# NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

## Study information

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| **Title** | Evaluation of the Effectiveness and Safety of Anticoagulants Among Sub-Groups of Venous Thromboembolism Patients |
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| **Research question and objectives** | **Aim 1:** Describe and compare the demographic and clinical characteristics among venous thromboembolism (VTE) patients overall and in key subgroups (e.g., age, obesity, renal disease, thrombophilia) of patients who were prescribed apixaban or warfarin.<br><br>**Aim 2:** Describe and compare the rate of recurrent VTE among VTE patients overall and in key subgroups of patients who were prescribed apixaban or warfarin.<br><br>**Aim 3:** Describe and compare the rate of major bleeding (MB) and clinically relevant non-major bleeding (CRNMB) among VTE patients overall and in key subgroups of patients who were prescribed apixaban or warfarin. |

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## ABSTRACT (STAND-ALONE DOCUMENT)

**Title:** Evaluation of the Effectiveness and Safety of Anticoagulants Among Sub-Groups of Venous Thromboembolism Patients

**Rationale and background:** Venous thromboembolism (VTE) is a major cause of morbidity and mortality. Each year in the United States, the annual incidence of VTE is 1 case per 1,000 patients. VTE accounts for more than 600,000 hospitalizations and 100,000 deaths and has a significant economic burden ($13.5 billion to $27.2 billion). Moreover, the incidence of VTE increases with age, with older adults being the most prone to develop a VTE.

Vitamin K antagonists (VKAs), such as warfarin, have been the treatment of choice in VTE patients. New non-VKA oral anticoagulants (NOACs) have emerged to treat VTE. NOACs have at least equal efficacy to warfarin but have a lower or similar risk of major bleeding (MB). In addition, NOACs have less complex pharmacodynamics with limited need for routine monitoring, an advantage over constant monitoring with VKAs. One such NOAC is apixaban, an oral factor Xa inhibitor that eliminates the need for initial parenteral anticoagulant, thus simplifying the treatment of VTE. The AMPLIFY randomized clinical trial demonstrated that a fixed-dose regimen of apixaban alone was associated with significantly less MB and was non-inferior to conventional therapy (subcutaneous enoxaparin, followed by warfarin) for the treatment of VTE. Subgroup analyses of the AMPLIFY trial indicated similar safety and effectiveness among some pre-specified subgroups (e.g., elderly and obese). A study using four US commercial claims databases showed that patients treated with apixaban had a significantly lower risk of MB and recurrent VTE compared with those treated with warfarin in routine clinical practice. However, there is a lack of evidence about the safety and effectiveness of apixaban vs. warfarin among high-risk subgroups of VTE patients (i.e. elderly, obese, renal disease, and thrombophilia) in routine clinical practice.

This study adds real-world evidence regarding the comparative risks of recurrent VTE, MB, and clinically relevant non-major bleeding (CRNMB) among VTE patients who initiated treatment with apixaban or warfarin, especially among some high-risk subgroups of patients (e.g., elderly, obese, renal disease, and thrombophilia).

**Objectives**:
The overall objective of this analysis was to understand patient characteristics and compare safety and effectiveness of apixaban vs. warfarin among high-risk subgroups of VTE patients.

**Aim 1:** Describe and compare the demographic and clinical characteristics among VTE patients overall and in key subgroups (e.g., age, obesity, renal disease, thrombophilia) of patients who were newly prescribed apixaban or warfarin.

**Aim 2:** Describe and compare the rate of recurrent VTE among VTE patients overall and in key subgroups of patients who were newly prescribed apixaban or warfarin.

**Aim 3:** Describe and compare the rate of MB and CRNMB among VTE patients overall and

in key subgroups of patients who were newly prescribed apixaban or warfarin.

**Study design:** The study was a longitudinal retrospective cohort analysis using a pooled (Humana, IMS, Optum, MarketScan, and CMS Medicare) database. The study period was from March 1, 2014 through December 31, 2017 for the CMS Medicare database and the most recent data cut available for each commercial database (MarketScan: 01MAR2014-30SEP2018; Optum & Humana: 01MAR2014-31DEC2018; PharMetrics: 01MAR2014-31MAR2019; Medicare: 01MAR2014-31DEC2017).

Patients were required to have a VTE diagnosis in any position in the inpatient or outpatient setting between September 1, 2014 and end of study period. Patients were also required to have a warfarin or apixaban prescription claim within 30 days of the index VTE event. The first prescription date for apixaban or warfarin was defined as the index date for the respective cohort.

The study had a 6-month baseline period prior to the index date. Patients were followed from the day after the index date until the earliest of treatment discontinuation, treatment switch, initiation of a new parenteral anticoagulant (PAC) treatment, death, disenrollment, study end, or 6 months after the index date.

**Population:** VTE patients in the Humana, Optum, IMS, MarketScan, and CMS Medicare databases who were newly prescribed apixaban or warfarin between September 1, 2014 and the end of the study period and had continuous health plan enrollment for 6 months prior to the initial apixaban or warfarin prescription.

**Subgroups:** The following subgroups were evaluated:

1) Demographic-socioeconomic (age [65-79 and 80+], sex, race [white and black]. Socioeconomic status, and Medicaid dual eligibility/ low income subsidy status on index date);

2) Obese and morbid obese prior to index;

3) Prior chronic kidney disease (CKD) [stage 1&2, stage 3, stage 4, stage 5/ESRD and unspecified];

4) High risk of bleeding (at least one risk factor: age 75+, prior drug use [antiplatelet, NSAID or corticosteroid], prior GI bleed or prior GI-related condition [peptic ulcer, helicobacter pylori infection, diverticulosis, angiodysplasias, history of GI cancer (stomach, colon, esophageal, or rectal), or other GI lesions], and prior late stage CKD [stage 3-5/ESRD]);

5) Bleeding (prior history of bleeding, prior thrombocytopenia) and VTE recurrence (prior thrombophilia, prior chronic liver disease and prior immune mediated disorder) risk factors.

**Variables:** Demographic and clinical characteristics and clinical outcomes including recurrent VTE, MB, and CRNMB.

**Data sources:** The study was conducted using member enrollment as well as medical and pharmacy claims from the Optum, Humana, IMS, MarketScan, and CMS Medicare 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. Stabilized inverse probability treatment weighting (IPTW) were used to balance treatment cohorts. Standard differences were used to determine if groups were balanced after IPTW (difference >10 indicated imbalance). Depending on sample size, subgroup analysis was either a comparative analysis within a specific subgroup of patients (e.g., obese subgroup) or a subgroup interaction analysis. For the comparative analysis, IPTW was applied to the specific subgroup of patients to balance patient characteristics between treatment cohorts and Cox models were used to compare outcomes between different cohorts. For the subgroup interaction analysis, the overall study population was stratified into the subgroups described above (e.g., age and sex) and the interaction between treatment and subgroup on outcomes was evaluated to assess whether treatment effects were different among subgroups. Appropriate tests (e.g., t-test, chi-square test) were used for comparisons based on the distribution of the measure. Kaplan-Meier survival curves were generated to illustrate the time to first MB, CRNMB, and recurrent VTE events for each treatment cohort. The cumulative incidence rates for clinical outcomes were calculated. Cox proportional hazard ratio models were used to compare the risk of clinical outcomes (recurrent VTE, MB, CRNMB) between treatment cohorts and adjusted for variables that were imbalanced after IPTW and subgroup stratification. Data analysis was executed using statistical software SAS version 9.4 (Cary, NC).

**Results:** Of the 155,119 VTE patients eligible for analysis, 94,333 (60.8%) were prescribed warfarin and 60,786 (39.2%) were prescribed apixaban. After IPTW, patient characteristics were generally balanced. Apixaban patients had a significantly lower risk of MB (hazard ratio [HR]: 0.70; 95% confidence interval [CI]: 0.64-0.76), CRNMB (HR: 0.83; 95% CI: 0.80-0.86), and recurrent VTE (HR: 0.72; 95% CI: 0.67-0.78) ($p < 0.001$).

*Demographic socioeconomic subgroup analysis* - Only Medicare data were used for the demographic socioeconomic subgroup analysis. Other databases lack information about race and socioeconomic status (SES). In the Medicare patients with VTE, apixaban treatment was associated with significantly lower risks of recurrent VTE (hazard ratio [HR] 0.64; 95% confidence interval [CI] 0.52-0.79), MB (HR 0.65; 95% CI 0.57-0.75), and CRNMB (HR 0.79; 95% CI 0.75-0.85) versus warfarin. When stratified by demographics and SES, higher incidence rates of recurrent VTE, MB, and CRNMB were observed for black vs white patients and patients with lower vs higher SES. Comparison of apixaban with warfarin by different demographic and SES subgroups showed generally consistent results with the overall analysis. For most subgroups, no significant interaction was observed between treatment and subgroup strata for recurrent VTE, MB, and CRNMB.

*Obese/morbid obese subgroup analysis* - When stratified by obesity status (non-obese, obese/non-morbid, morbidly obese) in the post-IPTW overall VTE population, no significant interactions were observed between the obesity status and treatment of apixaban vs warfarin on recurrent VTE or MB (interaction $p > 0.10$). Among post-IPTW obese and morbidly obese

patients with VTE, apixaban was associated with a significantly lower risk of recurrent VTE ([obese: HR 0.73; 95% CI 0.64–0.84], [morbidly obese: HR 0.65; 95% CI 0.53–0.80] and MB ([obese: HR 0.73; 95% CI 0.62–0.85], [morbidly obese: HR 0.68; 95% CI 0.54–0.86]) as compared with warfarin.

*CKD subgroup analysis* - Among post-IPTW CKD patients with VTE, the apixaban cohort had significantly lower risk of recurrent VTE (HR: 0.78; 95% confidence interval [CI]: 0.66, 0.92), MB (HR: 0.76; 95% CI: 0.65, 0.88), and CRNMB (HR: 0.86; 95% CI: 0.80, 0.93) than the warfarin cohort. When stratified by CKD stage (stage I/II: 8.2%; stage III: 49.4%; stage IV: 12.8%; stage V/ESRD: 12.0%; stage unspecified: 17.6%), no significant interaction was observed between CKD stages and treatment of apixaban versus warfarin on recurrent VTE and MB.

*High risk of bleeding subgroup analysis* - Among the subgroup of VTE patients at high-risk of bleeding after applying IPTW, apixaban was associated with significantly lower risk of recurrent VTE (HR 0.78; 95% CI 0.70-0.87), MB (HR 0.75 95% CI 0.67-0.83) and clinically relevant non-major bleeding (HR 0.89; 95% CI 0.85-0.93). No significant interactions were observed between treatment and number of risk factors on major bleeding and CRNMB or between treatment and type of bleeding risk factors on any of the outcomes.

*Bleeding and VTE Recurrence Risk Factor Subgroup Analysis* – The post-IPTW overall population was stratified by the presence and absence of each of the following risk factors: history of bleed, thrombocytopenia, thrombophilia, chronic liver disease and immune mediated disorders. For most of the subgroup interaction analyses, no significant interaction was observed between the treatment of apixaban vs. warfarin and the risk factor on recurrent VTE, MB or CRNMB (P value for interaction >0.1 for most of the analyses).

**Conclusions:** VTE patients who initiated apixaban had a significantly lower risk of MB, CRNMB, and recurrent VTE compared to warfarin patients in the overall and some specific high-risk subgroup of patients. Treatment effects of apixaban were generally consistent across various subgroups of patients.

## 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 |
| CRNMB | Clinically Relevant Non-Major Bleeding |
| DVT | Deep Vein Thrombosis |
| ER | Emergency Room |
| GI | Gastrointestinal |

| Abbreviation | Definition |
|---|---|
| GLM | Generalized Linear Models |
| GPP | Good Pharmacoepidemiology Practices |
| HCFA | Health Care Financing Agency |
| HCPCS | Common Procedure Coding System |
| HIPAA | Health Insurance Portability and Accountability Act |
| HR | Hazard Ratios |
| ICD-9-CM | International Classification of Disease, 9th Revision, Clinical Modification |
| ICD-10-CM | International Classification of Disease, 10th Revision, Clinical Modification |
| ICH | Intracranial Hemorrhage |
| IPTW | Inverse Probability Treatment Weights |
| INR | *International Normalized Ratio* |
| NOAC | Vitamin K antagonist Oral Anticoagulant |
| NDC | National Drug Codes |
| OAC | Oral Anticoagulant |
| PAC | Parenteral Anticoagulant |
| PE | Pulmonary Embolism |
| RCT | Randomized Controlled Trial |
| SES | Socioeconomic Status |
| UB | Uniform Bill |
| VKA | Vitamin K antagonist |
| VTE | Venous Thromboembolism |

## 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 |
|---|---|---|
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## OTHER RESPONSIBLE PARTIES

Not applicable

## RATIONALE AND BACKGROUND

Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), is a serious disease in the United States affecting ~1 in 1,000 patients each year. Studies have shown that every year >900,000 patients are diagnosed with VTE, and the disease accounts for 600,000 hospitalizations and 100,000 deaths.[1] The costs associated with VTE were assessed at $13.5-27.2 billion per year,[2] and the incidence of early recurrent VTE on treatment was estimated at nearly 3% at 3 months of follow-up.[3] Moreover, the incidence of VTE increases with age, with older adults having the highest incidence rates for VTE.

Vitamin K agonists (VKAs), such as warfarin, have been the treatment of choice among VTE patients. To maximize benefits and minimize complications such as bleeding, warfarin therapy needs to be monitored and adjusted within a narrow therapeutic index of international normalized ratio (INR) results.[4,5] The pharmacokinetic profile of warfarin is complex due to several drug-drug and drug-food interactions. It is difficult to achieve long-term stability among warfarin patients due to fluctuating INR values, which may be caused by factors such as diet, seasonal variation, and alcohol consumption.[6] The need for regular monitoring, the risk of hemorrhage, and poor control of INR levels may lead to medication non-adherence.[7,8]

Over the last several years, non-VKA oral anticoagulants (NOACs)—including dabigatran, apixaban, rivaroxaban, and edoxaban—were approved in the United States for the treatment of VTE. Clinical trials demonstrated that NOACs were as effective as warfarin and have similar or less major bleeding (MB).[9,10,11,12,13] Patients who are older or obese, or who have thrombophilia or renal disease, are at a higher risk of VTE.[14,15,16] An estimated 13% of Americans have kidney disease, and an estimated 35% of Americans are obese.[17] As the US population ages and rates of obesity and renal disease increase,[16] it is important to identify safe and effective VTE treatments for these sub-populations of VTE patients.

According to the American College of Chest Physician guidelines, DVT and PE patients who do not have cancer should be initiated on anticoagulation therapy with an oral VKA in preference to a non-oral VKA.[18] NOACs have two main drug classes: factor Xa inhibitors and direct thrombin inhibitors. Apixaban is an oral factor Xa inhibitor which eliminates the need for an initial parenteral anticoagulant, thus simplifying VTE treatment.[19] The AMPLIFY randomized clinical trial demonstrated that a 5mg twice-daily, fixed-dose oral regimen (after administering 10mg twice daily for 7 days) of apixaban alone was associated with significantly less risk of MB and was non-inferior to conventional therapy (subcutaneous enoxaparin, overlapped and followed by warfarin) for the treatment of VTE.[20] Additionally, the AMPLIFY trial demonstrated consistent treatment effects for apixaban vs. warfarin among certain clinically important subgroups, including elderly patients (aged >75 years) and obese patients (weighing >100kg).[20] A recent large-scale evaluation of VTE patients receiving outpatient treatment with apixaban or warfarin in routine clinical practice using four US claims databases found that patients treated with apixaban had a significantly lower risk of MB, clinically-relevant nonmajor bleeding (CRNMB), and recurrent VTE compared with those treated with warfarin over a mean 152-day follow-up period.[21]

There is insufficient real-world evidence on the effectiveness and safety of apixaban vs. warfarin in high-risk subgroups of VTE patients. Studies are needed to evaluate the comparative risks of MB, CRNMB, and recurrent VTE among VTE patients who initiated treatment with apixaban or warfarin, especially among some high-risk subgroups of patients (e.g., age range, obesity, renal disease, and thrombophilia).

## RESEARCH QUESTION AND OBJECTIVES

The overall objective of this analysis was to understand patient characteristics and compare effectiveness and safety of apixaban vs. warfarin among some high-risk subgroups of VTE patients.

**Aim 1:** Describe and compare the demographic and clinical characteristics among VTE patients overall and in key subgroups (e.g., age, obesity, renal disease, and thrombophilia) of patients who were newly prescribed apixaban or warfarin.

**Aim 2:** Describe and compare the rate of recurrent VTE among VTE patients overall and in key subgroups of patients who were prescribed newly apixaban or warfarin.

**Aim 3:** Describe and compare the rates of MB and CRNMB among VTE patients overall and in key subgroups of patients who were newly prescribed apixaban or warfarin.

## RESEARCH METHODS

### 8.1. Study Design

#### 8.1.1. Key Index Period Definitions

- **Study period:** The study period ranged from March 1, 2014 until the last date of the data cut available at the time of study execution for each database. The study end time may be different for each database based on the last available data cut as follows:
  - MarketScan: 01MAR2014 – 30SEP2018
  - Optum: 01MAR2014 – 31DEC2018
  - Humana: 01MAR2014 – 31DEC2018
  - PharMetrics: 01MAR2014 – 31MAR2019
  - CMS Medicare: 01MAR2014 – 31DEC2017
- **Patient identification period:** The identification period ranged from September 1, 2014 until the end of the study period.
- **Baseline period:** The baseline period was 6 months prior to and on the index date. (See the index date definition in 9.1.2.)
- **Follow-up period:** The follow-up period was defined as the period between the day after the index date through the earliest of the subsequent 6-month period, health plan

disenrollment, index therapy discontinuation, switch to another oral anticoagulant (OAC), initiation of (new) parenteral anticoagulant (PAC) treatment, death, or study end.

### 8.1.2. Key Index Point Definitions

- **Index VTE event:** The first evidence of a VTE diagnosis in any position in the inpatient or ambulatory setting during the identification period for each patient
- **Index therapy:** The apixaban or warfarin treatment prescribed within 30 days from the index VTE event
- **Index date:** The first prescription claim date for the index therapy

## 8.2. Setting

Adult patients prescribed apixaban or warfarin were selected between September 1, 2014 and the end of the study. Patients were required to have a VTE diagnosis in any position (index VTE event). Patients were also required to have an apixaban or warfarin prescription claim within 30 days of the index VTE event. Patients were required to have health plan enrollment for 6 months prior to the index date to ensure availability of complete patient medical history.

***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) PAC treatment, study end, or 6 months after the index date.

Discontinuation was defined as no evidence of index warfarin or apixaban use for 30 days from the last day of the days' supply of the last filled apixaban or warfarin prescription, respectively.[22] The discontinuation date was the last day of the days' supply of the last filled prescription. The follow-up was censored at 30 days after the index drug discontinuation date.

VTE patients who received a prescription for an OAC other than the index therapy during the follow-up period were considered switchers if this OAC prescription was ≤30 days of the last day of supply. The follow-up was censored as of the index drug switch date.

VTE patients who initiated a PAC including low-molecular-weight heparin (LMWH; dalteparin, enoxaparin, tinzaparin), heparin, or fondaparinux during the follow-up period were considered initiators of PAC if this prescription was within ≤30 days of the last day of supply of the index therapy. The follow-up was censored at the initiation of PAC.

**NOTE:** For warfarin patients that bridged therapy with LMWH and used LMWH ≤14 days from the index date, patients were censored if they initiated PAC after day 14. Since the days of supply for PAC is 1 day, a gap in therapy of ≥2 days was used to distinguish the censoring event from the bridging therapy.

## 8.3. Subjects

### 8.3.1. Inclusion Criteria

Patients were included in the study if they:

- 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 to the end of the study period);
    - ❖ If the event occurred in the outpatient setting, the service date was designated as the index VTE event date. If the event occurred in the inpatient setting, the discharge date was designated as the index VTE event date. Qualifying outpatient VTE events followed by qualifying inpatient VTE events within 7 days were considered inpatient episodes (unless warfarin or apixaban were initiated between VTE events—in which case it would be classified as an outpatient VTE event).
- had ≥1 pharmacy claim for apixaban or warfarin during the 30-day period following the index VTE event;
- were aged ≥18 years as of the index date (≥65 years for Medicare); and
- had continuous health plan enrollment for ≥6 months prior to the index VTE event through the index date.

**Table 1. Oral and Parenteral Anticoagulants**

| Drug | Anticoagulant Type | HCPCS Codes |
|---|---|---|
| **Low molecular weight heparin** | | |
| 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 | - |

### 8.3.2. Exclusion Criteria

The study required a VTE population that was treatment naïve; newly diagnosed; without evidence of pregnancy, mechanical heart valve, or inferior vena cava filter; and without active cancer (the American College of Chest Physicians recommends different treatment guidelines for cancer patients diagnosed with VTE). Therefore, patients were excluded if they:

- had evidence of atrial fibrillation/flutter on or before the 6-month period preceding the index date;

- had evidence of a mechanical heart valve on or before the 6-month period preceding the index date;
- 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);
  - ❖ Warfarin patients who bridged therapy with LMWH were included.
- had evidence of any OAC/PAC use during the 6-month period preceding the index VTE event unless it was determined that such therapy was administered prophylactically (see Appendix 2);
  - ❖ Prophylactic use of OAC/PAC was determined based on the duration and timing of use (e.g., relative to knee/hip replacement surgery, hip or bone fractures, pelvic or thoracic surgery, or medical inpatient admission).
- had ≥2 medical claims for a cancer diagnosis or 1 claim for cancer diagnosis and ≥1 claim for cancer treatment (e.g., chemotherapy, radiation, cancer-related surgery) 6 months before the index VTE event or 30 days after index VTE event;
- had a medical claim indicating a diagnosis code for VTE during the 6 months preceding the index VTE event. The only exception is patients with an outpatient VTE event within 7 days prior to the index VTE event or an index VTE event occurring in the inpatient setting. For these patients, the outpatient VTE event was likely to be related to the index VTE event.
- had evidence of inferior vena cava filter at any time during the study period;
- had evidence of pregnancy at any time during the study period; or
- had evidence of antiphospholipid syndrome (APS) at any time during the study period.
  - ❖ Only International Classification of Diseases, 10th Revision (ICD-10) diagnosis codes are available for APS.

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

### 8.3.3. Cohorts

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

- **Warfarin:** 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 LMWH) during the period between the index VTE event and the initiation of warfarin. Warfarin patients who bridged therapy with LMWH were included.
- **Apixaban:** 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.

## 8.4. 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 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 age groups (e.g., 18-54, 55-64, 65-74, 75-79, ≥80 years) |
| **Gender** | 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. |
| **Medicare/Medicaid Dual Eligibility** | A flag was created for patients who have Medicare/Medicaid dual eligibility with results reported as a percentage (for the Medicare database only). |
| **Part D Low-Income Subsidy** | A flag was created for patients who have a Part D low-income subsidy with results reported as a percentage (for the Medicare database only). |
| **Socioeconomic Status (SES)** | A flag was created for patients who have low, moderate, or high socioeconomic status (SES) with results reported as a percentage (for the Medicare database only). |
| **Race** | Race was identified and was categorized as white, black, and other (for Medicare only). |
| **Index Year** | A flag was created for the proportion of unique patients identified in 2014, 2015, 2016, 2017, 2018, and 2019 (only for PharMetrics). |
| **Setting of Index VTE Event** | Flags were created for patients with an index VTE event in inpatient or outpatient settings. Qualifying outpatient VTE events followed by qualifying inpatient VTE events within 7 days were considered an inpatient episode (unless warfarin or apixaban was initiated between events—in which case they were classified as an outpatient event). |
| **Position of VTE Diagnosis** | Flags were created for the position of VTE diagnosis including primary (principal 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 events were defined as events |

| Variable | Operational Definition |
|---|---|
| | 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 the index VTE event; unprovoked VTE events were 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 a central venous catheter. |
| **Cerebrovascular Disease** | A flag was created for patients with claims for cerebrovascular disease. |
| **Coagulation Defects** | A flag was created for patients with claims for coagulation defects. |
| **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. |
| **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. |

| Variable | Operational Definition |
|---|---|
| **Renal Disease** | A flag was created for patients with claims for renal disease.<br>A flag for chronic kidney disease (CKD) 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 was reported as a percentage. |
| **Fracture/Trauma Involving the Lower Extremities** | A flag was created for patients having a fracture or a trauma and was reported as a percentage. |
| **Selected Surgeries** | A flag was created for patients having a surgery and was reported as a percentage. |
| **Baseline Deyo-Charlson Comorbidity Index** | Deyo-Charlson comorbidity index scores were reported. |
| **Other Baseline Medications** | Flags were created for patients with prescription fills for antiarrhythmic, statin, antiplatelet, aromatase inhibitors, beta blockers, gastroprotective agents, selective estrogen receptor modulators, nonsteroidal anti-inflammatory drugs (NSAIDs), and hormone therapy. |
| **Apixaban Index Dose** | Standard dose (apixaban 5 mg) and lower dose (apixaban 2.5 mg) were based on the dose of the initial prescription of apixaban. |

**Table 3. Clinical and Outcome Variables (in the 6 Months After Index Date)**

| Variable | Operational Definition |
|---|---|
| **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—will not be considered a recurrent VTE event. |

| Variable | Operational Definition |
|---|---|
| **MB** | MB events observed during follow-up were identified using hospital records that had an MB diagnosis as the first listed diagnosis (commercial datasets) or primary diagnosis (Medicare) as listed by ICD-9-CM or ICD-10-CM diagnosis or procedure code. An MB event was a dichotomous variable that equals 1 if there was ≥1 bleeding event during the follow-up period. Time to the first MB event was calculated.<br><br>MB was stratified by gastrointestinal (GI) bleeding, intracranial hemorrhage (ICH), and other bleeding. |
| **CRNMB** | A CRNMB event was defined as a bleeding event not considered to be MB (without a principal diagnosis code for GI/ICH/other bleeding or a procedure code for bleeding treatment). This included:<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). |
| **Discontinuation** | Discontinuation was defined as no evidence of the index prescription for 30 days from the last day of supply of the last filled prescription. The date of discontinuation was the last day of supply of the last filled prescription. |
| **Time-to-discontinuation** | Time from the index date to the discontinuation date was evaluated among patients who discontinued index therapy. |
| **Switch among anticoagulants** | Patients who received a prescription for an anticoagulant other than the index drug prescription during the follow-up period were considered switchers if this prescription was ≤30 days of the last day of supply and was further categorized by switch drug: apixaban, dabigatran, edoxaban, rivaroxaban, warfarin, LMWH, unfractionated heparin, or fondaparinux. |

## 8.5. Data source

***MarketScan***

The IBM MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits database was 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 who 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 entire US Medicare population.

***Optum***

OptumInsight 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 (e.g., physicians) use the Health Care Financing Agency (HCFA)-1500 format. Claims for facility services submitted by institutions, (e.g., 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, 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 who used United Health Group for their health care services.

***IQVIA PharMetrics Plus***

The IQVIA 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. IQVIA 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 >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.

***US Centers for Medicare & Medicaid Services (CMS) Data***

*Medicare Inpatient Data:* The inpatient claim file contains final action claims data submitted by inpatient hospital providers for reimbursement of facility costs. Some information contained in this file includes diagnosis (International Classification of Diseases, 9$^{th}$ and 10$^{th}$ Revision, Clinical Modification [ICD-9-CM and ICD-10-CM] diagnosis code, procedure (ICD-9 and ICD-10 procedure code), diagnosis-related group, dates of service, reimbursement amount, hospital provider, 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 (ICD-9-CM diagnosis, ICD-9 procedure, ICD-10 diagnosis, ICD-10 procedure, and CMS HCPCS codes), dates of service, reimbursement amount, outpatient provider number, revenue center codes, and beneficiary demographic information. Each observation in this file is at the claim level.

*Medicare Part D Drug Events (PDE) Data:* The PDE data contains prescription drug costs and payment data (including out-of-pocket costs [co-payments and deductibles]) 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 but are summary extracts using CMS-defined standard fields.

*Skilled Nursing Facility (SNF) Research Identifiable File (RIF):* The SNF file contains final action, fee-for-service (FFS) claims data submitted by SNF providers. This file includes ICD-9-CM and ICD-10-CM diagnosis and procedure codes, dates of service, reimbursement amount, SNF provider number, and beneficiary demographic information.

*Home Health Agency (HHA) RIF:* The 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 and ICD-10-CM diagnosis), date of visit, reimbursement amount, HHA provider number, and beneficiary demographic information.

*Hospice RIF:* The Hospice file contains final action claims submitted by hospice providers. Once a beneficiary elects hospice care, all hospice-related claims were found in this file, regardless of if the beneficiary is in Medicare FFS or in a Medicare managed care plan. This file includes level of hospice care received (e.g., routine home care, inpatient respite care), terminal diagnosis (ICD-9-CM and ICD-10-CM diagnosis), dates of service, reimbursement amounts, hospice provider number, and beneficiary demographic information.

*Durable Medical Equipment (DME) RIF:* The DME file contains final action, FFS claims submitted by DME suppliers. This file includes diagnosis (ICD-9-CM and ICD-10-CM diagnosis), services provided (CMS HCPCS codes), dates of service, reimbursement amounts, DME provider number, and beneficiary demographic information.

