4% | 21.8 |
| Gastroprotective agents | 2,165 | 35.4% | 1,554 | 33.9% | 3.3 | 1,091 | 32.2% | 7.0 |
| Selective estrogen receptor modulator | 117 | 1.9% | 155 | 3.4% | 9.1 | 121 | 3.6% | 10.1 |
| Nonsteroidal anti-inflammatory drugs | 1,356 | 22.2% | 1,093 | 23.8% | 3.9 | 842 | 24.8% | 6.2 |
| Hormone therapy | 205 | 3.4% | 90 | 2.0% | 8.7 | 78 | 2.3% | 6.4 |
| Cancer site[f] | | | | | | | | |
| Leukemia | 302 | 4.9% | 208 | 4.5% | 1.9 | 145 | 4.3% | 3.2 |
| Bladder | 228 | 3.7% | 266 | 5.8% | 9.7 | 161 | 4.7% | 5.0 |
| Brain tumor | 537 | 8.8% | 230 | 5.0% | 14.9 | 122 | 3.6% | 21.7 |
| Gynecologic (uterus, cervix, placenta, ovary, other female genital organs) | 742 | 12.1% | 328 | 7.2% | 17.0 | 208 | 6.1% | 21.0 |
| Lung | 1,364 | 22.3% | 626 | 13.7% | 22.7 | 486 | 14.3% | 20.8 |
| Lymphoma | 638 | 10.4% | 451 | 9.8% | 2.0 | 314 | 9.3% | 4.0 |
| Pancreas | 528 | 8.6% | 140 | 3.1% | 24.0 | 144 | 4.2% | 18.0 |
| Renal cell carcinoma | 327 | 5.4% | 269 | 5.9% | 2.2 | 171 | 5.0% | 1.4 |
| Testicular | 67 | 1.1% | 31 | 0.7% | 4.5 | 22 | 0.6% | 4.8 |
| Upper GI cancer (esophagus, stomach) | 297 | 4.9% | 115 | 2.5% | 12.5 | 95 | 2.8% | 10.8 |
| | 783 | 12.8% | 561 | 12.2% | 1.8 | 394 | 11.6% | 3.7 |

(*Continued*)

| | Pre-IPTW | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | LMWH cohort (reference) | | Warfarin cohort | | | Apixaban cohort | | |
| | N/mean | %/SD | N/mean | %/SD | STD[a] | N/mean | %/SD | STD[a] |
| Lower GI cancer (small intestine, large intestine, rectum, and anus) | | | | | | | | |
| Female breast cancer | 833 | 13.6% | 791 | 17.3% | 10.0 | 689 | 20.3% | 17.8 |
| Prostate cancer | 346 | 5.7% | 699 | 15.2% | 31.7 | 541 | 15.9% | 33.6 |
| Multiple myeloma | 234 | 3.8% | 206 | 4.5% | 3.3 | 136 | 4.0% | 0.9 |
| Cancer metastasis[b,f] | 4,200 | 68.8% | 1,514 | 33.0% | 76.5 | 1,264 | 37.3% | 66.5 |
| Cancer type[b,f,g] | | | | | | | | |
| Hematological | 1,010 | 16.5% | 731 | 15.9% | 1.6 | 550 | 16.2% | 0.9 |
| Nonhematological | 5,098 | 83.5% | 3,847 | 83.9% | 1.2 | 2,831 | 83.4% | 0.1 |
| VTE risk scale[b,f] | | | | | | | | |
| Very high risk[h] | 1,259 | 20.6% | 439 | 9.6% | 31.2 | 322 | 9.5% | 31.5 |
| High risk[i] | 2,757 | 45.1% | 1,723 | 37.6% | 15.4 | 1,174 | 34.6% | 21.6 |
| Other cancers | 2,092 | 34.3% | 2,423 | 52.8% | 38.2 | 1,897 | 55.9% | 44.6 |
| Cancer-related treatment[f] | | | | | | | | |
| Number of patients who had cancer-related treatment during the baseline period until 30 days after the index date | 5,415 | 88.7% | 2,915 | 63.6% | 61.5 | 2,320 | 68.4% | 50.9 |
| Chemotherapy[b] | 4,908 | 80.4% | 2,158 | 47.1% | 73.8 | 1,752 | 51.6% | 63.6 |
| Hormone therapy[b] | 240 | 3.9% | 327 | 7.1% | 14.0 | 287 | 8.5% | 18.9 |
| Immunotherapy[b] | 186 | 3.0% | 34 | 0.7% | 17.0 | 60 | 1.8% | 8.3 |
| Radiation[b] | 2,546 | 41.7% | 1,225 | 26.7% | 31.9 | 1,072 | 31.6% | 21.1 |
| Cancer-related surgery[b] | 1,075 | 17.6% | 381 | 8.3% | 27.9 | 277 | 8.2% | 28.4 |

Abbreviations: IPTW, inverse probability of treatment weighing; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; SD, standard deviation; STD, standardized difference; VTE, venous thromboembolism.
[a]STD = 100 × |actual STD|. STD > 10.00 is considered significant.
[b]Variables that were adjusted in the IPTW to balance patient characteristics between apixaban, LMWH, and warfarin cohorts.
[c]After applying weights, the values for age category were not whole numbers; therefore, due to rounding the sum of patients does not equal 100%.
[d]Some patients in Optum and PharMetrics data have missing information on gender. Hence, the sum of male and female is not equal to 100%.
[e]A modified comorbidity index was used which included myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes, diabetes w/ complications, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, and acquired immune deficiency syndrome.
[f]Cancer-related variables will be measured 6 months prior to the index date until 30 days after the index date.
[g]The sum of hematological and nonhematological cancers was not equal to 100% since very small number of patients had a cancer diagnosis at month 6 before the index VTE event (month 7 before the index date) and not captured in the baseline period.
[h]Very high risk (brain, stomach, and pancreas).
[i]High risk (lung, lymphoma, gynecologic, bladder, testicular, and renal cell carcinoma).

## 7.3. Outcome Data

When the follow-up was censored at 6 months, the mean follow-up was 108.5 days, 93.3 days, and 117.8 days for apixaban, LMWH, and warfarin patients, respectively (Table 5). The unadjusted incidence rate of MB—including GI, ICH, and other bleeding—was 10.2 (apixaban), 20.7 (LMWH), and 14.3 (warfarin) per 100 person-years. The unadjusted incidence rate of recurrent VTE was 13.9 (apixaban), 26.6 (LMWH), and 19.7 (warfarin) per 100 person-years.

When using all available follow-up, before IPTW, the mean follow-up was 143.7 days, 113.5 days, and 177.1 days for apixaban, LMWH, and warfarin patients, respectively (Table 5). The

unadjusted incidence rate of MB—including GI, ICH, and other bleeding—was 8.2 (apixaban), 18.6 (LMWH), and 10.4 (warfarin) per 100 person-years. Similarly, the unadjusted incidence rate of recurrent VTE was 10.2 (apixaban), 22.0 (LMWH), and 13.9 (warfarin) per 100 person-years.

**Table 5. Phase 1 Pre-IPTW Outcomes**

| | LMWH Cohort | | Warfarin Cohort | | Apixaban Cohort | |
|---|---|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD | N/Mean | %/SD |
| **Sample Size** | **6,108** | | **4,585** | | **3,393** | |
| **FULL FOLLOW-UP** | | | | | | |
| **Follow-up Time (in days), (Mean, SD)** | 113.51 | 110.79 | 177.11 | 174.41 | 143.65 | 133.61 |
| **Major Bleeding Incidence Rate (per 100 person-years)** | 18.62 | | 10.44 | | 8.18 | |
| Gastrointestinal (GI) Bleeding | 4.82 | | 4.39 | | 3.12 | |
| Intracranial Hemorrhage | 3.13 | | 1.24 | | 0.37 | |
| Other Bleeding | 10.80 | | 5.26 | | 4.77 | |
| **CRNM Bleeding Incidence Rate (per 100 person-years)** | 45.03 | | 39.68 | | 36.13 | |
| Gastrointestinal (GI) Bleeding | 10.03 | | 9.50 | | 10.67 | |
| Other Bleeding | 34.34 | | 29.37 | | 24.45 | |
| **Recurrent VTE Incidence Rate (per 100 person-years)** | 21.98 | | 13.85 | | 10.19 | |
| DVT | 12.98 | | 8.38 | | 6.52 | |
| PE | 9.33 | | 5.69 | | 4.02 | |
| **CENSORED AT 6-MONTHS OF FOLLOW-UP** | | | | | | |
| **Follow-up Time (in days), (Mean, SD)** | 93.33 | 56.93 | 117.85 | 62.06 | 108.51 | 60.97 |
| **Major Bleeding Incidence Rate (per 100 person-years)** | 20.73 | | 14.33 | | 10.19 | |
| Gastrointestinal (GI) Bleeding | 4.69 | | 5.43 | | 4.14 | |
| Intracranial Hemorrhage | 3.17 | | 1.46 | | 0.51 | |
| Other Bleeding | 12.99 | | 7.88 | | 5.71 | |
| **CRNM Bleeding Incidence Rate (per 100 person-years)** | 49.96 | | 47.89 | | 41.20 | |
| Gastrointestinal (GI) Bleeding | 11.38 | | 12.08 | | 12.54 | |
| Other Bleeding | 38.28 | | 36.02 | | 28.05 | |
| **Recurrent VTE Incidence Rate (per 100 person-years)** | 26.59 | | 19.67 | | 13.92 | |
| DVT | 15.44 | | 12.19 | | 8.59 | |
| PE | 11.81 | | 7.97 | | 5.71 | |

## 7.4. Main Results

### 7.4.1. Post-IPTW Baseline Characteristics

Post-IPTW baseline characteristics among VTE cancer patients are described in Table 6. After applying IPTW, all patient characteristics were balanced. In the IPTW population, ~34% of

patients had a history of baseline bleed, 51% had metastatic cancer, and 63% received chemotherapy during the baseline period. Further, 15% had very high-risk cancer and 40% had high-risk cancer.

**Table 6: Phase 1 Post-IPTW patient characteristics**

| | LMWH cohort (reference) | | Warfarin cohort | | | Apixaban cohort | | |
|---|---|---|---|---|---|---|---|---|
| | *N*/mean | %/SD | *N*/mean | %/SD | STD[a] | *N*/mean | %/SD | STD[a] |
| Sample size | *6,108* | | *4,585* | | | *3,393* | | |
| Age[b] | 63.7 | 13.2 | 64.2 | 12.9 | 3.5 | 64.6 | 12.6 | 7.1 |
| 18–54 | 1,247 | 20.4% | 967 | 21.1% | 1.7 | 660 | 19.4% | 2.4 |
| 55–64 | 1,970 | 32.3% | 1,475 | 32.2% | 0.2 | 1,105 | 32.6% | 0.7 |
| 65–74 | 1,531 | 25.1% | 1,139 | 24.9% | 0.5 | 875 | 25.8% | 1.7 |
| 75–79 | 636 | 10.4% | 462 | 10.1% | 1.1 | 353 | 10.4% | 0.1 |
| ≥80 | 723 | 11.8% | 541 | 11.8% | 0.1 | 400 | 11.8% | 0.1 |
| Gender[c] | | | | | | | | |
| Male | 2,869 | 47.0% | 2,171 | 47.3% | 0.7 | 1,621 | 47.8% | 1.6 |
| Female | 3,237 | 53.0% | 2,412 | 52.6% | 0.8 | 1,772 | 52.2% | 1.6 |
| Setting of index VTE event | | | | | | | | |
| Inpatient | 3,017 | 49.4% | 2,313 | 50.4% | 2.1 | 1,679 | 49.5% | 0.2 |
| Outpatient | 3,091 | 50.6% | 2,272 | 49.6% | 2.1 | 1,714 | 50.5% | 0.2 |
| VTE diagnosis | | | | | | | | |
| DVT only | 3,605 | 59.0% | 2,643 | 57.6% | 2.8 | 1,938 | 57.1% | 3.9 |
| PE with or without DVT | 2,503 | 41.0% | 1,942 | 42.4% | 2.8 | 1,455 | 42.9% | 3.9 |
| Baseline comorbidity | | | | | | | | |
| Deyo–Charlson comorbidity index[d] | 2.0 | 2.1 | 1.9 | 2.0 | 1.9 | 2.0 | 2.0 | 0.5 |
| Central venous catheter | 1,790 | 29.3% | 1,314 | 28.7% | 1.4 | 985 | 29.0% | 0.6 |
| Cerebrovascular disease | 712 | 11.7% | 528 | 11.5% | 0.5 | 391 | 11.5% | 0.4 |
| Coagulation defects | 894 | 14.6% | 657 | 14.3% | 0.9 | 503 | 14.8% | 0.6 |
| Ischemic heart/coronary artery disease | 1,182 | 19.3% | 888 | 19.4% | 0.0 | 667 | 19.7% | 0.8 |
| Dyspepsia or stomach discomfort | 2,205 | 36.1% | 1,629 | 35.5% | 1.2 | 1,222 | 36.0% | 0.2 |

(*Continued*)

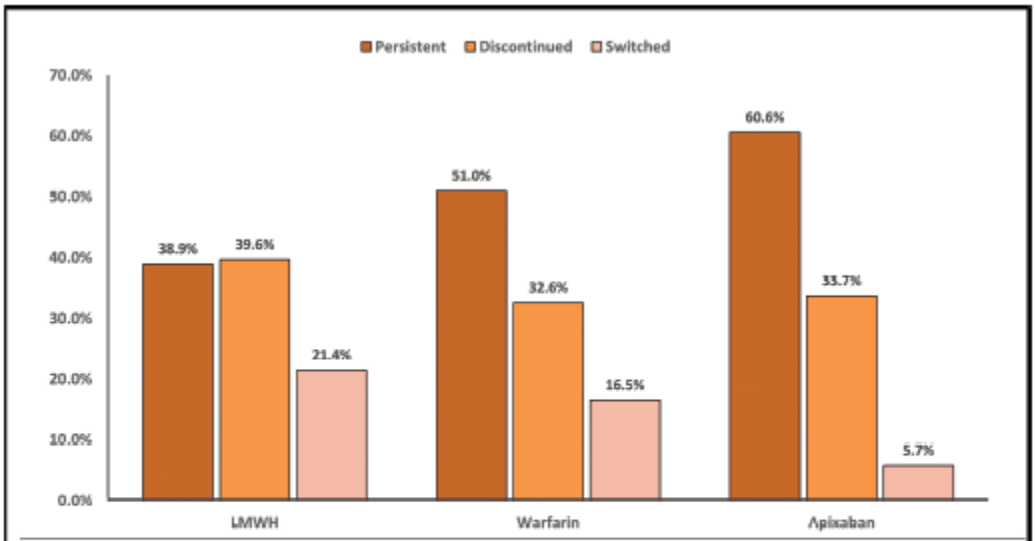
| | LMWH cohort (reference) | | Warfarin cohort | | | Apixaban cohort | | |
|---|---|---|---|---|---|---|---|---|
| | *N*/mean | %/SD | *N*/mean | %/SD | STD[a] | *N*/mean | %/SD | STD[a] |
| Hemiplegia or paraplegia | 171 | 2.8% | 126 | 2.8% | 0.3 | 93 | 2.7% | 0.4 |
| Hyperlipidemia | 2,424 | 39.7% | 1,864 | 40.6% | 2.0 | 1,391 | 41.0% | 2.7 |
| Obesity | 1,118 | 18.3% | 843 | 18.4% | 0.2 | 615 | 18.1% | 0.5 |
| Pneumonia | 1,040 | 17.0% | 791 | 17.2% | 0.6 | 586 | 17.3% | 0.7 |
| Sleep apnea | 593 | 9.7% | 460 | 10.0% | 1.1 | 365 | 10.8% | 3.5 |
| Thrombophilia | 328 | 5.4% | 268 | 5.9% | 2.1 | 210 | 6.2% | 3.5 |
| Congestive heart failure | 676 | 11.1% | 511 | 11.1% | 0.3 | 366 | 10.8% | 0.9 |
| Diabetes | 1,637 | 26.8% | 1,219 | 26.6% | 0.5 | 907 | 26.7% | 0.2 |
| Hypertension | 3,834 | 62.8% | 2,860 | 62.4% | 0.8 | 2,170 | 64.0% | 2.5 |
| Liver disease | 1,334 | 21.8% | 968 | 21.1% | 1.8 | 770 | 22.7% | 2.0 |
| Chronic obstructive pulmonary disease | 1,253 | 20.5% | 913 | 19.9% | 1.5 | 667 | 19.7% | 2.2 |
| Baseline any bleed | 2,088 | 34.2% | 1,575 | 34.3% | 0.3 | 1,132 | 33.4% | 1.8 |
| Recent history of falls | 259 | 4.2% | 176 | 3.8% | 2.1 | 147 | 4.3% | 0.5 |
| Fracture/trauma involving lower extremities | 530 | 8.7% | 364 | 7.9% | 2.7 | 288 | 8.5% | 0.7 |
| Selected surgeries | 2,966 | 48.6% | 2,105 | 45.9% | 5.3 | 1,586 | 46.7% | 3.7 |
| Cancer metastasis[e] | 3,172 | 51.9% | 2,344 | 51.1% | 1.6 | 1,727 | 50.9% | 2.1 |
| Cancer type[e,f] | | | | | | | | |
| Hematological | 992 | 16.2% | 749 | 16.3% | 0.3 | 543 | 16.0% | 0.7 |
| Nonhematological | 5,116 | 83.8% | 3,830 | 83.5% | 0.6 | 2,846 | 83.9% | 0.3 |
| VTE risk scale[e] | | | | | | | | |
| Very high risk[g] | 921 | 15.1% | 708 | 15.4% | 1.0 | 518 | 15.3% | 0.5 |
| High risk[h] | 2,502 | 41.0% | 1,849 | 40.3% | 1.3 | 1,343 | 39.6% | 2.8 |
| Other cancers | 2,685 | 44.0% | 2,028 | 44.2% | 0.6 | 1,532 | 45.2% | 2.4 |
| Cancer-related treatment[e] | | | | | | | | |
| Number of patients that had cancer-related treatment during the baseline period until 30 days after the index date | 4,722 | 77.3% | 3,494 | 76.2% | 2.6 | 2,560 | 75.4% | 4.4 |
| Chemotherapy | 3,895 | 63.8% | 2,889 | 63.0% | 1.6 | 2,139 | 63.0% | 1.5 |
| Hormone therapy | 364 | 6.0% | 270 | 5.9% | 0.3 | 201 | 5.9% | 0.2 |
| Immunotherapy | 125 | 2.0% | 94 | 2.0% | 0.0 | 64 | 1.9% | 1.3 |
| Radiation | 2197 | 36.0% | 1638 | 35.7% | 0.5 | 1,180 | 34.8% | 2.5 |
| Cancer-related surgery | 775 | 12.7% | 611 | 13.3% | 1.9 | 430 | 12.7% | 0.1 |

Abbreviations: DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; SD, standard deviation; STD, standardized difference; VTE, venous thromboembolism.
[a]STD = 100 × |actual STD|. STD > 10.00 is considered significant.
[b]After applying weights, the values for age category were not whole numbers; therefore, due to rounding the sum of patients does not equal 100%.
[c]Some patients in Optum and PharMetrics data have missing information on gender. Hence, the sum of male and female is not equal to 100%.
[d]A modified comorbidity index was used which included myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, rheumatologic disease, peptic ulcer disease, mild liver disease, diabetes, diabetes w/ complications, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, and acquired immune deficiency syndrome.
[e]Cancer-related variables will be measured 6 months prior to the index date until 30 days after the index date.
[f]The sum of hematological and nonhematological cancer was not equal to 100% since a very small number of patients had a cancer diagnosis at month 6 before the index VTE event (month 7 before the index date) and not captured in the baseline period.
[g]Very high risk (brain, stomach, and pancreas).
[h]High risk (lung, lymphoma, gynecologic, bladder, testicular, and renal cell carcinoma).