*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 Denominator File:* The denominator file contains demographic and enrollment information of Medicare beneficiaries enrolled or entitled 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, sex, race, age, monthly entitlement indicators (A/B/both), reasons for entitlement, state buy-in indicators, and monthly managed care indicators (yes/no). However, all Medicare files described above can be linked by de-identified patient ID and were included in the same CMS access request. Data are collected on an ongoing basis with files constructed annually. It does not contain data on all beneficiaries ever entitled to Medicare. The file contains data only 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.

### 8.6. Study Size

All eligible patients available for analysis were included.

The five databases described were pooled together to create a master pooled dataset. The advantages of using this pooled dataset include large study sample, diverse patient population, and increased generalizability of the data.

## 8.7. Data analysis

All data analysis were executed using statistical software SAS version 9.4 (Cary, NC).

### 8.7.1. Baseline patient characteristics

Baseline demographic and clinical factors such as age, sex, geographic region, type of index VTE event, position of VTE diagnosis, VTE diagnosis, VTE etiology, baseline medications, and comorbidities among VTE patients newly treated with apixaban 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.

### 8.7.2. Rate of recurrent VTE, MB, and CRNMB

The cumulative incidence rates for clinical outcomes (recurrent VTE, MB, and CRNMB) were calculated. MB was broken down to GI bleeding, ICH, and other bleeding; CRNMB was broken down to GI bleeding and other bleeding. The incidence rates were calculated as the number of patients who experience the event divided by the observed time at risk. The incidence rates were calculated per 100 person-years. Unadjusted Kaplan-Meier survival curves were generated to illustrate the time to first MB, CRNMB, and recurrent VTE events.

Inverse probability of treatment weights (IPTW) was used to balance patient characteristics when comparing outcomes among different cohorts. IPTW used propensity scores to obtain estimates of the average treatment effect. The propensity score was calculated using a logistic model with the treatment cohorts (apixaban and warfarin) included in the model, using warfarin 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. The propensity score acts as a balancing score between the cohorts. After calculating the propensity score, the distribution of the propensity scores was reviewed. Treated patients (apixaban) were assigned a weight of 1/ (propensity score) and control patients (warfarin) were assigned a weight of 1/(1-propensity score).

To stabilize the weights, the weights for the treatment and control cohorts were multiplied by a constant, equal to the mean of propensity score for each cohort (expected value of being in the treatment or comparison cohorts, respectively). This reduces the variability of the weights and reduces the variance of the treatment effect estimates.

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

Cox proportional hazards models were used to compare the time to MB, CRNMB, and recurrent VTE between the apixaban and warfarin cohorts after IPTW.

The proportional hazards proportionality assumption was evaluated by visually inspecting the Kaplan-Meier plot in the weighted population and confirmed by testing the significance of interactions between treatment and the log of time.

### 8.7.3. Subgroup Analyses

The following subgroup analyses were conducted to evaluate the effectiveness and safety in each subgroup. The subgroup analysis was an interaction analysis between treatment and subgroups on specific outcomes.

1. Demographic and socioeconomic subgroup analysis[23]: only CMS Medicare data were used for this subgroup analysis since other commercial databases lack information on race and socioeconomic status. Post-IPTW study population was stratified into the following demographic and socioeconomic subgroups:

- **Age**: ages 65 to 79 years vs. age 80 and older.
- **Gender**: Male vs. female.
- **Race**: Black vs. white vs. other
- **Socioeconomic Status:** Low vs. medium vs. high.
- **Dual Medicare/Medicaid Eligibility or Part D Low Income Subsidy (LIS):** Yes vs. no.

Interaction analyses were conducted using Cox models to evaluate whether treatment effects differ by age (65–79 vs 80 years), gender (male vs female), race (white vs black), SES (low vs medium vs high), and dual Medicare/Medicaid eligibility or Part-D LIS (yes vs no).

2. Obesity/morbid obesity subgroup analysis[24] Obese (ICD-9 278, V85.3 and V85.4; ICD-10 E66, Z68.3, Z68.4) and morbidly obese (ICD-9 278.01 and V85.4; ICD-10 E66.01, E66.2 and Z68.4) patients were identified based on diagnosis codes. IPTW was conducted to balance observed patient characteristics between treatment cohorts. Cox proportional hazard models were used to evaluate the risk of recurrent VTE and MB among IPTW weighted obese and morbidly obese patients.[25]

3. Chronic kidney disease (CKD) subgroup analysis[26]: Patients with CKD and different stages (stage 1-5) of CKD were identified based on ICD-9/10 diagnosis codes.[27] IPTW was used to balance patient characteristics between treatment cohorts among patients with CKD and Cox models were used to evaluate the risk of recurrent VTE, MB, and CRNMB among these patients. An interaction analysis was conducted to evaluate treatment effects across different stages of CKD.

4. High risk of bleeding subgroup analysis[28]: Patients at high risk of bleeding were defined as those with at least one of the risk factors below: age ≥75 years, medications on the index date that increase bleeding (antiplatelets, NSAIDs, corticosteroids), CKD stage III-V/ESRD, and GI-related conditions (peptic ulcer, GI bleeding, helicobacter pylori, diverticulosis, angiodysplasias, GI cancer, and other GI lesions)[29,30]. IPTW was used to balance patient characteristics among different treatment cohorts in patients at high risk of bleeding. Cox models were used to estimate the risk of recurrent VTE, MB, and CRNMB among these patients. Interaction analyses were conducted to evaluate treatment effects across different type of risk factors and different number of risk factors.

5. Bleeding or VTE recurrence risk factor subgroup analysis[31]: Two bleeding risk factors (thrombocytopenia and history of bleed) and three VTE recurrence risk factors (thrombophilia, chronic liver disease, and immune mediated disorders) were evaluated. Patients with VTE initiating apixaban or warfarin were identified from five claims databases. IPTW was used to balance characteristics between cohorts for the main analysis. Subgroup interaction analyses were conducted to evaluate treatment effects among patients with and without each of the conditions that increased the risk of bleeding (thrombocytopenia and history of bleed) or recurrent VTE (thrombophilia, chronic liver disease, and immune mediated disorders).

For those subgroups that were re-balanced using IPTW, the same methodology as the main analysis was utilized.

### 8.7.4. Amendments to the Statistical Analysis Plan

None

## 8.8. Quality Control

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

1. Sound scientific design and clinically rigorous review: a detailed study protocol that included definitions, codes, analyses, and table shells. A member of the STATinMED clinical team reviewed the appropriateness and validity of the coding strategy and identified relevant issues.
2. The protocol further provided STATinMED 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 were 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's analysis was performed by an analyst under the supervision of the project manager, lead analyst, and/or vice president. These team members reviewed 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.

## 8.9. Protection of Human Subjects

Subject information and consent

Not Applicable

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; it followed generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, Good Epidemiological Practice guidelines issued by the International Epidemiological Association, Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research, International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences, European Medicines Agency, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, the Guide on Methodological Standards in Pharmacoepidemiology, and the FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, or equivalents.

# RESULTS

## 9.1. OVERALL POPULATION

### 9.1.1. Participants

Of 155,119 patients eligible for analysis, 94,333 (60.8%) were prescribed warfarin and 60,786 (39.2%) were prescribed apixaban. Table 4 shows patient attrition after applying each eligibility criteria from individual database and pooled data sources.

**Table 4. Attrition Table – Pooled**

| Primary Analysis | | | | | | |
|---|---|---|---|---|---|---|
| **Inclusion Criteria** | **MarketScan** | **Optum** | **PharMetrics** | **Humana** | **Medicare** | **Pooled** |
| a) Patients with a VTE diagnosis in any position in the inpatient or outpatient setting between September 1, 2014 to end of study. The first VTE diagnosis was considered as the **'index VTE event**'. The index event was defined as the date of service if outpatient and the date of discharge if inpatient.<br>**NOTE**: Qualifying outpatient events followed by qualifying inpatient events within 7 days were considered an inpatient episode (unless warfarin or apixaban was initiated between events, in which case it was classified as an outpatient event)* | 311,404 | 499,206 | 566,911 | 293,110 | 1,453,486 | 3,124,117 |
| b) had ≥1 pharmacy claim for apixaban or warfarin during the 30-day period following the index VTE event. The first warfarin or apixaban prescription was designated as the **'index date'** | 55,646 | 105,366 | 103,655 | 64,360 | 310,471 | 639,498 |
| c) were age ≥18 years on the index date (for commercial database) and ≥65 years on the index date for Medicare database | 54,321 | 95,574 | 102,069 | 64,346 | 250,123 | 566,433 |
| d) had continuous health plan enrollment with medical and pharmacy benefits for at least 6 months before the index VTE event until the index date. | 42,365 | 68,016 | 72,026 | 49,024 | 231,337 | 462,768 |
| **Exclusion Criteria** | | | | | | |
| a) had medical claims indicating a diagnosis of atrial fibrillation/flutter during the 6-months prior to and on index date | 38,526 | 50,782 | 63,225 | 34,230 | 156,869 | 343,632 |
| b) had evidence of mechanical heart valve during the 6-month period prior to and on the index date | 38,491 | 50,631 | 63,052 | 34,123 | 156,426 | 342,723 |
| c) had evidence of receipt of another oral anticoagulant (OAC) or PAC on the index date (or during the period between the index VTE event and the index date)<br>**NOTE:** Warfarin patients who bridge therapy with LMWH will still be included.** | 35,407 | 47,423 | 57,396 | 31,330 | 145,923 | 317,479 |

| Primary Analysis | | | | | | |
|---|---|---|---|---|---|---|
| **Inclusion Criteria** | **MarketScan** | **Optum** | **PharMetrics** | **Humana** | **Medicare** | **Pooled** |
| d) pharmacy claim for OAC/parenteral anticoagulant (PAC) use during the 6-month period preceding the index VTE event unless it is determined that such therapy was administered prophylactically<br>**NOTE:** Prophylactic use of OAC/PAC was determined based on the duration of use and timing of use (e.g., relative to knee/hip replacement surgery or medical inpatient admission) | 24,879 | 34,481 | 41,994 | 21,749 | 95,414 | 218,517 |
| e) had ≥2 medical claims for cancer diagnosis or 1 claim for cancer diagnosis and ≥1 claim for cancer treatment (e.g., chemotherapy, radiation, cancer re-lated surgery) 6 months before the index VTE event or 30 days after index VTE event | 22,269 | 28,779 | 37,421 | 17,664 | 75,898 | 182,031 |
| f) had medical claims indicating a diagnosis code for VTE during the 6-months preceding index VTE event unless the index VTE event occurred in the inpatient setting and was preceded by an outpatient VTE event within 7 days of inpatient admission date | 21,023 | 25,373 | 35,913 | 14,817 | 74,925 | 172,051 |
| g) had medical claims indicating inferior vena cava (IVC) filter during the study period | 19,952 | 23,932 | 34,251 | 13,928 | 69,498 | 161,561 |
| h) had medical claims indicating pregnancy during the study period | 19,076 | 23,364 | 32,481 | 13,775 | 68,717 | 157,413 |
| i) had medical claims indicating antiphospholipid syndrome (APS) during the study period | 18,843 | 23,317 | 32,121 | 13,699 | 68,365 | 156,345 |
| j) had ICD-10: D68.62 during the study period | 18,674 | 23,030 | 31,852 | 13,588 | 67,975 | 155,119 |
| **Final Sample Size** | 18,674 | 23,030 | 31,852 | 13,588 | 67,975 | 155,119 |
| **Apixaban** | **7,983** | **9,944** | **14,505** | **6,219** | **22,135** | **60,786** |
| **Warfarin** | **10,691** | **13,086** | **17,347** | **7,369** | **45,840** | **94,333** |

*If outpatient, inpatient, and pharmacy claims occur on the same date, then inpatient will be considered as the index setting and the discharge date will be designated as the index date.

**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 will be designated as the index date. There should be no other anticoagulant (apixaban, dabigatran, edoxaban, rivaroxaban, UFH, fondaparinux) during the period between index VTE event and initiation of warfarin as well as for the duration of LMWH if it occurs 14 days after warfarin initiation.

MarketScan: The study period: March 1, 2014-September 30, 2018

Optum and Humana: The study period: March 1, 2014-December 31, 2018

PharMetrics: The study period: March 1, 2014-March 31, 2019

Medicare: The study period: March 1, 2014-December 31, 2017

### 9.1.2. Pre-IPTW Baseline Characteristics in Overall Population

Pre-IPTW baseline characteristics among VTE patients are described in **Table 5**. Before IPTW, warfarin patients were older (67.4 years), on average, than apixaban patients (65.4 years). Apixaban patients were more prevalent in the south (48.2%) than north central (22.2%) compared to warfarin patients who were evenly distributed between the south (31.6%) and north central (31.4%). Over half of warfarin and apixaban patients had the index VTE as DVT only (57% and 56% respectively). In addition, over half of the index VTE events for warfarin and apixaban patients were caused by a provoked event (58% and 53%, respectively). The mean Charlson Comorbidity Index (CCI) was 2.06 for apixaban patients and 2.28 for warfarin patients. Among VTE patients, 17.4% of apixaban patients and 22.6% of warfarin patients had evidence of baseline bleeding prior to initiation of anticoagulation; 6.9% of apixaban patients and 7.4% of warfarin patients had a history of a recent fall; 16% of apixaban patients and 15% of warfarin patients had a history of fracture or trauma involving the lower extremities; and 23.1% of apixaban patients and 25.6% of warfarin patients had a history of selected surgeries.

**Table 5. Pre-IPTW Baseline Characteristics Among VTE Patients Prescribed Apixaban vs Warfarin**

| | Warfarin Cohort (Reference) | | Apixaban Cohort | | | |
|---|---|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD | P-value | STD* |
| **Sample Size** | **94,333** | | **60,786** | | | **0** |
| **Age** | 67.43 | 15.71 | 65.39 | 16.26 | <.0001 | 12.76 |
| **18-54** | 18,924 | 20.06% | 14,876 | 24.47% | <.0001 | 10.62 |
| **55-64** | 13,976 | 14.82% | 11,517 | 18.95% | <.0001 | 11.05 |
| **65-74** | 28,334 | 30.04% | 15,491 | 25.48% | <.0001 | 10.18 |
| **75-79** | 12,064 | 12.79% | 6,853 | 11.27% | <.0001 | 4.66 |
| **≥80** | 21,035 | 22.30% | 12,049 | 19.82% | <.0001 | 6.08 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | | |
| **Gender** | | | | | | |
| **Male** | 41,850 | 44.36% | 28,261 | 46.49% | <.0001 | 4.28 |
| **Female** | 52,483 | 55.64% | 32,525 | 53.51% | <.0001 | 4.28 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | | |
| **Geographic Region** | | | | | | |
| **Northeast** | 15,071 | 15.98% | 9,302 | 15.30% | 0.0004 | 1.85 |
| **North Central** | 29,650 | 31.43% | 13,507 | 22.22% | <.0001 | 20.90 |
| **South** | 29,769 | 31.56% | 29,322 | 48.24% | <.0001 | 34.57 |
| **West** | 19,639 | 20.82% | 8,590 | 14.13% | <.0001 | 17.68 |
| **Other** | 204 | 0.22% | 65 | 0.11% | <.0001 | 2.72 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | | |
| **Index Year** | | | | | | |
| **2014** | 14,376 | 15.24% | 911 | 1.50% | <.0001 | 51.22 |
| **2015** | 34,809 | 36.90% | 7,507 | 12.35% | <.0001 | 59.45 |
| **2016** | 24,109 | 25.56% | 16,730 | 27.52% | <.0001 | 4.45 |
| **2017** | 16,591 | 17.59% | 21,090 | 34.70% | <.0001 | 39.69 |
| **(no Medicare, Marketscan until Q3 2018) 2018** | 4,211 | 4.46% | 13,305 | 21.89% | <.0001 | 53.31 |
| **(Pharmetrics only) 2019** | 237 | 0.25% | 1,243 | 2.04% | <.0001 | 16.90 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | | |
| **Type of Index Encounter** | | | | | | |
| **Inpatient** | 53,019 | 56.20% | 30,803 | 50.67% | <.0001 | 11.10 |
| **Outpatient** | 41,314 | 43.80% | 29,983 | 49.33% | <.0001 | 11.10 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | | |
| **ER Setting** | 29,870 | 31.66% | 20,475 | 33.68% | <.0001 | 4.31 |
| **VTE Diagnosis** | | | | | | |

| | Warfarin Cohort (Reference) | | Apixaban Cohort | | | |
|---|---|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD | P-value | STD* |
| **DVT only** | 53,645 | 56.87% | 33,971 | 55.89% | 0.0001 | 1.98 |
| **PE with or without DVT** | 40,688 | 43.13% | 26,815 | 44.11% | 0.0001 | 1.98 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | | |
| **PE with DVT** | 13,268 | 14.07% | 8,707 | 14.32% | 0.1534 | 0.74 |
| **PE without DVT** | 27,420 | 29.07% | 18,108 | 29.79% | 0.0023 | 1.59 |
| **Total** | 40,688 | 43.1% | 26,815 | 44.1% | | |
| **Position of VTE Diagnosis** | | | | | | |
| **Primary or first-listed** | 73,438 | 77.85% | 48,550 | 79.87% | <.0001 | 4.95 |
| **Secondary** | 20,895 | 22.15% | 12,236 | 20.13% | <.0001 | 4.95 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | | |
| **VTE Etiology** | | | | | | |
| **Provoked** | 55,058 | 58.37% | 32,147 | 52.89% | <.0001 | 11.05 |
| **Unprovoked** | 39,275 | 41.63% | 28,639 | 47.11% | <.0001 | 11.05 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | | |
| **Baseline Comorbidity** | | | | | | |
| **Deyo-Charlson Comorbidity Index** | 2.28 | 2.40 | 2.06 | 2.33 | <.0001 | 9.33 |
| **AIDS** | 389 | 0.41% | 241 | 0.40% | 0.6308 | 0.25 |
| **Alcohol abuse** | 3,115 | 3.30% | 1,768 | 2.91% | <.0001 | 2.27 |
| **Anemia** | 29,504 | 31.28% | 15,959 | 26.25% | <.0001 | 11.11 |
| **Central venous catheter** | 8,428 | 8.93% | 4,134 | 6.80% | <.0001 | 7.93 |
| **Cerebrovascular disease** | 12,626 | 13.38% | 6,694 | 11.01% | <.0001 | 7.25 |
| **Coagulation defects** | 8,318 | 8.82% | 4,103 | 6.75% | <.0001 | 7.72 |
| **Ischemic heart/ coronary artery disease** | 24,298 | 25.76% | 14,952 | 24.60% | <.0001 | 2.67 |
| **Dementia** | 5,964 | 6.32% | 4,119 | 6.78% | 0.0004 | 1.83 |
| **Dyspepsia or stomach discomfort** | 21,891 | 23.21% | 13,455 | 22.14% | <.0001 | 2.56 |
| **Hemiplegia or Paraplegia** | 2,143 | 2.27% | 1,142 | 1.88% | <.0001 | 2.76 |
| **Hyperlipidemia** | 45,702 | 48.45% | 28,856 | 47.47% | 0.0002 | 1.95 |
| **Obesity** | 25,602 | 27.14% | 17,493 | 28.78% | <.0001 | 3.65 |
| Morbid obesity | 12,340 | 13.08% | 7,411 | 12.19% | <.0001 | 2.68 |
| **Pneumonia** | 13,782 | 14.61% | 8,576 | 14.11% | 0.0061 | 1.43 |
| **Rheumatologic disease** | 4,620 | 4.90% | 2,651 | 4.36% | <.0001 | 2.55 |
| **Sleep apnea** | 12,725 | 13.49% | 8,065 | 13.27% | 0.2111 | 0.65 |
| **Spinal cord injury** | 279 | 0.30% | 136 | 0.22% | 0.0073 | 1.42 |
| **Thrombophilia** | 3,924 | 4.16% | 2,166 | 3.56% | <.0001 | 3.10 |
| **Varicose veins** | 3,754 | 3.98% | 2,817 | 4.63% | <.0001 | 3.23 |
| **Congestive heart failure** | 16,527 | 17.52% | 9,377 | 15.43% | <.0001 | 5.65 |
| **Diabetes** | 30,260 | 32.08% | 17,071 | 28.08% | <.0001 | 8.72 |
| **Hypertension** | 66,061 | 70.03% | 40,748 | 67.04% | <.0001 | 6.45 |
| **Non-ESRD renal disease** | 14,449 | 15.32% | 8,399 | 13.82% | <.0001 | 4.25 |
| Stage 1 and/or 2 | 2,561 | 2.71% | 1,765 | 2.90% | 0.0275 | 1.14 |
| Stage III | 11,572 | 12.27% | 6,793 | 11.18% | <.0001 | 3.39 |
| Stage IV | 3,570 | 3.78% | 1,510 | 2.48% | <.0001 | 7.47 |
| **End stage renal disease** | 2,666 | 2.83% | 904 | 1.49% | <.0001 | 9.23 |
| Stage V | 985 | 1.04% | 322 | 0.53% | <.0001 | 5.82 |
| ESRD | 2,328 | 2.47% | 775 | 1.27% | <.0001 | 8.81 |
| **Chronic liver disease** | 6,502 | 6.89% | 4,513 | 7.42% | <.0001 | 2.06 |
| **COPD** | 17,956 | 19.03% | 10,496 | 17.27% | <.0001 | 4.59 |
| **Peptic ulcer disease** | 2,130 | 2.26% | 1,102 | 1.81% | <.0001 | 3.15 |
| **Inflammatory bowel disease** | 1,850 | 1.96% | 1,052 | 1.73% | 0.0011 | 1.71 |
| **Peripheral vascular disease** | 18,777 | 19.91% | 10,805 | 17.78% | <.0001 | 5.45 |
| **Baseline bleed** | 21,339 | 22.62% | 10,589 | 17.42% | <.0001 | 13.02 |
| **Recent history of falls** | 7,007 | 7.43% | 4,204 | 6.92% | 0.0001 | 1.98 |
| **Fracture/trauma involving lower extremities** | 14,141 | 14.99% | 9,720 | 15.99% | <.0001 | 2.76 |
| **Selected surgeries** | 24,184 | 25.64% | 14,052 | 23.12% | <.0001 | 5.87 |
| **Baseline Medication Use** | | | | | | |

| | Warfarin Cohort (Reference) | | Apixaban Cohort | | | |
|---|---|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD | P-value | STD* |
| **Antiarrhythmic** | 9,111 | 9.66% | 5,747 | 9.45% | 0.1829 | 0.69 |
| **Statins** | 36,673 | 38.88% | 22,842 | 37.58% | <.0001 | 2.67 |
| **Anti-platelets** | 7,201 | 7.63% | 4,497 | 7.40% | 0.0864 | 0.89 |
| **Aromatase inhibitors (Anastrozole, exemestane, letrozole)** | 189 | 0.20% | 158 | 0.26% | 0.0153 | 1.24 |
| **Beta blockers** | 33,151 | 35.14% | 19,486 | 32.06% | <.0001 | 6.54 |
| **Gastroprotective agents** | 27,400 | 29.05% | 16,487 | 27.12% | <.0001 | 4.28 |
| **SERMS** | 539 | 0.57% | 398 | 0.65% | 0.0386 | 1.07 |
| **NSAIDs** | 23,751 | 25.18% | 17,052 | 28.05% | <.0001 | 6.51 |
| **Hormone therapy (estrogen)** | 4,652 | 4.93% | 3,970 | 6.53% | <.0001 | 6.89 |
| **Risk Factors for GI-Bleeding** | 55,336 | 58.7% | 32,945 | 54.20% | <.0001 | 9.01 |
| **Age ≥75 years (on index date)** | 33,099 | 35.1% | 18,902 | 31.1% | <.0001 | 8.49 |
| **Concurrent medications (on index date)** | 18,843 | 20.0% | 12,410 | 20.4% | 0.0346 | 1.10 |
| Antiplatelets | 4,858 | 5.1% | 3,074 | 5.1% | 0.4182 | 0.42 |
| NSAIDs | 8,303 | 8.8% | 5,944 | 9.8% | <.0001 | 3.37 |
| Corticosteroids | 7,063 | 7.5% | 4,410 | 7.3% | 0.0878 | 0.89 |
| **Prior GI conditions (during baseline period)** | 14,160 | 15.0% | 8,041 | 13.2% | <.0001 | 5.12 |
| Peptic ulcer | 2,092 | 2.2% | 1,085 | 1.8% | <.0001 | 3.09 |
| Prior GI bleeding | 5,564 | 5.9% | 2,776 | 4.6% | <.0001 | 5.98 |
| Helicobacter pylori | 338 | 0.4% | 184 | 0.3% | 0.0649 | 0.97 |
| Diverticulosis | 8,728 | 9.3% | 5,082 | 8.4% | <.0001 | 3.15 |
| Angiodysplasias | 183 | 0.2% | 74 | 0.1% | 0.0006 | 1.82 |
| GI cancer (Stomach, colon, esophageal, and rectal cancer) | 242 | 0.3% | 123 | 0.2% | 0.0315 | 1.13 |
| Other GI lesions | 696 | 0.7% | 564 | 0.9% | <.0001 | 2.09 |
| **Chronic Kidney Disease (during baseline period)** | 14,329 | 15.2% | 7,771 | 12.8% | <.0001 | 6.94 |
| Stage III | 11,572 | 12.3% | 6,793 | 11.2% | <.0001 | 3.39 |
| Stage IV | 3,570 | 3.8% | 1,510 | 2.5% | <.0001 | 7.47 |
| Stage V/ESRD | 2,666 | 2.8% | 904 | 1.5% | <.0001 | 9.23 |
| **Only 1 risk factor** | 34,855 | 36.9% | 21,364 | 35.1% | <.0001 | 3.76 |
| age at least 75 years | 16,756 | 17.8% | 9,585 | 15.8% | <.0001 | 5.34 |
| Concurrent medications (on index date) | 8,842 | 9.4% | 6,390 | 10.5% | <.0001 | 3.81 |
| Prior GI conditions | 5,440 | 5.8% | 3,322 | 5.5% | 0.0120 | 1.31 |
| CKD | 3,817 | 4.0% | 2,067 | 3.4% | <.0001 | 3.41 |
| **2 or more risk factors** | 20,481 | 21.7% | 11,581 | 19.1% | <.0001 | 6.61 |
| 2 | 16,233 | 17.2% | 9,201 | 15.1% | <.0001 | 5.63 |
| 3 | 3,882 | 4.1% | 2,162 | 3.6% | <.0001 | 2.91 |
| 4 | 366 | 0.4% | 218 | 0.4% | 0.3568 | 0.48 |
| **Apixaban Index Dose** | | | | | | |
| **On standard dose (apixaban 5mg)** | | | 57,003 | 93.78% | | |
| **Lower dose (2.5mg apixaban** | | | 3,783 | 6.22% | | |
| **Total** | | | 60,786 | 100.0% | | |
| **Race (only Medicare and Humana)** | | | | | | |
| **White** | 43,771 | 82.26% | 22,972 | 81.02% | <.0001 | 3.21 |
| **Black** | 6,445 | 12.11% | 3,647 | 12.86% | 0.0020 | 2.27 |
| **Other** | 2,993 | 5.62% | 1,735 | 6.12% | 0.0040 | 2.10 |

AIDS: Acquired immunodeficiency syndrome; COPD: Chronic obstructive pulmonary disorder; DVT: Deep vein thrombosis; ER: Emergency Room; NSAIDs: Nonsteroidal Anti-inflammatory Drugs; PE: Pulmonary embolism; SERMS: Selective estrogen receptor modulators; SD: Standard deviation; STD: Standardized differences; VTE: Venous thromboembolism

*Std Difference=100*|actual std diff|. Std Difference greater than 10 is considered significant

### 9.1.3. Pre-IPTW Outcome Data in Overall Population

The unadjusted outcome results are described in **Table 6**. The mean follow-up time was 119.4 days for apixaban and 126.4 days for warfarin. The unadjusted incidence rate (per 100 person-years) of MB (including GI bleeding, ICH, and other bleeding) was 3.82 for apixaban and 6.02 for warfarin. The unadjusted incidence rate (per 100 person-years) of recurrent VTE was 5.01 for apixaban and 6.37 for warfarin.

**Table 6. Pre-IPTW Outcomes Among VTE Patients Prescribed Apixaban vs Warfarin**

| | Warfarin Cohort (Reference) | | Apixaban Cohort | |
|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD |
| **Sample Size** | **94,333** | | **60,786** | |
| **Follow-up Time (in days)** | 126.36 | 61.00 | 119.39 | 59.66 |
| **minimum** | 1 | | 1 | |
| **Q1** | 67 | | 59 | |
| **median** | 146 | | 124 | |
| **Q3** | 183 | | 183 | |
| **maximum** | 183 | | 183 | |
| **Reason for Censoring** | | | | |
| **Disenrollment** | 6,248 | 6.62% | 5,005 | 8.23% |
| **Death** | 2,398 | 2.54% | 1,171 | 1.93% |
| **Discontinuation** | 31,046 | 32.91% | 22,688 | 37.32% |
| **Switch** | 11,466 | 12.15% | 2,679 | 4.41% |
| **End of study period** | 4,298 | 4.56% | 8,599 | 14.15% |
| **6 months post-index date** | 38,877 | 41.21% | 20,644 | 33.96% |
| **Major Bleeding** | 1,942 | 2.06% | 752 | 1.24% |
| **Gastrointestinal (GI) Bleeding** | 1,066 | 1.13% | 418 | 0.69% |
| **Intracranial Hemorrhage** | 244 | 0.26% | 86 | 0.14% |
| **Other Bleeding** | 693 | 0.73% | 266 | 0.44% |
| **Time to Major Bleeding** | 52.97 | 49.38 | 54.07 | 50.86 |
| **Major Bleeding – Time-at-Risk** | 125.09 | 61.72 | 118.68 | 60.01 |
| **Gastrointestinal (GI) Bleeding – Time-at-Risk** | 125.65 | 61.39 | 119.00 | 59.86 |
| **Intracranial Hemorrhage – Time-at-Risk** | 126.26 | 61.06 | 119.33 | 59.68 |
| **Other Bleeding – Time-at-Risk** | 125.85 | 61.31 | 119.11 | 59.80 |
| **Major Bleeding Incidence Rate (per 100 person-years)** | 6.02 | | 3.82 | |
| **Gastrointestinal (GI) Bleeding** | 3.29 | | 2.11 | |
| **Intracranial Hemorrhage** | 0.75 | | 0.43 | |
| **Other Bleeding** | 2.14 | | 1.34 | |
| **CRNM Bleeding** | 9,723 | 10.31% | 4,882 | 8.03% |
| **Gastrointestinal (GI) Bleeding** | 2,632 | 2.79% | 1,457 | 2.40% |
| **Other Bleeding** | 7,411 | 7.86% | 3,552 | 5.84% |
| **Time to CRNM Bleeding** | 50.24 | 49.08 | 51.58 | 48.94 |
| **CRNM Bleeding – Time-at-Risk** | 117.51 | 64.61 | 112.94 | 61.90 |
| **Gastrointestinal (GI) Bleeding Time-at-Risk** | 124.09 | 62.10 | 117.55 | 60.35 |
| **Other Bleeding Time-at-Risk** | 119.57 | 63.90 | 114.64 | 61.42 |
| **CRNM Bleeding Incidence Rate (per 100 person-years)** | 32.10 | | 26.03 | |
| **Gastrointestinal (GI) Bleeding** | 8.23 | | 7.46 | |
| **Other Bleeding** | 24.05 | | 18.66 | |
| **Recurrent VTE** | 2,048 | 2.17% | 984 | 1.62% |
| **DVT** | 1,274 | 1.35% | 552 | 0.91% |
| **PE** | 829 | 0.88% | 468 | 0.77% |

| | Warfarin Cohort (Reference) | | Apixaban Cohort | |
|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD |
| **Recurrent VTE Time-at-Risk** | 124.80 | 61.91 | 118.28 | 60.21 |
| **DVT – Time-at-Risk** | 125.44 | 61.55 | 118.81 | 59.96 |
| **PE – Time-at-Risk** | 125.69 | 61.40 | 118.82 | 59.93 |
| **Time to Recurrent VTE** | 40.81 | 42.87 | 38.28 | 41.28 |
| **Recurrent VTE Incidence Rate (per 100 person-years)** | 6.37 | | 5.01 | |
| **Patients that continued treatment during the follow-up period** | 51,821 | 54.93% | 35,419 | 58.27% |
| **Discontinuation without switch** | 31,046 | 32.91% | 22,688 | 37.32% |
| **Time-to-Discontinuation** | 75.45 | 41.56 | 68.81 | 41.02 |
| **Switch** | 11,466 | 12.15% | 2,679 | 4.41% |
| **Time-to-Switch** | 49.18 | 45.90 | 48.60 | 45.28 |
| Apixaban | 3,175 | 3.37% | | |
| Dabigatran | 401 | 0.43% | 130 | 0.21% |
| Edoxaban | 36 | 0.04% | 9 | 0.01% |
| Rivaroxaban | 5,349 | 5.67% | 954 | 1.57% |
| Warfarin | | | 870 | 1.43% |
| Unfractionated heparin (UFH) | 469 | 0.50% | 252 | 0.41% |
| LMWH | 1,982 | 2.10% | 455 | 0.75% |
| Fondaparinux | 54 | 0.06% | 9 | 0.01% |

CRNM: Clinically relevant non-major (bleeding); VTE: Venous thromboembolism

*Std Difference=100*|actual std diff|. Std Difference greater than 10 is considered significant.

### 9.1.4. Post-IPTW Baseline Characteristics in Overall Population

After applying IPTW, patient characteristics were generally balanced. For both treatment cohorts, most patients were aged 65-79 years (apixaban: 62.6%; warfarin: 62.6%), followed by ≥80 years (apixaban: 37.4%; warfarin: 37.4%) with mean ages of about 67 years for both cohorts (**Table 7**). A majority of patients across the two cohorts were female (54.9% for both cohorts), and the average CCI was 2.2 (**Table 7**).

**Table 7. Post-IPTW Baseline Characteristics among VTE Patients Prescribed Apixaban or Warfarin**

| | Warfarin Cohort (Reference) | | Apixaban Cohort | | |
|---|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD | STD* |
| **Sample Size** | **94,333** | **1** | **60,786** | **1** | **0** |
| **Age*** | 66.66 | 15.94 | 66.79 | 15.97 | 0.80 |
| **18-54** | 20,449 | 21.68% | 13,098 | 21.55% | 0.31 |
| **55-64** | 15,430 | 16.36% | 9,908 | 16.30% | 0.15 |
| **65-74** | 26,709 | 28.31% | 17,219 | 28.33% | 0.03 |
| **75-79** | 11,545 | 12.24% | 7,471 | 12.29% | 0.16 |
| **≥80** | 20,200 | 21.41% | 13,089 | 21.53% | 0.29 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | |
| **Gender*** | | | | | |
| **Male** | 42,590 | 45.15% | 27,410 | 45.09% | 0.11 |
| **Female** | 51,743 | 54.85% | 33,376 | 54.91% | 0.11 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | |

| | Warfarin Cohort (Reference) | | Apixaban Cohort | | |
|---|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD | STD* |
| **Geographic Region*** | | | | | |
| **Northeast** | 14,825 | 15.72% | 9,494 | 15.62% | 0.27 |
| **North Central** | 26,271 | 27.85% | 16,873 | 27.76% | 0.20 |
| **South** | 35,815 | 37.97% | 23,008 | 37.85% | 0.24 |
| **West** | 17,257 | 18.29% | 11,301 | 18.59% | 0.77 |
| **Other** | 165 | 0.17% | 110 | 0.18% | 0.16 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | |
| **Index Year** | | | | | |
| **2014** | 14,481 | 15.35% | 943 | 1.55% | 51.21 |
| **2015** | 34,922 | 37.02% | 7,609 | 12.52% | 59.20 |
| **2016** | 24,019 | 25.46% | 17,054 | 28.06% | 5.86 |
| **2017** | 16,305 | 17.28% | 21,472 | 35.32% | 41.86 |
| **(no Medicare, Marketscan until Q3 2018) 2018** | 4,356 | 4.62% | 12,582 | 20.70% | 49.84 |
| **(Pharmetrics only) 2019** | 250 | 0.27% | 1,126 | 1.85% | 15.55 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | |
| **Type of Index Encounter** | | | | | |
| **Inpatient*** | 51,097 | 54.17% | 33,030 | 54.34% | 0.35 |
| **Outpatient*** | 43,236 | 45.83% | 27,756 | 45.66% | 0.35 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | |
| **ER Setting (included in outpatient)** | 30,752 | 32.60% | 19,291 | 31.74% | 1.85 |
| **VTE Diagnosis** | | | | | |
| **DVT only*** | 53,279 | 56.48% | 34,367 | 56.54% | 0.12 |
| **PE with or without DVT** | 41,054 | 43.52% | 26,419 | 43.46% | 0.12 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | |
| **PE with DVT*** | 13,394 | 14.20% | 8,635 | 14.21% | 0.02 |
| **PE without DVT*** | 27,660 | 29.32% | 17,784 | 29.26% | 0.14 |
| **Total** | 41,054 | 43.5% | 26,419 | 43.5% | |
| **Position of VTE Diagnosis** | | | | | |
| **Primary or first-listed** | 74,307 | 78.77% | 47,392 | 77.97% | 1.96 |
| **Secondary** | 20,026 | 21.23% | 13,394 | 22.03% | 1.96 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | |
| **VTE Etiology*** | | | | | |
| **Provoked** | 53,076 | 56.26% | 34,264 | 56.37% | 0.21 |
| **Unprovoked** | 41,257 | 43.74% | 26,522 | 43.63% | 0.21 |
| **Total** | 94,333 | 100.0% | 60,786 | 100.0% | |
| **Baseline Comorbidity** | | | | | |
| **Deyo-Charlson Comorbidity Index*** | 2.21 | 2.37 | 2.22 | 2.41 | 0.71 |
| **AIDS** | 402 | 0.43% | 233 | 0.38% | 0.67 |
| **Alcohol abuse*** | 2,987 | 3.17% | 1,937 | 3.19% | 0.12 |
| **Anemia*** | 27,751 | 29.42% | 17,985 | 29.59% | 0.37 |
| **Central venous Catheter*** | 7,672 | 8.13% | 4,977 | 8.19% | 0.20 |
| **Cerebrovascular disease** | 12,162 | 12.89% | 7,293 | 12.00% | 2.71 |
| **Coagulation defects*** | 7,611 | 8.07% | 5,000 | 8.23% | 0.58 |
| Thrombocytopenia | 5,006 | 5.31% | 3,431 | 5.64% | 1.48 |
| **Ischemic heart/ coronary artery disease*** | 23,951 | 25.39% | 15,491 | 25.48% | 0.22 |
| **Dementia** | 5,676 | 6.02% | 4,601 | 7.57% | 6.17 |
| **Dyspepsia or stomach discomfort*** | 21,551 | 22.85% | 13,960 | 22.97% | 0.28 |
| **Hemiplegia or Paraplegia** | 2,035 | 2.16% | 1,297 | 2.13% | 0.17 |
| **Hyperlipidemia*** | 45,444 | 48.17% | 29,333 | 48.26% | 0.16 |
| **Obesity*** | 26,218 | 27.79% | 16,896 | 27.80% | 0.01 |

| | Warfarin Cohort (Reference) | | Apixaban Cohort | | |
|---|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD | STD* |
| Morbid obesity | 12,662 | 13.42% | 7,209 | 11.86% | 4.71 |
| **Pneumonia*** | 13,641 | 14.46% | 8,819 | 14.51% | 0.13 |
| **Rheumatologic disease*** | 4,430 | 4.70% | 2,854 | 4.69% | 0.01 |
| **Sleep apnea*** | 12,634 | 13.39% | 8,118 | 13.35% | 0.11 |
| **Spinal cord injury*** | 253 | 0.27% | 168 | 0.28% | 0.15 |
| **Thrombophilia*** | 3,718 | 3.94% | 2,420 | 3.98% | 0.21 |
| **Varicose Veins*** | 3,988 | 4.23% | 2,560 | 4.21% | 0.08 |
| **Congestive Heart Failure** | 15,900 | 16.86% | 10,319 | 16.98% | 0.32 |
| **Diabetes** | 29,708 | 31.49% | 17,789 | 29.26% | 4.85 |
| **Hypertension*** | 65,067 | 68.98% | 42,014 | 69.12% | 0.31 |
| **Non-ESRD CKD Disease*** | 12,837 | 13.61% | 8,297 | 13.65% | 0.12 |
| Stage 1 and/or 2 | 2,533 | 2.69% | 1,861 | 3.06% | 2.26 |
| Stage III | 11,188 | 11.86% | 7,343 | 12.08% | 0.68 |
| Stage IV | 3,332 | 3.53% | 1,769 | 2.91% | 3.52 |
| **End Stage Renal Disease (ESRD and stage V)*** | 2,179 | 2.31% | 1,434 | 2.36% | 0.33 |
| Stage V | 805 | 0.85% | 522 | 0.86% | 0.06 |
| ESRD | 1,898 | 2.01% | 1,238 | 2.04% | 0.18 |
| **Unspecified Renal Disease** | | | | | |
| Stage IV | 2,543 | 2.70% | 1,288 | 2.12% | 3.76 |
| Stage III | 8,870 | 9.40% | 5,965 | 9.81% | 1.39 |
| Stage 1 and/or 2 | 1,424 | 1.51% | 1,044 | 1.72% | 1.65 |
| Non CKD patients | 81,496 | 86.39% | 52,489 | 86.35% | |
| **Chronic Liver Disease** | 6,320 | 6.70% | 4,766 | 7.84% | 4.39 |
| **COPD** | 17,465 | 18.51% | 11,277 | 18.55% | 0.10 |
| **Peptic Ulcer Disease** | 1,970 | 2.09% | 1,270 | 2.09% | 0.01 |
| **Inflammatory Bowel Disease*** | 1,769 | 1.88% | 1,132 | 1.86% | 0.10 |
| **Peripheral vascular disease** | 18,212 | 19.31% | 11,605 | 19.09% | 0.55 |
| **Baseline bleed*** | 19,481 | 20.65% | 12,611 | 20.75% | 0.24 |
| **Recent History of Falls*** | 6,853 | 7.26% | 4,426 | 7.28% | 0.06 |
| **Fracture/trauma involving Lower Extremities*** | 14,515 | 15.39% | 9,346 | 15.37% | 0.03 |
| **Selected Surgeries*** | 23,353 | 24.76% | 15,109 | 24.86% | 0.23 |
| **Baseline Medication Use*** | | | | | |
| **Antiarrhythmic** | 9,044 | 9.59% | 5,841 | 9.61% | 0.07 |
| **Statins** | 36,293 | 38.47% | 23,437 | 38.56% | 0.17 |
| **Anti-platelets** | 7,140 | 7.57% | 4,613 | 7.59% | 0.08 |
| **Aromatase Inhibitors (Anastrozole, exemestane, letrozole)** | 207 | 0.22% | 131 | 0.22% | 0.06 |
| **Beta Blockers** | 32,108 | 34.04% | 20,784 | 34.19% | 0.33 |
| **Gastroprotective Agents** | 26,741 | 28.35% | 17,274 | 28.42% | 0.16 |
| **SERMS** | 567 | 0.60% | 364 | 0.60% | 0.04 |
| **NSAIDs** | 24,770 | 26.26% | 15,951 | 26.24% | 0.04 |
| **Hormone Therapy (estrogen)** | 5,207 | 5.52% | 3,344 | 5.50% | 0.08 |
| **Apixaban Index Dose** | | | | | |
| **On Standard Dose (Apixaban 5mg)** | | | 56,642 | 93.18% | |
| **Lower Dose (2.5mg Apixaban** | | | 4,144 | 6.82% | |
| **Total** | | | 60,786 | 100.0% | |

*Included in the propensity score model

### 9.1.5. Post-IPTW Outcomes Data in Overall Population

Post-IPTW outcome characteristics among VTE patients are described in **Table 8**. The mean follow-up was 119 days (4 months) for apixaban and 126 days (4.2 months) for warfarin. The adjusted incidence rate of MB—including GI, ICH, and other bleeding—was 4.2 (apixaban) and 5.8 (warfarin) per 100 person-years when the follow-up was censored at 6 months. The adjusted incidence rate of CRNMB—including GI bleeding and other bleeding—was 27.0 (apixaban) and 31.6 (warfarin) per 100 person-years. The adjusted incidence rate of recurrent VTE, including DVT and PE, was 4.9 (apixaban) and 6.5 (warfarin) per 100 person-years. The Kaplan-Meier curves on cumulative incidence rates for MB, CRNMB, and recurrent VTE in the post-IPTW population are shown in **Figures 1-3**. Compared to warfarin patients, apixaban patients had a significantly lower risk of MB (hazard ratio [HR]: 0.70; 95% confidence interval [CI]: 0.64-0.76), CRNMB (HR: 0.83; 95% CI: 0.80-0.86), and recurrent VTE (HR: 0.72; 95% CI: 0.67-0.78) (p <0.001) **(Figures 1-3)**.

**Table 8. Post-IPTW Outcomes among VTE Patients Prescribed Apixaban or Warfarin**

| | Warfarin Cohort (Reference) | | Apixaban Cohort | |
|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD |
| **Sample Size** | **94,333** | **1** | **60,786** | **1** |
| **Follow-up Time (in days)** | 125.84 | 61.23 | 119.26 | 59.74 |
| **minimum** | 1 | | 1 | |
| **Q1** | 67 | | 59 | |
| **median** | 146 | | 124 | |
| **Q3** | 183 | | 183 | |
| **maximum** | 183 | | 183 | |
| **Reason for Censoring** | | | | |
| **Disenrollment** | 6,607 | 7.00% | 4,519 | 7.43% |
| **Death** | 2,254 | 2.39% | 1,321 | 2.17% |
| **Discontinuation** | 30,906 | 32.76% | 22,665 | 37.29% |
| **Switch** | 11,800 | 12.51% | 2,728 | 4.49% |
| **End of study period** | 4,113 | 4.36% | 8,902 | 14.65% |
| **6 months post-index date** | 38,653 | 40.98% | 20,650 | 33.97% |
| **Total** | 94,333 | 100.00% | 60,786 | 100.00% |
| **Major Bleeding** | 1,873 | 1.99% | 822 | 1.35% |
| **Gastrointestinal Bleeding** | 1,008 | 1.07% | 471 | 0.78% |
| **Intracranial Hemorrhage** | 233 | 0.25% | 93 | 0.15% |
| **Other Bleeding** | 691 | 0.73% | 281 | 0.46% |
| **Time to Major Bleeding** | 53.14 | 48.53 | 54.34 | 53.39 |
| **Major Bleeding – Time-at-Risk** | 124.62 | 61.90 | 118.49 | 60.12 |
| **Gastrointestinal Bleeding – Time-at-Risk** | 125.17 | 61.58 | 118.83 | 59.95 |
| **Intracranial Hemorrhage – Time-at-Risk** | 125.75 | 61.28 | 119.19 | 59.77 |
| **Other Bleeding – Time-at-Risk** | 125.33 | 61.53 | 118.96 | 59.90 |
| **Major Bleeding Incidence Rate (per 100 person-years)** | 5.83 | | 4.18 | |
| **Gastrointestinal Bleeding** | 3.12 | | 2.39 | |
| **Intracranial Hemorrhage** | 0.72 | | 0.47 | |
| **Other Bleeding** | 2.14 | | 1.42 | |
| **CRNM Bleeding** | 9,551 | 10.13% | 5,043 | 8.30% |
| **Gastrointestinal Bleeding** | 2,555 | 2.71% | 1,561 | 2.57% |
| **Other Bleeding** | 7,300 | 7.74% | 3,623 | 5.96% |
| **Time to CRNM Bleeding** | 50.42 | 48.68 | 50.91 | 49.43 |
| **CRNM Bleeding – Time-at-Risk** | 117.16 | 64.68 | 112.61 | 62.07 |
| **Gastrointestinal Bleeding Time-at-Risk** | 123.64 | 62.25 | 117.29 | 60.51 |

| | Warfarin Cohort (Reference) | | Apixaban Cohort | |
|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD |
| **Other Bleeding Time-at-Risk** | 119.16 | 64.01 | 114.43 | 61.54 |
| **CRNM Bleeding Incidence Rate (per 100 person-years)** | 31.63 | | 26.97 | |
| **Gastrointestinal Bleeding** | 8.02 | | 8.02 | |
| **Other Bleeding** | 23.77 | | 19.06 | |
| **Recurrent VTE** | 2,080 | 2.20% | 960 | 1.58% |
| **DVT** | 1,278 | 1.35% | 547 | 0.90% |
| **PE** | 862 | 0.91% | 445 | 0.73% |
| **Recurrent VTE Time-at-Risk** | 124.25 | 62.13 | 118.17 | 60.28 |
| **DVT – Time-at-Risk** | 124.91 | 61.77 | 118.68 | 60.04 |
| **PE – Time-at-Risk** | 125.14 | 61.63 | 118.72 | 60.00 |
| **Time to Recurrent VTE** | 40.39 | 42.95 | 38.86 | 41.15 |
| **Recurrent VTE Incidence Rate (per 100 person-years)** | 6.49 | | 4.89 | |
| **Patients that continued treatment during the follow-up period** | 51,627 | 54.73% | 35,392 | 58.22% |
| **Discontinuation without switch** | 30,906 | 32.76% | 22,665 | 37.29% |
| **Time-to-Discontinuation** | 75.25 | 41.44 | 68.66 | 40.97 |
| **Switch** | 11,800 | 12.51% | 2,728 | 4.49% |
| **Time-to-Switch** | 48.57 | 46.29 | 49.03 | 45.84 |
| Apixaban | 3,282 | 3.48% | | |
| Dabigatran | 411 | 0.44% | 129 | 0.21% |
| Edoxaban | 40 | 0.04% | 9 | 0.01% |
| Rivaroxaban | 5,595 | 5.93% | 939 | 1.54% |
| Warfarin | | | 902 | 1.48% |
| Unfractionated heparin (UFH) | 438 | 0.46% | 282 | 0.46% |
| LMWH | 1,978 | 2.10% | 459 | 0.76% |
| Fondaparinux | 56 | 0.06% | 9 | 0.01% |
| Total | 11,800 | 12.51% | 2,728 | 4.49% |

CRNM: Clinically relevant non-major (bleeding); VTE: Venous thromboembolism; DVT: Deep vein thrombosis; PE: Pulmonary embolism.

*Std Difference=100*|actual std diff|. Std Difference greater than 10 is considered significant.

**Figure 1. Kaplan-Meier Curve: Risk of MB for Apixaban vs. Warfarin**

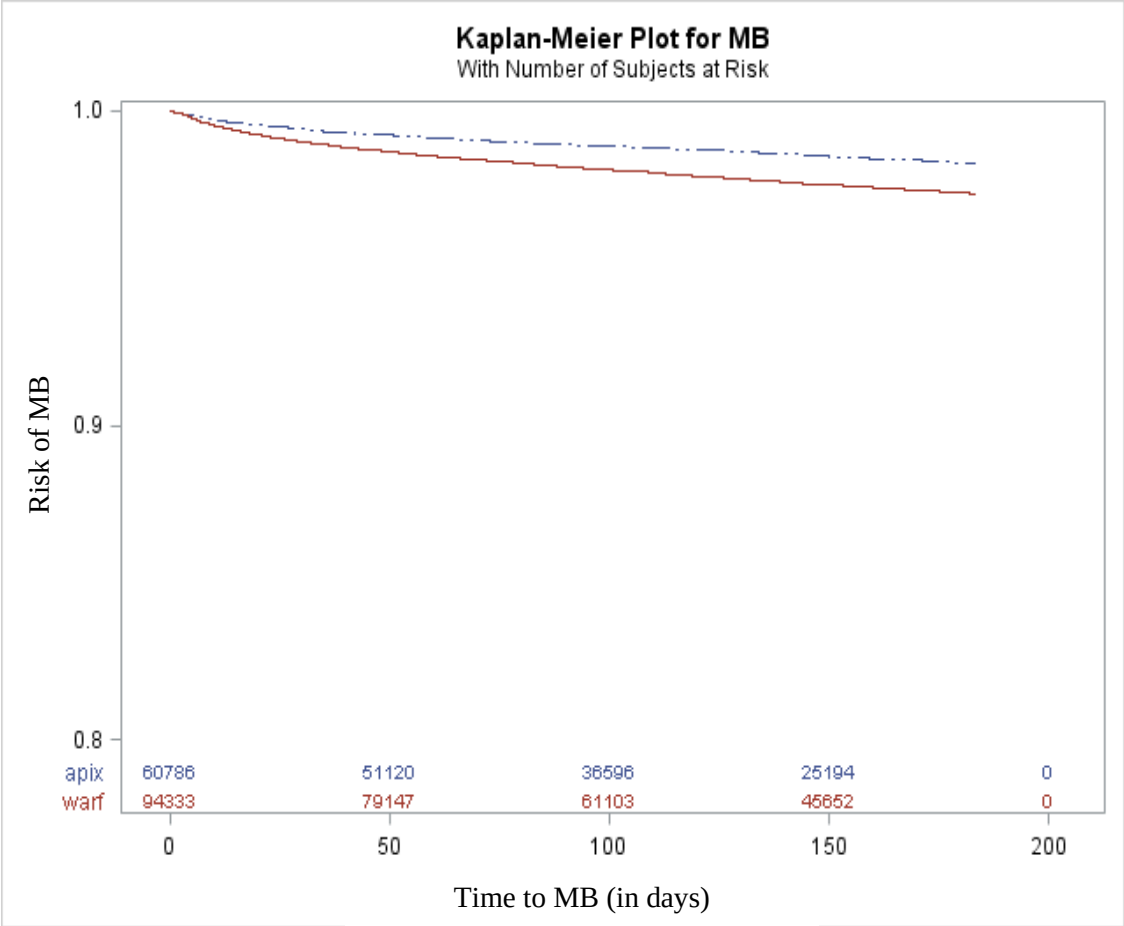


**Figure 2. Kaplan-Meier Curve: Risk of CRNM Bleeding for Apixaban vs. Warfarin**

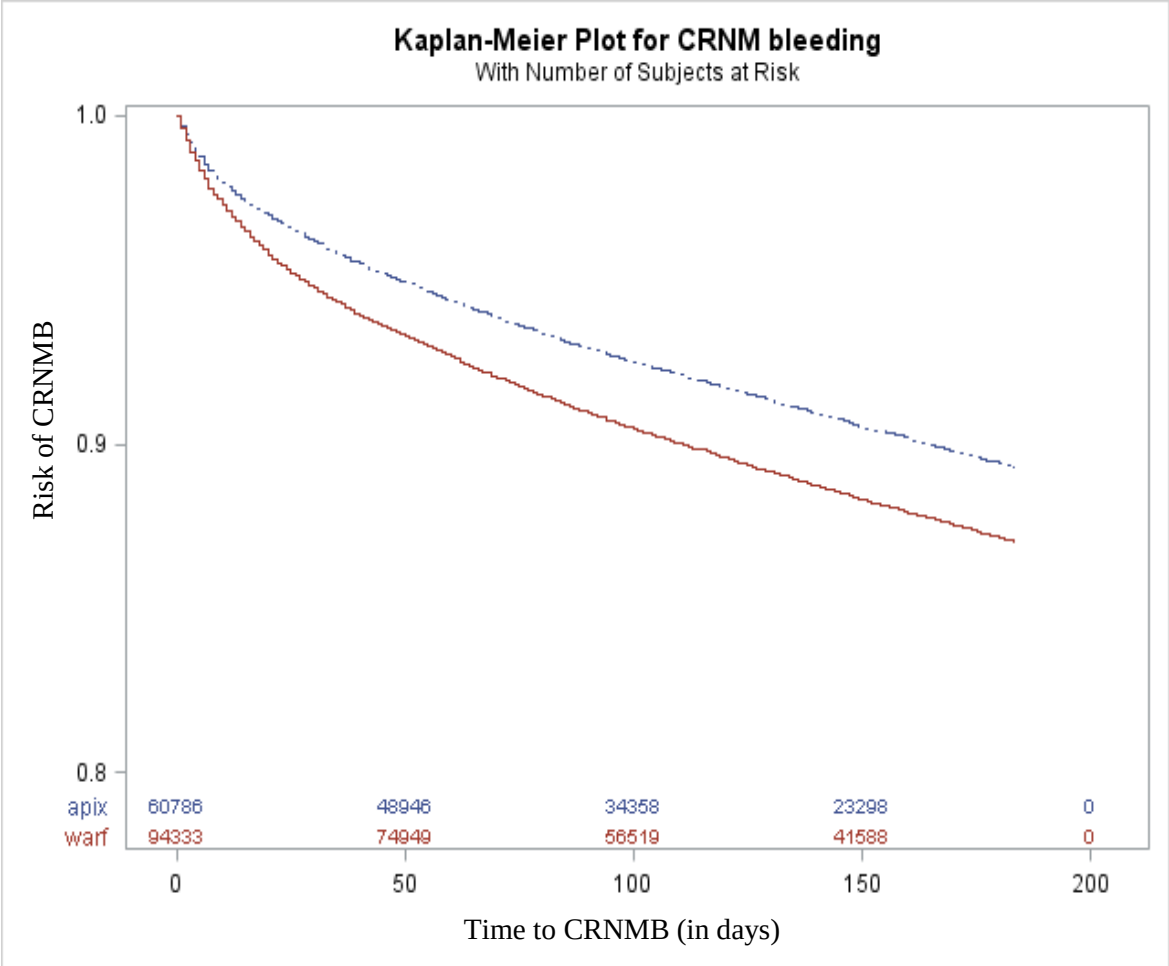
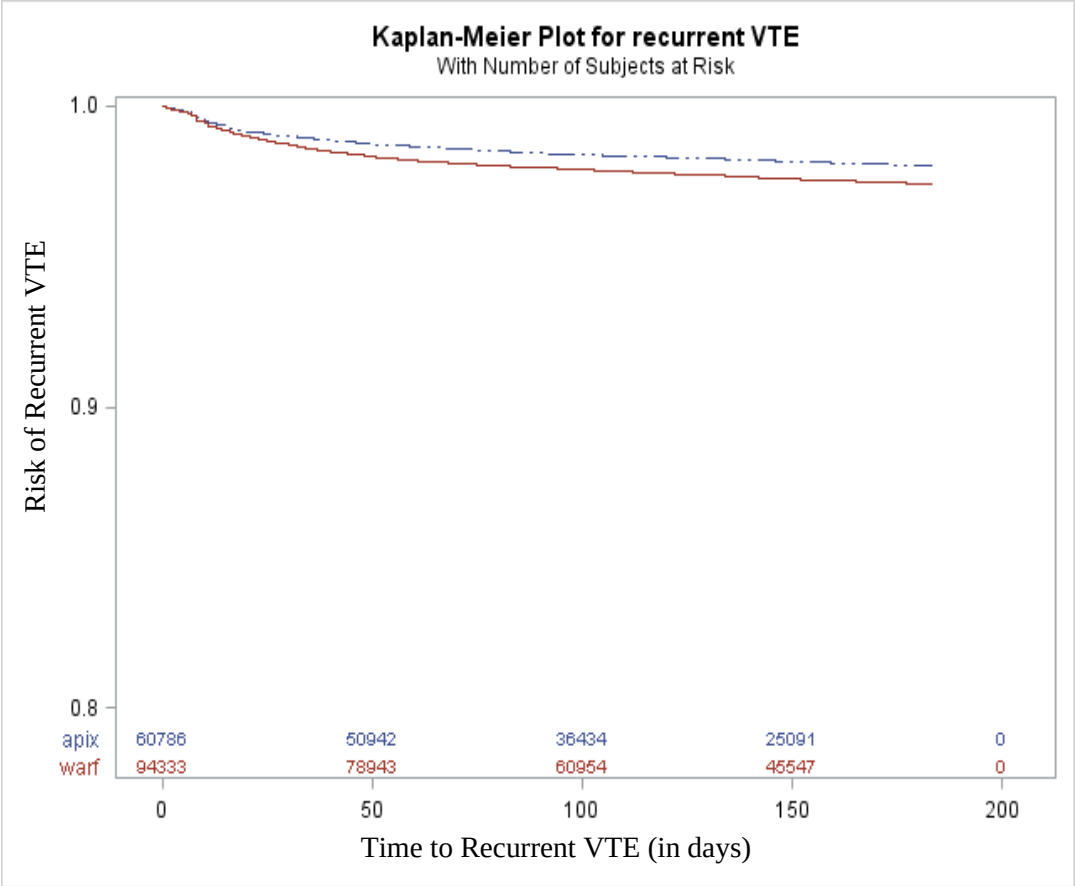


**Figure 3. Kaplan-Meier Curve: Risk of Recurrent VTE for Apixaban vs. Warfarin**




## 9.2. SUBGROUP ANALYSES

### 9.2.1. Findings for Demographic Socioeconomic Subgroup Analysis

Only Medicare data were used for the demographic socioeconomic subgroup analysis. Other databases lack information about race and socioeconomic status (SES). During the study period, approximately 1.4 million patients in the Medicare database had a VTE event. After applying the selection criteria, a total of 22,135 (32.6%) patients who initiated apixaban and 45,840 (67.4%) patients who initiated warfarin were included in the study (Table 4). After applying IPTW but before stratification by subgroups, patient characteristics were generally balanced. For both treatment cohorts, most patients were aged 65-79 years (apixaban: 62.6%; warfarin: 62.6%), followed by ≥80 years (apixaban: 37.4%; warfarin: 37.4%) with mean ages of about 67 years for both cohorts (**Table 7**). A majority of patients across the two cohorts were female (54.9% for both cohorts), and the average CCI was 2.2 (**Table 7**).