### 7.4.2. Treatment Patterns

Figure 6 shows treatment patterns when patients were censored at 6 months of follow-up. Apixaban patients had the largest proportion who were persistent and lowest proportion of switching compared to LMWH and warfarin. When the follow-up was censored at 6 months, apixaban (HR: 0.52; 95% [CI]: 0.48-0.56) and warfarin (HR: 0.60; 95% CI: 0.56-0.64) patients had a lower risk of non-persistence compared to LMWH patients (Table 7). Additionally, apixaban patients also had a lower risk of non-persistence compared to warfarin patients (HR: 0.87; 95% CI: 0.80-0.94). Consistent results were observed when using all available follow-up: apixaban (hazard ratio [HR]: 0.51; 95% confidence interval [CI]: 0.48-0.55) and warfarin (HR: 0.64; 95%CI: 0.60-0.68) patients had a lower risk of non-persistence compared to LMWH patients (Table 7). Apixaban patients also had a lower risk of non-persistence compared to warfarin patients (HR: 0.89; 95% CI: 0.84-0.94) using all available follow-up.

**Figure 6: Treatment patterns of apixaban, LMWH and warfarin**




| Switched to | | | |
|---|---|---|---|
| Apixaban | 5.2% | 2.5% | - |
| Dabigatran | 0.6% | 0.2% | 0.1% |
| Rivaroxaban | 8.2% | 4.6% | 0.9% |
| Warfarin | 4.6% | - | 0.7% |
| LMWH | - | 6.4% | 2.4% |
| UFH | 2.4% | 2.3% | 1.5% |
| Fondaparinux | 0.3% | 0.4% | 0.1% |

**Table 7. Risk of Non-persistence among VTE cancer patients with LMWH, warfarin or apixaban, post-IPTW**

| | Risk of Non-Persistence | | |
|---|---|---|---|
| | Hazard Ratio | 95% CI | P-value |
| **Censoring Follow-up at 6 Months** | | | |
| **Apixaban vs LMWH (ref)** | 0.52 | 0.48 - 0.56 | <0.001 |
| **Warfarin vs LMWH (ref)** | 0.6 | 0.56 - 0.64 | <0.001 |
| **Apixaban vs Warfarin (ref)** | 0.87 | 0.80 - 0.94 | 0.001 |
| **During Entire Follow-Up** | | | |
| **Apixaban vs LMWH (ref)** | 0.53 | 0.50 - 0.57 | <0.001 |
| **Warfarin vs LMWH (ref)** | 0.64 | 0.60 - 0.67 | <0.001 |
| **Apixaban vs Warfarin (ref)** | 0.84 | 0.79 - 0.91 | <0.001 |

### 7.4.3. Post-IPTW Outcomes Characteristics

Figure 7 shows incidence rates and hazard ratios of recurrent VTE, major bleeding, and CRNM bleeding among VTE cancer patients prescribed apixaban, LMWH, or warfarin in the IPTW-weighted population censoring follow-up at 6 months. When patients were censored at 6 months of follow-up, the mean follow-up was 105 days (3.5 months), 88 days (2.9 months), and 113 days (3.8 months) for apixaban, LMWH, and warfarin, respectively. The adjusted incidence rate of MB—including GI, ICH, and other bleeding—was 11.8 (apixaban), 20.1 (LMWH), and 15.7 (warfarin) per 100 person-years when the follow-up was censored at 6 months. The adjusted incidence rate of recurrent VTE was 15.8 (apixaban), 28.8 (LMWH), and 22.2 (warfarin) per 100 person-years.

Compared to LMWH, apixaban patients had a lower risk of MB (HR: 0.63; 95% CI: 0.47-0.86), CRNM bleeding (HR: 0.81; 95% CI: 0.70-0.94), and recurrent VTE (HR: 0.61; 95% CI: 0.47-0.81; Figure 7). Warfarin patients had a similar risk of MB (HR: 0.87; 95% CI: 0.68-1.12), CRNM bleeding (HR: 0.90; 95% CI: 0.79-1.04), and recurrent VTE (HR: 0.91; 95% CI: 0.72-1.15) compared to LMWH patients. Apixaban patients had a lower risk of recurrent VTE (HR: 0.68; 95% CI: 0.52-0.90) but a similar risk of MB (HR: 0.73; 95% CI: 0.53-1.00) and CRNM bleeding (HR; 0.89; 95% CI: 0.77-1.04) compared to warfarin patients.

**Figure 7: Phase 1 incidence rates and HRs in the IPTW-weighted population censoring follow-up at 6 months.**

| | Comparator | Reference | Hazard Ratio (95% CI) | P-value |
|---|---|---|---|---|
| | No. of events (incidence per 100 person-years) | | | |
| **Apixaban vs LMWH (ref)** | **(N = 3,393** | **vs N = 6,108)** | | |
| Recurrent VTE[a] | 114 (15.8) | 314 (28.8) | 0.61 (0.47-0.81) | 0.001 |
| Major bleeding[b] | 85 (11.8) | 224 (20.1) | 0.63 (0.47-0.86) | 0.003 |
| GI bleeding | 29 (3.9) | 49 (4.3) | 0.97 (0.59-1.58) | 0.892 |
| ICH | 5 (0.6) | 33 (2.9) | 0.22 (0.07-0.70) | 0.011 |
| Other bleeding | 54 (7.4) | 147 (13.1) | 0.62 (0.41-0.92) | 0.018 |
| CRNM bleeding[c] | 387 (42.4) | 773 (56.4) | 0.81 (0.70-0.94) | 0.006 |
| GI bleeding | 129 (13.4) | 163 (11.1) | 1.30 (0.98-1.72) | 0.069 |
| Other bleeding | 266 (28.3) | 627 (45.0) | 0.68 (0.57-0.81) | <0.001 |
| **Warfarin vs LMWH (ref)** | **(N = 4,585** | **vs N = 6,108)** | | |
| Recurrent VTE[a] | 240 (22.2) | 314 (28.8) | 0.91 (0.72-1.15) | 0.421 |
| Major bleeding[b] | 171 (15.7) | 224 (20.1) | 0.87 (0.68-1.12) | 0.282 |
| GI bleeding | 54 (4.8) | 49 (4.3) | 1.25 (0.82-1.90) | 0.297 |
| ICH | 16 (1.4) | 33 (2.9) | 0.50 (0.25-1.00) | 0.050 |
| Other bleeding | 108 (9.8) | 147 (13.1) | 0.85 (0.61-1.19) | 0.354 |
| CRNM bleeding[c] | 606 (46.6) | 773 (56.4) | 0.90 (0.79-1.04) | 0.146 |
| GI bleeding | 151 (10.8) | 163 (11.1) | 1.08 (0.83-1.39) | 0.580 |
| Other bleeding | 476 (35.9) | 627 (45.0) | 0.88 (0.75-1.03) | 0.098 |
| **Apixaban vs Warfarin (ref)** | **(N = 3,393** | **vs N = 4,585)** | | |
| Recurrent VTE[a] | 114 (15.8) | 240 (22.2) | 0.68 (0.52-0.90) | 0.007 |
| Major bleeding[b] | 85 (11.8) | 171 (15.7) | 0.73 (0.53-1.00) | 0.051 |
| GI bleeding | 29 (3.9) | 54 (4.8) | 0.78 (0.49-1.26) | 0.308 |
| ICH | 5 (0.6) | 16 (1.4) | 0.42 (0.12-1.43) | 0.166 |
| Other bleeding | 54 (7.4) | 108 (9.8) | 0.72 (0.47-1.11) | 0.140 |
| CRNM bleeding[c] | 387 (42.4) | 606 (46.6) | 0.89 (0.77-1.04) | 0.145 |
| GI bleeding | 129 (13.4) | 151 (10.8) | 1.21 (0.93-1.57) | 0.163 |
| Other bleeding | 266 (28.3) | 476 (35.9) | 0.78 (0.65-0.93) | 0.005 |

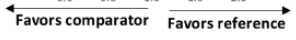
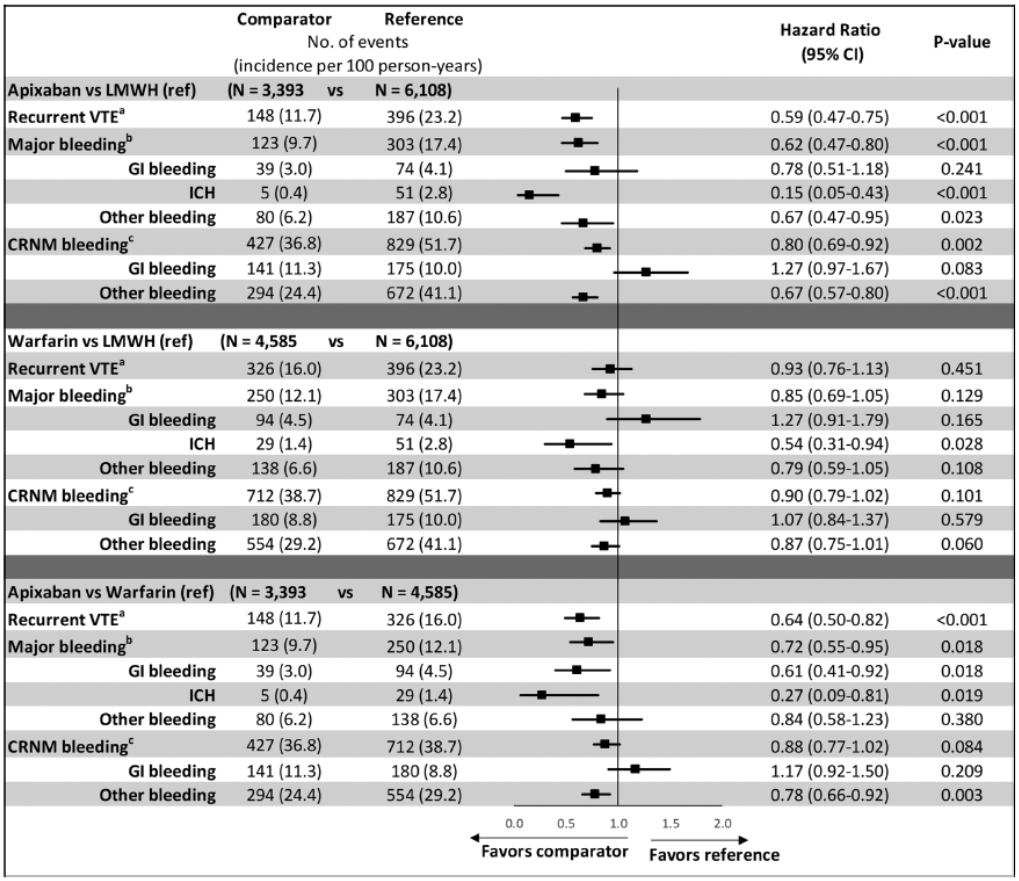



Figure 8 shows incidence rates and hazard ratios of outcomes in the IPTW-weighted population during the entire follow-up. When the entire available follow-up was evaluated, the mean follow-up was 137 days (4.6 months), 105 days (3.5 months), and 166 days (5.5 months) for the apixaban, LMWH, and warfarin cohorts, respectively. The maximum length of follow-up was about 3 years for apixaban and LMWH and 3.3 years for warfarin. Findings when using the entire follow-up period were generally consistent compared to the outcomes when follow-up was censored at 6 months. One difference is that apixaban patients had a significantly lower risk of MB (HR: 0.72; 95% CI: 0.55-0.95) compared to warfarin patients during the entire follow-up.

**Figure 8: Phase 1 incidence rates and HRs in the IPTW-weighted population during the entire follow-up**



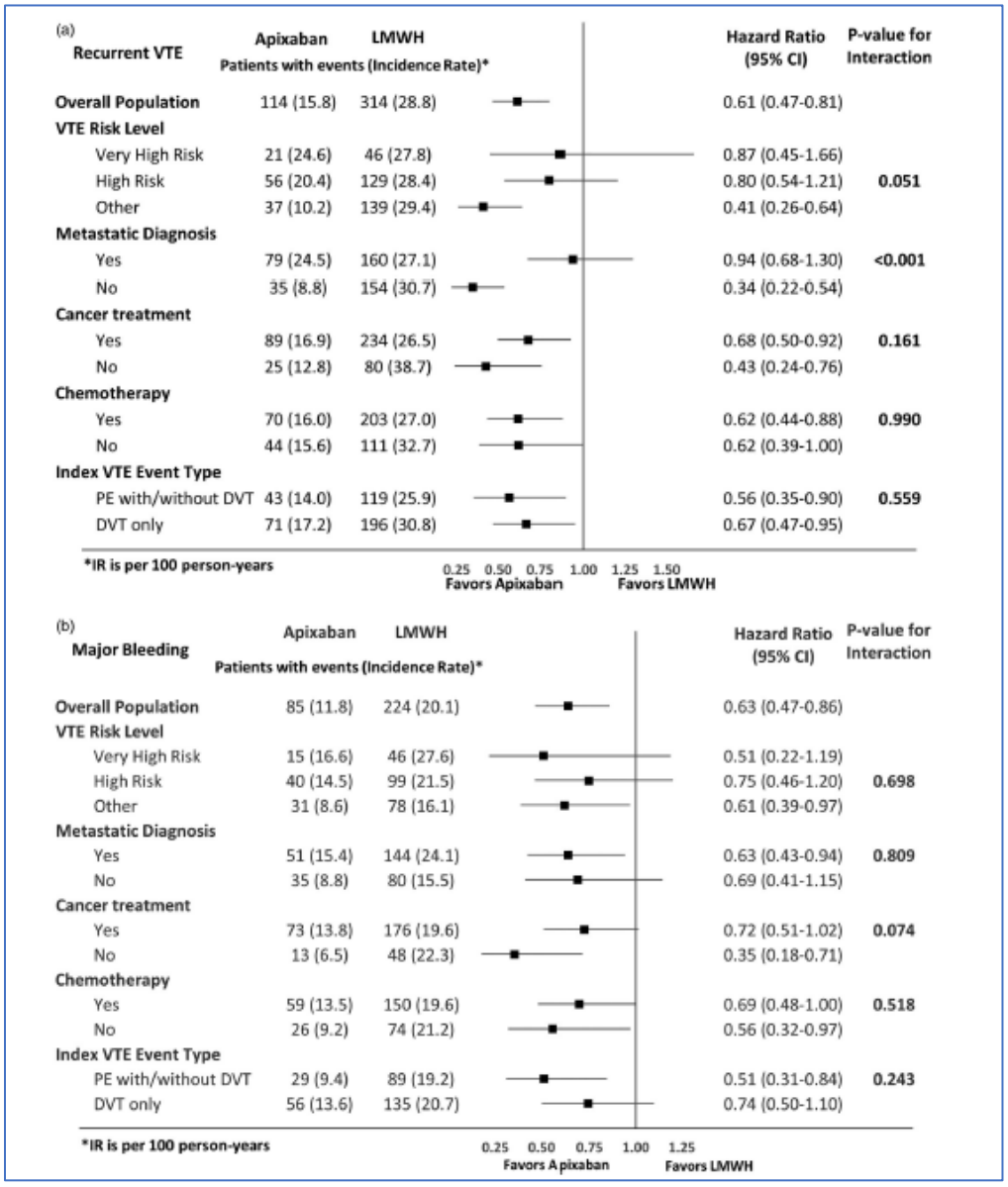
| | Comparator No. of events (incidence per 100 person-years) | Reference No. of events (incidence per 100 person-years) | Hazard Ratio (95% CI) | P-value |
|---|---|---|---|---|
| **Apixaban vs LMWH (ref)** | **(N = 3,393 vs** | **N = 6,108)** | | |
| Recurrent VTE[a] | 148 (11.7) | 396 (23.2) | 0.59 (0.47-0.75) | <0.001 |
| Major bleeding[b] | 123 (9.7) | 303 (17.4) | 0.62 (0.47-0.80) | <0.001 |
| GI bleeding | 39 (3.0) | 74 (4.1) | 0.78 (0.51-1.18) | 0.241 |
| ICH | 5 (0.4) | 51 (2.8) | 0.15 (0.05-0.43) | <0.001 |
| Other bleeding | 80 (6.2) | 187 (10.6) | 0.67 (0.47-0.95) | 0.023 |
| CRNM bleeding[c] | 427 (36.8) | 829 (51.7) | 0.80 (0.69-0.92) | 0.002 |
| GI bleeding | 141 (11.3) | 175 (10.0) | 1.27 (0.97-1.67) | 0.083 |
| Other bleeding | 294 (24.4) | 672 (41.1) | 0.67 (0.57-0.80) | <0.001 |
| **Warfarin vs LMWH (ref)** | **(N = 4,585 vs** | **N = 6,108)** | | |
| Recurrent VTE[a] | 326 (16.0) | 396 (23.2) | 0.93 (0.76-1.13) | 0.451 |
| Major bleeding[b] | 250 (12.1) | 303 (17.4) | 0.85 (0.69-1.05) | 0.129 |
| GI bleeding | 94 (4.5) | 74 (4.1) | 1.27 (0.91-1.79) | 0.165 |
| ICH | 29 (1.4) | 51 (2.8) | 0.54 (0.31-0.94) | 0.028 |
| Other bleeding | 138 (6.6) | 187 (10.6) | 0.79 (0.59-1.05) | 0.108 |
| CRNM bleeding[c] | 712 (38.7) | 829 (51.7) | 0.90 (0.79-1.02) | 0.101 |
| GI bleeding | 180 (8.8) | 175 (10.0) | 1.07 (0.84-1.37) | 0.579 |
| Other bleeding | 554 (29.2) | 672 (41.1) | 0.87 (0.75-1.01) | 0.060 |
| **Apixaban vs Warfarin (ref)** | **(N = 3,393 vs** | **N = 4,585)** | | |
| Recurrent VTE[a] | 148 (11.7) | 326 (16.0) | 0.64 (0.50-0.82) | <0.001 |
| Major bleeding[b] | 123 (9.7) | 250 (12.1) | 0.72 (0.55-0.95) | 0.018 |
| GI bleeding | 39 (3.0) | 94 (4.5) | 0.61 (0.41-0.92) | 0.018 |
| ICH | 5 (0.4) | 29 (1.4) | 0.27 (0.09-0.81) | 0.019 |
| Other bleeding | 80 (6.2) | 138 (6.6) | 0.84 (0.58-1.23) | 0.380 |
| CRNM bleeding[c] | 427 (36.8) | 712 (38.7) | 0.88 (0.77-1.02) | 0.084 |
| GI bleeding | 141 (11.3) | 180 (8.8) | 1.17 (0.92-1.50) | 0.209 |
| Other bleeding | 294 (24.4) | 554 (29.2) | 0.78 (0.66-0.92) | 0.003 |



## 7.5. Subgroup analysis

Findings on subgroup analysis for apixaban vs. LMWH (Figure 9), apixaban vs. warfarin (Figure 10), and warfarin vs. LMWH (Figure 11) can be found below. The subgroup analyses' results were generally consistent with those of the main analysis. P values for subgroup interaction analyses, and incidence rates and hazard ratios of MB, and recurrent VTE for each subgroup strata can be found in Figure 9, Figure 10, and Figure 11.

## Figure 9: Subgroup analysis for apixaban vs. LMWH



## Figure 10: Subgroup analysis for apixaban vs. warfarin

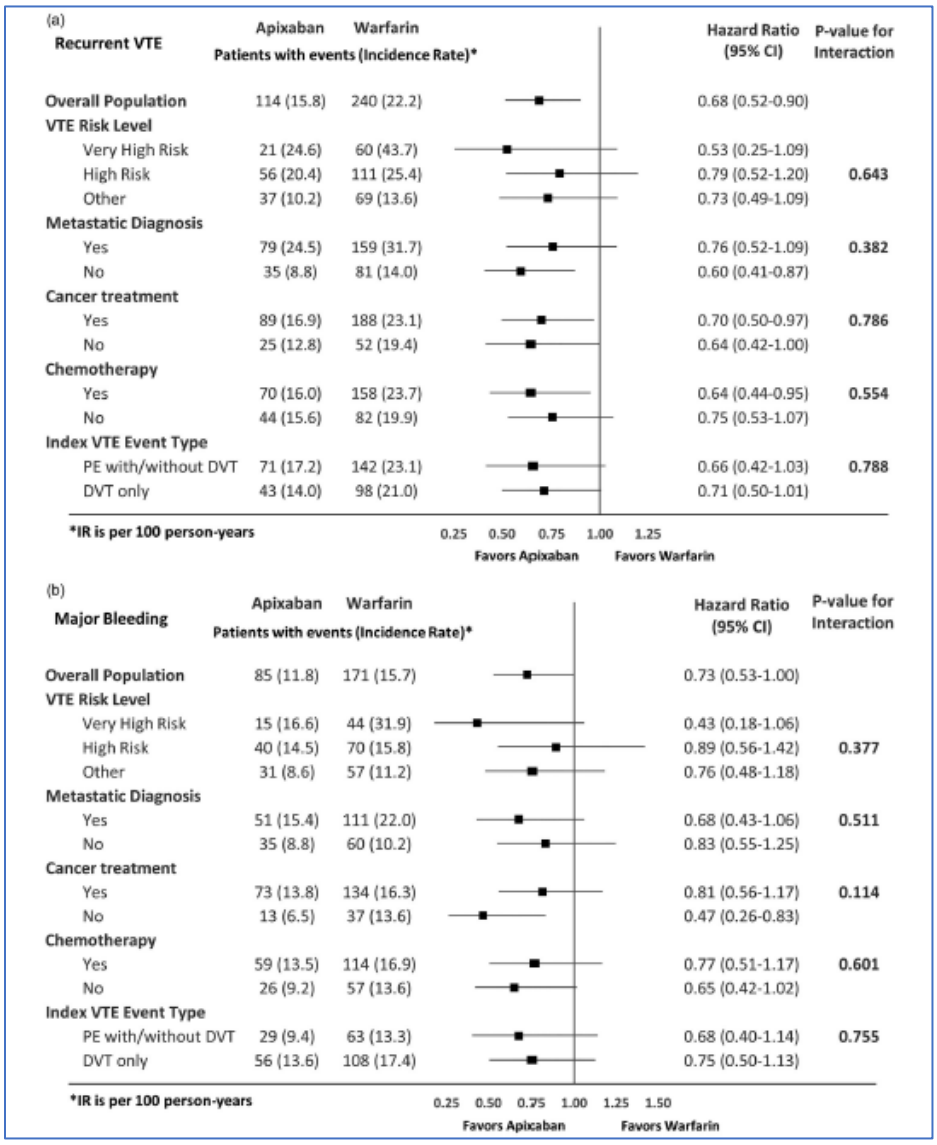
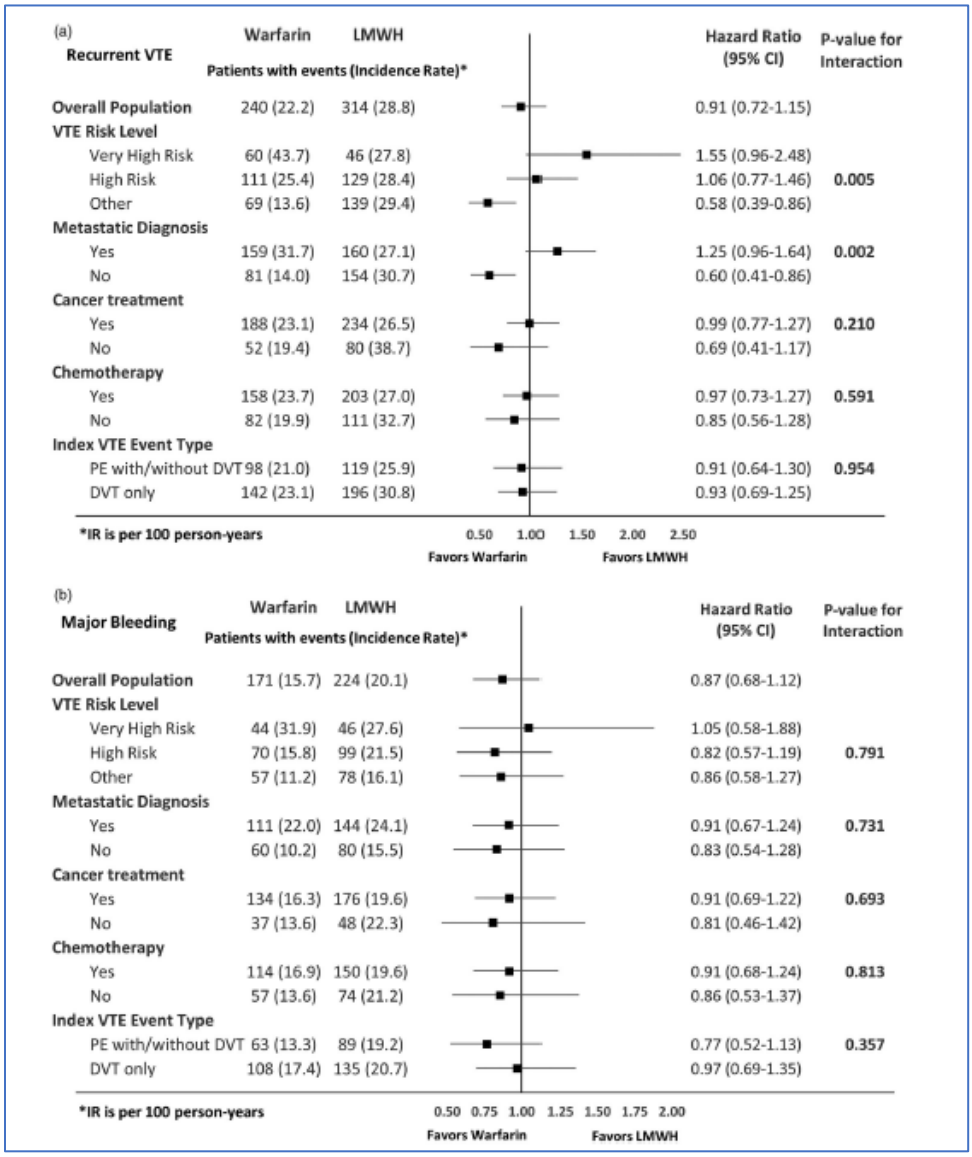


**Figure 11: Subgroup analysis for warfarin vs. LMWH**




No significant interaction was observed between anticoagulant treatment and VTE risk level for MB (Figure 9, Figure 10, and Figure 11). Two significant interactions were evident for recurrent VTE: apixaban trended towards a lower risk of recurrent VTE compared to LMWH across all three subgroups (p interaction=0.051), but the magnitude of the difference was larger in the other cancer group vs. very high-risk and high-risk cancer groups (Figure 8). For warfarin vs. LMWH, different trends in recurrent VTE risk were observed among patients with different VTE risk levels (p interaction=0.005) (Figure 11).

No significant interaction was observed between anticoagulant treatment and metastatic diagnosis for MB, but two significant interactions were observed for recurrent VTE (Figure 9, Figure 10, and Figure 11). Apixaban and warfarin patients had a lower risk of recurrent VTE vs. LMWH in

patients without a metastatic diagnosis whereas apixaban and warfarin had similar risk of recurrent VTE vs LMWH in patients with a metastatic diagnosis (Figure 9 and Figure 11).

There was a significant interaction between anticoagulant treatment and cancer treatment strata on MB: apixaban trended towards a lower risk of MB vs. LMWH with or without cancer treatment; however, patients without cancer treatment had a larger difference vs. patients with cancer treatment (p interaction=0.074) (Figure 9). No other significant interactions were seen between anticoagulant treatment and cancer treatment across comparisons (Figure 9, Figure 10, and Figure 11).

No significant interaction was observed between anticoagulant treatment and chemotherapy, between anticoagulant treatment and VTE event type, and between anticoagulant treatment and GI cancer for MB and recurrent VTE (Figure 9, Figure 10, and Figure 11).

No significant interaction was seen between anticoagulant treatment and GI/bladder cancer for MB (Figure 9, Figure 10, and Figure 11). Two significant interactions were observed for recurrent VTE: apixaban patients had a lower risk of recurrent VTE vs warfarin and LMWH in patients with no GI/bladder cancer whereas the risk of recurrent VTE was similar for apixaban vs warfarin and apixaban vs LMWH among patients with GI/bladder cancer (Figure 9 and Figure 10).

# 8. PHASE 2 RESULTS

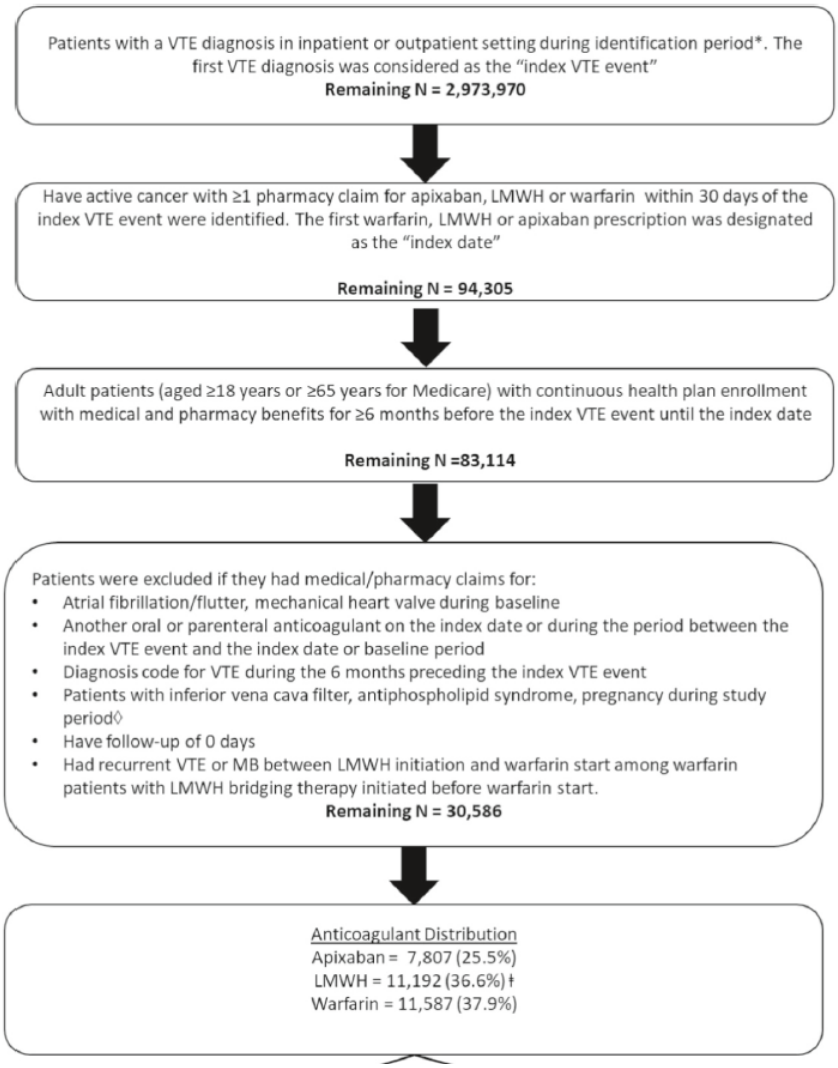
## 8.1. Participants

Figure 12 shows patient selection process in phase 2 analysis. After adding Medicare to the phase 2 analysis, a total of 30,586 patients met all eligibility criteria, 11,587 (37.9%) were prescribed warfarin, 11,192 (36.6%) were prescribed LMWH, and 7,807 (25.5%) were prescribed apixaban.

## 8.2. Baseline Characteristics

Pre-IPTW-weighted baseline characteristics among VTE cancer patients are described in Table 8. Before IPTW, warfarin patients were older with mean age of 73.10 years. A majority (55%) of patients had their index VTE as DVT only. The mean CCI ranged from 2.30 (LMWH), to 3.17 (warfarin). Prior bleed was prevalent among apixaban (29.03%), LMWH (35.90%) and warfarin (36.14%). Patients with LMWH were more likely to have very high risk or high-risk cancer than patients with apixaban or warfarin. Most patients (>50%) received cancer-related treatment.