Table 9 shows demographics, SES, and clinical characteristics for the apixaban and warfarin cohorts before and after IPTW.

After IPTW, all patient characteristics were well balanced (Table 9). For both treatment cohorts, most patients were aged 65-79 years (apixaban: 62.6%; warfarin: 62.6%), followed by ≥80 years (apixaban: 37.4%; warfarin: 37.4%). The majority were female (apixaban:62.9%; warfarin: 62.9%) and most of them were white (apixaban: 84.2%; warfarin: 83.7%) across the two cohorts. The largest proportion of patients had a high SES (apixaban: 45.2%; warfarin: 42.2%), followed by medium (apixaban: 30.2%; warfarin: 32.6%), and low (apixaban: 22.7%; warfarin: 23.4%). One third of patients also had Medicare/Medicaid Dual-eligibility and/or Part D low-income subsidy (apixaban: 28.5%; warfarin: 30.5%) during the baseline period. During the follow-up period, apixaban patients had significantly lower risk of recurrent VTE (hazard ratio [HR]: 0.64; 95% confidence interval [CI]: 0.52-0.79), MB (HR: 0.65; 95% CI: 0.57-0.75), and CRNMB (HR: 0.79; 95% CI: 0.75-0.85) compared to warfarin patients.

The baseline characteristics for the apixaban vs warfarin study population stratified by age, gender, race, SES status, and dual eligibility/ Part-D LIS are listed in Tables 10-14. For both apixaban and warfarin cohorts, higher mean comorbidity index was observed in patients aged ≥80 vs. 65-79 years (apixaban: 3.2 vs 2.7; warfarin: 3.2 vs 2.7), low vs. high SES (apixaban: 3.5 vs 2.6; warfarin: 3.3 vs 2.7), dual eligibility/ Part-D LIS yes vs. no (apixaban: 3.9 vs 2.5; warfarin: 3.8 vs 2.5) and black vs. white patients (apixaban: 4.1 vs 2.7; warfarin: 4.1 vs 2.7). Additionally, during the follow-up, the incidence rates per 100 person-years for recurrent VTE were numerically higher for black vs. white patients (apixaban: 2.0 vs 1.4; warfarin: 3.3 vs 2.2), patients with low vs. high SES (apixaban: 2.6 vs 1.3 ; warfarin: 3.2 vs 2.0 ) and dual eligibility/ Part-D LIS yes vs. no (apixaban: 2.2 vs 1.3; warfarin: 3.1 vs 2.0) (Figure 4). Similarly, the incidence rates per 100 person-years for MB were numerically higher for patients aged ≥80 vs. 65-79 years (apixaban: 5.4 vs 3.1; warfarin: 7.4 vs 5.0), females vs. males (apixaban: 4.5 vs 3.1; warfarin: 6.4 vs 5.0), black vs. white patients (apixaban: 7.4 vs 3.5; warfarin 10.1 vs 5.3), low vs. high SES (apixaban: 5.7 vs 3.2; warfarin: 7.0 vs 5.1 ), and dual eligibility/ Part-D LIS yes vs. no (apixaban: 6.3 vs 3.1; warfarin: 8.6 vs 4.8) (Figure 5).

Figures 4-6 show the data of apixaban vs. warfarin on risks of recurrent VTE, MB and CRNMB stratified by demographic and SES factors. No significant interaction was observed between the treatment and the following subgroups on recurrent VTE (Figure 4) and MB (Figure 5): age, sex, race, SES, and dual eligibility/LIS. Across all subgroup strata, apixaban patients had a lower incidence rate of recurrent VTE and MB compared to warfarin patients. For CRNMB, no significant interaction was observed between the treatment and the following subgroups: sex, race, and dual eligibility/LIS (Figure 6). However, there were significant interactions between the treatment and age (interaction p-value=0.001) and between the treatment and SES (interaction p-value=0.012) on CRNMB. Apixaban trended towards a lower risk of CRNMB across both age groups, but the risk of CRNMB was larger for patients aged 65-79 years. Similarly, apixaban trended towards a lower risk of CRNMB across all three SES strata, but the risk was larger for those with medium and high SES (Figure 6).

## Table 9. Baseline and Clinical Characteristics Among Medicare VTE Patients that Initiated Apixaban vs Warfarin Pre- and Post-IPTW

| | Pre-IPTW | | | Post IPTW | | |
|---|---|---|---|---|---|---|
| | Warfarin Cohort | Apixaban Cohort | STD* | Warfarin Cohort | Apixaban Cohort | STD* |
| **Sample Size** | **45,840** | **22,135** | | **45,840** | **22,135** | |
| **Age** | 77.2 (8.1) | 77.7 (8.2) | 6.01 | 77.3 (8.1) | 77.4 (8.2) | 1.57 |
| 65-79 | 29,021 (63%) | 13,548 (61%) | 4.34 | 28,703 (63%) | 13,848 (63%) | 0.11 |
| ≥80 | 16,819 (36.7%) | 8,587 (38.8%) | 4.34 | 17,137 (37.4%) | 8,287 (37.4%) | 0.11 |
| **Sex** | | | | | | |
| Male | 16,959 (37.0%) | 8,300 (37.5%) | 1.04 | 17,019 (37.1%) | 8,202 (37.1%) | 0.15 |
| Female | 28,881 (63.0%) | 13,835 (62.5%) | 1.04 | 28,821 (62.9%) | 13,933 (62.9%) | 0.15 |
| **Race** | | | | | | |
| White | 38,487 (84.0%) | 18,575 (83.9%) | 0.12 | 38,371 (83.7%) | 18,636 (84.2%) | 1.33 |
| African American | 5,239 (11.4%) | 2,535 (11.5%) | 0.07 | 5,404 (11.8%) | 2,428 (11.0%) | 2.58 |
| Other Categories | 2,114 (4.6%) | 1,025 (4.6%) | 0.09 | 0 (0.0%) | 0 (0.0%) | |
| **SES Status** | | | | | | |
| Low | 10,374 (22.6%) | 5,320 (24.0%) | 3.32 | 10,733 (23.4%) | 5,029 (22.7%) | 1.65 |
| Medium | 15,083 (32.9%) | 6,600 (29.8%) | 6.66 | 14,959 (32.6%) | 6,684 (30.2%) | 5.25 |
| High | 19,567 (42.7%) | 9,792 (44.2%) | 3.13 | 19,324 (42.2%) | 10,008 (45.2%) | 6.17 |
| Missing | 816 (1.8%) | 423 (1.9%) | 0.97 | 824 (1.8%) | 414 (1.9%) | 0.52 |
| **Medicare/Medicaid Dual-eligibility and/or Part D low income subsidy during the baseline period** | 13,857 (30.2%) | 6,385 (28.8%) | 3.03 | 13,990 (30.5%) | 6,319 (28.5%) | 4.32 |
| **Type of Index Encounter** | | | | | | |
| Inpatient | 29,977 (65.4%) | 14,391 (65.0%) | 0.80 | 29,907 (65.2%) | 14,418 (65.1%) | 0.22 |
| Outpatient | 15,863 (34.6%) | 7,744 (35.0%) | 0.80 | 15,933 (34.8%) | 7,717 (34.9%) | 0.22 |
| **VTE Diagnosis** | | | | | | |
| DVT only | 24,772 (54.0%) | 11,669 (52.7%) | 2.65 | 24,601 (53.7%) | 11,913 (53.8%) | 0.31 |
| PE with DVT | 7,091 (15.5%) | 3,502 (15.8%) | 0.97 | 7,145 (15.6%) | 3,448 (15.6%) | 0.02 |
| PE without DVT | 13,977 (30.5%) | 6,964 (31.5%) | 2.10 | 14,094 (30.7%) | 6,773 (30.6%) | 0.32 |
| **Deyo-Charlson Comorbidity Index** | 2.9 (2.5) | 2.9 (2.5) | 1.40 | 2.9 (2.5) | 2.9 (2.5) | 0.37 |
| **Baseline Comorbidity** | | | | | | |
| AIDS | 128 (0.3%) | 46 (0.2%) | 1.45 | 130 (0.3%) | 48 (0.2%) | 1.29 |
| Alcohol abuse | 1,178 (2.6%) | 525 (2.4%) | 1.28 | 1,152 (2.5%) | 561 (2.5%) | 0.13 |
| Anemia | 17,520 (38.2%) | 8,026 (36.3%) | 4.06 | 17,246 (37.6%) | 8,340 (37.7%) | 0.11 |
| Central venous Catheter | 4,047 (8.8%) | 1,597 (7.2%) | 5.94 | 3,810 (8.3%) | 1,835 (8.3%) | 0.08 |
| Cerebrovascular disease | 7,918 (17.3%) | 3,786 (17.1%) | 0.45 | 8,006 (17.5%) | 3,724 (16.8%) | 1.70 |
| Coagulation defects | 4,429 (9.7%) | 1,870 (8.4%) | 4.23 | 4,254 (9.3%) | 2,064 (9.3%) | 0.15 |
| Ischemic heart/ coronary artery disease | 15,724 (34.3%) | 8,111 (36.6%) | 4.90 | 16,071 (35.1%) | 7,757 (35.0%) | 0.03 |
| Dementia | 4,868 (10.6%) | 3,041 (13.7%) | 9.55 | 4,934 (10.8%) | 2,996 (13.5%) | 8.48 |
| Dyspepsia or stomach discomfort | 11,168 (24.4%) | 5,336 (24.1%) | 0.60 | 11,150 (24.3%) | 5,413 (24.5%) | 0.31 |
| Hemiplegia or Paraplegia | 1,157 (2.5%) | 542 (2.4%) | 0.48 | 1,157 (2.5%) | 562 (2.5%) | 0.11 |
| Hyperlipidemia | 27,678 (60.4%) | 14,048 (63.5%) | 6.36 | 28,129 (61.4%) | 13,563 (61.3%) | 0.19 |
| Obesity | 11,558 (25.2%) | 5,794 (26.2%) | 2.20 | 11,689 (25.5%) | 5,631 (25.4%) | 0.14 |
| Pneumonia | 7,893 (17.2%) | 3,912 (17.7%) | 1.20 | 7,980 (17.4%) | 3,868 (17.5%) | 0.17 |
| Rheumatologic disease | 3,060 (6.7%) | 1,455 (6.6%) | 0.41 | 3,044 (6.6%) | 1,465 (6.6%) | 0.08 |
| Sleep apnea | 6,394 (13.9%) | 3,086 (13.9%) | 0.02 | 6,375 (13.9%) | 3,054 (13.8%) | 0.32 |
| Spinal cord injury | 130 (0.3%) | 46 (0.2%) | 1.53 | 119 (0.3%) | 59 (0.3%) | 0.10 |
| Thrombophilia | 1,450 (3.2%) | 627 (2.8%) | 1.94 | 1,397 (3.0%) | 670 (3.0%) | 0.11 |
| Varicose Veins | 1,999 (4.4%) | 1,059 (4.8%) | 2.03 | 2,065 (4.5%) | 996 (4.5%) | 0.02 |
| Congestive Heart Failure | 10,648 (23.2%) | 5,233 (23.6%) | 0.97 | 10,731 (23.4%) | 5,221 (23.6%) | 0.42 |
| Diabetes | 17,825 (38.9%) | 8,031 (36.3%) | 5.38 | 17,978 (39.2%) | 7,900 (35.7%) | 7.29 |
| Hypertension | 38,312 (83.6%) | 18,691 (84.4%) | 2.36 | 38,446 (83.9%) | 18,571 (83.9%) | 0.08 |
| Non-ESRD Renal Disease | 9,408 (20.5%) | 4,615 (20.8%) | 0.80 | 9,466 (20.6%) | 4,585 (20.7%) | 0.16 |
| End Stage Renal Disease | 1,588 (3.5%) | 449 (2.0%) | 8.79 | 1,375 (3.0%) | 675 (3.0%) | 0.28 |
| Chronic Liver Disease | 2,861 (6.2%) | 1,570 (7.1%) | 3.41 | 2,807 (6.1%) | 1,610 (7.3%) | 4.59 |
| COPD | 11,754 (25.6%) | 5,814 (26.3%) | 1.43 | 11,858 (25.9%) | 5,800 (26.2%) | 0.76 |
| Peptic Ulcer Disease | 1,296 (2.8%) | 533 (2.4%) | 2.63 | 1,267 (2.8%) | 564 (2.5%) | 1.35 |
| Inflammatory Bowel Disease | 853 (1.9%) | 378 (1.7%) | 1.16 | 829 (1.8%) | 395 (1.8%) | 0.19 |
| Peripheral vascular disease | 11,958 (26.1%) | 5,840 (26.4%) | 0.68 | 12,052 (26.3%) | 5,760 (26.0%) | 0.61 |
| Baseline bleed | 11,159 (24.3%) | 4,544 (20.5%) | 9.15 | 10,590 (23.1%) | 5,112 (23.1%) | 0.02 |
| **Recent History of Falls** | 4,488 (9.8%) | 2,198 (9.9%) | 0.47 | 4,522 (9.9%) | 2,184 (9.9%) | 0.01 |
| **Fracture/trauma involving Lower Extremities** | 7,075 (15.4%) | 3,636 (16.4%) | 2.71 | 7,245 (15.8%) | 3,523 (15.9%) | 0.30 |
| **Selected Surgeries** | 12,264 (26.8%) | 5,844 (26.4%) | 0.80 | 12,210 (26.6%) | 5,885 (26.6%) | 0.11 |
| **Baseline Medication Use** | | | | | | |
| Antiarrhythmic | 4,804 (10.5%) | 2,354 (10.6%) | 0.50 | 4,829 (10.5%) | 2,333 (10.5%) | 0.03 |
| Statins | 21,848 (47.7%) | 11,057 (50.0%) | 4.58 | 22,189 (48.4%) | 10,706 (48.4%) | 0.07 |
| Anti-platelets | 4,649 (10.1%) | 2,562 (11.6%) | 4.61 | 4,859 (10.6%) | 2,337 (10.6%) | 0.14 |
| Aromatase Inhibitors | 103 (0.2%) | 53 (0.2%) | 0.31 | 105 (0.2%) | 50 (0.2%) | 0.07 |
| Beta Blockers | 19,886 (43.4%) | 9,739 (44.0%) | 1.24 | 19,978 (43.6%) | 9,652 (43.6%) | 0.04 |
| Gastroprotective Agents | 15,790 (34.4%) | 7,643 (34.5%) | 0.17 | 15,811 (34.5%) | 7,646 (34.5%) | 0.11 |
| SERMS | 378 (0.8%) | 233 (1.1%) | 2.36 | 410 (0.9%) | 197 (0.9%) | 0.04 |
| NSAIDs | 10,052 (21.9%) | 5,433 (24.5%) | 6.20 | 10,438 (22.8%) | 5,031 (22.7%) | 0.10 |
| Hormone Therapy | 1,138 (2.5%) | 578 (2.6%) | 0.82 | 1,164 (2.5%) | 573 (2.6%) | 0.31 |

AIDS: Acquired immuno deficiency syndrome; COPD: Chronic obstructive pulmonary disorder; DVT: Deep vein thrombosis; IPTW: Inverse Probability of Treatment Weighting NSAIDs: Nonsteroidal Anti-inflammatory Drugs; PE: Pulmonary embolism; SERMS: Selective estrogen receptor modulators; SD: Standard deviation; STD: Standardized differences; VTE: Venous
*Std Difference=100*|actual std diff|. Std Difference greater than 10 is considered significant.

## Table 10. Baseline Characteristics Among Medicare VTE Patients that Initiated Apixaban vs Warfarin Stratified by Age

| | Age 65-79 Years | | | Age ≥80 Years | | |
|---|---|---|---|---|---|---|
| | Warfarin | Apixaban | STD* | Warfarin | Apixaban | STD* |
| **Sample Size** | **28,703** | **13,848** | | **17,137** | **8,287** | |
| **Sex** | | | | | | |
| Male | 12,287 (43%) | 5,951 (43%) | 0.33 | 4,732 (28%) | 2,251 (27%) | 1.00 |
| Female | 16,416 (57%) | 7,898 (57%) | 0.33 | 12,405 (72%) | 6,035 (73%) | 1.00 |
| **VTE Diagnosis** | | | | | | |
| DVT only | 14,859 (52%) | 7,156 (52%) | 0.19 | 9,742 (57%) | 4,757 (57%) | 1.14 |
| PE with DVT | 4,534 (16%) | 2,291 (17%) | 2.02 | 2,610 (15%) | 1,157 (14%) | 3.60 |
| PE without DVT | 9,309 (32%) | 4,401 (32%) | 1.40 | 4,785 (28%) | 2,372 (29%) | 1.57 |
| **Deyo-Charlson Comorbidity Index** | 2.7 (2.5) | 2.7 (2.6) | 0.18 | 3.2 (2.4) | 3.2 (2.4) | 1.32 |
| **Baseline Comorbidity** | | | | | | |
| Anemia | 9,965 (35%) | 4,836 (35%) | 0.42 | 7,281 (42%) | 3,504 (42%) | 0.41 |
| Cerebrovascular disease | 4,496 (16%) | 2,040 (15%) | 2.58 | 3,510 (20%) | 1,684 (20%) | 0.41 |
| Coagulation defects | 2,719 (9%) | 1,311 (9%) | 0.03 | 1,535 (9%) | 753 (9%) | 0.47 |
| Ischemic heart/ coronary artery disease | 9,375 (33%) | 4,543 (33%) | 0.30 | 6,696 (39%) | 3,214 (39%) | 0.60 |
| Dementia | 1,445 (5%) | 960 (7%) | 7.99 | 3,489 (20%) | 2,035 (25%) | 10.12 |
| Hyperlipidemia | 17,825 (62%) | 8,552 (62%) | 0.71 | 10,305 (60%) | 5,011 (60%) | 0.69 |
| Obesity | 9,110 (32%) | 4,356 (31%) | 0.61 | 2,579 (15%) | 1,275 (15%) | 0.93 |
| Pneumonia | 4,762 (17%) | 2,282 (16%) | 0.29 | 3,218 (19%) | 1,585 (19%) | 0.90 |
| Rheumatologic disease | 1,859 (6%) | 877 (6%) | 0.60 | 1,185 (7%) | 589 (7%) | 0.74 |
| Sleep apnea | 5,103 (18%) | 2,409 (17%) | 1.00 | 1,273 (7%) | 645 (8%) | 1.35 |
| Thrombophilia | 1,018 (4%) | 491 (4%) | 0.02 | 379 (2%) | 179 (2%) | 0.31 |
| Varicose Veins | 1,331 (5%) | 655 (5%) | 0.44 | 733 (4%) | 341 (4%) | 0.82 |
| Congestive Heart Failure | 5,782 (20%) | 2,833 (20%) | 0.77 | 4,949 (29%) | 2,388 (29%) | 0.12 |
| Diabetes | 11,271 (39%) | 5,062 (37%) | 5.58 | 6,708 (39%) | 2,838 (34%) | 10.19 |
| Hypertension | 23,389 (81%) | 11,255 (81%) | 0.54 | 15,057 (88%) | 7,316 (88%) | 1.30 |
| Non-ESRD Renal Disease | 5,024 (18%) | 2,512 (18%) | 1.66 | 4,442 (26%) | 2,073 (25%) | 2.08 |
| End Stage Renal Disease | 1,018 (4%) | 504 (4%) | 0.50 | 358 (2%) | 171 (2%) | 0.17 |
| Chronic Liver Disease | 2,128 (7%) | 1,217 (9%) | 5.02 | 680 (4%) | 393 (5%) | 3.80 |
| Baseline bleed | 6,666 (23%) | 3,190 (23%) | 0.44 | 3,924 (23%) | 1,921 (23%) | 0.68 |

*Std Difference=100*|actual std diff|. Std Difference greater than 10 is considered significant.

DVT: Deep vein thrombosis; PE: Pulmonary embolism;

## Table 11. Baseline Characteristics Among Medicare VTE Patients that Initiated Apixaban vs Warfarin Stratified by Gender

| | Gender — Male | | | Gender — Female | | |
|---|---|---|---|---|---|---|
| | Warfarin | Apixaban | STD* | Warfarin | Apixaban | STD* |
| **Sample Size** | **17,019** | **8,202** | | **28,821** | **13,933** | |
| **Age** | 75.5 (7.3) | 75.5 (7.3) | 0.31 | 78.4 (8.4) | 78.5 (8.5) | 2.21 |
| 65-79 | 12,287 (72%) | 5,951 (73%) | 0.80 | 16,416 (57%) | 7,898 (57%) | 0.56 |
| ≥80 | 4,732 (28%) | 2,251 (27%) | 0.80 | 12,405 (43%) | 6,035 (43%) | 0.56 |
| **VTE Diagnosis** | | | | | | |
| DVT only | 9,212 (54%) | 4,441 (54%) | 0.04 | 15,389 (53%) | 7,473 (54%) | 0.47 |
| PE with DVT | 2,896 (17%) | 1,437 (18%) | 1.34 | 4,249 (15%) | 2,011 (14%) | 0.87 |
| PE without DVT | 4,911 (29%) | 2,324 (28%) | 1.16 | 9,183 (32%) | 4,449 (32%) | 0.15 |
| **Deyo-Charlson Comorbidity Index** | 2.9 (2.6) | 2.9 (2.6) | 0.16 | 2.9 (2.5) | 2.9 (2.5) | 0.70 |
| **Baseline Comorbidity** | | | | | | |
| Anemia | 5,596 (33%) | 2,646 (32%) | 1.31 | 11,650 (40%) | 5,694 (41%) | 0.90 |
| Cerebrovascular disease | 3,032 (18%) | 1,342 (16%) | 3.87 | 4,974 (17%) | 2,382 (17%) | 0.43 |
| Coagulation defects | 1,888 (11%) | 948 (12%) | 1.46 | 2,367 (8%) | 1,117 (8%) | 0.72 |
| Ischemic heart/ coronary artery disease | 6,979 (41%) | 3,385 (41%) | 0.54 | 9,092 (32%) | 4,372 (31%) | 0.37 |
| Dementia | 1,312 (8%) | 716 (9%) | 3.70 | 3,622 (13%) | 2,280 (16%) | 10.79 |
| Hyperlipidemia | 10,561 (62%) | 5,143 (63%) | 1.36 | 17,569 (61%) | 8,419 (60%) | 1.09 |
| Obesity | 3,950 (23%) | 1,982 (24%) | 2.26 | 7,739 (27%) | 3,649 (26%) | 1.50 |
| Pneumonia | 3,044 (18%) | 1,465 (18%) | 0.04 | 4,936 (17%) | 2,402 (17%) | 0.30 |
| Rheumatologic disease | 663 (4%) | 319 (4%) | 0.00 | 2,381 (8%) | 1,146 (8%) | 0.14 |
| Sleep apnea | 3,087 (18%) | 1,543 (19%) | 1.75 | 3,288 (11%) | 1,511 (11%) | 1.80 |
| Thrombophilia | 572 (3%) | 293 (4%) | 1.17 | 825 (3%) | 377 (3%) | 0.95 |
| Varicose Veins | 650 (4%) | 314 (4%) | 0.01 | 1,414 (5%) | 683 (5%) | 0.04 |
| Congestive Heart Failure | 3,741 (22%) | 1,819 (22%) | 0.48 | 6,990 (24%) | 3,402 (24%) | 0.38 |
| Diabetes | 6,810 (40%) | 3,078 (38%) | 5.11 | 11,168 (39%) | 4,822 (35%) | 8.59 |
| Hypertension | 13,934 (82%) | 6,731 (82%) | 0.51 | 24,512 (85%) | 11,840 (85%) | 0.20 |
| Non-ESRD Renal Disease | 3,717 (22%) | 1,838 (22%) | 1.36 | 5,749 (20%) | 2,747 (20%) | 0.57 |
| End Stage Renal Disease | 577 (3%) | 319 (4%) | 2.67 | 799 (3%) | 356 (3%) | 1.34 |
| Chronic Liver Disease | 1,173 (7%) | 653 (8%) | 4.11 | 1,634 (6%) | 956 (7%) | 4.91 |
| Baseline bleed | 3,947 (23%) | 1,881 (23%) | 0.62 | 6,643 (23%) | 3,231 (23%) | 0.32 |

*Std Difference=100*|actual std diff|. Std Difference greater than 10 is considered significant.