## Figure 12: Patient selection process for phase 2 analysis




## Table 8: Phase 2 Pre-IPTW patient characteristics

| | Apixaban | LMWH | Warfarin | Apixaban vs LMWH | Apixaban vs Warfarin | LMWH vs Warfarin |
|---|---|---|---|---|---|---|
| | N=7,807 | N=11,192 | N=11,587 | STD | STD | STD |
| **Age (years)** | 72.7 (11.4) | 66.7 (12.4) | 73.1 (10.9) | 50.03 | 3.83 | 54.71 |
| 18-54 | 541 (6.9%) | 1,638 (14.6%) | 654 (5.6%) | 26.51 | 3.35 | 29.88 |
| 55-64 | 935 (12.0%) | 2,332 (20.8%) | 1,149 (10.0%) | 21.78 | 3.74 | 25.56 |
| 65-74 | 2,762 (35.4%) | 4,273 (38.2%) | 4,407 (38.0%) | 5.81 | 5.51 | 0.30 |
| 75-79 | 1,428 (18.3%) | 1,536 (13.7%) | 2,194 (18.9%) | 12.48 | 1.65 | 14.13 |

| | | | | | | |
|---|---|---|---|---|---|---|
| ≥80 | 2,141 (27.4%) | 1,413 (12.6%) | 3,183 (27.5%) | 37.63 | 0.10 | 37.73 |
| **Gender** | | | | | | |
| Male | 3,617 (46.3%) | 4,920 (44.0%) | 5,527 (47.7%) | 4.76 | 2.74 | 7.51 |
| Female | 4,190 (53.7%) | 6,272 (56.0%) | 6,060 (52.3%) | 4.76 | 2.74 | 7.51 |
| **Geographic Region** | | | | | | |
| Northeast | 1,293 (16.6%) | 2,893 (25.8%) | 2,064 (17.8%) | 22.87 | 3.32 | 19.54 |
| South | 3,761 (48.2%) | 3,698 (33.0%) | 3,745 (32.3%) | 31.19 | 32.76 | 1.54 |
| Midwest | 1,687 (21.6%) | 2,700 (24.1%) | 3,552 (30.7%) | 5.99 | 20.70 | 14.68 |
| West | 1,061 (13.6%) | 1,880 (16.8%) | 2,211 (19.1%) | 8.94 | 14.89 | 5.96 |
| Other | 5 (0.1%) | 21 (0.2%) | 15 (0.1%) | 3.49 | 2.10 | 1.46 |
| **Index VTE Setting** | | | | | | |
| Inpatient | 4,519 (57.9%) | 5,059 (45.2%) | 7,027 (60.6%) | 25.58 | 5.62 | 31.32 |
| Outpatient | 3,288 (42.1%) | 6,133 (54.8%) | 4,560 (39.4%) | 25.58 | 5.62 | 31.32 |
| ER | 2,773 (35.5%) | 5,288 (47.2%) | 4,020 (34.7%) | 23.98 | 1.73 | 25.74 |
| **Position of VTE Diagnosis** | | | | | | |
| Primary | 5,492 (70.3%) | 6,968 (62.3%) | 7,961 (68.7%) | 17.17 | 3.57 | 13.59 |
| Secondary | 2,315 (29.7%) | 4,224 (37.7%) | 3,626 (31.3%) | 17.17 | 3.57 | 13.59 |
| **VTE Diagnosis** | | | | | | |
| DVT only | 4,243 (54.3%) | 5,981 (53.4%) | 6,479 (55.9%) | 1.82 | 3.15 | 4.98 |
| PE with DVT | 1,030 (13.2%) | 1,127 (10.1%) | 1,518 (13.1%) | 9.75 | 0.27 | 9.48 |
| PE without DVT | 2,534 (32.5%) | 4,084 (36.5%) | 3,590 (31.0%) | 8.49 | 3.17 | 11.67 |
| **Provoked factors*** ** | 5,055 (64.7%) | 6,488 (58.0%) | 7,995 (69.0%) | 13.96 | 9.04 | 23.06 |
| **NCI Comorbidity Index** | 2.6 (2.5) | 2.1 (2.1) | 2.9 (2.5) | 21.88 | 8.98 | 31.04 |
| **Baseline Comorbidity** | | | | | | |
| Anemia | 3,579 (45.8%) | 5,483 (49.0%) | 5,759 (49.7%) | 6.30 | 7.73 | 4.85 |
| Central venous Catheter | 1,411 (18.1%) | 3,224 (28.8%) | 2,230 (19.2%) | 25.54 | 3.01 | 17.84 |
| Cerebrovascular disease | 1,089 (13.9%) | 1,392 (12.4%) | 1,828 (15.8%) | 4.47 | 5.14 | 9.51 |
| Hematologic disorders | 1,001 (12.8%) | 1,790 (16.0%) | 1,832 (15.8%) | 9.04 | 8.54 | 0.74 |
| Thrombocytopenia | 780 (10.0%) | 1,495 (13.4%) | 1,296 (11.2%) | 10.50 | 3.88 | 5.39 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Ischemic heart/ coronary artery disease | 2,338 (29.9%) | 2,304 (20.6%) | 3,518 (30.4%) | 21.67 | 0.90 | 22.91 |
| Dementia | 489 (6.3%) | 200 (1.8%) | 614 (5.3%) | 22.92 | 4.13 | 18.22 |
| Dyspepsia | 2,407 (30.8%) | 4,339 (38.8%) | 3,830 (33.1%) | 16.72 | 4.77 | 8.01 |
| Hyperlipidemia | 4,342 (55.6%) | 4,986 (44.5%) | 6,408 (55.3%) | 22.27 | 0.63 | 21.74 |
| Obesity | 1,515 (19.4%) | 1,712 (15.3%) | 2,383 (20.6%) | 10.87 | 2.90 | 15.41 |
| Pneumonia | 1,430 (18.3%) | 1,923 (17.2%) | 2,302 (19.9%) | 2.97 | 3.94 | 8.53 |
| Rheumatologic disease | 408 (5.2%) | 303 (2.7%) | 570 (4.9%) | 12.93 | 1.40 | 11.54 |
| Sleep apnea | 945 (12.1%) | 1,054 (9.4%) | 1,464 (12.6%) | 8.68 | 1.61 | 10.89 |
| Thrombophilia | 463 (5.9%) | 625 (5.6%) | 810 (7.0%) | 1.49 | 4.31 | 5.95 |
| Congestive Heart Failure | 1,360 (17.4%) | 1,102 (9.8%) | 2,186 (18.9%) | 22.21 | 3.75 | 25.93 |
| Diabetes | 2,533 (32.4%) | 3,002 (26.8%) | 4,166 (36.0%) | 12.34 | 7.40 | 19.86 |
| Hypertension | 6,051 (77.5%) | 7,077 (63.2%) | 9,160 (79.1%) | 31.65 | 3.75 | 32.79 |
| Renal Disease | 2,573 (33.0%) | 2,361 (21.1%) | 3,990 (34.4%) | 26.95 | 3.13 | 29.19 |
| Liver Disease | 1,237 (15.8%) | 3,051 (27.3%) | 1,842 (15.9%) | 28.03 | 0.14 | 23.33 |
| COPD | 2,062 (26.4%) | 2,243 (20.0%) | 3,201 (27.6%) | 15.13 | 2.73 | 18.14 |
| Peripheral vascular disease | 1,728 (22.1%) | 1,772 (15.8%) | 2,818 (24.3%) | 16.12 | 5.18 | 21.12 |
| Baseline any bleed | 2,266 (29.0%) | 4,018 (35.9%) | 4,187 (36.1%) | 14.72 | 15.21 | 2.41 |
| **Recent History of Falls** | 495 (6.3%) | 437 (3.9%) | 837 (7.2%) | 11.07 | 3.51 | 13.26 |
| **Fracture/trauma** | 874 (11.2%) | 740 (6.6%) | 1,275 (11.0%) | 16.14 | 0.61 | 15.76 |
| **Selected Surgeries** | 3,095 (39.6%) | 5,050 (45.1%) | 4,718 (40.7%) | 11.10 | 2.19 | 4.80 |
| **Baseline Medication Use** | | | | | | |
| Antiarrhythmic | 1,300 (16.7%) | 2,600 (23.2%) | 1,762 (15.2%) | 16.52 | 3.95 | 16.51 |
| Statins | 3,259 (41.7%) | 3,678 (32.9%) | 4,852 (41.9%) | 18.44 | 0.26 | 18.83 |
| Anti-platelets | 624 (8.0%) | 471 (4.2%) | 918 (7.9%) | 15.86 | 0.26 | 15.03 |
| Aromatase Inhibitors | 569 (7.3%) | 434 (3.9%) | 707 (6.1%) | 14.90 | 4.75 | 10.74 |
| Beta Blockers | 2,922 (37.4%) | 3,023 (27.0%) | 4,553 (39.3%) | 22.43 | 3.84 | 25.90 |
| Gastroprotective Agents | 2,676 (34.3%) | 4,165 (37.2%) | 4,124 (35.6%) | 6.13 | 2.76 | 1.72 |

| | | | | | | |
|---|---|---|---|---|---|---|
| NSAIDs | 1,717 (22.0%) | 2,237 (20.0%) | 2,367 (20.4%) | 4.93 | 3.83 | 2.69 |
| Hormone Therapy | 142 (1.8%) | 304 (2.7%) | 182 (1.6%) | 6.03 | 1.92 | 6.67 |
| **Cancer Metastasis+** | 3,426 (43.9%) | 8,644 (77.2%) | 5,011 (43.2%) | 72.59 | 1.28 | 78.24 |
| **Cancer Type+** | | | | | | |
| Hematological | 1,411 (18.1%) | 2,079 (18.6%) | 2,098 (18.1%) | 1.30 | 0.09 | 1.00 |
| Non-Hematological | 6,396 (81.9%) | 9,113 (81.4%) | 9,489 (81.9%) | 1.30 | 0.09 | 1.00 |
| **Khorana Risk Scale** | | | | | | |
| Very high risk | 845 (10.8%) | 2,773 (24.8%) | 1,302 (11.2%) | 37.10 | 1.32 | 35.72 |
| High risk | 3,134 (40.1%) | 5,474 (48.9%) | 4,927 (42.5%) | 17.71 | 4.83 | 15.99 |
| Other | 3,828 (49.0%) | 2,945 (26.3%) | 5,358 (46.2%) | 48.23 | 5.59 | 42.08 |
| **Cancer-related Treatment+** | | | | | | |
| Cancer treatment | 4,581 (58.7%) | 8,322 (74.4%) | 6,217 (53.7%) | 33.69 | 10.14 | 43.67 |
| Chemotherapy | 3,265 (41.8%) | 6,603 (59.0%) | 4,426 (38.2%) | 34.87 | 7.40 | 48.23 |
| Hormone Therapy | 53 (0.7%) | 80 (0.7%) | 100 (0.9%) | 0.43 | 2.11 | 14.55 |
| Immunotherapy | 89 (1.1%) | 230 (2.1%) | 60 (0.5%) | 7.30 | 6.87 | 13.73 |
| Radiation | 2,412 (30.9%) | 4,428 (39.6%) | 3,003 (25.9%) | 18.22 | 11.06 | 29.44 |
| Cancer-related Surgery | 485 (6.2%) | 1,553 (13.9%) | 693 (6.0%) | 25.70 | 0.97 | 26.63 |

## 8.3. Outcome Characteristics

When the follow-up was censored at 6 months, the mean follow-up was 112.5 days, 91.3 days, and 122.5 days for apixaban, LMWH, and warfarin patients, respectively (Table 9). The unadjusted incidence rate of MB—including GI, ICH, and other bleeding—was 8.97 (apixaban), 18.89 (LMWH), and 11.88 (warfarin) per 100 person-years. The unadjusted incidence rate of recurrent VTE was 6.84 (apixaban), 14.67 (LMWH), and 8.22 (warfarin) per 100 person-years.

When using all available follow-up, before IPTW, the mean follow-up was 159 days, 113 days, and 198 days for apixaban, LMWH, and warfarin patients, respectively (Table 9). The unadjusted incidence rate of MB—including GI, ICH, and other bleeding—was 7.5 (apixaban), 16.9 (LMWH), and 8.8 (warfarin) per 100 person-years. Similarly, the unadjusted incidence rate of recurrent VTE was 5.1 (apixaban), 12.8 (LMWH), and 5.7 (warfarin) per 100 person-years.

**Table 9. Phase 2 Pre-IPTW Outcomes During Full Follow-up and Censored at 6-months**

| | Apixaban Cohort | | LMWH Cohort | | Warfarin Cohort | |
|---|---|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD | N/Mean | %/SD |
| **Sample Size** | 7807 | | 11192 | | 11587 | |
| **Follow-up Time (in days), (Mean, SD)** | 159 | 154.95 | 113 | 118.87 | 198 | 199.32 |
| **Major Bleeding Incidence Rate (per 100 person-years)** | 7.50 | | 16.93 | | 8.84 | |
| Gastrointestinal (GI) Bleeding | 2.48 | | 4.20 | | 3.26 | |
| Intracranial Hemorrhage | 0.38 | | 2.73 | | 1.18 | |
| Other Bleeding | 4.88 | | 10.28 | | 4.72 | |
| **CRNM Bleeding Incidence Rate (per 100 person-years)** | 25.61 | | 40.63 | | 28.85 | |
| Gastrointestinal (GI) Bleeding | 7.65 | | 9.01 | | 6.91 | |
| Other Bleeding | 18.00 | | 31.05 | | 21.79 | |
| **Recurrent VTE Incidence Rate (per 100 person-years)** | 5.13 | | 12.79 | | 5.71 | |
| DVT | 3.15 | | 7.23 | | 3.42 | |
| PE | 2.09 | | 5.83 | | 2.40 | |
| **Follow-up Time (in days), (Mean, SD)** | 112.46 | 62.15 | 91.29 | 58.00 | 122.48 | 62.14 |
| **Major Bleeding Incidence Rate (per 100 person-years)** | 8.97 | | 18.89 | | 11.88 | |
| Gastrointestinal (GI) Bleeding | 2.84 | | 4.43 | | 4.45 | |
| Intracranial Hemorrhage | 0.45 | | 3.11 | | 1.55 | |
| Other Bleeding | 5.95 | | 11.68 | | 6.25 | |
| **CRNM Bleeding Incidence Rate (per 100 person-years)** | 30.24 | | 44.85 | | 36.58 | |
| Gastrointestinal (GI) Bleeding | 9.10 | | 9.99 | | 9.15 | |
| Other Bleeding | 21.60 | | 34.69 | | 27.99 | |
| **Recurrent VTE Incidence Rate (per 100 person-years)** | 6.84 | | 14.67 | | 8.22 | |
| DVT | 4.25 | | 8.17 | | 4.93 | |
| PE | 2.76 | | 6.88 | | 3.44 | |

## 8.4. Post-IPTW Baseline Characteristics

Post-IPTW baseline characteristics among VTE cancer patients are described in Table 10. After applying IPTW, all patient characteristics were balanced. In the IPTW population, ~35% of patients had prior bleed, 48% had metastatic cancer, and 52% received chemotherapy during the baseline period across cohorts. Further, 14% had very high-risk cancer and 41% had high-risk cancer across cohorts.

### 8.4.1. Post-IPTW Outcome Characteristics

When patients were censored at 6 months of follow-up, the mean follow-up was 108 days (3.5 months), 89 days (2.9 months), and 118 days (3.8 months) for apixaban, LMWH, and warfarin,

respectively. The adjusted incidence rate of MB—including GI, ICH, and other bleeding—was 8.97 (apixaban), 18.89 (LMWH), and 11.88 (warfarin) per 100 person-years when the follow-up was censored at 6 months. The adjusted incidence rate of recurrent VTE was 6.84 (apixaban), 14.67 (LMWH), and 8.22 (warfarin) per 100 person-years.

During the follow-up of up to 6 months, compared to LMWH, apixaban patients had a lower risk of MB (HR: 0.68; 95% CI: 0.56-0.83), CRNM bleeding (HR: 0.74; 95% CI: 0.66-0.83), and recurrent VTE (HR: 0.66; 95% CI: 0.53-0.83). Warfarin patients had a lower risk of MB (HR: 0.84; 95% CI: 0.72-0.99), CRNM bleeding (HR: 0.88; 95% CI: 0.79-0.98), and similar risk of recurrent VTE (HR: 0.95; 95% CI: 0.77-1.17) compared to LMWH patients. Apixaban patients had a significantly 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 CRNM bleeding (HR; 0.85; 95% CI: 0.77-0.94) compared to warfarin patients.

## Table 10: Phase 2 Post-IPTW patient characteristics

| 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)

| 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.

### 8.4.2. Subgroup Analysis

#### 8.4.2.1. Brain Cancer subgroup analysis

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).

##### 8.4.2.1.1. Patient Characteristics by Brain Cancer Status

Table 11 shows patient characteristics after stratifying the post-IPTW population by brain cancer status. Mean age tended to be lower for brain cancer patients (63–68 years across medication groups) compared to other cancer patients (69–72 years). Patients with brain cancer and other cancers had similar common comorbidities (mean NCI comorbidity index scores ranged from 2.7–3.4) and the presence of each comorbidity was generally similar across treatment cohorts by brain cancer status. 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.

## Table 11: Patient characteristics by brain cancer status

| 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)

| 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 %) |

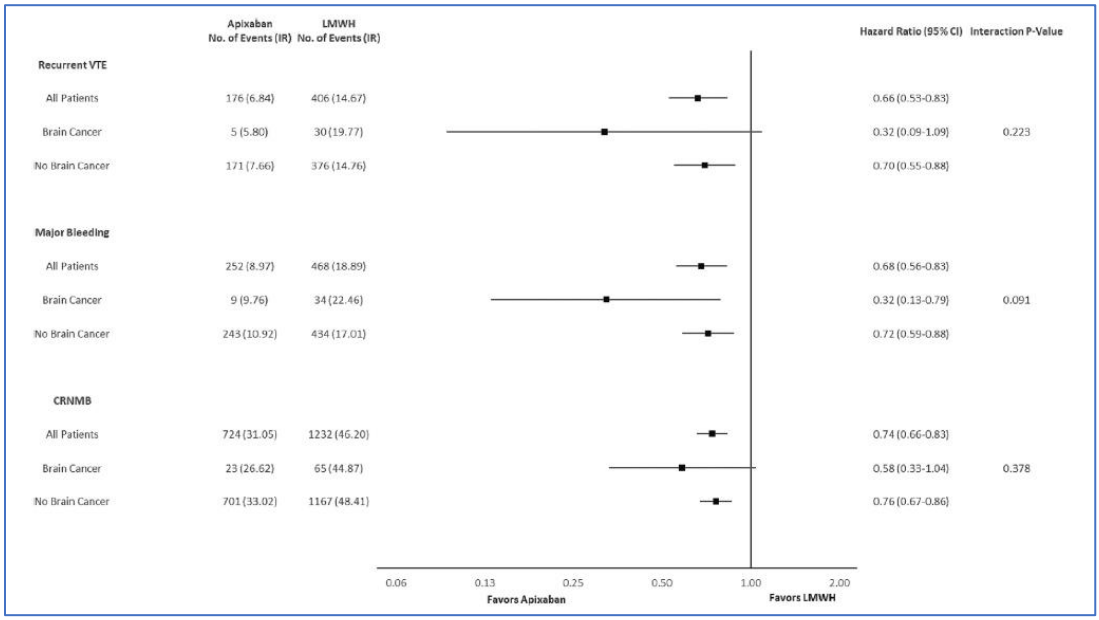
[a] Due to rounding from IPTW, patient counts and proportions may be off slightly.
[b] Defined as a VTE that is preceded by hormone therapy, fracture/trauma involving lower extremities, pelvic/orthopedic surgery, or hospitalization for any reason for ≥3 days during 3 months prior to VTE.
[c] Measured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

### 8.4.2.1.2. Evaluation of Outcomes by Brain Cancer Status

*Apixaban vs LMWH*

As shown in Figure 13, 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), MB (9.76 vs 22.46), and CRNMB (26.62 vs 44.87). Likewise, among other cancer patients, incidence rates were numerically lower for apixaban vs LMWH patients for recurrent VTE (7.66 vs 14.76), MB (10.92 vs 17.01), and CRNMB (33.02 vs 48.41). There were no significant interactions between treatment (apixaban vs. LMWH) and brain cancer status on recurrent VTE and CRNMB (Figure 13, p-value for interactions > 0.1). A significant interaction was observed for MB (Figure 13, p 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.