DVT: Deep vein thrombosis; PE: Pulmonary embolism;

## Table 12. Baseline Characteristics Among Medicare VTE Patients that Initiated Apixaban vs Warfarin Stratified by Race

| | Race — White | | | Race — Black | | | Race — Other | | |
|---|---|---|---|---|---|---|---|---|---|
| | Warfarin | Apixaban | STD* | Warfarin | Apixaban | STD* | Warfarin | Apixaban | STD* |
| **Sample Size** | **38,371** | **18,636** | | **5,404** | **2,428** | | **2,065** | **1,070** | |
| **Age** | 77.4 (8.0) | 77.5 (8.1) | 2.22 | 77.2 (8.4) | 77.0 (8.3) | 2.07 | 76.5 (8.5) | 76.4 (9.0) | 0.57 |
| 65-79 | 23,933 (62%) | 11,603 (62%) | 0.23 | 3,405 (63%) | 1,545 (64%) | 1.29 | 1,366 (66%) | 701 (65%) | 1.40 |
| ≥80 | 14,439 (38%) | 7,034 (38%) | 0.23 | 1,999 (37%) | 883 (36%) | 1.29 | 699 (34%) | 370 (35%) | 1.40 |
| **Sex** | | | | | | | | | |
| Male | 14,371 (37%) | 6,970 (37%) | 0.11 | 1,734 (32%) | 775 (32%) | 0.35 | 914 (44%) | 457 (43%) | 3.14 |
| Female | 24,000 (63%) | 11,667 (63%) | 0.11 | 3,670 (68%) | 1,653 (68%) | 0.35 | 1,151 (56%) | 613 (57%) | 3.14 |
| **VTE Diagnosis** | | | | | | | | | |
| DVT only | 20,310 (53%) | 9,981 (54%) | 1.25 | 3,041 (56%) | 1,316 (54%) | 4.20 | 1,250 (61%) | 617 (58%) | 5.93 |
| PE with DVT | 6,141 (16%) | 2,957 (16%) | 0.37 | 761 (14%) | 353 (15%) | 1.28 | 243 (12%) | 138 (13%) | 3.49 |
| PE without DVT | 11,920 (31%) | 5,698 (31%) | 1.06 | 1,603 (30%) | 760 (31%) | 3.56 | 572 (28%) | 315 (29%) | 3.91 |
| **Deyo-Charlson Comorbidity Index** | 2.7 (2.4) | 2.7 (2.4) | 0.30 | 4.1 (2.9) | 4.1 (2.8) | 0.97 | 3.3 (2.7) | 3.5 (2.8) | 7.51 |
| **Baseline Comorbidity** | | | | | | | | | |
| Anemia | 13,567 (35%) | 6,609 (35%) | 0.22 | 2,798 (52%) | 1,241 (51%) | 1.35 | 882 (43%) | 490 (46%) | 6.24 |
| Cerebrovascular disease | 6,283 (16%) | 2,904 (16%) | 2.16 | 1,338 (25%) | 604 (25%) | 0.31 | 386 (19%) | 216 (20%) | 3.69 |
| Coagulation defects | 3,453 (9%) | 1,670 (9%) | 0.13 | 577 (11%) | 258 (11%) | 0.14 | 224 (11%) | 136 (13%) | 5.63 |
| Ischemic heart/ coronary artery disease | 13,130 (34%) | 6,366 (34%) | 0.12 | 2,188 (40%) | 981 (40%) | 0.18 | 753 (36%) | 409 (38%) | 3.67 |
| Dementia | 3,875 (10%) | 2,379 (13%) | 8.38 | 811 (15%) | 482 (20%) | 12.89 | 249 (12%) | 135 (13%) | 1.55 |
| Hyperlipidemia | 23,357 (61%) | 11,320 (61%) | 0.27 | 3,473 (64%) | 1,555 (64%) | 0.46 | 1,299 (63%) | 687 (64%) | 2.67 |
| Obesity | 9,604 (25%) | 4,622 (25%) | 0.54 | 1,609 (30%) | 736 (30%) | 1.21 | 476 (23%) | 273 (25%) | 5.68 |
| Pneumonia | 6,593 (17%) | 3,226 (17%) | 0.34 | 974 (18%) | 424 (17%) | 1.53 | 412 (20%) | 217 (20%) | 0.86 |
| Rheumatologic disease | 2,573 (7%) | 1,236 (7%) | 0.29 | 367 (7%) | 155 (6%) | 1.59 | 104 (5%) | 73 (7%) | 7.72 |
| Sleep apnea | 5,480 (14%) | 2,603 (14%) | 0.91 | 659 (12%) | 333 (14%) | 4.56 | 236 (11%) | 118 (11%) | 1.38 |
| Thrombophilia | 1,199 (3%) | 547 (3%) | 1.10 | 139 (3%) | 78 (3%) | 3.97 | 59 (3%) | 44 (4%) | 7.00 |
| Varicose Veins | 1,774 (5%) | 886 (5%) | 0.63 | 194 (4%) | 70 (3%) | 3.99 | 96 (5%) | 40 (4%) | 4.82 |
| Congestive Heart Failure | 8,254 (22%) | 4,031 (22%) | 0.29 | 1,952 (36%) | 890 (37%) | 1.12 | 524 (25%) | 299 (28%) | 5.77 |
| Diabetes | 13,959 (36%) | 6,079 (33%) | 7.92 | 2,977 (55%) | 1,281 (53%) | 4.74 | 1,042 (50%) | 541 (51%) | 0.21 |
| Hypertension | 31,532 (82%) | 15,340 (82%) | 0.36 | 5,152 (95%) | 2,310 (95%) | 1.08 | 1,761 (85%) | 921 (86%) | 2.19 |
| Non-ESRD Renal Disease | 7,418 (19%) | 3,612 (19%) | 0.12 | 1,603 (30%) | 725 (30%) | 0.39 | 445 (22%) | 249 (23%) | 4.09 |
| End Stage Renal Disease | 720 (2%) | 372 (2%) | 0.87 | 507 (9%) | 211 (9%) | 2.43 | 148 (7%) | 92 (9%) | 5.16 |
| Chronic Liver Disease | 2,274 (6%) | 1,297 (7%) | 4.22 | 363 (7%) | 218 (9%) | 8.48 | 171 (8%) | 94 (9%) | 1.89 |
| Baseline bleed | 8,702 (23%) | 4,207 (23%) | 0.25 | 1,406 (26%) | 609 (25%) | 2.16 | 482 (23%) | 295 (28%) | 9.72 |

*Std Difference=100*|actual std diff|. Std Difference greater than 10 is considered significant.
DVT: Deep vein thrombosis; PE: Pulmonary embolism;

## Table 13. Baseline Characteristics Among Medicare VTE Patients that Initiated Apixaban vs Warfarin Stratified by SES

| | Socioeconomic Status — Low | | | Socioeconomic Status — Medium | | | Socioeconomic Status — High | | | Socioeconomic Status — Missing | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Warfarin | Apixaban | STD* | Warfarin | Apixaban | STD* | Warfarin | Apixaban | STD* | Warfarin | Apixaban | STD* |
| **Sample Size** | **10,733** | **5,029** | | **14,959** | **6,684** | | **19,324** | **10,008** | | **824** | **414** | |
| **Age** | 77.0 (8.2) | 77.1 (7.9) | 1.56 | 77.2 (8.0) | 77.3 (8.2) | 2.22 | 77.6 (8.1) | 77.7 (8.3) | 0.87 | 76.8 (8.2) | 76.7 (8.0) | 1.21 |
| 65-79 | 6,853 (64%) | 3,206 (64%) | 0.21 | 9,420 (63%) | 4,207 (63%) | 0.05 | 11,899 (62%) | 6,164 (62%) | 0.04 | 531 (64%) | 270 (65%) | 1.79 |
| ≥80 | 3,879 (36%) | 1,823 (36%) | 0.21 | 5,539 (37%) | 2,477 (37%) | 0.05 | 7,426 (38%) | 3,844 (38%) | 0.04 | 293 (36%) | 143 (35%) | 1.79 |
| **Sex** | | | | | | | | | | | | |
| Male | 3,819 (36%) | 1,743 (35%) | 1.96 | 5,559 (37%) | 2,436 (36%) | 1.48 | 7,291 (38%) | 3,839 (38%) | 1.29 | 351 (43%) | 184 (45%) | 4.04 |
| Female | 6,914 (64%) | 3,286 (65%) | 1.96 | 9,400 (63%) | 4,248 (64%) | 1.48 | 12,034 (62%) | 6,169 (62%) | 1.29 | 474 (57%) | 229 (55%) | 4.04 |
| **VTE Diagnosis** | | | | | | | | | | | | |
| DVT only | 6,125 (57%) | 2,755 (55%) | 4.62 | 7,808 (52%) | 3,637 (54%) | 4.43 | 10,204 (53%) | 5,295 (53%) | 0.22 | 464 (56%) | 226 (55%) | 3.47 |
| PE with DVT | 1,472 (14%) | 675 (13%) | 0.82 | 2,391 (16%) | 1,015 (15%) | 2.18 | 3,176 (16%) | 1,697 (17%) | 1.39 | 106 (13%) | 60 (15%) | 5.04 |
| PE without DVT | 3,136 (29%) | 1,598 (32%) | 5.60 | 4,760 (32%) | 2,032 (30%) | 3.07 | 5,944 (31%) | 3,015 (30%) | 1.36 | 254 (31%) | 128 (31%) | 0.02 |
| **Deyo-Charlson Comorbidity Index** | 3.3 (2.7) | 3.5 (2.6) | 4.21 | 2.9 (2.5) | 2.9 (2.5) | 0.45 | 2.7 (2.4) | 2.6 (2.4) | 0.12 | 3.1 (2.6) | 3.1 (2.6) | 3.48 |
| **Baseline Comorbidity** | | | | | | | | | | | | |
| Anemia | 4,561 (42%) | 2,175 (43%) | 1.52 | 5,309 (35%) | 2,431 (36%) | 1.83 | 7,039 (36%) | 3,578 (36%) | 1.41 | 338 (41%) | 157 (38%) | 6.24 |
| Cerebrovascular disease | 2,120 (20%) | 989 (20%) | 0.24 | 2,520 (17%) | 1,109 (17%) | 0.67 | 3,222 (17%) | 1,540 (15%) | 3.50 | 145 (18%) | 87 (21%) | 8.58 |
| Coagulation defects | 979 (9%) | 458 (9%) | 0.06 | 1,342 (9%) | 568 (8%) | 1.67 | 1,856 (10%) | 996 (10%) | 1.17 | 77 (9%) | 42 (10%) | 2.80 |
| Ischemic heart/ coronary artery disease | 4,136 (39%) | 2,054 (41%) | 4.73 | 5,241 (35%) | 2,279 (34%) | 1.97 | 6,407 (33%) | 3,273 (33%) | 0.96 | 288 (35%) | 151 (36%) | 3.27 |
| Dementia | 1,269 (12%) | 776 (15%) | 10.59 | 1,506 (10%) | 904 (14%) | 10.73 | 2,056 (11%) | 1,248 (12%) | 5.71 | 103 (12%) | 67 (16%) | 10.86 |
| Hyperlipidemia | 6,676 (62%) | 3,150 (63%) | 0.89 | 9,202 (62%) | 4,046 (61%) | 2.04 | 11,753 (61%) | 6,136 (61%) | 1.02 | 499 (60%) | 231 (56%) | 9.53 |
| Obesity | 2,915 (27%) | 1,453 (29%) | 3.86 | 3,987 (27%) | 1,728 (26%) | 1.82 | 4,582 (24%) | 2,348 (23%) | 0.58 | 205 (25%) | 102 (25%) | 0.47 |
| Pneumonia | 2,112 (20%) | 990 (20%) | 0.01 | 2,625 (18%) | 1,159 (17%) | 0.54 | 3,077 (16%) | 1,646 (16%) | 1.42 | 166 (20%) | 73 (18%) | 6.70 |
| Rheumatologic disease | 725 (7%) | 366 (7%) | 2.07 | 982 (7%) | 442 (7%) | 0.22 | 1,293 (7%) | 632 (6%) | 1.50 | 45 (5%) | 25 (6%) | 2.20 |
| Sleep apnea | 1,372 (13%) | 685 (14%) | 2.48 | 2,217 (15%) | 911 (14%) | 3.42 | 2,681 (14%) | 1,409 (14%) | 0.61 | 105 (13%) | 49 (12%) | 3.25 |
| Thrombophilia | 276 (3%) | 142 (3%) | 1.57 | 428 (3%) | 167 (3%) | 2.22 | 662 (3%) | 353 (4%) | 0.57 | 31 (4%) | 7 (2%) | 11.77 |
| Varicose Veins | 470 (4%) | 208 (4%) | 1.22 | 650 (4%) | 275 (4%) | 1.18 | 916 (5%) | 498 (5%) | 1.10 | 29 (3%) | 16 (4%) | 1.60 |
| Congestive Heart Failure | 3,164 (29%) | 1,526 (30%) | 1.88 | 3,415 (23%) | 1,531 (23%) | 0.18 | 3,940 (20%) | 2,060 (21%) | 0.50 | 212 (26%) | 104 (25%) | 1.34 |
| Diabetes | 4,942 (46%) | 2,195 (44%) | 4.86 | 5,871 (39%) | 2,400 (36%) | 6.88 | 6,821 (35%) | 3,162 (32%) | 7.84 | 344 (42%) | 143 (35%) | 14.70 |
| Hypertension | 9,578 (89%) | 4,497 (89%) | 0.62 | 12,477 (83%) | 5,642 (84%) | 2.73 | 15,687 (81%) | 8,085 (81%) | 1.01 | 704 (85%) | 347 (84%) | 4.53 |
| Non-ESRD Renal Disease | 2,458 (23%) | 1,194 (24%) | 2.00 | 3,176 (21%) | 1,378 (21%) | 1.52 | 3,672 (19%) | 1,934 (19%) | 0.81 | 159 (19%) | 79 (19%) | 0.39 |
| End Stage Renal Disease | 511 (5%) | 255 (5%) | 1.44 | 415 (3%) | 153 (2%) | 3.06 | 425 (2%) | 247 (2%) | 1.76 | 25 (3%) | 20 (5%) | 9.43 |
| Chronic Liver Disease | 740 (7%) | 372 (7%) | 1.93 | 895 (6%) | 498 (7%) | 5.84 | 1,116 (6%) | 706 (7%) | 5.21 | 56 (7%) | 34 (8%) | 5.44 |

*Std Difference=100*|actual std diff|. Std Difference greater than 10 is considered significant.
DVT: Deep vein thrombosis; PE: Pulmonary embolism;

## Table 14. Baseline Characteristics Among Medicare VTE Patients that Initiated Apixaban vs Warfarin Stratified by Dual Eligibility/Part D

| | Dual Eligibility/Part D - Yes | | | Dual Eligibility/Part D - No | | |
|---|---|---|---|---|---|---|
| | Warfarin | Apixaban | STD* | Warfarin | Apixaban | STD* |
| **Sample Size** | **13,990** | **6,319** | | **31,850** | **15,816** | |
| **Age** | 77.8 (8.8) | 77.8 (8.8) | 0.02 | 77.1 (7.8) | 77.3 (7.9) | 2.53 |
| 65-79 | 8,251 (59%) | 3,765 (60%) | 1.22 | 20,452 (64%) | 10,084 (64%) | 0.95 |
| ≥80 | 5,739 (41%) | 2,554 (40%) | 1.22 | 11,398 (36%) | 5,732 (36%) | 0.95 |
| **Sex** | | | | | | |
| Male | 4,019 (29%) | 1,719 (27%) | 3.38 | 13,000 (41%) | 6,482 (41%) | 0.35 |
| Female | 9,971 (71%) | 4,600 (73%) | 3.38 | 18,850 (59%) | 9,334 (59%) | 0.35 |
| **VTE Diagnosis** | | | | | | |
| DVT only | 8,334 (60%) | 3,653 (58%) | 3.59 | 16,267 (51%) | 8,261 (52%) | 2.32 |
| PE with DVT | 1,665 (12%) | 727 (12%) | 1.22 | 5,480 (17%) | 2,721 (17%) | 0.00 |
| PE without DVT | 3,991 (29%) | 1,939 (31%) | 4.73 | 10,103 (32%) | 4,834 (31%) | 2.50 |
| **Deyo-Charlson Comorbidity Index** | 3.8 (2.7) | 3.9 (2.7) | 6.04 | 2.5 (2.3) | 2.5 (2.3) | 0.79 |
| **Baseline Comorbidity** | | | | | | |
| Anemia | 6,481 (46%) | 2,995 (47%) | 2.15 | 10,765 (34%) | 5,345 (34%) | 0.01 |
| Cerebrovascular disease | 3,186 (23%) | 1,456 (23%) | 0.64 | 4,821 (15%) | 2,269 (14%) | 2.23 |
| Coagulation defects | 1,331 (10%) | 615 (10%) | 0.71 | 2,923 (9%) | 1,450 (9%) | 0.04 |
| Ischemic heart/ coronary artery disease | 5,587 (40%) | 2,586 (41%) | 2.01 | 10,484 (33%) | 5,171 (33%) | 0.48 |
| Dementia | 2,552 (18%) | 1,462 (23%) | 12.12 | 2,383 (7%) | 1,533 (10%) | 7.91 |
| Hyperlipidemia | 8,494 (61%) | 3,835 (61%) | 0.04 | 19,636 (62%) | 9,728 (62%) | 0.30 |
| Obesity | 3,732 (27%) | 1,714 (27%) | 1.01 | 7,957 (25%) | 3,917 (25%) | 0.50 |
| Pneumonia | 3,133 (22%) | 1,459 (23%) | 1.64 | 4,846 (15%) | 2,409 (15%) | 0.04 |
| Rheumatologic disease | 883 (6%) | 460 (7%) | 3.84 | 2,161 (7%) | 1,005 (6%) | 1.73 |
| Sleep apnea | 1,582 (11%) | 702 (11%) | 0.62 | 4,794 (15%) | 2,352 (15%) | 0.51 |
| Thrombophilia | 335 (2%) | 164 (3%) | 1.25 | 1,062 (3%) | 506 (3%) | 0.74 |
| Varicose Veins | 609 (4%) | 279 (4%) | 0.32 | 1,456 (5%) | 717 (5%) | 0.18 |
| Congestive Heart Failure | 4,659 (33%) | 2,203 (35%) | 3.30 | 6,072 (19%) | 3,018 (19%) | 0.04 |
| Diabetes | 6,842 (49%) | 3,004 (48%) | 2.72 | 11,137 (35%) | 4,896 (31%) | 8.54 |
| Hypertension | 12,453 (89%) | 5,691 (90%) | 3.45 | 25,993 (82%) | 12,880 (81%) | 0.45 |
| Non-ESRD Renal Disease | 3,369 (24%) | 1,550 (25%) | 1.05 | 6,097 (19%) | 3,035 (19%) | 0.12 |
| End Stage Renal Disease | 732 (5%) | 384 (6%) | 3.65 | 643 (2%) | 291 (2%) | 1.31 |
| Chronic Liver Disease | 966 (7%) | 543 (9%) | 6.33 | 1,841 (6%) | 1,066 (7%) | 3.97 |

*Std Difference=100*|actual std diff|. Std Difference greater than 10 is considered significant.

DVT: Deep vein thrombosis; PE: Pulmonary embolism;

**Figure 4. Risk of Recurrent VTE Stratified by Demographic and SES Factors**

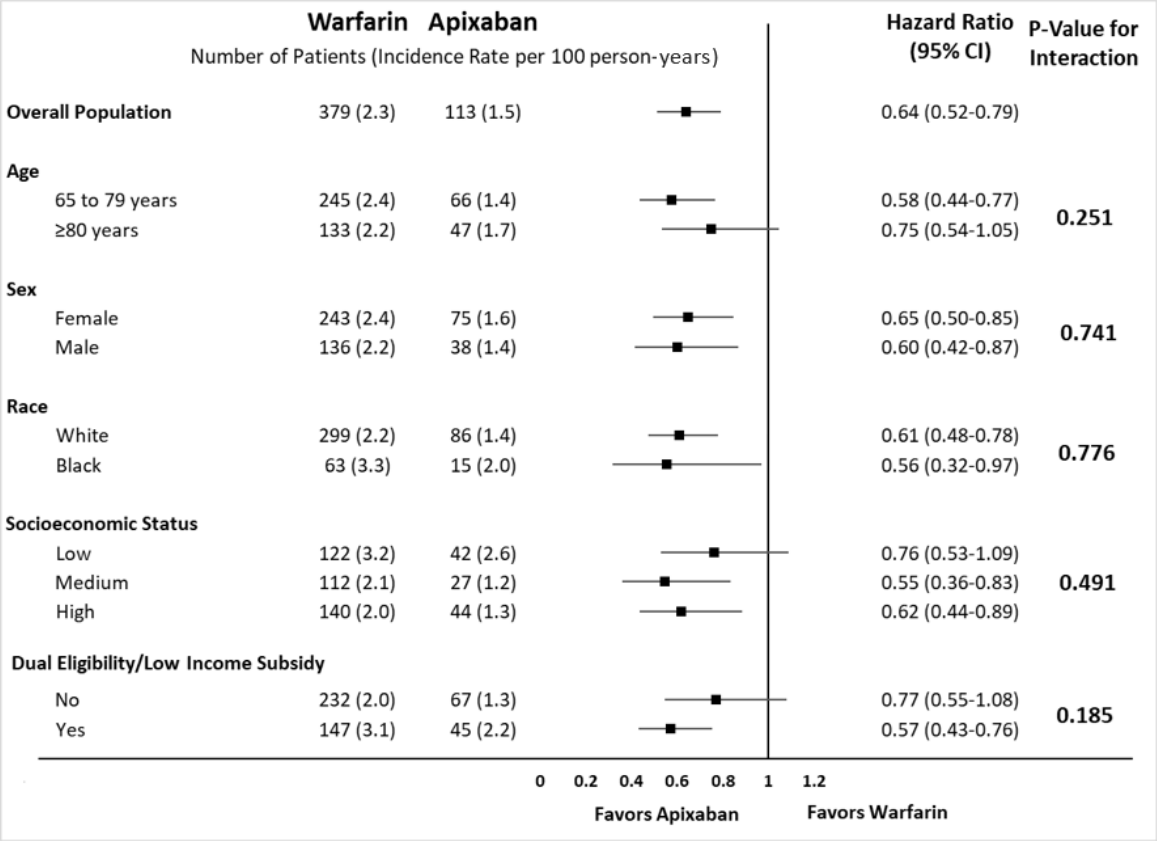


**Figure 5. Risk of Major Bleeding Among VTE Patients Stratified by Demographic and SES Factors**

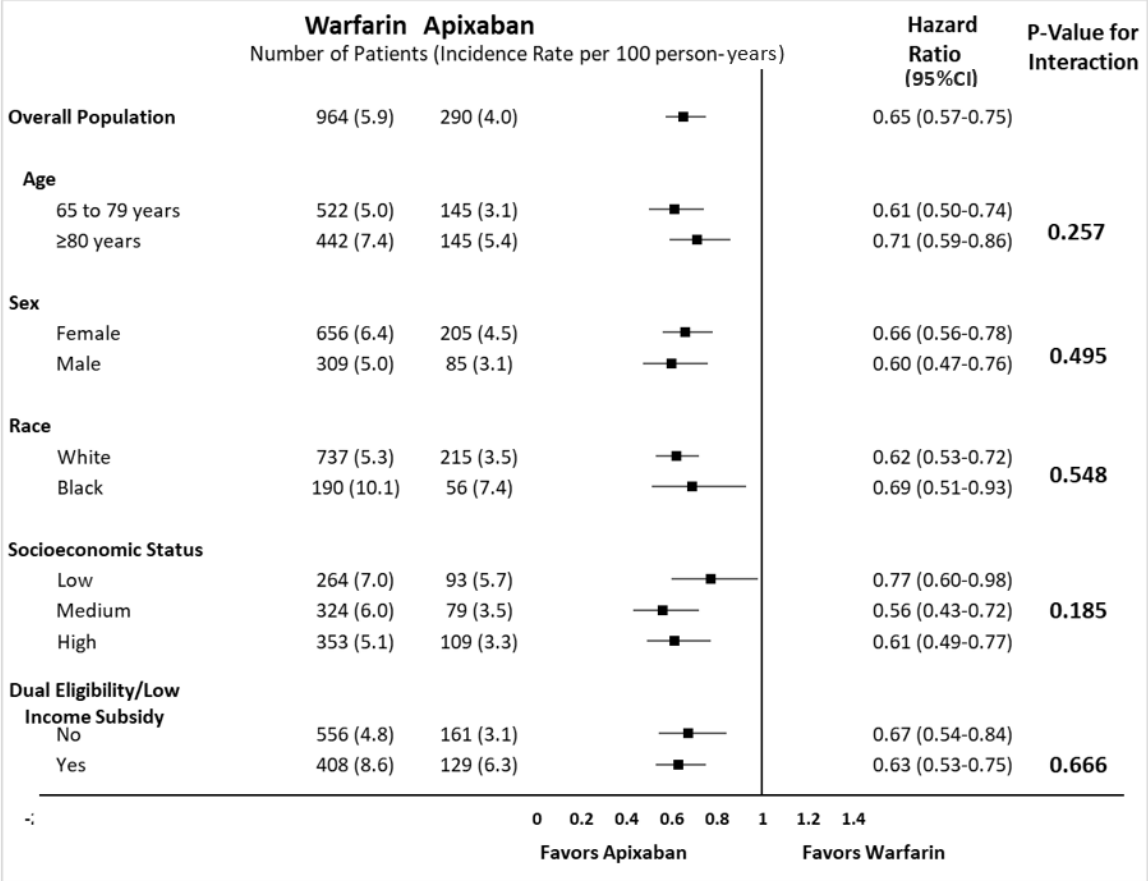
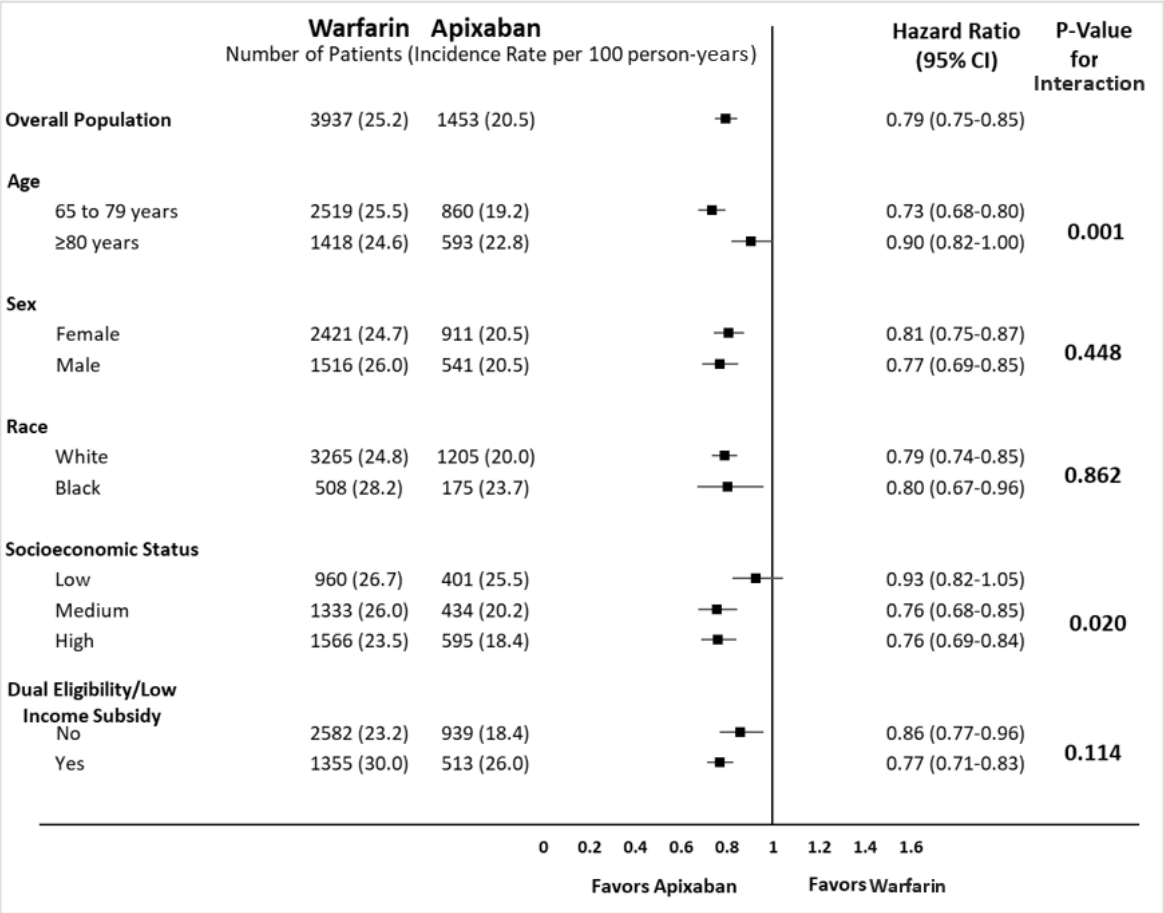


**Figure 6. Risk of CRNM Bleeding Among VTE Patients Stratified by Demographic and SES Factors**




### 9.2.2. Findings for Obesity and Morbid Obesity Subgroup Analysis

After applying the selection criteria, a total of 155,119 VTE patients including 60,786 (39.2%) who initiated apixaban and 94,333 (60.8%) who initiated warfarin were identified in the pooled database (Table 4). Of the total population, 112,024 (72.2%) were categorized as non-obese, 23,344 (15.0%) as obese/non-morbid, and 19,751 (12.7%) as morbidly obese VTE patients (Table 15). After applying IPTW but before stratification by obesity subgroups, patient characteristics were generally balanced. For both treatment cohorts, most patients were aged 65-79 years (apixaban: 62.6%; warfarin: 62.6%), followed by ≥80 years (apixaban: 37.4%; warfarin: 37.4%) with mean ages of about 67 years for both cohorts (**Table 7**). A majority of patients across the two cohorts were female (54.9% for both cohorts), and the average CCI was 2.2 (**Table 7**).

Table 15 shows the baseline characteristics of non-obese, obese/non-morbid, and morbidly obese patients receiving apixaban or warfarin before IPTW across subgroups: morbidly obese (mean age: 62 years; CCI: 2.9) and obese/non-morbid (mean age: 66 years; CCI: 2.5) patients were younger and had a higher baseline CCI compared to non-obese (mean age: 68 years; CCI: 2.0) patients. Morbidly obese and obese/non-morbid patients were more likely to be diagnosed with PE (57.2% and 48.2% vs. 40.1%) and higher proportions experienced provoked VTE events (65.7% and 61.8% vs. 53.4%) compared to non-obese patients. Morbidly obese and obese/non-morbid patients were also more likely to have comorbidities such as hypertension (82.9% and 77.7% vs. 64.5%), hyperlipidemia (55.5% and 58.7% vs. 44.6%), and diabetes (48.7% and 38.2% vs. 25.7%) compared to non-obese patients.

After applying IPTW for the apixaban and warfarin cohorts, baseline patient characteristics were balanced between the two cohorts (Table 16). Figure 7 represents the hazard ratios for the comparison of recurrent VTE, MB, and CRNM bleeding between apixaban and warfarin in the IPTW weighted population stratified by non-obese vs. obese/non-morbid vs. morbidly obese. No significant interaction was observed between treatment and obesity status for recurrent VTE (interaction p = 0.170) and MB (interaction p = 0.674). One significant interaction was observed for CRNM bleeding (interaction p = 0.023): while apixaban trended towards lower risk of CRNM bleeding compared to warfarin across non-obese, obese/non-morbid, and morbidly obese patients; the magnitude of the difference was bigger for morbidly obese patients vs. the other two subgroups.