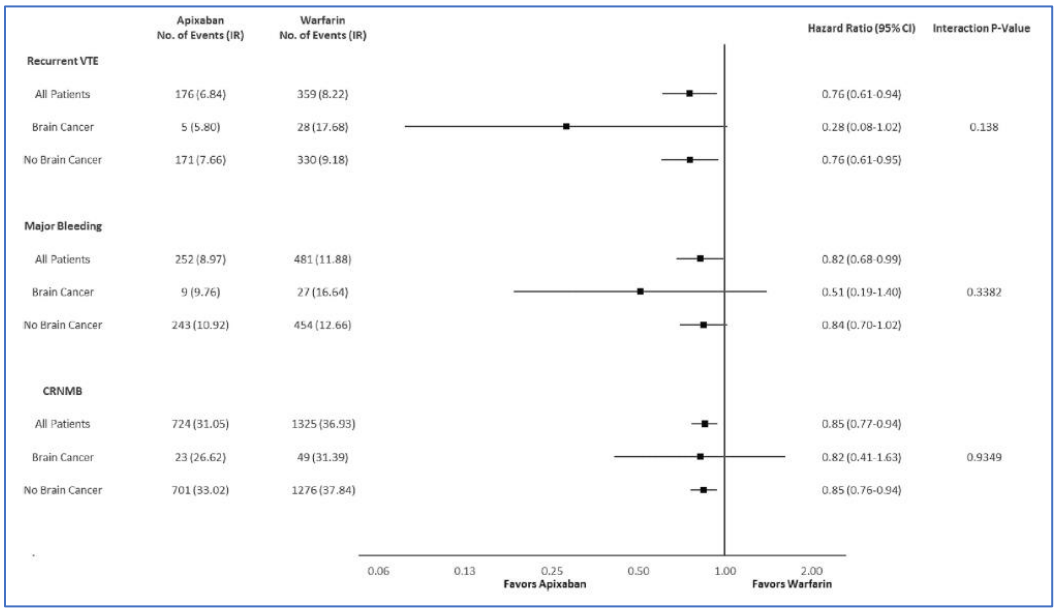
**Figure 13: Brain cancer subgroup analysis for apixaban vs. LMWH**



*Apixaban vs Warfarin*

As shown in Figure 14, 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), MB (9.76 vs 16.64), and CRNMB (26.62 vs 31.39). 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), MB (10.92 vs 12.66), and CRNMB (33.02 vs 37.84).

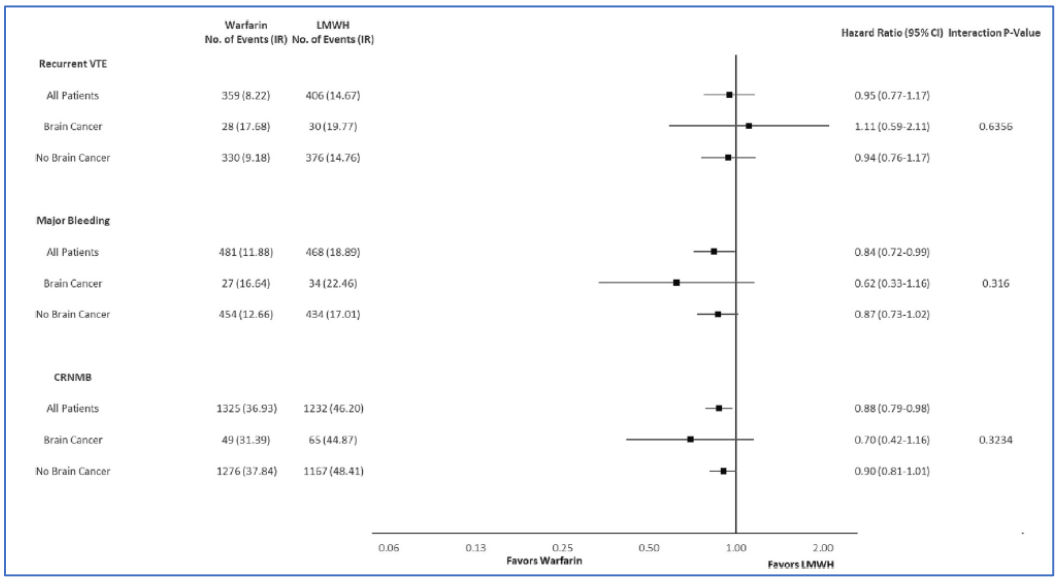
**Figure 14: Brain cancer subgroup analysis for warfarin vs. apixaban**




*Warfarin vs LMWH*

As shown in Figure 15, 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), and CRNMB (31.39 vs 44.87). Likewise, the incidence rates were numerically lower for warfarin patients (vs LMWH) among those with other cancer for MB (12.66 vs 17.01), and CRNMB (37.84 vs 48.41).

**Figure 15: Brain cancer subgroup analysis for warfarin vs. LMWH**




## 8.4.2.2. Subgroup Analysis on High Risk and Common Cancer Patient

**Figure 16: Patient selection for common and high risk cancer patients**

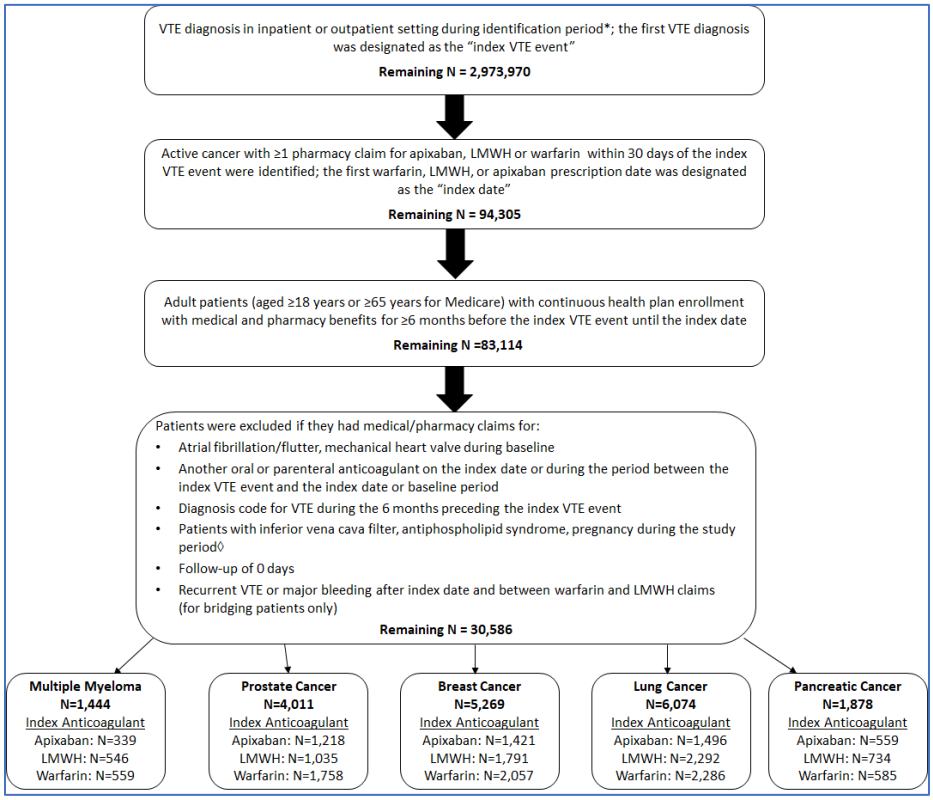


Figure 16 shows sample size and anticoagulant treatments for the common (breast, prostate, and lung) and high-risk cancer (pancreatic, multiple myeloma). Of the 30,586 patients with all types of cancer, patients with lung cancer accounted for 19.9%, breast cancer 17.2%, prostate cancer 13.1%, pancreatic cancer 6.1% and multiple myeloma 4.7%. The percentage of patients using apixaban ranged from 23% (multiple myeloma) to 30% (prostate and pancreatic), using LMWH ranged from 26% (prostate) to 39% (pancreatic), and using warfarin ranged from 31% (pancreatic) to 44% (prostate).

#### 8.4.2.2.1. Patient Characteristics of High Risk and Common Cancer Patients

**Table 12: Patient characteristics for patients with common cancer types**

| | Lung Cancer | | | Prostate Cancer | | | Breast Cancer | | |
|---|---|---|---|---|---|---|---|---|---|
| | Apixaban | LMWH | Warfarin | Apixaban | LMWH | Warfarin | Apixaban | LMWH | Warfarin |
| | N=1,496 | N=2,292 | N=2,286 | N=1,218 | N=1,035 | N=1,758 | N=1,421 | N=1,791 | N=2,057 |
| **Age, Mean (SD)** | 71.9 (10.9) | 69.9 (9.8) | 71.5 (10.8) | 75.1 (8.0) | 74.4 (11.1) | 75.6 (7.6) | 71.4 (10.9) | 68.4 (13.3) | 72.3 (10.8) |
| **Gender, N (%)** | | | | | | | | | |
| Male | 619 (41.4%) | 1,042 (45.5%) | 988 (43.2%) | 1,212 (99.5%) | 1,032 (99.8%) | 1,749 (99.5%) | 23 (1.6%) | 43 (2.4%) | 19 (0.9%) |
| Female | 877 (58.6%) | 1,250 (54.5%) | 1,298 (56.8%) | 6 (0.5%) | 2 (0.2%) | 9 (0.5%) | 1,398 (98.4%) | 1,748 (97.6%) | 2,038 (99.1%) |
| **Setting of Index VTE Event** | | | | | | | | | |
| Inpatient | 823 (55.0%) | 1,302 (56.8%) | 1,251 (54.7%) | 707 (58.0%) | 583 (56.4%) | 997 (56.7%) | 763 (53.7%) | 922 (51.5%) | 1,036 (50.4%) |
| Outpatient | 673 (45.0%) | 990 (43.2%) | 1,035 (45.3%) | 511 (42.0%) | 452 (43.6%) | 761 (43.3%) | 658 (46.3%) | 869 (48.5%) | 1,020 (49.6%) |
| ER | 597 (39.9%) | 885 (38.6%) | 933 (40.8%) | 443 (36.4%) | 393 (38.0%) | 680 (38.7%) | 557 (39.2%) | 733 (40.9%) | 845 (41.1%) |
| **VTE Diagnosis** | | | | | | | | | |
| DVT only | 676 (45.2%) | 1,002 (43.7%) | 953 (41.7%) | 655 (53.7%) | 599 (57.9%) | 947 (53.8%) | 766 (53.9%) | 1,036 (57.8%) | 1,130 (54.9%) |
| PE with DVT | 178 (11.9%) | 304 (13.3%) | 256 (11.2%) | 185 (15.2%) | 128 (12.4%) | 267 (15.2%) | 181 (12.7%) | 213 (11.9%) | 259 (12.6%) |
| PE without DVT | 642 (42.9%) | 986 (43.0%) | 1,076 (47.1%) | 379 (31.1%) | 308 (29.8%) | 545 (31.0%) | 474 (33.3%) | 543 (30.3%) | 668 (32.5%) |
| **NCI Comorbidity Index, Mean (SD)** | 3.5 (2.9) | 3.3 (2.3) | 3.5 (2.9) | 3.1 (2.4) | 3.3 (3.3) | 3.2 (2.5) | 2.7 (2.4) | 2.7 (2.9) | 2.8 (2.5) |
| **Baseline any bleed** | 525 (35.1%) | 754 (32.9%) | 775 (33.9%) | 424 (34.8%) | 419 (40.5%) | 614 (34.9%) | 375 (26.4%) | 462 (25.8%) | 536 (26.1%) |
| **Cancer Metastasis+** | 1,120 (74.8%) | 1,658 (72.3%) | 1,761 (77.0%) | 354 (29.1%) | 473 (45.8%) | 577 (32.8%) | 633 (44.5%) | 905 (50.5%) | 887 (43.1%) |

\+ Measured in the 6 months prior through 30 days after VTE

**Table 13: Patient characteristics for high-risk cancer patients**

| | Pancreatic Cancer | | | Multiple Myeloma | | |
|---|---|---|---|---|---|---|
| | Apixaban | LMWH | Warfarin | Apixaban | LMWH | Warfarin |
| | N=559 | N=734 | N=585 | N=339 | N=546 | N=559 |
| **Age, Mean (SD)** | 71.0 (12.8) | 69.1 (8.5) | 70.6 (12.3) | 72.5 (9.4) | 70.5 (12.0) | 72.3 (11.1) |
| **Gender, N (%)** | | | | | | |
| Male | 264 (47.3%) | 355 (48.4%) | 218 (37.3%) | 185 (54.5%) | 321 (58.8%) | 277 (49.6%) |
| Female | 295 (52.7%) | 378 (51.6%) | 367 (62.7%) | 154 (45.5%) | 225 (41.2%) | 281 (50.4%) |
| **Setting of Index VTE Event** | | | | | | |
| Inpatient | 245 (43.9%) | 368 (50.2%) | 300 (51.2%) | 163 (48.1%) | 271 (49.7%) | 307 (55.0%) |
| Outpatient | 313 (56.1%) | 365 (49.8%) | 285 (48.8%) | 176 (51.9%) | 275 (50.3%) | 251 (45.0%) |
| ER | 284 (50.8%) | 311 (42.3%) | 263 (45.0%) | 154 (45.5%) | 236 (43.2%) | 227 (40.6%) |
| **VTE Diagnosis** | | | | | | |
| DVT only | 319 (57.0%) | 396 (53.9%) | 311 (53.2%) | 217 (64.0%) | 366 (67.1%) | 364 (65.2%) |
| PE with DVT | 73 (13.1%) | 100 (13.6%) | 73 (12.6%) | 30 (8.7%) | 77 (14.1%) | 56 (10.0%) |
| PE without DVT | 167 (29.9%) | 238 (32.4%) | 200 (34.3%) | 93 (27.3%) | 102 (18.8%) | 138 (24.8%) |
| **NCI Comorbidity Index, Mean (SD)** | 3.4 (3.6) | 3.4 (2.0) | 3.5 (3.4) | 3.0 (2.5) | 2.9 (2.7) | 3.1 (2.7) |
| **Baseline any bleed** | 215 (38.5%) | 234 (31.9%) | 220 (37.6%) | 121 (35.7%) | 163 (29.8%) | 186 (33.3%) |
| **Cancer Metastasis+** | 489 (87.5%) | 532 (72.5%) | 495 (84.6%) | 126 (37.0%) | 110 (20.2%) | 201 (36.0%) |

\+ Measured in the 6 months prior to VTE through 30 days after VTE

Table 12 and Table 13 show demographics and clinical characteristics for patients with VTE and the selected cancer after IPTW for the overall population. Mean age in years ranged from 71.0 (pancreatic) to 75.1 (prostate) for apixaban patients, 68.4 (breast) to 74.4 (prostate) for LMWH patients, and 70.6 (pancreatic) to 75.6 (prostate) for warfarin patients. Patient gender varied by tumor type. Multiple myeloma tended to be more common for males, whereas lung, and pancreatic cancers were more common for females. The setting in which the index VTE event was diagnosed was mostly inpatient (43.9-58.0%) or emergency room (ER; 36.4-50.8%) across tumor types.

The index VTE event was more likely to be DVT only across different tumor types except for lung cancer which had more PE with or without DVT. The mean NCI comorbidity index score ranged from 2.7 (breast) to 3.5 (lung) for apixaban patients, 2.7 (breast) to 3.4 (pancreatic) for LMWH patients, and 2.8 (breast) to 3.5 (lung and pancreatic) for warfarin patients. The percentage of patients with a documented bleed during baseline ranged from 26.4% (breast) to 38.5% (pancreatic) for apixaban patients, 25.8% (breast) to 40.5% (prostate) for LMWH patients, and 26.1% (breast) to 37.6% (pancreatic) for warfarin patients. Cancer metastasis was higher for pancreatic (72.5-87.5%) and lung (72.3-77.0%) cancer compared to breast (43.1-50.5%), multiple myeloma (20.2-37%) and prostate cancer (29.1%-45.8%).

### 8.4.2.2.2. Subgroup Analysis on Recurrent VTE

**Figure 17: Effects on recurrent VTE by the presence and absence of each selected cancer**

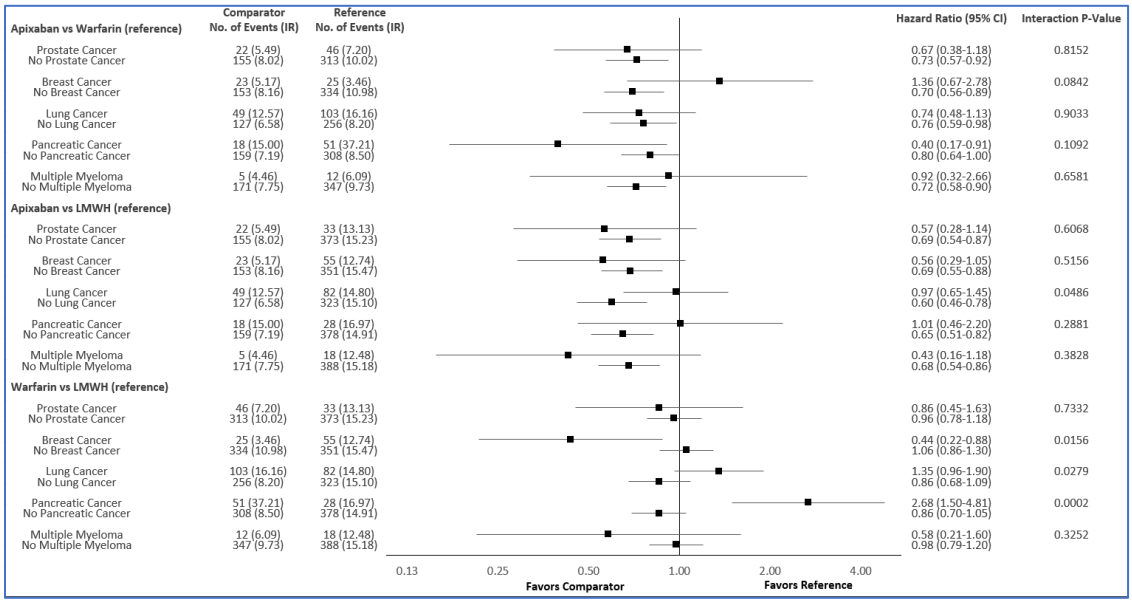



Figure 17 shows the effects of anticoagulants on recurrent VTE after stratifying overall cancer population by the presence and absence of each selected cancer. In general, effects of apixaban vs warfarin, apixaban vs. LMWH, and warfarin vs. LMWH on recurrent VTE were not significantly different (p's > 0.1 for most of the interactions) between patients with a specific tumor vs. patients without the specific tumor for each of the five tumor types (multiple myeloma, prostate cancer,

breast cancer, lung cancer, and pancreatic cancer). For most of the tumor types, apixaban tended to have lower incidence rates of recurrent VTE vs. warfarin and vs. LMWH regardless of tumor status.