Patients with obesity and morbid obesity were further selected. The pre- and post-IPTW baseline characteristics among VTE patients who were obese or morbidly obese are listed in Tables 17 and 18, respectively. After applying IPTW to the obese patients, baseline patient characteristics were balanced between the apixaban and warfarin cohorts; the mean age was 64 years with a mean CCI score of 2.7, approximately 64% of patients had provoked VTE events, and 23% of patients had a history of bleeding at baseline. In the post-IPTW morbidly obese population, the baseline patient characteristics were balanced between the two treatment cohorts and the mean age was 62 years with a mean CCI score of 2.9.

Table 19 shows the incidence rate of recurrent VTE, major bleeding, and CRNM bleeding among obese and morbidly obese VTE patients that initiated apixaban vs. warfarin. Among obese patients, apixaban was associated with a significantly lower risk of recurrent VTE (HR: 0.73; 95% CI: 0.64–0.84), MB (HR: 0.73; 95% CI: 0.62–0.85), and CRNM bleeding (HR: 0.82; 95% CI: 0.77–0.88) compared to warfarin (Figure 3). Similarly, among morbidly obese patients, apixaban was associated with a significantly lower risk of recurrent VTE (HR: 0.65; 95% CI: 0.53–0.80), MB (HR: 0.68; 95% CI: 0.54–0.86), and CRNM bleeding (HR: 0.76; 95% CI: 0.69–0.83) compared to warfarin (Figure 8).

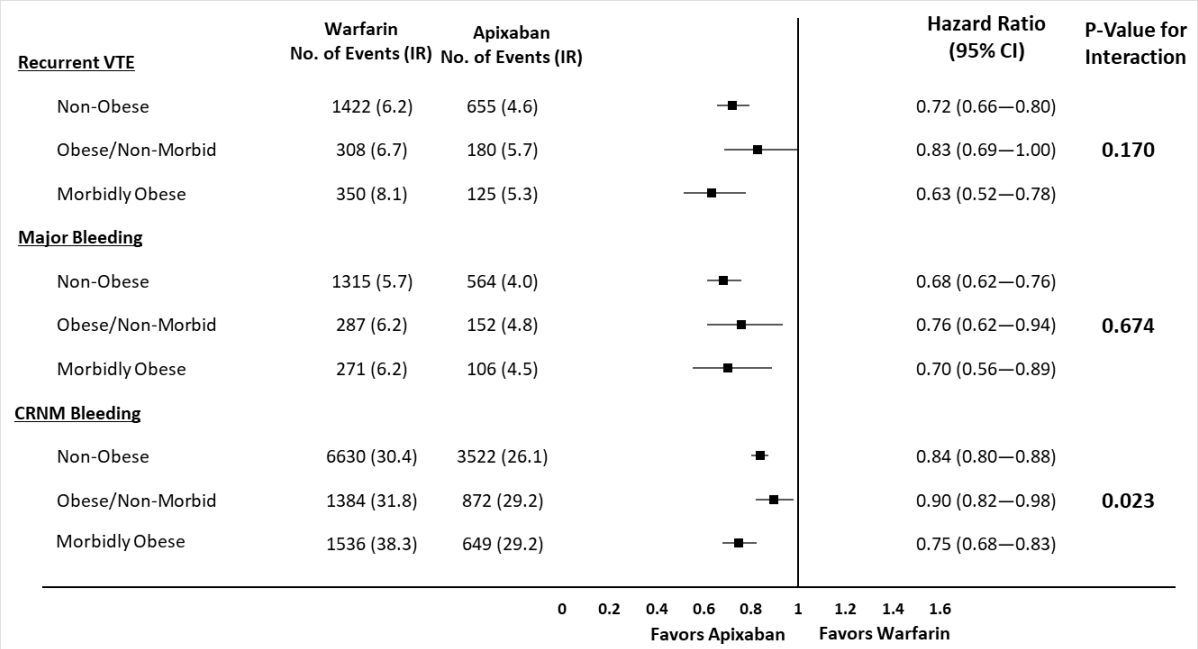
## Table 15. Baseline Characteristics Among Non-Obese, Obese/Non-Morbid and Obese/Morbid Patients

| | Non-Obese | Obese/Non-Morbid | STD* | Obese/Morbid | STD* |
|---|---|---|---|---|---|
| **Sample Size** | **112,024** | **23,344** | | **19,751** | |
| **Age, Mean (SD)** | 67.5 (16.5) | 66.2 (14.2) | 8.77 | 62.1 (14.0) | 35.31 |
| **Age Categories, n(%)** | | | | | |
| **18-54** | 23,553 (21.0%) | 4,737 (20.3%) | 1.81 | 5,510 (27.9%) | 16.04 |
| **55-64** | 17,641 (15.7%) | 3,915 (16.8%) | 2.77 | 3,937 (19.9%) | 10.95 |
| **65-74** | 29,065 (25.9%) | 7,890 (33.8%) | 17.22 | 6,870 (34.8%) | 19.31 |
| **75-79** | 13,840 (12.4%) | 3,129 (13.4%) | 3.13 | 1,948 (9.9%) | 7.94 |
| **≥80** | 27,925 (24.9%) | 3,673 (15.7%) | 22.99 | 1,486 (7.5%) | 48.58 |
| **Gender, n(%)** | | | | | |
| **Male** | 52,410 (46.8%) | 10,482 (44.9%) | 3.78 | 7,219 (36.6%) | 20.87 |
| **Female** | 59,614 (53.2%) | 12,862 (55.1%) | 3.78 | 12,532 (63.4%) | 20.87 |
| **Index VTE Setting, n(%)** | | | | | |
| **Inpatient** | 56,065 (50.0%) | 14,103 (60.4%) | 20.96 | 13,654 (69.1%) | 39.64 |
| **Outpatient** | 55,959 (50.0%) | 9,241 (39.6%) | 20.96 | 6,097 (30.9%) | 39.64 |
| **Index VTE Event Type, n(%)** | | | | | |
| **DVT only** | 67,055 (59.9%) | 12,103 (51.8%) | 16.19 | 8,458 (42.8%) | 34.59 |
| **PE with or without DVT** | 44,969 (40.1%) | 11,241 (48.2%) | 16.19 | 11,293 (57.2%) | 34.59 |
| **Index VTE Etiology, n(%)** | | | | | |
| **Provoked** | 59,790 (53.4%) | 14,437 (61.8%) | 17.21 | 12,978 (65.7%) | 25.33 |
| **Unprovoked** | 52,234 (46.6%) | 8,907 (38.2%) | 17.21 | 6,773 (34.3%) | 25.33 |
| **Deyo-Charlson Comorbidity Index, Mean (SD)** | 2.0 (2.3) | 2.5 (2.5) | 21.89 | 2.9 (2.6) | 36.28 |
| **Baseline Comorbidity, n(%)** | | | | | |
| **Anemia** | 31,341 (28.0%) | 7,616 (32.6%) | 10.13 | 6,506 (32.9%) | 10.80 |
| **Central venous Catheter** | 7,925 (7.1%) | 2,144 (9.2%) | 7.73 | 2,493 (12.6%) | 18.70 |
| **Coagulation defects** | 8,612 (7.7%) | 2,099 (9.0%) | 4.72 | 1,710 (8.7%) | 3.54 |
| **Ischemic heart/ coronary artery disease** | 26,614 (23.8%) | 6,931 (29.7%) | 13.44 | 5,705 (28.9%) | 11.66 |
| **Dementia** | 8,584 (7.7%) | 965 (4.1%) | 15.02 | 534 (2.7%) | 22.51 |
| **Dyspepsia or stomach discomfort** | 24,365 (21.7%) | 6,049 (25.9%) | 9.78 | 4,932 (25.0%) | 7.62 |
| **Hyperlipidemia** | 49,908 (44.6%) | 13,695 (58.7%) | 28.53 | 10,955 (55.5%) | 21.96 |
| **Sleep apnea** | 8,597 (7.7%) | 4,717 (20.2%) | 36.79 | 7,476 (37.9%) | 77.14 |
| **Thrombophilia** | 4,214 (3.8%) | 1,028 (4.4%) | 3.24 | 848 (4.3%) | 2.70 |
| **Varicose Veins** | 4,357 (3.9%) | 1,082 (4.6%) | 3.69 | 1,132 (5.7%) | 8.62 |
| **Congestive Heart Failure** | 16,465 (14.7%) | 4,384 (18.8%) | 10.95 | 5,055 (25.6%) | 27.42 |
| **Diabetes** | 28,796 (25.7%) | 8,921 (38.2%) | 27.07 | 9,614 (48.7%) | 48.93 |
| **Hypertension** | 72,297 (64.5%) | 18,148 (77.7%) | 29.46 | 16,364 (82.9%) | 42.53 |
| **Non-ESRD Renal Disease** | 14,803 (13.2%) | 4,199 (18.0%) | 13.18 | 3,846 (19.5%) | 16.99 |
| **End Stage Renal Disease** | 2,442 (2.2%) | 587 (2.5%) | 2.21 | 541 (2.7%) | 3.61 |
| **Chronic Liver Disease** | 6,917 (6.2%) | 2,117 (9.1%) | 10.92 | 1,981 (10.0%) | 14.16 |
| **Chronic obstructive pulmonary disease** | 19,315 (17.2%) | 4,560 (19.5%) | 5.92 | 4,577 (23.2%) | 14.81 |
| **Baseline bleed** | 22,089 (19.7%) | 5,418 (23.2%) | 8.51 | 4,421 (22.4%) | 6.54 |

DVT: deep vein thrombosis; ESRD: End Stage Renal Disease; NSAIDs: Nonsteroidal anti-inflammatory drug; SERMS: Selective

*STD=100*|actual STD|. STD >10.00 is

**Figure 7. Risk of Recurrent VTE, MB, and CRNM Bleeding Among VTE Patients Stratified by Obesity Status**



## Table 16. Post-IPTW Characteristics Among Overall VTE Patients who Initiated Apixaban and Warfarin

| | Post-IPTW | | |
|---|---|---|---|
| | Warfarin Cohort (Reference) | Apixaban Cohort | STD[a] |
| **Sample Size** | **94,333** | **60,786** | |
| **Age, Mean (SD)** | 66.7 (15.9) | 66.8 (16.0) | 0.80 |
| **Age Categories,[b] n(%)** | | | |
| **18-54** | 20,449 (21.7%) | 13,098 (21.5%) | 0.31 |
| **55-64** | 15,430 (16.4%) | 9,908 (16.3%) | 0.15 |
| **65-74** | 26,709 (28.3%) | 17,219 (28.3%) | 0.03 |
| **75-79** | 11,545 (12.2%) | 7,471 (12.3%) | 0.16 |
| **≥80** | 20,200 (21.4%) | 13,089 (21.5%) | 0.29 |
| **Gender, n(%)** | | | |
| **Male** | 42,590 (45.1%) | 27,410 (45.1%) | 0.11 |
| **Female** | 51,743 (54.9%) | 33,376 (54.9%) | 0.11 |
| **Geographic Region,[c] n(%)** | | | |
| **Northeast** | 14,825 (15.7%) | 9,494 (15.6%) | 0.27 |
| **North Central** | 26,271 (27.8%) | 16,873 (27.8%) | 0.20 |
| **South** | 35,815 (38.0%) | 23,008 (37.9%) | 0.24 |
| **West** | 17,257 (18.3%) | 11,301 (18.6%) | 0.77 |
| **Other** | 165 (0.2%) | 110 (0.2%) | 0.16 |
| **Index VTE Setting, n(%)** | | | |
| **Inpatient** | 51,097 (54.2%) | 33,030 (54.3%) | 0.35 |
| **Outpatient** | 43,236 (45.8%) | 27,756 (45.7%) | 0.35 |
| **Index VTE Event Type, n(%)** | | | |
| **DVT only** | 53,279 (56.5%) | 34,367 (56.5%) | 0.12 |
| **PE with or without DVT** | 41,054 (43.5%) | 26,419 (43.5%) | 0.12 |
| **Index VTE Etiology, n(%)** | | | |
| **Provoked** | 53,076 (56.3%) | 34,264 (56.4%) | 0.21 |
| **Unprovoked** | 41,257 (43.7%) | 26,522 (43.6%) | 0.21 |
| **Deyo-Charlson Comorbidity Index, Mean (SD)** | 2.2 (2.4) | 2.2 (2.4) | 0.71 |
| **Baseline Comorbidity, n(%)** | | | |
| **Alcohol abuse** | 2,987 (3.2%) | 1,937 (3.2%) | 0.12 |
| **Anemia** | 27,751 (29.4%) | 17,985 (29.6%) | 0.37 |
| **Central venous Catheter** | 7,672 (8.1%) | 4,977 (8.2%) | 0.20 |
| **Coagulation defects** | 7,611 (8.1%) | 5,000 (8.2%) | 0.58 |
| **Ischemic heart/ coronary artery disease** | 23,951 (25.4%) | 15,491 (25.5%) | 0.22 |
| **Dyspepsia or stomach discomfort** | 21,551 (22.8%) | 13,960 (23.0%) | 0.28 |
| **Hyperlipidemia** | 45,444 (48.2%) | 29,333 (48.3%) | 0.16 |
| **Obesity** | 26,218 (27.8%) | 16,896 (27.8%) | 0.01 |
| **Pneumonia** | 13,641 (14.5%) | 8,819 (14.5%) | 0.13 |
| **Rheumatologic disease** | 4,430 (4.7%) | 2,854 (4.7%) | 0.01 |
| **Sleep apnea** | 12,634 (13.4%) | 8,118 (13.4%) | 0.11 |
| **Spinal cord injury** | 253 (0.3%) | 168 (0.3%) | 0.15 |
| **Thrombophilia** | 3,718 (3.9%) | 2,420 (4.0%) | 0.21 |
| **Varicose Veins** | 3,988 (4.2%) | 2,560 (4.2%) | 0.08 |
| **Hypertension** | 65,067 (69.0%) | 42,014 (69.1%) | 0.31 |
| **Non-ESRD Renal Disease** | 12,837 (13.6%) | 8,297 (13.6%) | 0.12 |
| **End Stage Renal Disease** | 2,179 (2.3%) | 1,434 (2.4%) | 0.33 |
| **Inflammatory Bowel Disease** | 1,769 (1.9%) | 1,132 (1.9%) | 0.10 |
| **Baseline bleed** | 19,481 (20.7%) | 12,611 (20.7%) | 0.24 |
| **Recent History of Falls, n(%)** | 6,853 (7.3%) | 4,426 (7.3%) | 0.06 |
| **Fracture/trauma involving Lower Extremities, n(%)** | 14,515 (15.4%) | 9,346 (15.4%) | 0.03 |
| **Selected Surgeries, n(%)** | 23,353 (24.8%) | 15,109 (24.9%) | 0.23 |
| **Baseline Medication Use, n(%)** | | | |
| **Antiarrhythmic** | 9,044 (9.6%) | 5,841 (9.6%) | 0.07 |
| **Statins** | 36,293 (38.5%) | 23,437 (38.6%) | 0.17 |
| **Anti-platelets** | 7,140 (7.6%) | 4,613 (7.6%) | 0.08 |
| **Aromatase Inhibitors** | 207 (0.2%) | 131 (0.2%) | 0.06 |
| **Beta Blockers** | 32,108 (34.0%) | 20,784 (34.2%) | 0.33 |
| **Gastroprotective Agents** | 26,741 (28.3%) | 17,274 (28.4%) | 0.16 |
| **SERMS** | 567 (0.6%) | 364 (0.6%) | 0.04 |
| **NSAIDs** | 24,770 (26.3%) | 15,951 (26.2%) | 0.04 |
| **Hormone Therapy (estrogen)** | 5,207 (5.5%) | 3,344 (5.5%) | 0.08 |

DVT: Deep vein thrombosis; ESRD: End Stage Renal Disease; IPTW: Inverse probability treatment weighting;NSAIDs: Nonsteroidal anti-inflammatory drug; SERMS: Selective estrogen receptor modulator; PE: Pulmonary embolism; SD: Standard deviation; STD: Standardized differences; VTE: Venous thromboembolism

[a] Std Difference=100*|actual std diff|. Std Difference greater than 10 is considered significant.

[b] After applying weights, the values for age category were not whole numbers; therefore, due to r

[c] After applying weights, the values for region category were not whole numbers; therefore, due t

# Table 17. Pre- and Post-IPTW Characteristics Among VTE Patients with Obesity who Initiated Apixaban and Warfarin

| | Pre-IPTW | | | Post-IPTW | | |
|---|---|---|---|---|---|---|
| | Warfarin Cohort (Reference) | Apixaban Cohort | STD[a] | Warfarin Cohort (Reference) | Apixaban Cohort | STD[a] |
| **Sample Size** | **25,602** | **17,493** | | **25,602** | **17,493** | |
| **Age, Mean (SD)** | 64.9 (14.1) | 63.5 (14.5) | 9.61 | 64.3 (14.3) | 64.5 (14.2) | 1.41 |
| **Age Categories,[b] n(%)** | | | | | | |
| **18-54** | 5,702 (22.3%) | 4,545 (26.0%) | 8.68 | 6,074 (23.7%) | 4,130 (23.6%) | 0.27 |
| **55-64** | 4,276 (16.7%) | 3,576 (20.4%) | 9.63 | 4,635 (18.1%) | 3,155 (18.0%) | 0.18 |
| **65-74** | 9,358 (36.6%) | 5,402 (30.9%) | 12.02 | 8,781 (34.3%) | 6,008 (34.3%) | 0.10 |
| **75-79** | 3,120 (12.2%) | 1,957 (11.2%) | 3.11 | 3,034 (11.9%) | 2,089 (11.9%) | 0.27 |
| **≥80** | 3,146 (12.3%) | 2,013 (11.5%) | 2.41 | 3,078 (12.0%) | 2,112 (12.1%) | 0.15 |
| **Gender, n(%)** | | | | | | |
| **Male** | 10,120 (39.5%) | 7,581 (43.3%) | 7.74 | 10,504 (41.0%) | 7,167 (41.0%) | 0.12 |
| **Female** | 15,482 (60.5%) | 9,912 (56.7%) | 7.74 | 15,098 (59.0%) | 10,326 (59.0%) | 0.12 |
| **Geographic Region,[c] n(%)** | | | | | | |
| **Northeast** | 4,059 (15.9%) | 2,463 (14.1%) | 4.97 | 3,869 (15.1%) | 2,626 (15.0%) | 0.28 |
| **North Central** | 8,088 (31.6%) | 3,845 (22.0%) | 21.83 | 7,094 (27.7%) | 4,831 (27.6%) | 0.20 |
| **South** | 8,829 (34.5%) | 9,162 (52.4%) | 36.69 | 10,667 (41.7%) | 7,275 (41.6%) | 0.15 |
| **West** | 4,584 (17.9%) | 2,011 (11.5%) | 18.17 | 3,940 (15.4%) | 2,737 (15.6%) | 0.71 |
| **Other** | 42 (0.2%) | 12 (0.1%) | 2.80 | 32 (0.1%) | 23 (0.1%) | 0.19 |
| **Index VTE Setting, n(%)** | | | | | | |
| **Inpatient** | 17,155 (67.0%) | 10,602 (60.6%) | 13.35 | 16,530 (64.6%) | 11,321 (64.7%) | 0.32 |
| **Outpatient** | 8,447 (33.0%) | 6,891 (39.4%) | 13.35 | 9,072 (35.4%) | 6,172 (35.3%) | 0.32 |
| **Index VTE Event Type, n(%)** | | | | | | |
| **DVT only** | 12,183 (47.6%) | 8,378 (47.9%) | 0.62 | 12,214 (47.7%) | 8,359 (47.8%) | 0.16 |
| **PE with or without DVT** | 13,419 (52.4%) | 9,115 (52.1%) | 0.62 | 13,388 (52.3%) | 9,134 (52.2%) | 0.16 |
| **Index VTE Etiology, n(%)** | | | | | | |
| **Provoked** | 17,000 (66.4%) | 10,415 (59.5%) | 14.25 | 16,298 (63.7%) | 11,146 (63.7%) | 0.13 |
| **Unprovoked** | 8,602 (33.6%) | 7,078 (40.5%) | 14.25 | 9,304 (36.3%) | 6,347 (36.3%) | 0.13 |
| **Deyo-Charlson Comorbidity Index, Mean (SD)** | 2.8 (2.6) | 2.5 (2.5) | 10.11 | 2.7 (2.6) | 2.7 (2.6) | 0.53 |
| **Baseline Comorbidity, n(%)** | | | | | | |
| **Alcohol abuse** | 684 (2.7%) | 456 (2.6%) | 0.40 | 684 (2.7%) | 475 (2.7%) | 0.26 |
| **Anemia** | 8,958 (35.0%) | 5,164 (29.5%) | 11.72 | 8,405 (32.8%) | 5,765 (33.0%) | 0.27 |
| **Central venous Catheter** | 3,033 (11.8%) | 1,604 (9.2%) | 8.74 | 2,772 (10.8%) | 1,909 (10.9%) | 0.28 |
| **Coagulation defects** | 2,521 (9.8%) | 1,288 (7.4%) | 8.87 | 2,270 (8.9%) | 1,564 (8.9%) | 0.25 |
| **Ischemic heart/ coronary artery disease** | 7,599 (29.7%) | 5,037 (28.8%) | 1.95 | 7,551 (29.5%) | 5,189 (29.7%) | 0.37 |
| **Dyspepsia or stomach discomfort** | 6,608 (25.8%) | 4,373 (25.0%) | 1.87 | 6,549 (25.6%) | 4,508 (25.8%) | 0.43 |
| **Hyperlipidemia** | 14,732 (57.5%) | 9,918 (56.7%) | 1.71 | 14,683 (57.3%) | 10,048 (57.4%) | 0.19 |
| **Pneumonia** | 3,955 (15.4%) | 2,639 (15.1%) | 1.01 | 3,930 (15.4%) | 2,681 (15.3%) | 0.07 |
| **Rheumatologic disease** | 1,332 (5.2%) | 845 (4.8%) | 1.71 | 1,297 (5.1%) | 891 (5.1%) | 0.14 |
| **Sleep apnea** | 7,448 (29.1%) | 4,745 (27.1%) | 4.38 | 7,239 (28.3%) | 4,932 (28.2%) | 0.18 |
| **Spinal cord injury** | 67 (0.3%) | 47 (0.3%) | 0.14 | 67 (0.3%) | 44 (0.3%) | 0.21 |
| **Thrombophilia** | 1,180 (4.6%) | 696 (4.0%) | 3.11 | 1,125 (4.4%) | 784 (4.5%) | 0.42 |
| **Varicose Veins** | 1,267 (4.9%) | 947 (5.4%) | 2.10 | 1,310 (5.1%) | 896 (5.1%) | 0.03 |
| **Hypertension** | 20,774 (81.1%) | 13,738 (78.5%) | 6.50 | 20,529 (80.2%) | 14,042 (80.3%) | 0.22 |
| **Non-ESRD Renal Disease** | 4,965 (19.4%) | 3,080 (17.6%) | 4.60 | 4,810 (18.8%) | 3,309 (18.9%) | 0.33 |
| **End Stage Renal Disease** | 835 (3.3%) | 293 (1.7%) | 10.24 | 673 (2.6%) | 469 (2.7%) | 0.33 |
| **Inflammatory Bowel Disease** | 447 (1.7%) | 280 (1.6%) | 1.13 | 433 (1.7%) | 291 (1.7%) | 0.21 |
| **Baseline bleed** | 6,395 (25.0%) | 3,444 (19.7%) | 12.73 | 5,858 (22.9%) | 4,012 (22.9%) | 0.13 |
| **Recent History of Falls, n(%)** | 1,670 (6.5%) | 1,077 (6.2%) | 1.50 | 1,645 (6.4%) | 1,127 (6.4%) | 0.09 |
| **Fracture/trauma involving Lower Extremities, n(%** | 3,798 (14.8%) | 2,682 (15.3%) | 1.39 | 3,844 (15.0%) | 2,619 (15.0%) | 0.12 |
| **Selected Surgeries, n(%)** | 8,225 (32.1%) | 5,193 (29.7%) | 5.28 | 8,015 (31.3%) | 5,491 (31.4%) | 0.18 |
| **Baseline Medication Use, n(%)** | | | | | | |
| **Antiarrhythmic** | 2,955 (11.5%) | 1,905 (10.9%) | 2.07 | 2,881 (11.3%) | 1,964 (11.2%) | 0.09 |
| **Statins** | 11,332 (44.3%) | 7,562 (43.2%) | 2.08 | 11,268 (44.0%) | 7,728 (44.2%) | 0.33 |
| **Anti-platelets** | 2,084 (8.1%) | 1,452 (8.3%) | 0.58 | 2,110 (8.2%) | 1,441 (8.2%) | 0.02 |
| **Aromatase Inhibitors** | 51 (0.2%) | 36 (0.2%) | 0.15 | 52 (0.2%) | 34 (0.2%) | 0.19 |
| **Beta Blockers** | 10,283 (40.2%) | 6,555 (37.5%) | 5.53 | 10,026 (39.2%) | 6,874 (39.3%) | 0.27 |
| **Gastroprotective Agents** | 8,402 (32.8%) | 5,514 (31.5%) | 2.78 | 8,278 (32.3%) | 5,666 (32.4%) | 0.12 |
| **SERMS** | 99 (0.4%) | 83 (0.5%) | 1.34 | 110 (0.4%) | 75 (0.4%) | 0.02 |
| **NSAIDs** | 8,035 (31.4%) | 5,990 (34.2%) | 6.09 | 8,311 (32.5%) | 5,671 (32.4%) | 0.09 |
| **Hormone Therapy (estrogen)** | 1,225 (4.8%) | 1,045 (6.0%) | 5.27 | 1,331 (5.2%) | 903 (5.2%) | 0.15 |

DVT: Deep vein thrombosis; ESRD: End Stage Renal Disease; IPTW: Inverse probability treatment weighting; NSAIDs: Nonsteroidal anti-inflammatory drug; SERMS: Selective estrogen receptor modulator; PE: Pulmonary embolism; SD: Standard deviation; STD: Standardized differences; VTE: Venous thromboembolism

[a] Std Difference=100*|actual std diff|. Std Difference greater than 10 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

[c] After applying weights, the values for region category were not whole numbers; therefore, due to rounding the sum of patients does n