There were few significant interactions between some treatments and some tumor types on recurrent VTE. For apixaban vs. warfarin, there was a significant interaction between the treatment and breast cancer status (yes or no) on recurrent VTE ($p < 0.1$). Compared to warfarin, apixaban was associated with a lower incidence of recurrent VTE for patients without breast cancer, but higher incidence for patients with breast cancer. For apixaban vs. LMWH, apixaban was associated with lower incidence of recurrent VTE for patients without lung cancer, but similar risk for those with lung cancer (p interaction = 0.049). For warfarin vs. LMWH, the treatment effect on recurrent VTE was significantly different between patients with or without a specific tumor for 3 of the 5 tumor types (breast, lung and pancreatic). For each of the 3 tumor types, there was a significant interaction between treatment of warfarin vs. LMWH and the specific tumor status (yes or no) on recurrent VTE (p for interactions < 0.1) with different trends in treatment effects between patients with and without the tumor (Figure 17).

### 8.4.2.2.3. Major Bleeding (MB)

**Figure 18: Effects on MB by the presence and absence of each selected cancer**

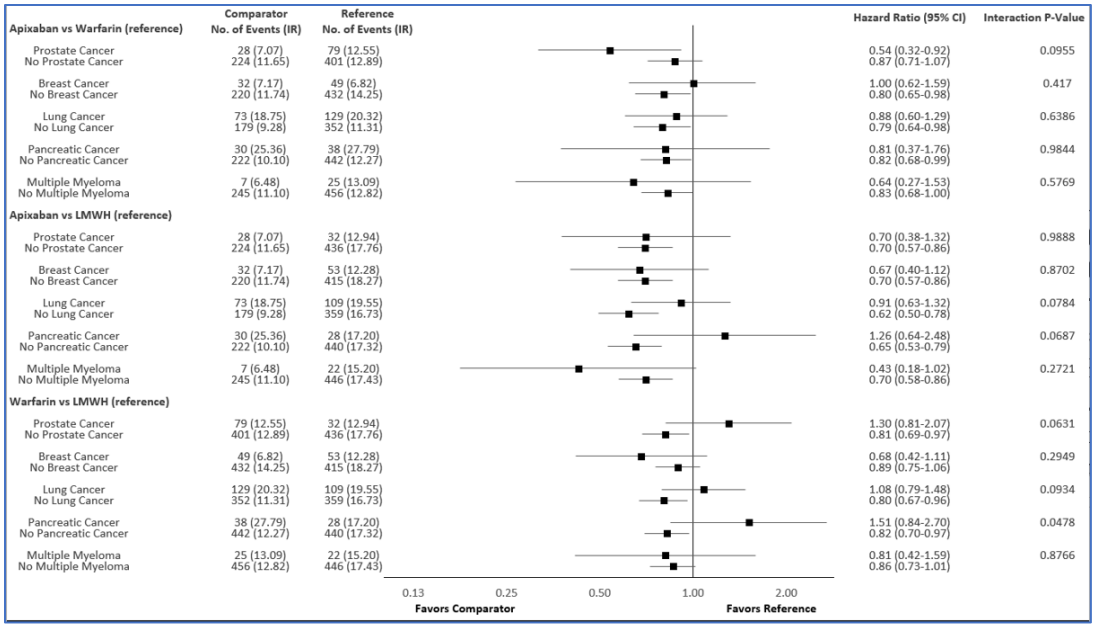



Figure 18 shows the effects of anticoagulants on MB after stratifying overall cancer population by the presence and absence of each selected cancer. In general, the effects of apixaban vs warfarin, apixaban vs. LMWH, and warfarin vs. LMWH on MB were mostly not significantly different ($p > 0.1$ for most of the interactions) between patients with a specific tumor and patients without the specific tumor for each of the five tumor types. Regardless of tumor status, incidence rates of MB were in general, numerically lower for apixaban vs. warfarin or vs. LMWH (Figure 18). However, for lung and pancreatic cancer, there were significant interactions between the treatment of

apixaban vs. LMWH and treatment of warfarin vs. LMWH and tumor status (yes or no) on MB (p for interactions < 0.1). In general, the treatment effects trended differently for patients with lung cancer vs. those without lung cancer and for patients with pancreatic cancer vs. those without pancreatic cancer (Figure 17). There were also significant interactions between prostate cancer status (yes or no) and treatment of apixaban vs. warfarin and treatment of warfarin vs. LMWH on MB (Figure 18).

#### 8.4.2.2.4. Clinically Relevant Non-Major Bleeding (CRNMB)

**Figure 19: Effects on CRNMB by the presence and absence of each selected cancer**

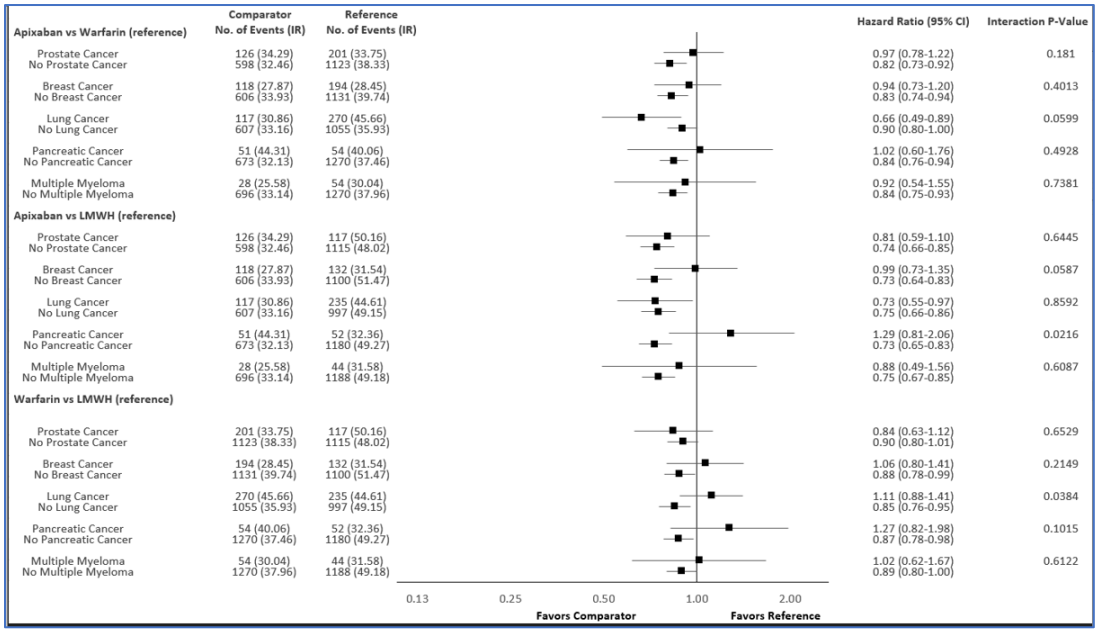



Figure 19 shows effects of anticoagulants on CRNMB by the presence and absence of each selected cancer. In general, the effects of apixaban vs warfarin, apixaban vs. LMWH, and warfarin vs. LMWH on CRNMB were not significantly different (p > 0.1 for most of the interactions) between patients with a specific tumor and patients without the specific tumor (Figure 18). Apixaban was generally associated with lower incidence of CRNMB vs. warfarin and vs. LMWH in patients with or without a specific tumor (Figure 19).

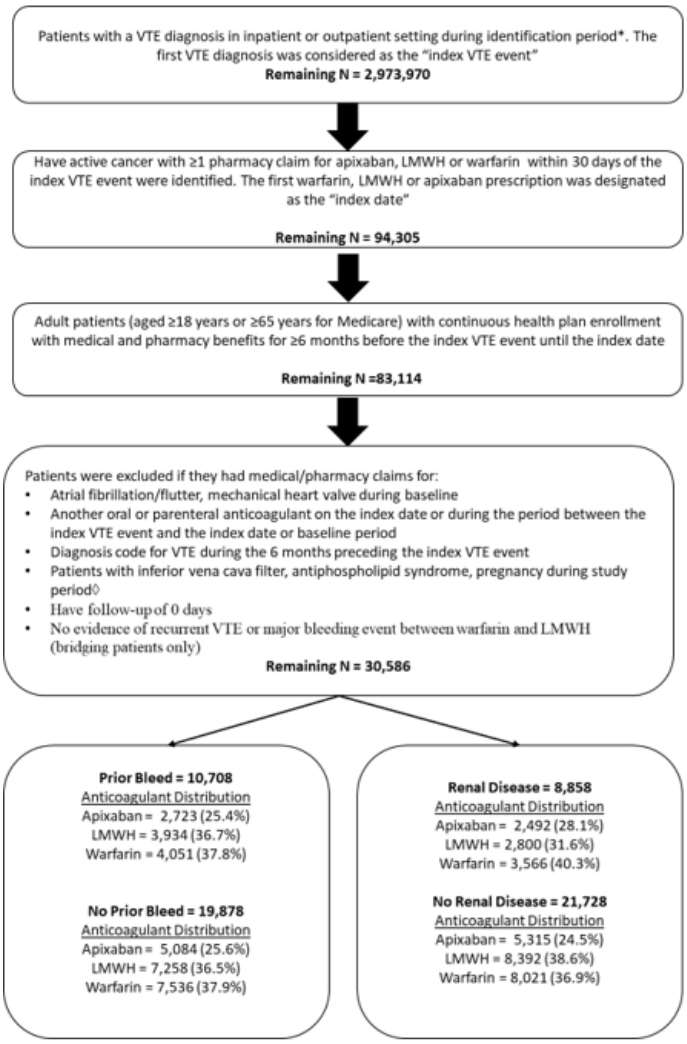
Significant interactions were observed for some of the treatments and some tumor types on CRNMB. For apixaban vs. LMWH, there was a significant interaction between the treatment and pancreatic cancer and breast cancer (Figure 19). For apixaban vs. warfarin, there was a significant interaction between the treatment and lung cancer (Figure 19). For warfarin vs. LMWH, there was a significant interaction between the treatment and lung cancer (Figure 19).

### 8.4.2.3. Prior Bleed and Renal Disease

Among the 30,586 VTE cancer patients who met all study criteria, 10,708 (35.0%) had prior bleed, and 19,878 (65.0%) had no prior bleed (Figure 20). Use of warfarin, LMWH and apixaban was similar between those with prior bleed (37.8%, 36.7%, and 25.4%, respectively) and without

prior bleed (37.9%, 36.5%, and 25.6%, respectively). A total of 8,858 patients (29.0%) had renal disease and 21,728 (71.0%) did not have renal disease (Figure 20). Patients with renal disease were more likely to use warfarin (40.3% vs. 36.9%), apixaban (28.1% vs. 24.5%) and less likely to use LMWH (31.6% vs. 38.6%) compared to those without renal disease. Renal disease was further classified into the following types: chronic kidney disease (CKD) Stage 1 and 2, CKD Stage 3, CKD Stage 4/5/ESRD, CKD Unknown, Other Renal (nephrotic syndrome, chronic glomerulonephritis, nephritis, and nephropathy [lupus nephritis etc.], hypertensive chronic kidney disease and renal failure). Most of the patients were either in CKD Stage 3 (apixaban: 38.8%, LMWH: 31.9% and warfarin: 37.8%) or had other renal disease (apixaban: 30.5%, LMWH: 36.1% and warfarin: 23.7%).

**Figure 20: Selection of VTE cancer patients with prior bleed or renal disease**




### 8.4.2.3.1. Patient Characteristics by Prior Bleed Status

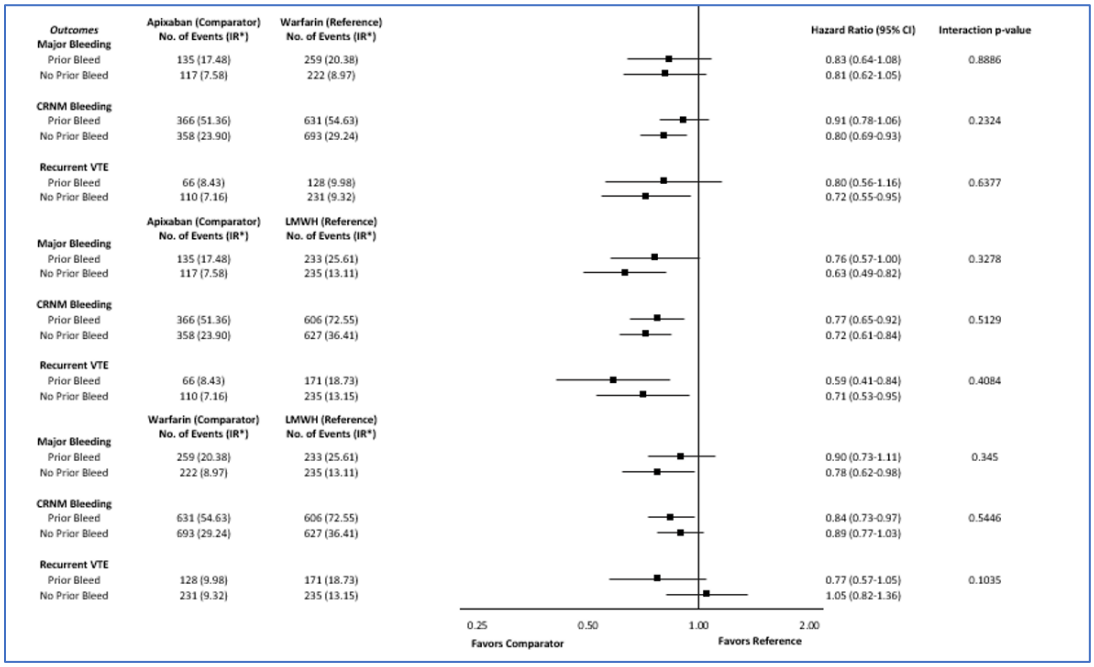
## Table 14: Patient characteristics by prior bleed status