## Table 18. Pre- and Post-IPTW Characteristics Among VTE Patients with Morbid Obesity who Initiated Apixaban and Warfarin

| | Pre-IPTW | | | Post-IPTW | | |
|---|---|---|---|---|---|---|
| | Warfarin Cohort (Reference) | Apixaban Cohort | STD[a] | Warfarin Cohort (Reference) | Apixaban Cohort | STD[a] |
| **Sample Size** | **12,340** | **7,411** | | **12,340** | **7,411** | |
| **Age, Mean (SD)** | 62.4 (13.9) | 61.7 (14.0) | 4.60 | 62.1 (14.0) | 62.3 (13.9) | 1.81 |
| **Age Categories,[b] n(%)** | | | | | | |
| **18-54** | 3,356 (27.2%) | 2,154 (29.1%) | 4.16 | 3,438 (27.9%) | 2,051 (27.7%) | 0.41 |
| **55-64** | 2,325 (18.8%) | 1,612 (21.8%) | 7.24 | 2,453 (19.9%) | 1,467 (19.8%) | 0.22 |
| **65-74** | 4,481 (36.3%) | 2,389 (32.2%) | 8.60 | 4,297 (34.8%) | 2,590 (35.0%) | 0.28 |
| **75-79** | 1,250 (10.1%) | 698 (9.4%) | 2.40 | 1,221 (9.9%) | 738 (10.0%) | 0.21 |
| **≥80** | 928 (7.5%) | 558 (7.5%) | 0.03 | 932 (7.6%) | 565 (7.6%) | 0.28 |
| **Gender, n(%)** | | | | | | |
| **Male** | 4,408 (35.7%) | 2,811 (37.9%) | 4.58 | 4,511 (36.6%) | 2,702 (36.5%) | 0.19 |
| **Female** | 7,932 (64.3%) | 4,600 (62.1%) | 4.58 | 7,829 (63.4%) | 4,709 (63.5%) | 0.19 |
| **Geographic Region,[c] n(%)** | | | | | | |
| **Northeast** | 1,835 (14.9%) | 988 (13.3%) | 4.42 | 1,761 (14.3%) | 1,050 (14.2%) | 0.28 |
| **North Central** | 4,050 (32.8%) | 1,661 (22.4%) | 23.44 | 3,568 (28.9%) | 2,139 (28.9%) | 0.13 |
| **South** | 4,226 (34.2%) | 3,931 (53.0%) | 38.60 | 5,095 (41.3%) | 3,058 (41.3%) | 0.06 |
| **West** | 2,210 (17.9%) | 823 (11.1%) | 19.41 | 1,899 (15.4%) | 1,154 (15.6%) | 0.51 |
| **Other** | 19 (0.2%) | 8 (0.1%) | 1.27 | 17 (0.1%) | 10 (0.1%) | 0.05 |
| **Index VTE Setting, n(%)** | | | | | | |
| **Inpatient** | 8,691 (70.4%) | 4,963 (67.0%) | 7.47 | 8,544 (69.2%) | 5,146 (69.4%) | 0.44 |
| **Outpatient** | 3,649 (29.6%) | 2,448 (33.0%) | 7.47 | 3,796 (30.8%) | 2,265 (30.6%) | 0.44 |
| **Index VTE Event Type, n(%)** | | | | | | |
| **DVT only** | 5,242 (42.5%) | 3,216 (43.4%) | 1.85 | 5,294 (42.9%) | 3,183 (43.0%) | 0.10 |
| **PE with or without DVT** | 7,098 (57.5%) | 4,195 (56.6%) | 1.85 | 7,046 (57.1%) | 4,228 (57.0%) | 0.10 |
| **Index VTE Etiology, n(%)** | | | | | | |
| **Provoked** | 8,305 (67.3%) | 4,673 (63.1%) | 8.92 | 8,108 (65.7%) | 4,875 (65.8%) | 0.14 |
| **Unprovoked** | 4,035 (32.7%) | 2,738 (36.9%) | 8.92 | 4,232 (34.3%) | 2,536 (34.2%) | 0.14 |
| **Deyo-Charlson Comorbidity Index, Mean (SD)** | 2.9 (2.6) | 2.8 (2.6) | 3.73 | 2.9 (2.6) | 2.9 (2.6) | 0.45 |
| **Baseline Comorbidity, n(%)** | | | | | | |
| **Alcohol abuse** | 269 (2.2%) | 161 (2.2%) | 0.05 | 272 (2.2%) | 169 (2.3%) | 0.49 |
| **Anemia** | 4,253 (34.5%) | 2,253 (30.4%) | 8.69 | 4,062 (32.9%) | 2,440 (32.9%) | 0.03 |
| **Central venous Catheter** | 1,677 (13.6%) | 816 (11.0%) | 7.86 | 1,561 (12.7%) | 939 (12.7%) | 0.03 |
| **Coagulation defects** | 1,165 (9.4%) | 545 (7.4%) | 7.53 | 1,068 (8.7%) | 643 (8.7%) | 0.06 |
| **Ischemic heart/ coronary artery disease** | 3,557 (28.8%) | 2,148 (29.0%) | 0.35 | 3,576 (29.0%) | 2,157 (29.1%) | 0.26 |
| **Dyspepsia or stomach discomfort** | 3,086 (25.0%) | 1,846 (24.9%) | 0.23 | 3,090 (25.0%) | 1,869 (25.2%) | 0.40 |
| **Hyperlipidemia** | 6,773 (54.9%) | 4,182 (56.4%) | 3.11 | 6,854 (55.5%) | 4,122 (55.6%) | 0.15 |
| **Pneumonia** | 2,011 (16.3%) | 1,257 (17.0%) | 1.79 | 2,043 (16.6%) | 1,225 (16.5%) | 0.10 |
| **Rheumatologic disease** | 604 (4.9%) | 364 (4.9%) | 0.08 | 606 (4.9%) | 366 (4.9%) | 0.11 |
| **Sleep apnea** | 4,715 (38.2%) | 2,761 (37.3%) | 1.97 | 4,674 (37.9%) | 2,804 (37.8%) | 0.09 |
| **Spinal cord injury** | 27 (0.2%) | 21 (0.3%) | 1.29 | 30 (0.2%) | 18 (0.2%) | 0.14 |
| **Thrombophilia** | 554 (4.5%) | 294 (4.0%) | 2.60 | 532 (4.3%) | 326 (4.4%) | 0.41 |
| **Varicose Veins** | 675 (5.5%) | 457 (6.2%) | 2.98 | 707 (5.7%) | 427 (5.8%) | 0.11 |
| **Hypertension** | 10,233 (82.9%) | 6,131 (82.7%) | 0.52 | 10,235 (82.9%) | 6,155 (83.1%) | 0.31 |
| **Non-ESRD Renal Disease** | 2,431 (19.7%) | 1,415 (19.1%) | 1.53 | 2,416 (19.6%) | 1,463 (19.7%) | 0.41 |
| **End Stage Renal Disease** | 409 (3.3%) | 132 (1.8%) | 9.74 | 339 (2.7%) | 207 (2.8%) | 0.26 |
| **Inflammatory Bowel Disease** | 176 (1.4%) | 101 (1.4%) | 0.54 | 173 (1.4%) | 102 (1.4%) | 0.21 |
| **Baseline bleed** | 2,961 (24.0%) | 1,460 (19.7%) | 10.41 | 2,767 (22.4%) | 1,665 (22.5%) | 0.10 |
| **Recent History of Falls, n(%)** | 741 (6.0%) | 436 (5.9%) | 0.51 | 737 (6.0%) | 443 (6.0%) | 0.05 |
| **Fracture/trauma involving Lower Extremities, n(%** | 1,800 (14.6%) | 1,126 (15.2%) | 1.70 | 1,824 (14.8%) | 1,092 (14.7%) | 0.13 |
| **Selected Surgeries, n(%)** | 3,912 (31.7%) | 2,292 (30.9%) | 1.67 | 3,888 (31.5%) | 2,332 (31.5%) | 0.08 |
| **Baseline Medication Use, n(%)** | | | | | | |
| **Antiarrhythmic** | 1,453 (11.8%) | 862 (11.6%) | 0.45 | 1,446 (11.7%) | 868 (11.7%) | 0.04 |
| **Statins** | 5,277 (42.8%) | 3,188 (43.0%) | 0.51 | 5,306 (43.0%) | 3,205 (43.2%) | 0.50 |
| **Anti-platelets** | 895 (7.3%) | 568 (7.7%) | 1.57 | 917 (7.4%) | 548 (7.4%) | 0.15 |
| **Aromatase Inhibitors** | 25 (0.2%) | 17 (0.2%) | 0.58 | 27 (0.2%) | 16 (0.2%) | 0.12 |
| **Beta Blockers** | 5,001 (40.5%) | 2,985 (40.3%) | 0.51 | 4,993 (40.5%) | 3,006 (40.6%) | 0.22 |
| **Gastroprotective Agents** | 4,022 (32.6%) | 2,388 (32.2%) | 0.79 | 4,009 (32.5%) | 2,408 (32.5%) | 0.02 |
| **SERMS** | 37 (0.3%) | 27 (0.4%) | 1.12 | 41 (0.3%) | 25 (0.3%) | 0.18 |
| **NSAIDs** | 3,983 (32.3%) | 2,682 (36.2%) | 8.25 | 4,156 (33.7%) | 2,490 (33.6%) | 0.16 |
| **Hormone Therapy (estrogen)** | 610 (4.9%) | 446 (6.0%) | 4.72 | 651 (5.3%) | 385 (5.2%) | 0.36 |

DVT: Deep vein thrombosis; ESRD: End Stage Renal Disease; IPTW: Inverse probability treatment weighting; NSAIDs: Nonsteroidal anti-inflammatory drug; SERMS: Selective estrogen receptor modulator; PE: Pulmonary embolism; SD: Standard deviation; STD: Standardized differences; VTE: Venous thromboembolism

[a] Std Difference=100*|actual std diff|. Std Difference greater than 10 is considered significant.

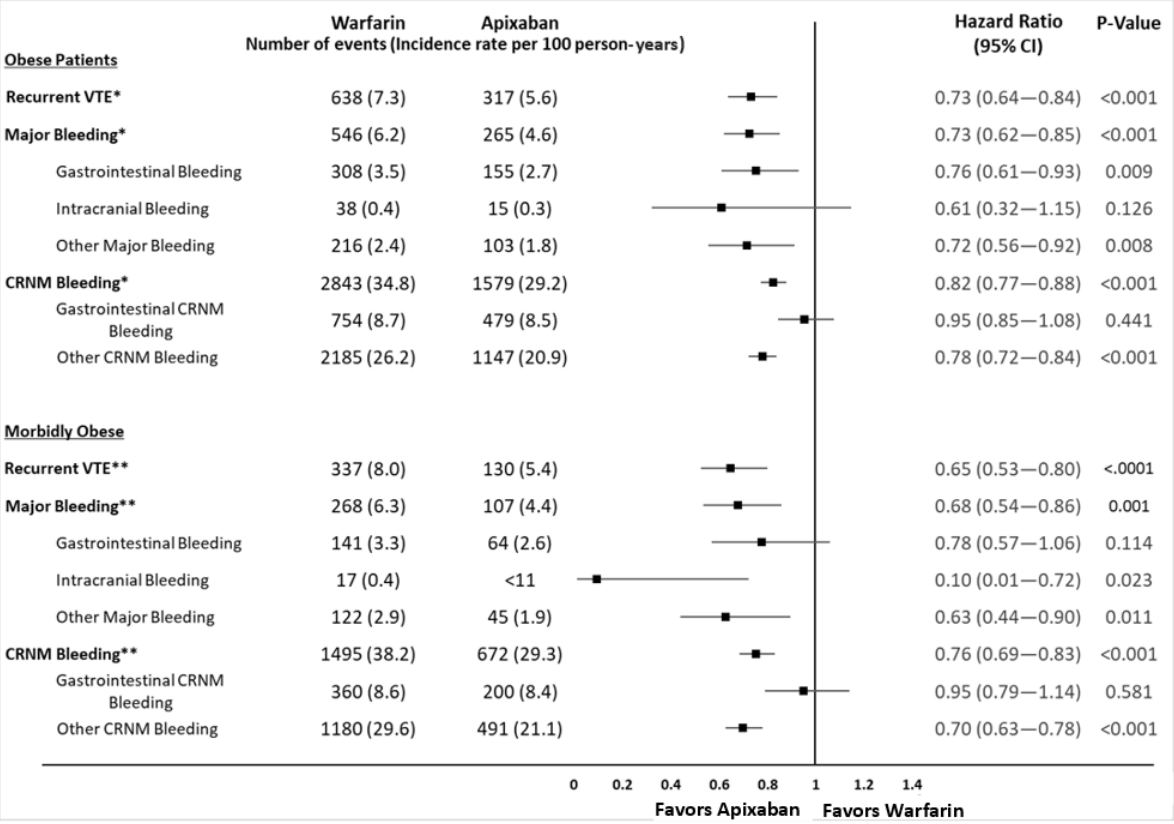
[b] After applying weights, the values for age category were not whole numbers; there

[c] After applying weights, the values for region category were not whole numbers; the

**Table 19. Post IPTW Incidence Rate of Recurrent VTE, MB, and CRNM Bleeding Among Obese and Morbid Obese VTE Patients who Initiated Apixaban and Warfarin**

| | Warfarin Cohort (Reference) | Apixaban Cohort |
|---|---|---|
| **Obese Patients** | | |
| **Sample Size** | **25,602** | **17,493** |
| **Recurrent VTE** | 638 (2.5%) | 317 (1.8%) |
| Incidence rate per 100 person-years (95% CI) | 7.3 (6.8,7.9) | 5.6 (5.0,6.2) |
| Number of person-years | 8,735.4 | 5,688.5 |
| **Major Bleeding** | 546 (2.1%) | 265 (1.5%) |
| Incidence rate per 100 person-years (95% CI) | 6.2 (5.7,6.8) | 4.6 (4.1,5.2) |
| Number of person-years | 8,762.4 | 5,706.6 |
| **CRNM Bleeding** | 2,843 (11.1%) | 1,579 (9.0%) |
| Incidence rate per 100 person-years (95% CI) | 34.8 (33.5,36.1) | 29.2 (27.8, 30.7) |
| Number of person-years | 8,181.5 | 5,397.7 |
| **Morbid Obese Patients** | | |
| **Sample Size** | **12,340** | **7,411** |
| **Recurrent VTE** | 337 (2.7%) | 130 (1.8%) |
| Incidence rate per 100 person-years (95% CI) | 8.0 (7.2,8.9) | 5.4 (4.5,6.4) |
| Number of person-years | 4,212.2 | 2,412.9 |
| **Major Bleeding** | 268 (2.2%) | 107 (1.4%) |
| Incidence rate per 100 person-years (95% CI) | 6.3 (5.6,7.2) | 4.4 (3.6,5.33) |
| Number of person-years | 4,230.8 | 2,418.8 |
| **CRNM Bleeding** | 1,495 (12.1%) | 672 (9.1%) |
| Incidence rate per 100 person-years (95% CI) | 38.2 (36.3,40.1) | 29.3 (27.2,31.6) |
| Number of person-years | 3,919.5 | 2,290.4 |
| CRNM: Clinically Relevant Non-Major (Bleeding); VTE: Venous Thromboembolism | | |

## Figure 8. Risk of Recurrent VTE, MB, and CRNM Bleeding Among Obese and Morbidly Obese VTE Patients




* Incidence rate for recurrent VTE (per 100 person years [95% confidence interval]) : Warfarin (7.3 [6.8,7.9]); Apixaban (5.6 [5.0,6.2])

Total person-years for recurrent VTE: Warfarin (8,735.4); Apixaban (5,688.5)
Incidence rate for major bleeding (per 100 person years [95% confidence interval]): Warfarin (6.2 [5.73,6.8]); Apixaban (4.6 [4.1,5.2])

Total person-years for major bleeding: Warfarin (8,762.4); Apixaban (5,706.6)
Incidence rate for CRNM bleeding (per 100 person years [95% confidence interval]): Warfarin (34.8 [33.5,36.1]); Apixaban (29.2 [27.8,30.7])

Total person-years for CRNM bleeding: Warfarin (8,181.4); Apixaban (5,397.7)
** Incidence rate for recurrent VTE (per 100 person years [95% confidence interval]): Warfarin (8.0 [7.2,8.9]); Apixaban (5.4 [4.5,6.4])

Total person-years for recurrent VTE: Warfarin (4,212.2); Apixaban (2,412.9)
Incidence rate for major bleeding (per 100 person years[95% confidence interval]): Warfarin (6.3 [5.6,7.2]); Apixaban (4.4 [3.6,5.33])

Total person-years for major bleeding: Warfarin (4,230.8); Apixaban (2,418.8)

Incidence rate for CRNM bleeding (per 100 person years [95% confidence interval]): Warfarin (38.2 [36.3,40.1]); Apixaban (29.3 [27.2,31.6])

Total person-years for CRNM bleeding: Warfarin (3,919.5); Apixaban (2,290.4)

### 9.2.3. Findings for CKD Subgroup Analysis

A total of 29,790 VTE patients with CKD were identified after applying the selection criteria, of which 10,669 (35.8%) initiated apixaban and 19,121 (64.2%) initiated warfarin (Figure 9). The pre- and post-IPTW baseline characteristics among VTE patients with CKD who initiated apixaban or warfarin are shown in Table 20. After applying IPTW but before stratification by CKD subgroups, patient characteristics were generally balanced. For both treatment cohorts, most patients were aged 65-79 years (apixaban: 62.6%; warfarin: 62.6%), followed by ≥80 years (apixaban: 37.4%; warfarin: 37.4%) with mean ages of about 67 years for both cohorts (**Table 7**). A majority of patients across the two cohorts were female (54.9% for both cohorts), and the average CCI was 2.2 (**Table 7**).

After applying IPTW across CKD subgroups, baseline characteristics were well balanced between the apixaban and warfarin cohorts among VTE patients with CKD. The effectiveness and safety outcomes of apixaban vs. warfarin among VTE patients with CKD are shown in Figure 10. VTE patients with CKD who initiated apixaban had a significantly lower risk of recurrent VTE (hazard ratio [HR]: 0.78; 95% confidence interval [CI]: 0.66, 0.92), MB (HR: 0.76; 95% CI: 0.65, 0.88) and CRNMB (HR: 0.86; 95% CI: 0.80, 0.93) compared to warfarin patients.

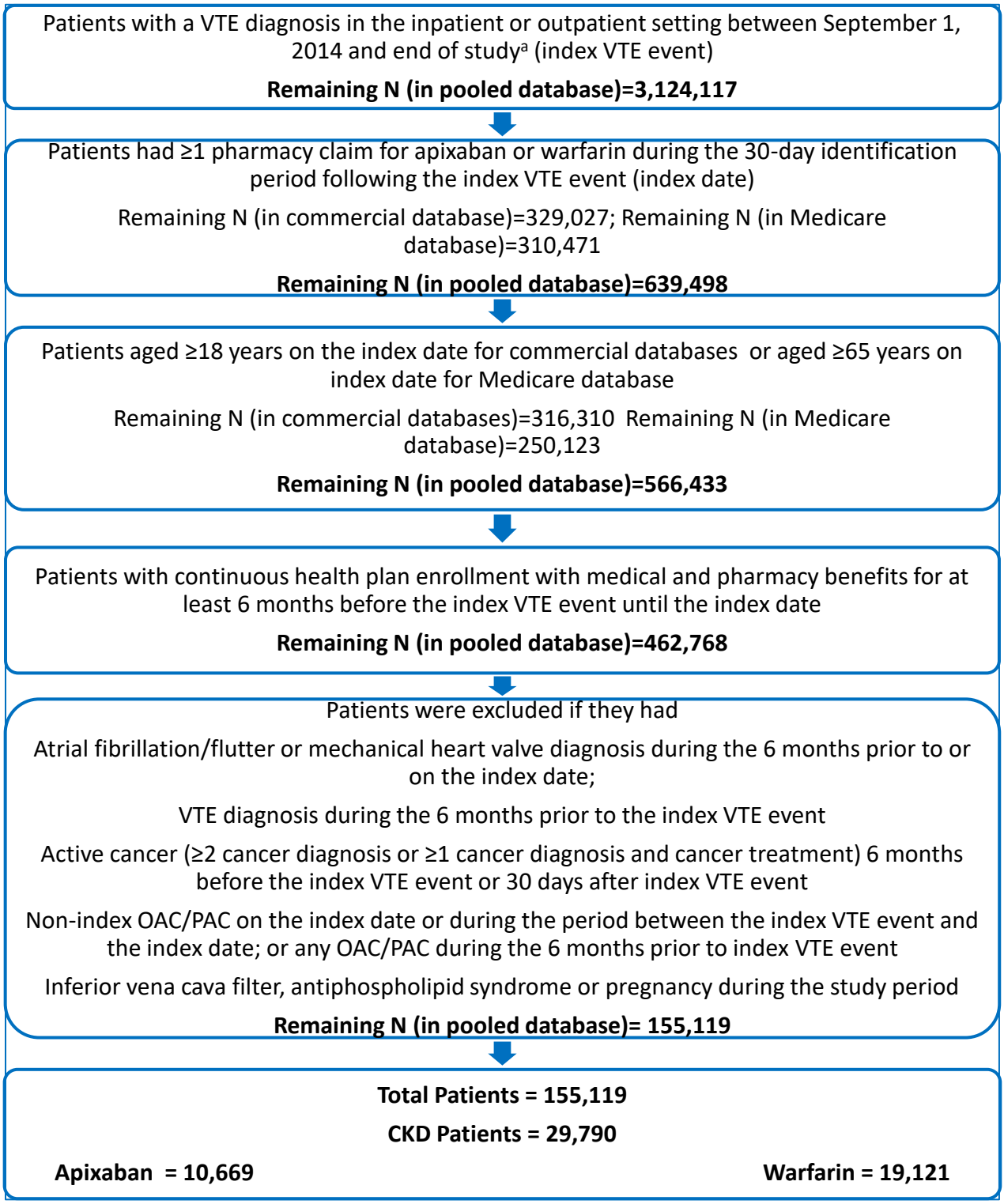
To gain a better understanding of the impact of CKD stage on clinical outcomes, patients were stratified by different CKD stages. Table 21 shows the demographic and clinical characteristics of patients stratified by different stages of CKD. Among the 29,790 VTE patients with CKD in both the apixaban and warfarin cohorts, the largest proportion of patients had CKD stage III (49.4%) followed by stage unspecified (17.6%), stage IV (12.8%), stage V/ESRD (12.0%), and stage I/II (8.2%). Patients with CKD stage IV were older (77.1-78.5 years), followed by stage III (76.4-76.5 years), stage unspecified (75.1-75.5 years), stage I/II (72.4-73.3 years), and stage V/ESRD (68.9 years); in contrast, the mean CCI score was the highest for stages V/ESRD (6.1-6.2) and decreased with the stages (stage IV: 5.6-5.7; stage III: 5.1; stage unspecified: 5.0; stage I/II: 4.9). For type of index VTE event, the proportion of patients that had an index DVT event or provoked event was highest for stage V/ESRD patients (DVT: 76.0-77.2%; provoked: 76.0-78.3%) followed by stage IV (DVT: 64.5-67.4%; provoked: 70.4-74.0%), stage unspecified (DVT: 54.7-55.8%; provoked: 72.2-72.6%), stage III (DVT: 55.2%; provoked: 68.1-68.7%), and stage I/II (DVT: 51.5-54.2%; provoked: 63.5-66.8%). Other demographic characteristics with notable differences between patients with stage V/ESRD CKD and those with stage I/II CKD were a substantially greater proportion of selected surgeries (58.9%-62.5% vs 28.6%-31.1%) and a two-fold increase in the rates of anemia (84.2%-87.1% vs 38.2%-43.9%).

Figure 11 shows the incidence rates and HRs of recurrent VTE, MB, and CRNMB for apixaban compared to warfarin across different stages of CKD. During the follow-up, patients with stage V/ESRD had the highest incidence rate of recurrent VTE, MB, and CRNMB (Figure 3). Across all stages of CKD, patients who received apixaban had a lower incidence of recurrent VTE (stage V/ESRD [7.7 vs 11.6], stage IV [5.8 vs 7.8], stage III [6.2 vs 6.9], stage I/II [5.2 vs 7.6]) and MB (stage V/ESRD [16.9 vs 18.0], stage IV [12.6 vs 12.8], stage III [7.3 vs 9.6], and stage I/II [2.9 vs 6.6]) compared to patients who received warfarin. The apixaban group also experienced lower incidences of CRNMB for patients

with CKD (stage V/ESRD [38.0 vs 52.0], stage IV [31.1 vs 40.9], stage III [33.2 vs 33.9], and stage I/II [28.0 vs 33.0]).

When stratified by CKD staging, no significant interaction was observed between CKD stage and the treatment effects of apixaban versus warfarin on recurrent VTE (interaction P=0.570) or MB (interaction P=0.124). However, there was a significant interaction between CKD stage and treatment effects on CRNMB: while patients treated with apixaban trended towards a lower risk of CRNMB compared to patients treated with warfarin across all CKD stages, the magnitude of difference was bigger for those with CKD stage IV or V/ESRD than for those with CKD stage I/II or III (Figure 11).

**Figure 9. CKD Patient Selection**



## Table 20. Pre- and Post-IPTW Patient Characteristics of VTE Patients with CKD who Initiated Apixaban and Warfarin

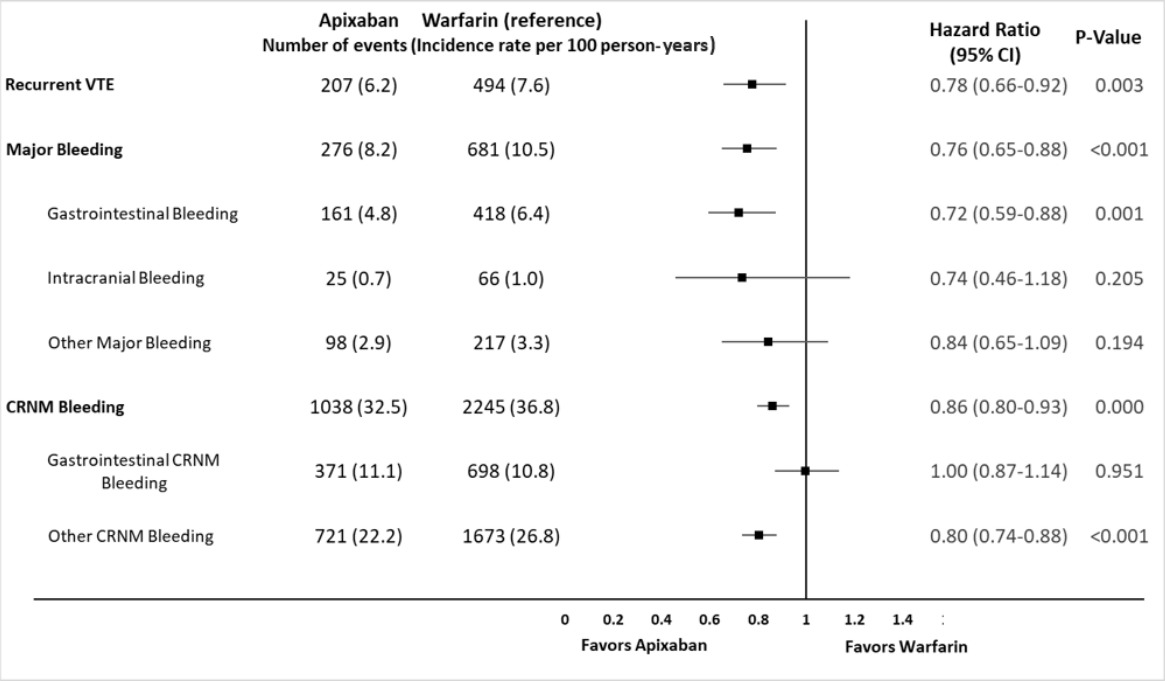
| | Pre-IPTW | | | Post-IPTW[b] | | |
|---|---|---|---|---|---|---|
| | Warfarin Cohort | Apixaban Cohort | STD[a] | Warfarin Cohort | Apixaban Cohort | STD[a] |
| **Sample Size** | **19,121** | **10,669** | | **19,121** | **10,669** | |
| **Age, Mean (SD)** | 75.1 (12.1) | 75.2 (12.2) | 0.79 | 75.1 (12.1) | 75.3 (12.2) | 1.54 |
| **18-54** | 1,092 (5.7%) | 608 (5.7%) | 0.05 | 1,085 (5.7%) | 603 (5.7%) | 0.11 |
| **55-64** | 1,536 (8.0%) | 1,013 (9.5%) | 5.17 | 1,626 (8.5%) | 907 (8.5%) | 0.01 |
| **65-74** | 6,057 (31.7%) | 3,201 (30.0%) | 3.63 | 5,942 (31.1%) | 3,311 (31.0%) | 0.08 |
| **75-79** | 3,356 (17.6%) | 1,879 (17.6%) | 0.16 | 3,369 (17.6%) | 1,889 (17.7%) | 0.23 |
| **≥80** | 7,080 (37.0%) | 3,968 (37.2%) | 0.34 | 7,099 (37.1%) | 3,959 (37.1%) | 0.04 |
| **Gender, n(%)** | | | | | | |
| **Male** | 8,267 (43.2%) | 4,804 (45.0%) | 3.61 | 8,393 (43.9%) | 4,686 (43.9%) | 0.06 |
| **Female** | 10,854 (56.8%) | 5,865 (55.0%) | 3.61 | 10,728 (56.1%) | 5,983 (56.1%) | 0.06 |
| **Geographic Region, n(%)** | | | | | | |
| **Northeast** | 2,897 (15.2%) | 1,337 (12.5%) | 7.59 | 2,714 (14.2%) | 1,496 (14.0%) | 0.48 |
| **Midwest** | 5,596 (29.3%) | 2,168 (20.3%) | 20.83 | 4,986 (26.1%) | 2,779 (26.0%) | 0.07 |
| **South** | 7,227 (37.8%) | 5,636 (52.8%) | 30.54 | 8,245 (43.1%) | 4,595 (43.1%) | 0.11 |
| **West** | 3,371 (17.6%) | 1,516 (14.2%) | 9.36 | 3,149 (16.5%) | 1,783 (16.7%) | 0.66 |
| **Other** | 30 (0.2%) | 12 (0.1%) | 1.21 | 27 (0.1%) | 16 (0.2%) | 0.21 |
| **Type of Index Encounter, n(%)** | | | | | | |
| **Inpatient** | 13,805 (72.2%) | 7,044 (66.0%) | 13.39 | 13,367 (69.9%) | 7,433 (69.7%) | 0.52 |
| **Outpatient** | 5,316 (27.8%) | 3,625 (34.0%) | 13.39 | 5,754 (30.1%) | 3,236 (30.3%) | 0.52 |
| **VTE Diagnosis, n(%)** | | | | | | |
| **DVT only** | 11,405 (59.6%) | 6,144 (57.6%) | 4.18 | 11,264 (58.9%) | 6,292 (59.0%) | 0.13 |
| **PE with or without DVT** | 7,716 (40.4%) | 4,525 (42.4%) | 4.18 | 7,857 (41.1%) | 4,377 (41.0%) | 0.13 |
| **VTE Etiology, n(%)** | | | | | | |
| **Provoked** | 13,955 (73.0%) | 7,038 (66.0%) | 15.28 | 13,467 (70.4%) | 7,501 (70.3%) | 0.27 |
| **Unprovoked** | 5,166 (27.0%) | 3,631 (34.0%) | 15.28 | 5,654 (29.6%) | 3,168 (29.7%) | 0.27 |
| **Deyo-Charlson Comorbidity Index, Mean (SD)** | 5.3 (2.3) | 5.2 (2.3) | 1.70 | 5.3 (2.3) | 5.3 (2.3) | 0.11 |
| **Baseline Comorbidity, n(%)** | | | | | | |
| **AIDS** | 114 (0.6%) | 62 (0.6%) | 0.20 | 120 (0.6%) | 57 (0.5%) | 1.22 |
| **Alcohol abuse** | 505 (2.6%) | 269 (2.5%) | 0.76 | 499 (2.6%) | 278 (2.6%) | 0.01 |
| **Anemia** | 10,497 (54.9%) | 5,250 (49.2%) | 11.41 | 10,106 (52.9%) | 5,630 (52.8%) | 0.17 |
| **Central venous Catheter** | 3,214 (16.8%) | 1,353 (12.7%) | 11.66 | 2,931 (15.3%) | 1,627 (15.2%) | 0.22 |
| **Cerebrovascular disease** | 3,965 (20.7%) | 2,111 (19.8%) | 2.36 | 3,927 (20.5%) | 2,142 (20.1%) | 1.15 |
| **Coagulation defects** | 2,594 (13.6%) | 1,179 (11.1%) | 7.66 | 2,431 (12.7%) | 1,370 (12.8%) | 0.38 |
| **Ischemic heart/ coronary artery disease** | 8,457 (44.2%) | 4,781 (44.8%) | 1.17 | 8,493 (44.4%) | 4,727 (44.3%) | 0.23 |
| **Dementia** | 2,024 (10.6%) | 1,402 (13.1%) | 7.91 | 2,021 (10.6%) | 1,434 (13.4%) | 8.83 |
| **Dyspepsia or stomach discomfort** | 5,323 (27.8%) | 2,860 (26.8%) | 2.32 | 5,261 (27.5%) | 2,947 (27.6%) | 0.24 |
| **Hemiplegia or Paraplegia** | 543 (2.8%) | 303 (2.8%) | 0.00 | 534 (2.8%) | 313 (2.9%) | 0.84 |
| **Hyperlipidemia** | 13,055 (68.3%) | 7,457 (69.9%) | 3.50 | 13,169 (68.9%) | 7,338 (68.8%) | 0.20 |
| **Obesity** | 6,371 (33.3%) | 3,818 (35.8%) | 5.19 | 6,534 (34.2%) | 3,641 (34.1%) | 0.10 |
| **Pneumonia** | 4,077 (21.3%) | 2,219 (20.8%) | 1.28 | 4,033 (21.1%) | 2,238 (21.0%) | 0.29 |
| **Rheumatologic disease** | 1,244 (6.5%) | 683 (6.4%) | 0.42 | 1,232 (6.4%) | 677 (6.3%) | 0.40 |
| **Sleep apnea** | 3,303 (17.3%) | 1,854 (17.4%) | 0.27 | 3,306 (17.3%) | 1,843 (17.3%) | 0.04 |
| **Spinal cord injury** | 49 (0.3%) | 31 (0.3%) | 0.66 | 51 (0.3%) | 28 (0.3%) | 0.09 |
| **Thrombophilia** | 647 (3.4%) | 354 (3.3%) | 0.37 | 641 (3.4%) | 354 (3.3%) | 0.19 |
| **Varicose Veins** | 749 (3.9%) | 486 (4.6%) | 3.17 | 788 (4.1%) | 437 (4.1%) | 0.12 |
| **Congestive Heart Failure** | 7,242 (37.9%) | 3,754 (35.2%) | 5.59 | 7,156 (37.4%) | 3,851 (36.1%) | 2.75 |
| **Diabetes** | 10,544 (55.1%) | 5,564 (52.2%) | 6.00 | 10,560 (55.2%) | 5,563 (52.1%) | 6.20 |
| **Hypertension** | 18,098 (94.6%) | 10,051 (94.2%) | 1.93 | 18,068 (94.5%) | 10,077 (94.5%) | 0.16 |
| **Stage I&II CKD** | 1,401 (7.3%) | 1,031 (9.7%) | 8.39 | 1,569 (8.2%) | 879 (8.2%) | 0.09 |
| **Stage III CKD** | 9,059 (47.4%) | 5,659 (53.0%) | 11.35 | 9,445 (49.4%) | 5,267 (49.4%) | 0.05 |
| **Stage IV CKD** | 2,604 (13.6%) | 1,208 (11.3%) | 6.95 | 2,445 (12.8%) | 1,363 (12.8%) | 0.02 |
| **Stage V/ESRD CKD** | 2,666 (13.9%) | 904 (8.5%) | 17.40 | 2,291 (12.0%) | 1,277 (12.0%) | 0.04 |
| **CKD Unspecified stage** | 3,391 (17.7%) | 1,867 (17.5%) | 0.62 | 3,371 (17.6%) | 1,883 (17.6%) | 0.04 |
| **Chronic Liver Disease** | 1,574 (8.2%) | 920 (8.6%) | 1.41 | 1,531 (8.0%) | 958 (9.0%) | 3.50 |
| **COPD** | 5,495 (28.7%) | 3,023 (28.3%) | 0.89 | 5,496 (28.7%) | 3,056 (28.6%) | 0.21 |
| **Peptic Ulcer Disease** | 645 (3.4%) | 287 (2.7%) | 3.99 | 615 (3.2%) | 314 (2.9%) | 1.57 |
| **Inflammatory Bowel Disease** | 387 (2.0%) | 188 (1.8%) | 1.92 | 369 (1.9%) | 204 (1.9%) | 0.13 |
| **Peripheral vascular disease** | 6,192 (32.4%) | 3,366 (31.5%) | 1.79 | 6,183 (32.3%) | 3,380 (31.7%) | 1.40 |
| **Baseline bleed** | 5,594 (29.3%) | 2,583 (24.2%) | 11.42 | 5,247 (27.4%) | 2,925 (27.4%) | 0.06 |
| **Recent History of Falls, n(%)** | 1,855 (9.7%) | 1,076 (10.1%) | 1.29 | 1,875 (9.8%) | 1,036 (9.7%) | 0.32 |
| **Fracture/trauma involving Lower Extremities, n(%)** | 3,057 (16.0%) | 1,773 (16.6%) | 1.71 | 3,105 (16.2%) | 1,732 (16.2%) | 0.01 |
| **Selected Surgeries, n(%)** | 6,684 (35.0%) | 3,343 (31.3%) | 7.70 | 6,441 (33.7%) | 3,588 (33.6%) | 0.11 |
| **Baseline Medication Use, n(%)** | | | | | | |
| **Antiarrhythmic** | 2,448 (12.8%) | 1,355 (12.7%) | 0.31 | 2,435 (12.7%) | 1,351 (12.7%) | 0.21 |
| **Statins** | 10,770 (56.3%) | 6,101 (57.2%) | 1.73 | 10,829 (56.6%) | 6,042 (56.6%) | 0.00 |
| **Anti-platelets** | 2,742 (14.3%) | 1,578 (14.8%) | 1.28 | 2,765 (14.5%) | 1,529 (14.3%) | 0.37 |
| **Aromatase Inhibitors** | 38 (0.2%) | 24 (0.2%) | 0.57 | 39 (0.2%) | 22 (0.2%) | 0.08 |
| **Beta Blockers** | 10,968 (57.4%) | 5,916 (55.5%) | 3.85 | 10,830 (56.6%) | 6,043 (56.6%) | 0.00 |
| **Gastroprotective Agents** | 7,340 (38.4%) | 3,996 (37.5%) | 1.92 | 7,282 (38.1%) | 4,062 (38.1%) | 0.02 |
| **SERMS** | 102 (0.5%) | 62 (0.6%) | 0.64 | 106 (0.6%) | 60 (0.6%) | 0.13 |
| **NSAIDs** | 3,680 (19.2%) | 2,458 (23.0%) | 9.30 | 3,940 (20.6%) | 2,198 (20.6%) | 0.01 |
| **Hormone Therapy (estrogen)** | 362 (1.9%) | 193 (1.8%) | 0.62 | 353 (1.8%) | 195 (1.8%) | 0.15 |
| **Apixaban Index Dose, n(%)** | | | | | | |
| **On Standard Dose (Apixaban 5mg)** | | 9,109 (85.4%) | | | 8,997 (84.3%) | |
| **Lower Dose (Apixaban 2.5mg)** | | 1,560 (14.6%) | | | 1,672 (15.7%) | |