| Characteristics | Prior Bleed | | | No Prior Bleed | | |
|---|---|---|---|---|---|---|
| | Apixaban N=2,723 | LMWH N=3,934 | Warfarin N=4,051 | Apixaban N=5,084 | LMWH N=7,258 | Warfarin N=7,536 |
| **Age in years, mean (sd)** | 72.3 (11.9) | 68.9 (12.9) | 71.8 (11.2) | 71.4 (10.8) | 68.2 (12.8) | 72.1 (11.1) |
| **Age in years, n (%)** | | | | | | |
| 18-54 | 163 (6.0%) | 496 (12.6%) | 313 (7.7%) | 411 (8.1%) | 906 (12.5%) | 492 (6.5%) |
| 55-64 | 352 (12.9%) | 718 (18.3%) | 435 (10.7%) | 659 (13.0%) | 1,472 (20.3%) | 836 (11.1%) |
| 65-74 | 1,038 (38.1%) | 1,291 (32.8%) | 1,601 (39.5%) | 1,995 (39.2%) | 2,535 (34.9%) | 3,049 (40.5%) |
| 75-79 | 497 (18.3%) | 594 (15.1%) | 764 (18.9%) | 893 (17.6%) | 1,002 (13.8%) | 1,329 (17.6%) |
| ≥80 | 672 (24.7%) | 835 (21.2%) | 939 (23.2%) | 1,126 (22.2%) | 1,343 (18.5%) | 1,830 (24.3%) |
| **Gender, n (%)** | | | | | | |
| Male | 1,266 (46.5%) | 1,902 (48.3%) | 1,925 (47.5%) | 2,275 (44.7%) | 3,144 (43.3%) | 3,338 (44.3%) |
| Female | 1,456 (53.5%) | 2,032 (51.7%) | 2,126 (52.5%) | 2,809 (55.3%) | 4,115 (56.7%) | 4,198 (55.7%) |
| **Setting of Index VTE Event, n (%)** | | | | | | |
| Inpatient | 1,642 (60.3%) | 2,417 (61.5%) | 2,610 (64.4%) | 2,544 (50.0%) | 3,546 (48.9%) | 3,718 (49.3%) |
| Outpatient‡ | 1,081 (39.7%) | 1,516 (38.5%) | 1,441 (35.6%) | 2,540 (50.0%) | 3,712 (51.1%) | 3,818 (50.7%) |
| ER | 998 (36.7%) | 1,369 (34.8%) | 1,321 (32.6%) | 2,164 (42.6%) | 3,112 (42.9%) | 3,270 (43.4%) |
| **VTE Diagnosis, n (%)** | | | | | | |
| DVT only | 1,529 (56.2%) | 2,273 (57.8%) | 2,227 (55.0%) | 2,785 (54.8%) | 4,051 (55.8%) | 4,076 (54.1%) |
| PE with DVT | 327 (12.0%) | 412 (10.5%) | 498 (12.3%) | 618 (12.2%) | 830 (11.4%) | 933 (12.4%) |
| PE without DVT | 867 (31.8%) | 1,249 (31.7%) | 1,326 (32.7%) | 1,681 (33.1%) | 2,378 (32.8%) | 2,527 (33.5%) |
| **NCI Comorbidity Index, mean (sd)** | 3.7 (3.0) | 3.5 (2.7) | 3.8 (2.7) | 2.8 (2.4) | 2.6 (2.5) | 2.8 (2.5) |
| **Baseline Comorbidity, n (%)** | | | | | | |
| Anemia | 1,862 (68.4%) | 2,659 (67.6%) | 2,794 (69.0%) | 2,018 (39.7%) | 2,865 (39.5%) | 2,968 (39.4%) |
| Central venous catheter | 859 (31.5%) | 1,227 (31.2%) | 1,247 (30.8%) | 960 (18.9%) | 1,585 (21.8%) | 1,320 (17.5%) |
| Cerebrovascular disease | 535 (19.6%) | 720 (18.3%) | 870 (21.5%) | 543 (10.7%) | 761 (10.5%) | 893 (11.9%) |
| Hematologic disorders associated with bleeding | 579 (21.3%) | 758 (19.3%) | 813 (20.1%) | 687 (13.5%) | 981 (13.5%) | 974 (12.9%) |
| Thrombocytopenia | 455 (16.7%) | 624 (15.9%) | 584 (14.4%) | 535 (10.5%) | 813 (11.2%) | 701 (9.3%) |
| Ischemic heart/ coronary artery disease | 852 (31.3%) | 1,167 (29.7%) | 1,335 (32.9%) | 1,287 (25.3%) | 1,598 (22.0%) | 1,896 (25.2%) |
| Dyspepsia or stomach discomfort | 1,300 (47.7%) | 1,752 (44.5%) | 1,814 (44.8%) | 1,467 (28.8%) | 2,221 (30.6%) | 2,178 (28.9%) |
| Hyperlipidemia | 1,534 (56.4%) | 1,942 (49.4%) | 2,342 (57.8%) | 2,563 (50.4%) | 3,361 (46.3%) | 3,859 (51.2%) |
| Obesity | 520 (19.1%) | 827 (21.0%) | 795 (19.6%) | 898 (17.7%) | 1,223 (16.9%) | 1,336 (17.7%) |
| Pneumonia | 661 (24.3%) | 886 (22.5%) | 961 (23.7%) | 818 (16.1%) | 1,195 (16.5%) | 1,221 (16.2%) |
| Congestive heart failure | 499 (18.3%) | 636 (16.2%) | 788 (19.5%) | 728 (14.3%) | 853 (11.8%) | 1,120 (14.9%) |
| Diabetes | 909 (33.4%) | 1,337 (34.0%) | 1,463 (36.1%) | 1,531 (30.1%) | 2,059 (28.4%) | 2,399 (31.8%) |
| Hypertension | 2,141 (78.6%) | 2,929 (74.5%) | 3,199 (79.0%) | 3,657 (71.9%) | 4,843 (66.7%) | 5,439 (72.2%) |
| Liver disease | 672 (24.7%) | 1,306 (33.2%) | 1,029 (25.4%) | 827 (16.3%) | 1,511 (20.8%) | 927 (12.3%) |
| Renal disease | 1,015 (37.3%) | 1,192 (30.3%) | 1,499 (37.0%) | 1,477 (29.0%) | 1,608 (22.2%) | 2,067 (27.4%) |
| COPD | 792 (29.1%) | 934 (23.8%) | 1,175 (29.0%) | 1,274 (25.1%) | 1,515 (20.9%) | 1,958 (26.0%) |
| **Selected Surgeries, n (%)** | 1,599 (58.7%) | 2,326 (59.1%) | 2,329 (57.5%) | 1,769 (34.8%) | 2,729 (37.6%) | 2,383 (31.6%) |
| **Cancer Metastasis+, n (%)** | 1,403 (51.5%) | 1,989 (50.6%) | 2,072 (51.2%) | 2,357 (46.4%) | 3,648 (50.3%) | 3,430 (45.5%) |
| **Cancer Type+, n (%)** | | | | | | |
| Hematological | 453 (16.6%) | 592 (15.1%) | 630 (15.6%) | 825 (16.2%) | 1,332 (18.3%) | 1,276 (16.9%) |
| Non-Hematological | 2,270 (83.4%) | 3,341 (84.9%)0? | 3,421 (84.4%) | 4,259 (83.8%) | 5,927 (81.7%)0? | 6,260 (83.1%) |
| **VTE Risk , n (%)** | | | | | | |
| Very high risk (brain, stomach, and pancreas) | 445 (16.3%) | 554 (14.1%) | 675 (16.7%) | 646 (12.7%) | 1,039 (14.3%) | 894 (11.9%) |
| High risk (lung, lymphoma, gynecologic, bladder, testicular, renal cell carcinoma) | 1,181 (43.4%) | 1,706 (43.4%) | 1,742 (43.0%) | 1,996 (39.3%) | 2,989 (41.2%) | 3,073 (40.8%) |
| Other | 1,096 (40.3%) | 1,674 (42.6%) | 1,635 (40.3%) | 2,442 (48.0%) | 3,230 (44.5%) | 3,569 (47.4%) |
| **Cancer-related Treatment+, n (%)** | | | | | | |
| Chemotherapy | 1,344 (49.4%) | 2,058 (52.3%) | 1,941 (47.9%) | 2,248 (44.2%) | 3,779 (52.1%) | 3,264 (43.3%) |
| Hormone therapy | 106 (3.9%) | 197 (5.0%) | 187 (4.6%) | 387 (7.6%) | 507 (7.0%) | 558 (7.4%) |

Table 14 shows patient characteristics by prior bleed status. Patients with and without prior bleed were generally 68-72 years old, and more than half were female. Patients with prior bleed were more likely to have their index VTE diagnosed in the inpatient setting (≥60%) compared to patients without prior bleed (≤50%). A majority (~55%) of patients had their index VTE as DVT only regardless of their prior bleed status. Patients with prior bleed had higher mean NCI Comorbidity Index score [NCI score] (3.5-3.8) and higher prevalence of comorbidities (Table 14) compared to patients without prior bleed who had a mean NCI score of 2.6-2.8. Patient characteristics were generally balanced between treatment groups after IPTW and when stratified by prior bleed status.

### 8.4.2.3.2. Evaluation of Outcomes by Prior Bleed Status

Figure 20: Effects by prior bleed status




Note: Additional adjustment in the cox model resulted in a direction shift of the hazard ratio for recurrent VTE (LMWH vs warfarin)

As shown in Figure 20, those with prior bleed vs. those without prior bleed had a higher incidence rate across all 3 drug cohorts (apixaban, LMWH and warfarin) for major bleeding (17.48 vs 7.58, 25.61 vs 13.11, and 20.38 vs 8.97 events per 100 person-years) and CRNM bleeding (51.36 vs 23.90, 72.55 vs 36.41, and 54.63 vs 29.24). When comparing different anticoagulants, the incidence rates of major bleeding, CRNM bleeding and recurrent VTE events were numerically lower in the apixaban cohort compared to warfarin or LMWH regardless of prior bleed status. There was no significant interaction between treatment (apixaban vs warfarin, apixaban vs LMWH and warfarin vs LMWH) and prior bleed status on any of the outcomes: recurrent VTE, MB, and

CRNMB (P > 0.1 for all interactions). Treatment effects were not significantly different between those with and without prior bleed.

#### 8.4.2.3.3. Patient Characteristics by Renal Disease Status

Table 15 shows patient characteristics by renal disease status. Those with renal disease were older (age 72–75 years across medication groups) and more than half were male compared to those without renal disease. Patients with renal disease were more likely to have their index VTE diagnosed in the inpatient setting (≥64%) compared to those without renal disease (~48%). A majority (52-63%) of patients had their index VTE as DVT only regardless of renal disease status. Patients with renal disease had a higher mean NCI score (~5.0) and higher prevalence of comorbidities compared to those without renal disease (mean NCI score of ~2.3). Patients with renal disease (vs without renal disease) were more likely to have a prior bleed (~41% vs ~32.0%), but less likely to have metastasis (~44% vs ~50%), respectively (Table 15).

**Table 15: Patient characteristics by renal disease status**

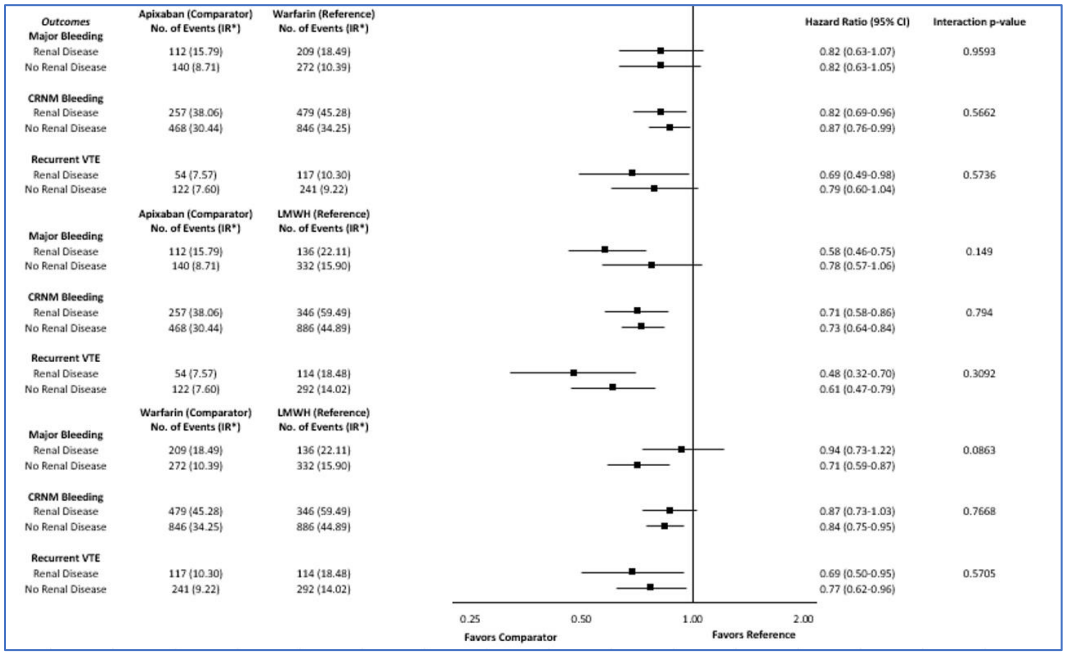
| Characteristics | Renal Disease | | | No Renal Disease | | |
|---|---|---|---|---|---|---|
| | Apixaban N=2,492 | LMWH N=2,800 | Warfarin N=3,566 | Apixaban N=5,315 | LMWH N=8,392 | Warfarin N=8,021 |
| **Age (years)** | 74.3 (10.1) | 72.4 (12.3) | 74.9 (9.9) | 70.6 (11.5) | 67.1 (12.7) | 70.7 (11.4) |
| 18-54 | 107 (4.3%) | 171 (6.1%) | 130 (3.6%) | 467 (8.8%) | 1,231 (14.7%) | 675 (8.4%) |
| 55-64 | 202 (8.1%) | 362 (12.9%) | 263 (7.4%) | 809 (15.2%) | 1,828 (21.8%) | 1,007 (12.6%) |
| 65-74 | 933 (37.4%) | 1,007 (36.0%) | 1,265 (35.5%) | 2,101 (39.5%) | 2,819 (33.6%) | 3,385 (42.2%) |
| 75-79 | 507 (20.3%) | 469 (16.7%) | 750 (21.0%) | 883 (16.6%) | 1,127 (13.4%) | 1,343 (16.7%) |
| ≥80 | 743 (29.8%) | 792 (28.3%) | 1,158 (32.5%) | 1,055 (19.9%) | 1,386 (16.5%) | 1,612 (20.1%) |
| **Gender** | | | | | | |
| Male | 1,259 (50.5%) | 1,432 (51.1%) | 1,859 (52.1%) | 2,282 (42.9%) | 3,614 (43.1%) | 3,403 (42.4%) |
| Female | 1,232 (49.5%) | 1,369 (48.9%) | 1,707 (47.9%) | 3,034 (57.1%) | 4,778 (56.9%) | 4,618 (57.6%) |
| **Setting of Index VTE Event** | | | | | | |
| Inpatient | 1,627 (65.3%) | 1,792 (64.0%) | 2,472 (69.3%) | 2,559 (48.1%) | 4,172 (49.7%) | 3,855 (48.1%) |
| Outpatient | 865 (34.7%) | 1,009 (36.0%) | 1,094 (30.7%) | 2,757 (51.9%) | 4,220 (50.3%) | 4,166 (51.9%) |
| ER | 811 (32.6%) | 926 (33.1%) | 1,021 (28.6%) | 2,351 (44.2%) | 3,555 (42.4%) | 3,570 (44.5%) |
| **VTE Diagnosis** | | | | | | |
| DVT only | 1,473 (59.1%) | 1,773 (63.3%) | 2,088 (58.5%) | 2,841 (53.4%) | 4,550 (54.2%) | 4,215 (52.5%) |
| PE with DVT | 320 (12.8%) | 339 (12.1%) | 484 (13.6%) | 626 (11.8%) | 903 (10.8%) | 947 (11.8%) |
| PE without DVT | 698 (28.0%) | 688 (24.6%) | 994 (27.9%) | 1,849 (34.8%) | 2,939 (35.0%) | 2,859 (35.6%) |
| **NCI Comorbidity Index** | 4.9 (2.7) | 4.9 (3.2) | 5.0 (2.7) | 2.3 (2.1) | 2.3 (2.1) | 2.3 (2.2) |
| **Baseline Comorbidity** | | | | | | |
| Anemia | 1,675 (67.2%) | 1,845 (65.9%) | 2,385 (66.9%) | 2,205 (41.5%) | 3,678 (43.8%) | 3,377 (42.1%) |
| Central venous catheter | 665 (26.7%) | 725 (25.9%) | 869 (24.4%) | 1,154 (21.7%) | 2,088 (24.9%) | 1,697 (21.2%) |
| Cerebrovascular disease | 431 (17.3%) | 512 (18.3%) | 694 (19.5%) | 646 (12.2%) | 970 (11.6%) | 1,069 (13.3%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| Hematologic disorders associated with bleeding | 525 (21.1%) | 607 (21.7%) | 691 (19.4%) | 741 (13.9%) | 1,132 (13.5%) | 1,097 (13.7%) |
| Thrombocytopenia | 434 (17.4%) | 515 (18.4%) | 517 (14.5%) | 556 (10.5%) | 922 (11.0%) | 767 (9.6%) |
| Ischemic heart/ coronary artery disease | 903 (36.3%) | 1,009 (36.0%) | 1,421 (39.9%) | 1,236 (23.3%) | 1,756 (20.9%) | 1,810 (22.6%) |
| Dyspepsia or stomach discomfort | 1,035 (41.5%) | 1,109 (39.6%) | 1,438 (40.3%) | 1,732 (32.6%) | 2,864 (34.1%) | 2,554 (31.8%) |
| Hyperlipidemia | 1,596 (64.1%) | 1,727 (61.7%) | 2,317 (65.0%) | 2,501 (47.1%) | 3,576 (42.6%) | 3,884 (48.4%) |
| Obesity | 587 (23.6%) | 627 (22.4%) | 802 (22.5%) | 831 (15.6%) | 1,423 (17.0%) | 1,330 (16.6%) |
| Pneumonia | 579 (23.2%) | 703 (25.1%) | 829 (23.3%) | 900 (16.9%) | 1,378 (16.4%) | 1,353 (16.9%) |
| Congestive heart failure | 646 (25.9%) | 668 (23.9%) | 969 (27.2%) | 581 (10.9%) | 821 (9.8%) | 939 (11.7%) |
| Diabetes | 1,142 (45.8%) | 1,258 (44.9%) | 1,660 (46.6%) | 1,297 (24.4%) | 2,137 (25.5%) | 2,202 (27.5%) |
| Hypertension | 2,222 (89.2%) | 2,429 (86.7%) | 3,228 (90.5%) | 3,576 (67.3%) | 5,343 (63.7%) | 5,410 (67.4%) |
| Liver disease | 484 (19.4%) | 723 (25.8%) | 578 (16.2%) | 1,015 (19.1%) | 2,094 (25.0%) | 1,378 (17.2%) |
| COPD | 750 (30.1%) | 748 (26.7%) | 1,079 (30.2%) | 1,315 (24.7%) | 1,701 (20.3%) | 2,055 (25.6%) |
| Peripheral vascular disease | 696 (27.9%) | 843 (30.1%) | 1,079 (30.3%) | 967 (18.2%) | 1,359 (16.2%) | 1,494 (18.6%) |
| Baseline any bleed | 1,015 (40.7%) | 1,192 (42.6%) | 1,499 (42.0%) | 1,708 (32.1%) | 2,742 (32.7%) | 2,553 (31.8%) |
| **Selected Surgeries** | 1,242 (49.8%) | 1,435 (51.2%) | 1,700 (47.7%) | 2,126 (40.0%) | 3,621 (43.1%) | 3,012 (37.6%) |
| **Cancer Metastasis+** | 1,086 (43.6%) | 1,281 (45.8%) | 1,491 (41.8%) | 2,674 (50.3%) | 4,356 (51.9%) | 4,011 (50.0%) |
| **Cancer Type+** | | | | | | |
| Hematological | 476 (19.1%) | 605 (21.6%) | 694 (19.5%) | 802 (15.1%) | 1,319 (15.7%) | 1,212 (15.1%) |
| Non-hematological | 2,016 (80.9%) | 2,195 (78.4%) | 2,872 (80.5%) | 4,513 (84.9%) | 7,073 (84.3%) | 6,809 (84.9%) |
| **VTE Risk** | | | | | | |
| Very high risk (brain, stomach, and pancreas) | 290 (11.6%) | 316 (11.3%) | 358 (10.0%) | 801 (15.1%) | 1,277 (15.2%) | 1,211 (15.1%) |
| High risk (lung, lymphoma, gynecologic, bladder, testicular, renal cell carcinoma) | 1,085 (43.6%) | 1,241 (44.3%) | 1,636 (45.9%) | 2,092 (39.4%) | 3,453 (41.2%) | 3,179 (39.6%) |
| Other | 1,116 (44.8%) | 1,243 (44.4%) | 1,572 (44.1%) | 2,423 (45.6%) | 3,661 (43.6%) | 3,631 (45.3%) |
| **Cancer-related Treatment+** | 00 (0.0%) | 00 (0.0%) | 00 (0.0%) | 00 (0.0%) | 00 (0.0%) | 00 (0.0%) |
| Chemotherapy | 1,062 (42.6%) | 1,385 (49.4%) | 1,503 (42.2%) | 2,530 (47.6%) | 4,452 (53.0%) | 3,701 (46.1%) |
| Hormone therapy | 134 (5.4%) | 189 (6.7%) | 190 (5.3%) | 359 (6.8%) | 515 (6.1%) | 555 (6.9%) |

### 8.4.2.3.4. Evaluation of Outcomes by Renal Disease Status

As shown in Figure 21, those with renal disease vs. those without renal disease had much higher incidence rates across all 3 drug cohorts (apixaban, LMWH and warfarin) for major bleeding (15.79 vs 8.71, 22.11 vs 15.90, and 18.49 vs 10.39) and CRNM bleeding (38.06 vs 30.44, 59.49 vs 44.89 and 45.28 vs 34.25), respectively. When comparing different anticoagulants, the incidence rates of major bleeding, CRNM bleeding and recurrent VTE events were numerically lower in the apixaban cohort compared to warfarin or LMWH regardless of renal disease status. In general, there was no significant interaction between the treatment (apixaban vs warfarin, apixaban vs LMWH, and warfarin vs LMWH) and renal disease status on any of the outcomes: recurrent VTE, MB, and CRNMB ($P > 0.1$ for most of the interactions). Treatment effects were generally not significantly different between those with and without renal disease. One significant interaction was observed between the treatment of warfarin (vs. LMWH) and renal disease status on MB (p value of interaction=0.0863). Warfarin had a lower risk of MB vs. LMWH (0.71 [0.59-0.87]) in patients without renal disease, but a similar risk (0.94 [0.73-1.22]) in those with renal disease (Figure 21).

**Figure 21：Effects by renal disease status**




# 9. DISCUSSION

## 9.1. PHASE 1 DISCUSSION

### 9.1.1. Key Results

For the phase 1 analysis, all eligibility criteria were fulfilled by 3,393 apixaban, 6,108 LMWH, and 4,585 warfarin patients. After IPTW, all patient characteristics were balanced. When the follow-up was censored at 6 months, apixaban patients had a lower risk of MB, CRNM bleeding, and recurrent VTE vs. LMWH. Apixaban patients had a lower risk of recurrent VTE and similar risk of MB and CRNM bleeding vs. warfarin. Warfarin patients had a similar risk of MB, CRNM bleeding, and recurrent VTE vs. LMWH. The trends were similar when the entire follow-up was used; however, apixaban patients were also associated with a lower risk of MB vs. warfarin patients.

Findings from the subgroup analyses were generally consistent with the main analyses. Analyses stratified by VTE risk scale, metastatic diagnosis, cancer treatment, chemotherapy, VTE event type, GI cancer and GI/bladder cancer showed generally consistent results across the subgroups (most of the p values for interaction >0.10)

### 9.1.2. Limitations

As a retrospective observational analysis, only associations could be concluded from this study. Diagnoses for DVT and PE were identified using ICD-9/10-CM codes; the presence of a diagnosis code on a medical claim may not indicate a positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. Given the lack of

clinical information in claims data, cancer stage, laboratory test results (such as international normalized ratio values and serum creatinine/creatinine clearance levels), and biomarkers (such as body weight) were not available. Duplicates were not excluded from the pooled database. However, prior literature reported only 0.5% duplicates between two databases[62]. Hence, they should not impact the study results. Transfusion codes were one criterion used to identify MB, which could have resulted in overestimation of MB since cancer patients are likely to receive transfusions for other reasons. However, the codes have been derived from a validated MB definition which had a positive predictive value of ≥89%[63]. Since hemoglobin values were not known and significant hemoglobin drop cannot be identified from the databases, MB also could have been underestimated. The commercial databases do not have complete death information for the patients; hence, we could not evaluate mortality and fatal recurrent VTE among this population, and mortality may be a competing risk in this population. Medications prescribed during hospitalization could not be identified in the commercial databases. Finally, the results may not be generalizable to the entire US VTE cancer population since uninsured patients or patients with governmental insurances such as Medicare, Medicaid, and Veterans Affairs were not evaluated.

### 9.1.3. Interpretation

This study, pooling 4 large US commercial claims databases, demonstrated that apixaban was associated with significantly lower risks of MB, CRNM bleeding, and recurrent VTE compared to LMWH. Additionally, apixaban was associated with a lower risk of recurrent VTE compared to warfarin initiators. Warfarin was associated with similar risks of MB, CRNM bleeding, and recurrent VTE compared to LMWH patients. Furthermore, patients prescribed apixaban had higher persistence compared to patients prescribed LMWH or warfarin. Warfarin patients had higher persistence compared to LMWH patients. Findings were consistent when follow-up was censored at 6 months and when the entire follow-up was used to evaluate the outcomes. Subgroup analyses showed generally consistent results as the main analyses.

The clinical guidelines, until very recently, had recommended primarily the use of LMWH for the first 6 months for the treatment of VTE in cancer patients. Despite the recommendation, LMWH remains under-utilized. In a review of published surveys, registries, and observational studies, only 50% of patients were treated with LMWH for cancer-associated VTE[40]. Additionally, a real-world study among commercially insured patients showed that 50% of the cancer patients who developed VTE used warfarin, 40% used LMWH, and ~10% used DOACs or fondaparinux[63]. The study also reported that during the 6 months of observation, 44% of LMWH patients and 28% of warfarin patients switched to other anticoagulants[63]. In our study, a higher proportion of LMWH (21.4%) patients switched their index treatment compared to apixaban (5.7%) and warfarin (16.5%) patients. Non-adherence to clinical guidelines could be due to the inconvenience associated with the use of LMWH, risk of bleeding, reluctance to impose daily injections on fragile patients, and personal preference[64,65]. DOACs, on the other hand, offer quick onset of action, higher bioavailability, and shorter half-lives; additionally, rivaroxaban and apixaban do not require concomitant LMWH therapy[66,67].

The choice of anticoagulation among VTE cancer patients is based on a balance between the risk of bleeding and of VTE recurrence. The recommendation to use LMWH as the standard of care

treatment among VTE patients with cancer is based on clinical trials that compared LMWH to VKAs for the initial management of cancer-associated VTE[68-70]. In the LITE trial, tinzaparin was associated with a lower rate of recurrent VTE and a similar rate of MB compared to VKAs[61]. In the CATCH trial, once-daily tinzaparin was associated with a similar risk of MB and recurrent VTE, and a lower risk of CRNM bleeding compared to warfarin patients who bridged therapy with tinzaparin[71]. In the CLOT trial, dalteparin had a significantly lower risk of recurrent VTE and a similar risk of bleeding compared to oral anticoagulation (warfarin LMWH bridging therapy)[72]. While these clinical trials provide important information about the efficacy and safety of LMWH vs VKA in VTE cancer patients, the current study offers complementary evidence about the effects of parenteral and oral anticoagulants in routine clinical practice.

The last decade has seen an emergence of DOACs for the treatment of VTE. Clinical trials have demonstrated the effectiveness and safety of DOACs in comparison to LWMH for VTE patients with cancer[40,45]. A meta-analysis of randomized control trials comparing the safety and efficacy of DOACs (apixaban, dabigatran, edoxaban, rivaroxaban) with conventional therapy (heparin/VKA) in patients with VTE and mainly inactive cancer reported that recurrent VTE (3.9% vs 6.0%) and MB (3.2% vs 4.2%) were similar between the two groups[73]. Another meta-analysis found that DOACs (edoxaban or rivaroxaban) significantly reduced the risk of recurrent VTE by 28% and 54% compared to LMWH and VKA[74]. However, DOACs (edoxaban or rivaroxaban) were associated with a 15% increase in the risk of MB compared to LMWH[71].

There is limited evidence in the literature regarding the use of apixaban among VTE cancer patients. In the ADAM trial, which studied 300 cancer patients with VTE, apixaban was associated with very low rates of MB and recurrent VTE compared to dalteparin[68]. The CARAVAGGIO trial which included more patients than the ADAM trial found that apixaban was noninferior to dalteparin for the treatment of cancer-associated VTE without an increased risk of MB[67]. Compared to the CARAVAGGIO, this claims database analysis included a larger sample size and showed generally consistent trends for apixaban vs LMWH on recurrent VTE and MB. The current analysis provides complementary information to CARAVAGGIO. This combined evidence may help inform the shared decision-making process for the treatment of VTE among cancer patients.

Other retrospective observational studies comparing LMWH to oral anticoagulants have also been conducted. A retrospective study using the electronic medical records of adult patients with cancer related VTE reported similar risks of MB and recurrent VTE among patients who initiated DOACs vs LMWH[65]. Another study conducted in a clinical setting that compared apixaban, enoxaparin, and rivaroxaban among patients with cancer associated VTE reported that the risk of MB and recurrent VTE was similar across apixaban, enoxaparin, and rivaroxaban[75]. However, rivaroxaban was associated with an increased risk of CRNM bleeding compared to apixaban and enoxaparin[32].

Studies have also evaluated the risk of MB in high-risk patients such as those with gastrointestinal cancers. The Hokusai cancer study reported a significant interaction between edoxaban and GI cancer on MB with increased MB in patients with GI cancer[32]. Results from Select-D trial report that in patients with bladder tumor, 10% patients on edoxaban had MB compared to 0% in patients prescribed LMWH[45]. In this study, no significant interaction was reported between treatment and

GI cancer for MB and recurrent VTE. Further exploration is needed to evaluate the safety and effectiveness of DOACs in VTE patients with high-risk cancers.

The use of LMWH remains challenging due to its risk-to-benefit ratio, cost, and inconvenience of use. This study found that apixaban had a significantly better safety and effectiveness profile compared to LMWH in VTE patients with active cancer. Safety and effectiveness of anticoagulation treatment also depends on the risk stratification for VTE at the time of cancer diagnosis, which may play an important role in the assessment of the risk-to-benefit ratio among VTE cancer patients[61,71]. Subgroup analyses stratified based on VTE risk scale and other risk factors such as metastatic diagnosis, cancer treatment and chemotherapy showed generally consistent findings as the main analyses and across the strata. Further studies are needed to evaluate the clinical outcomes of anticoagulation treatment among VTE cancer patients at high risk of recurrent VTE.

# 10. PHASE 2 DISCUSSION

## 10.1. Key Results

For the phase 2 analysis, all eligibility criteria were fulfilled by 7,807 apixaban, 11,192 LMWH, and 11,587 warfarin patients. After IPTW, all patient characteristics were balanced. When the follow-up was censored at 6 months, apixaban patients had a lower risk of MB, CRNM bleeding, and recurrent VTE vs. LMWH and vs. warfarin. Warfarin patients had a lower risk of MB, CRNM bleeding, and similar risk of recurrent VTE vs. LMWH.

Findings from the subgroup analyses were consistent with the main analyses. Analyses stratified by brain cancer, pancreas cancer, lung cancer, breast cancer, prostate cancer, multiple myeloma, prior bleed and renal disease showed generally consistent results across the subgroups (most of the p values for interaction >0.10).

## 10.2. Strengths and Limitations

A key strength is that retrospective observational analyses provide a better understanding about the study population in real-world clinical practice and offer complimentary information to controlled clinical trials. Retrospective observational studies also allow the evaluation of patients who are often under-represented in clinical trials, such as those with comorbidities and the elderly. Since prescribing patterns in the real-world can be complex, the retrospective analysis provides a comprehensive picture of how medications are used by clinicians in routine practice. The national claims databases incorporate all medical and pharmacy claims of patients and allow for longitudinal analysis of a nationally representative sample. Pooling five databases together increases study sample size and improve generalizability of study findings.

There are certain limitations associated with the use of claims data. First, the presence of a claim for a filled prescription does not indicate whether the medication was actually consumed or taken as prescribed. Second, the presence of a diagnosis code on a medical claim is not a positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. Third, certain information is not readily available in claims data that could influence study outcomes, such as INR tests. Fourth, this retrospective observational study

can only demonstrate association and not causality. Fifth, we did not exclude duplicates from the database. However, prior literature reported only 0.5% duplicates between two the databases.[1] Hence, it should not impact our study results. Finally, the results may not be generalizable to the entire US VTE cancer population such as the uninsured, self-insured, or those that are insured under Veterans Affairs or Medicaid.

## 10.3. Interpretation

### 10.3.1. High Risk and Common Tumor Types

In general, effects of apixaban vs. warfarin, apixaban vs. LMWH, and warfarin vs. LMWH on recurrent VTE, MB or CRNMB were not significantly different between patients with vs. without a specific tumor type. Apixaban was generally associated with lower incidence rates of recurrent VTE, MB and CRNMB compared to LMWH or warfarin regardless of tumor status (yes or no). In a few cases, treatment effects significantly differed between patients with and without a specific cancer. The effects of apixaban vs. LMWH on MB; and effects of warfarin vs. LMWH on recurrent VTE, MB, and CRNMB were significantly different between patients with lung cancer and patients without lung cancer. There were also significant differences in the effects of apixaban vs. LMWH on MB and CRNMB and effects of warfarin vs. LMWH on recurrent VTE and MB between patients with pancreatic cancer and without pancreatic cancer.

Limited studies have systematically examined the efficacy/effectiveness and safety of anticoagulant treatments as a function of tumor type. A post hoc analysis of the Hokusai VTE Cancer study that compared edoxaban with LMWH found a similar benefit-risk profile for lung, breast, hematological, and gynecological cancers [43]. But that post hoc analysis, as well as the SELECT-D trial, did report an increased risk of MB for edoxaban (Hokusai VTE Cancer) and rivaroxaban (SELECT-D), respectively, for gastrointestinal cancers, suggesting different treatment effect on MB for this tumor type [45,76]. A subgroup analysis of the CARVAGGIO trial compared apixaban with LMWH and found that the effects of apixaban were not different for gynecological, lung, genitourinary, and gastrointestinal cancer [41]. A subgroup analysis of a recent observational study which evaluated the effectiveness and safety of anticoagulants including apixaban, LMWH and warfarin in patients with VTE and active cancer found consistent treatment effects on recurrent VTE and MB for patients with and without gastrointestinal cancer [46]. Consistent with the previous publications, our current study found that the treatment effects of apixaban, LMWH and warfarin were mostly not significantly different between patients with VTE who had a specific tumor vs. patients without a specific tumor for most tumor types, including prostate, breast, lung, multiple myeloma, and pancreatic cancer.

The findings from our study also suggest there may be tumor specific treatment effects for some of the medications and some of the tumor types. One example is the comparison of apixaban or warfarin with LMWH for patients with or without lung cancer. Our study shows that the effects of apixaban vs. LMWH and effects of warfarin vs. LMWH on recurrent VTE and MB were significantly different between patients with vs. without lung cancer. The treatment effects trended differently with lung cancer patients showing more favorable treatment effects of apixaban or warfarin (vs. LMWH) than those without lung cancer. However, these findings are for hypothesis generation and require additional studies to confirm this observation.

### 10.3.2. Brain Cancer

When stratified by brain cancer status (brain cancer vs. other types of cancer), treatment effects of apixaban, LMWH and warfarin 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 [13,16,]. 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.

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 [16]. 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.

### 10.3.3. Prior Bleed and Renal Disease

This real-world study of patients with VTE and with active cancer showed that those with prior bleed or renal disease were more likely to have comorbidities and had a higher incidence rate of MB and CRNM bleeding compared to those without prior bleed or without renal disease respectively. The treatment effects of apixaban, warfarin and LMWH were in general not significantly different between those with and without prior bleed or between those with or without renal disease. Apixaban consistently had numerically lower incidence of recurrent VTE, MB, and CRNM bleeding compared to LMWH and warfarin regardless of the prior bleed or renal disease status.

Patients with cancer are at increased risk for VTE (either new or recurrent)[78,79]. Patients with cancer and VTE are also predisposed to bleeding events due to various cancer treatments or due to the cancer itself, which makes it challenging to treat these patients with anticoagulants [80]. Compounding this problem is the history of bleeding in some of these patients, which can increase the risk of another major bleeding event[81]. Consistently our current study found that patients with prior bleed had much higher incidence rates of MB and CRNM bleeding compared to those without prior bleed regardless of the anticoagulant they received. Additionally, patients with a prior bleed tended to have a higher comorbidity index and higher prevalence of comorbidities, indicating potential challenges for anticoagulant therapy in this patient population. However, our study showed no significant interactions between the treatment (apixaban vs. LMWH, warfarin vs. LMWH and apixaban vs. warfarin) and prior bleed status on recurrent VTE, MB and CRNM bleeding, suggesting that the treatment effects of apixaban, LMWH and warfarin were not significantly different between patients with and without prior bleed.

Patients with cancer and VTE who also had renal disease is another highly vulnerable population. These patients have been shown to be at increased risk for mortality, recurrent VTE, and MB[57]. In this study, we also found that patients with renal disease had higher incidence of MB and CRNM bleeding vs. those without renal disease. Additionally, patients with renal disease were more likely to be aged 75 years or older, more likely to have VTE been diagnosed in the hospital and have a markedly higher comorbidity index than those without renal disease. While these patients need careful considerations when being prescribed an anticoagulant, there is a knowledge gap on optimal anticoagulant treatment for these patients[82]. In this study, we found that there was no significant interaction between the treatment (apixaban vs. LMWH, warfarin vs. LMWH and apixaban vs. warfarin) and renal disease status on recurrent VTE, MB, and CRNM bleeding. The lack of a significant interaction indicates the treatment effect of apixaban, LMWH and warfarin were not significantly different between patients with and without renal disease. Our results are consistent with the renal sub-analysis of the CARRIVAGIO trial which found no significant interaction between the treatment of apixaban vs. dalteparin and the presence of renal insufficiency (estimated glomerular filtration rate [eGFR] <60 or <50) on recurrent VTE or bleeding [53].

## 11. OTHER INFORMATION

Not Applicable

## 12. CONCLUSIONS

To the best of our knowledge, this is the largest observational study of apixaban comparing LMWH and warfarin among VTE patients with active cancer. When using 5 US claims databases (4 commercial + Medicare), Apixaban was associated with lower risks of MB, CRNM bleeding, and recurrent VTE compared to LMWH and warfarin. Warfarin was associated with lower risks of MB, CRNM bleeding, and similar risk of recurrent VTE compared to LMWH patients. Analyses stratified by GI, brain, lung, pancreatic, breast, prostate cancer, renal disease and prior bleed showed generally consistent results across the subgroups. These results may be helpful for clinicians in evaluating different anticoagulation treatments for VTE patients with active cancer. Further research is needed to explore if there is a need for tumor specific anticoagulant treatment and to fully understand outcomes of anticoagulant treatment among subgroups of VTE cancer patients.

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