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

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

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

**Figure 10. Risk of Recurrent VTE, MB and CRNM Bleeding Among CKD Patients**



# Table 21. Pre- and Post-IPTW Patient Characteristics of VTE Patients with CKD by CKD Stage

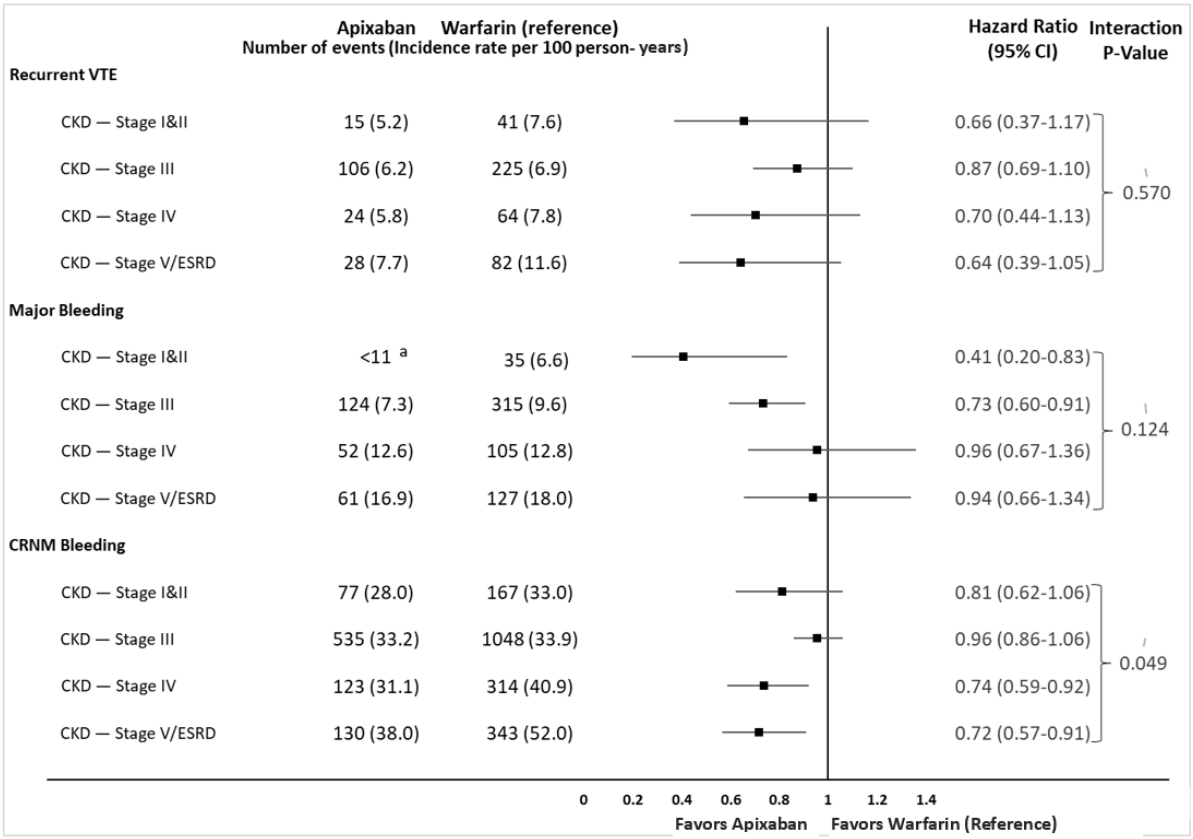
| | Stage I&II CKD[b] | | | Stage III CKD[b] | | | Stage IV CKD[b] | | | Stage V/ESRD CKD[b] | | | Stage Unspecified CKD[b] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Warfarin Cohort (Reference) | Apixaban Cohort | STD[a] | Warfarin Cohort (Reference) | Apixaban Cohort | STD[a] | Warfarin Cohort (Reference) | Apixaban Cohort | STD[a] | Warfarin Cohort (Reference) | Apixaban Cohort | STD[a] | Warfarin Cohort (Reference) | Apixaban Cohort | STD[a] |
| **Sample Size** | **1,569** | **879** | **0** | **9,445** | **5,267** | **0** | **2,445** | **1,363** | **0** | **2,291** | **1,277** | **0** | **3,371** | **1,883** | **0** |
| **Age, Mean (SD)** | 73.3 (13.2) | 72.4 (12.2) | 7.46 | 76.4 (11.4) | 76.5 (10.6) | 0.43 | 77.1 (11.3) | 78.5 (12.4) | 11.38 | 68.9 (12.2) | 68.9 (16.2) | 0.23 | 75.1 (12.4) | 75.5 (12.4) | 2.99 |
| **18-54** | 115 (7.4%) | 84 (9.6%) | 8.10 | 344 (3.6%) | 173 (3.3%) | 1.94 | 102 (4.2%) | 42 (3.0%) | 6.04 | 302 (13.2%) | 189 (14.8%) | 4.32 | 221 (6.6%) | 115 (6.1%) | 1.88 |
| **55-64** | 173 (11.0%) | 103 (11.7%) | 2.25 | 694 (7.4%) | 405 (7.7%) | 1.31 | 168 (6.9%) | 89 (6.5%) | 1.23 | 316 (13.8%) | 162 (12.7%) | 2.98 | 275 (8.2%) | 147 (7.8%) | 1.32 |
| **65-74** | 531 (33.8%) | 286 (32.6%) | 2.72 | 2,831 (30.0%) | 1,610 (30.6%) | 1.27 | 641 (26.2%) | 350 (25.7%) | 1.23 | 932 (40.7%) | 495 (38.7%) | 3.71 | 1,006 (29.9%) | 571 (30.3%) | 1.00 |
| **75-79** | 269 (17.1%) | 150 (17.1%) | 0.22 | 1,786 (18.9%) | 1,000 (19.0%) | 0.19 | 426 (17.4%) | 246 (18.1%) | 1.68 | 320 (14.0%) | 183 (14.3%) | 0.99 | 568 (16.9%) | 310 (16.5%) | 1.07 |
| **≥80** | 481 (30.6%) | 255 (29.1%) | 3.46 | 3,789 (40.1%) | 2,079 (39.5%) | 1.32 | 1,108 (45.3%) | 636 (46.6%) | 2.65 | 421 (18.4%) | 248 (19.4%) | 2.46 | 1,300 (38.6%) | 740 (39.3%) | 1.56 |
| **Gender, n(%)** | | | | | | | | | | | | | | | |
| **Male** | 799 (50.9%) | 419 (47.6%) | 6.55 | 4,061 (43.0%) | 2,292 (43.5%) | 1.04 | 954 (39.0%) | 495 (36.3%) | 5.46 | 1,074 (46.9%) | 631 (49.4%) | 4.85 | 1,505 (44.7%) | 849 (45.1%) | 0.88 |
| **Female** | 771 (49.1%) | 460 (52.4%) | 6.55 | 5,383 (57.0%) | 2,975 (56.5%) | 1.04 | 1,491 (61.0%) | 868 (63.7%) | 5.46 | 1,218 (53.1%) | 646 (50.6%) | 4.85 | 1,865 (55.3%) | 1,034 (54.9%) | 0.88 |
| **Geographic Region, n(%)** | | | | | | | | | | | | | | | |
| **Northeast** | 216 (13.8%) | 118 (13.5%) | 0.85 | 1,262 (13.4%) | 702 (13.3%) | 0.07 | 370 (15.2%) | 186 (13.6%) | 4.33 | 350 (15.3%) | 175 (13.7%) | 4.25 | 516 (15.3%) | 315 (16.7%) | 3.95 |
| **Midwest** | 336 (21.4%) | 202 (23.0%) | 3.76 | 2,680 (28.4%) | 1,454 (27.6%) | 1.70 | 610 (24.9%) | 369 (27.1%) | 4.74 | 474 (20.7%) | 257 (20.2%) | 1.29 | 885 (26.3%) | 496 (26.3%) | 0.17 |
| **South** | 742 (47.2%) | 406 (46.2%) | 2.13 | 3,890 (41.2%) | 2,189 (41.6%) | 0.76 | 1,087 (44.5%) | 609 (44.7%) | 0.44 | 1,112 (48.5%) | 617 (48.3%) | 0.42 | 1,415 (42.0%) | 774 (41.1%) | 1.77 |
| **West** | 274 (17.4%) | 153 (17.4%) | 0.22 | 1,600 (16.9%) | 914 (17.4%) | 1.12 | 374 (15.3%) | 196 (14.4%) | 2.45 | 353 (15.4%) | 226 (17.7%) | 5.77 | 549 (16.3%) | 294 (15.6%) | 1.84 |
| **Other** | <11 | <11 | 4.61 | 13 (0.1%) | <11 | 0.27 | <11 | <11 | 2.00 | <11 | <11 | 1.63 | <11 | <11 | 0.45 |
| **Type of Index Encounter, n(%)** | | | | | | | | | | | | | | | |
| **Inpatient** | 1,026 (65.4%) | 605 (68.8%) | 7.43 | 6,407 (67.8%) | 3,626 (68.8%) | 2.18 | 1,775 (72.6%) | 943 (69.2%) | 7.36 | 1,784 (77.9%) | 896 (70.1%) | 16.41 | 2,375 (70.5%) | 1,363 (72.4%) | 4.25 |
| **Outpatient** | 544 (34.6%) | 274 (31.2%) | 7.43 | 3,037 (32.2%) | 1,641 (31.2%) | 2.18 | 670 (27.4%) | 420 (30.8%) | 7.36 | 507 (22.1%) | 382 (29.9%) | 16.41 | 996 (29.5%) | 520 (27.6%) | 4.25 |
| **VTE Diagnosis, n(%)** | | | | | | | | | | | | | | | |
| **DVT only** | 851 (54.2%) | 452 (51.5%) | 5.51 | 5,212 (55.2%) | 2,905 (55.2%) | 0.05 | 1,578 (64.5%) | 918 (67.4%) | 5.84 | 1,741 (76.0%) | 986 (77.2%) | 2.63 | 1,883 (55.8%) | 1,030 (54.7%) | 2.24 |
| **PE with or without DVT** | 719 (45.8%) | 426 (48.5%) | 5.51 | 4,233 (44.8%) | 2,362 (44.8%) | 0.05 | 867 (35.5%) | 445 (32.6%) | 5.84 | 550 (24.0%) | 292 (22.8%) | 2.63 | 1,488 (44.2%) | 852 (45.3%) | 2.24 |
| **VTE Etiology, n(%)** | | | | | | | | | | | | | | | |
| **Provoked** | 996 (63.5%) | 587 (66.8%) | 7.11 | 6,435 (68.1%) | 3,617 (68.7%) | 1.17 | 1,808 (74.0%) | 960 (70.4%) | 7.69 | 1,793 (78.3%) | 970 (76.0%) | 5.14 | 2,434 (72.2%) | 1,366 (72.6%) | 0.77 |
| **Unprovoked** | 573 (36.5%) | 291 (33.2%) | 7.11 | 3,010 (31.9%) | 1,650 (31.3%) | 1.17 | 637 (26.0%) | 403 (29.6%) | 7.69 | 498 (21.7%) | 307 (24.0%) | 5.14 | 936 (27.8%) | 516 (27.4%) | 0.77 |
| **Deyo-Charlson Comorbidity Index, Mean (SD)** | 4.9 (2.4) | 4.9 (2.0) | 0.89 | 5.1 (2.3) | 5.1 (2.1) | 0.16 | 5.6 (2.2) | 5.7 (2.5) | 6.14 | 6.2 (2.3) | 6.1 (3.0) | 4.35 | 5.0 (2.2) | 5.0 (2.2) | 0.42 |
| **Baseline Comorbidity, n(%)** | | | | | | | | | | | | | | | |
| **AIDS** | 18 (1.1%) | <11 | 7.72 | 47 (0.5%) | 21 (0.4%) | 1.52 | 13 (0.5%) | <11 | 0.38 | 25 (1.1%) | 13 (1.0%) | 0.51 | 17 (0.5%) | 11 (0.6%) | 1.40 |
| **Alcohol abuse** | 47 (3.0%) | 22 (2.5%) | 3.01 | 222 (2.3%) | 125 (2.4%) | 0.15 | 47 (1.9%) | 32 (2.3%) | 2.73 | 76 (3.3%) | 35 (2.8%) | 2.96 | 108 (3.2%) | 65 (3.4%) | 1.30 |
| **Anemia** | 600 (38.2%) | 386 (43.9%) | 11.79 | 4,426 (46.9%) | 2,440 (46.3%) | 1.10 | 1,589 (65.0%) | 894 (65.6%) | 1.17 | 1,995 (87.1%) | 1,075 (84.2%) | 7.66 | 1,497 (44.4%) | 835 (44.4%) | 0.09 |
| **Central venous Catheter** | 146 (9.3%) | 80 (9.1%) | 0.88 | 963 (10.2%) | 541 (10.3%) | 0.25 | 310 (12.7%) | 190 (13.9%) | 3.67 | 1,051 (45.9%) | 564 (44.2%) | 3.23 | 461 (13.7%) | 252 (13.4%) | 0.80 |
| **Cerebrovascular disease** | 307 (19.5%) | 171 (19.5%) | 0.06 | 1,780 (18.8%) | 987 (18.7%) | 0.29 | 523 (21.4%) | 311 (22.8%) | 3.35 | 616 (26.9%) | 296 (23.1%) | 8.13 | 702 (20.8%) | 377 (20.0%) | 1.95 |
| **Coagulation defects** | 170 (10.8%) | 84 (9.6%) | 4.12 | 1,099 (11.6%) | 612 (11.6%) | 0.03 | 285 (11.7%) | 191 (14.0%) | 6.77 | 468 (20.4%) | 282 (22.1%) | 3.76 | 409 (12.1%) | 201 (10.7%) | 4.59 |
| **Ischemic heart/ coronary artery disease** | 589 (37.5%) | 350 (39.9%) | 4.86 | 4,057 (43.0%) | 2,255 (42.8%) | 0.30 | 1,220 (49.9%) | 672 (49.3%) | 1.17 | 1,174 (51.3%) | 638 (49.9%) | 2.50 | 1,452 (43.1%) | 811 (43.1%) | 0.04 |
| **Dementia** | 150 (9.6%) | 96 (11.0%) | 4.67 | 1,008 (10.7%) | 683 (13.0%) | 7.18 | 254 (10.4%) | 236 (17.3%) | 19.54 | 181 (7.9%) | 135 (10.6%) | 8.52 | 428 (12.7%) | 284 (15.1%) | 6.84 |
| **Dyspepsia or stomach discomfort** | 395 (25.2%) | 234 (26.6%) | 3.27 | 2,471 (26.2%) | 1,336 (25.4%) | 1.86 | 640 (26.2%) | 384 (28.1%) | 4.31 | 779 (34.0%) | 445 (34.9%) | 1.76 | 976 (29.0%) | 549 (29.2%) | 0.44 |
| **Hemiplegia or Paraplegia** | 44 (2.8%) | 29 (3.3%) | 3.07 | 218 (2.3%) | 128 (2.4%) | 0.86 | 60 (2.4%) | 24 (1.8%) | 4.65 | 87 (3.8%) | 53 (4.2%) | 1.86 | 126 (3.7%) | 78 (4.1%) | 2.09 |
| **Hyperlipidemia** | 1,047 (66.7%) | 596 (67.8%) | 2.40 | 6,678 (70.7%) | 3,689 (70.0%) | 1.47 | 1,744 (71.3%) | 993 (72.8%) | 3.23 | 1,566 (68.3%) | 842 (65.9%) | 4.81 | 2,134 (63.3%) | 1,218 (64.7%) | 2.90 |
| **Obesity** | 577 (36.8%) | 314 (35.8%) | 2.12 | 3,300 (34.9%) | 1,879 (35.7%) | 1.53 | 859 (35.1%) | 467 (34.3%) | 1.78 | 738 (32.2%) | 388 (30.4%) | 3.72 | 1,060 (31.4%) | 593 (31.5%) | 0.09 |
| **Pneumonia** | 278 (17.7%) | 154 (17.5%) | 0.54 | 1,823 (19.3%) | 1,053 (20.0%) | 1.74 | 527 (21.6%) | 290 (21.3%) | 0.73 | 663 (28.9%) | 318 (24.9%) | 8.60 | 742 (22.0%) | 424 (22.5%) | 1.16 |
| **Rheumatologic disease** | 92 (5.9%) | 54 (6.2%) | 1.41 | 621 (6.6%) | 346 (6.6%) | 0.02 | 181 (7.4%) | 96 (7.0%) | 1.34 | 100 (4.4%) | 54 (4.2%) | 0.85 | 238 (7.1%) | 126 (6.7%) | 1.38 |
| **Sleep apnea** | 249 (15.8%) | 154 (17.5%) | 4.51 | 1,689 (17.9%) | 936 (17.8%) | 0.29 | 428 (17.5%) | 242 (17.7%) | 0.51 | 365 (15.9%) | 209 (16.4%) | 1.20 | 575 (17.0%) | 302 (16.0%) | 2.73 |
| **Spinal cord injury** | <11 (0.2%) | <11 (0.4%) | 2.43 | 21 (0.2%) | 11 (0.2%) | 0.42 | <11 | <11 | 3.54 | 11 (0.5%) | <11 | 3.50 | 13 (0.4%) | <11 | 0.04 |
| **Thrombophilia** | 59 (3.8%) | 41 (4.6%) | 4.28 | 328 (3.5%) | 170 (3.2%) | 1.43 | 70 (2.9%) | 33 (2.4%) | 2.84 | 81 (3.5%) | 53 (4.2%) | 3.04 | 102 (3.0%) | 57 (3.0%) | 0.17 |
| **Varicose Veins** | 70 (4.5%) | 37 (4.2%) | 1.36 | 406 (4.3%) | 229 (4.4%) | 0.27 | 113 (4.6%) | 59 (4.3%) | 1.31 | 60 (2.6%) | 30 (2.3%) | 1.69 | 139 (4.1%) | 82 (4.3%) | 1.12 |
| **Congestive Heart Failure** | 420 (26.8%) | 228 (25.9%) | 1.94 | 3,244 (34.4%) | 1,757 (33.4%) | 2.12 | 1,146 (46.9%) | 639 (46.9%) | 0.03 | 1,171 (51.1%) | 593 (46.4%) | 8.83 | 1,174 (34.8%) | 635 (33.7%) | 2.33 |
| **Diabetes** | 810 (51.6%) | 428 (48.7%) | 5.79 | 5,017 (53.1%) | 2,637 (50.1%) | 6.16 | 1,493 (61.1%) | 815 (59.8%) | 2.63 | 1,579 (68.9%) | 823 (64.4%) | 8.93 | 1,661 (49.3%) | 860 (45.7%) | 7.20 |
| **Hypertension** | 1,424 (90.7%) | 788 (89.7%) | 3.40 | 8,923 (94.5%) | 5,004 (95.0%) | 2.32 | 2,384 (97.5%) | 1,326 (97.3%) | 1.35 | 2,234 (97.5%) | 1,232 (96.5%) | 5.53 | 3,104 (92.1%) | 1,727 (91.8%) | 1.16 |
| **Chronic Liver Disease** | 125 (8.0%) | 86 (9.7%) | 6.34 | 672 (7.1%) | 414 (7.9%) | 2.88 | 164 (6.7%) | 109 (8.0%) | 4.86 | 311 (13.6%) | 183 (14.4%) | 2.08 | 259 (7.7%) | 166 (8.8%) | 4.16 |
| **COPD** | 398 (25.4%) | 225 (25.6%) | 0.60 | 2,663 (28.2%) | 1,416 (26.9%) | 2.97 | 754 (30.8%) | 457 (33.5%) | 5.61 | 665 (29.0%) | 371 (29.0%) | 0.03 | 1,015 (30.1%) | 588 (31.2%) | 2.36 |
| **Peptic Ulcer Disease** | 40 (2.6%) | 17 (1.9%) | 4.21 | 274 (2.9%) | 138 (2.6%) | 1.73 | 83 (3.4%) | 29 (2.1%) | 7.81 | 107 (4.7%) | 61 (4.8%) | 0.37 | 111 (3.3%) | 70 (3.7%) | 2.30 |
| **Inflammatory Bowel Disease** | 21 (1.4%) | 14 (1.6%) | 1.78 | 180 (1.9%) | 83 (1.6%) | 2.58 | 49 (2.0%) | 36 (2.6%) | 4.24 | 55 (2.4%) | 24 (1.9%) | 3.21 | 63 (1.9%) | 47 (2.5%) | 4.10 |
| **Peripheral vascular disease** | 492 (31.4%) | 266 (30.2%) | 2.50 | 2,901 (30.7%) | 1,611 (30.6%) | 0.26 | 844 (34.5%) | 466 (34.2%) | 0.74 | 894 (39.0%) | 502 (39.3%) | 0.62 | 1,052 (31.2%) | 535 (28.4%) | 6.08 |
| **Baseline bleed** | 372 (23.7%) | 231 (26.3%) | 6.17 | 2,343 (24.8%) | 1,300 (24.7%) | 0.27 | 649 (26.6%) | 372 (27.3%) | 1.65 | 921 (40.2%) | 519 (40.6%) | 0.81 | 963 (28.6%) | 502 (26.7%) | 4.22 |
| **Recent History of Falls, n(%)** | 137 (8.7%) | 80 (9.1%) | 1.41 | 912 (9.7%) | 507 (9.6%) | 0.08 | 270 (11.1%) | 143 (10.5%) | 1.71 | 198 (8.6%) | 90 (7.0%) | 5.73 | 358 (10.6%) | 216 (11.5%) | 2.68 |
| **Fracture/trauma involving Lower Extremities, r** | 227 (14.5%) | 133 (15.1%) | 1.92 | 1,494 (15.8%) | 854 (16.2%) | 1.07 | 434 (17.8%) | 245 (17.9%) | 0.47 | 425 (18.5%) | 190 (14.9%) | 9.35 | 525 (15.6%) | 311 (16.5%) | 2.54 |
| **Selected Surgeries, n(%)** | 488 (31.1%) | 251 (28.6%) | 5.45 | 2,718 (28.8%) | 1,530 (29.1%) | 0.61 | 728 (29.8%) | 448 (32.9%) | 6.54 | 1,433 (62.5%) | 753 (58.9%) | 6.90 | 1,073 (31.8%) | 605 (32.1%) | 0.66 |
| **Baseline Medication Use, n(%)** | | | | | | | | | | | | | | | |
| **Antiarrhythmic** | 177 (11.3%) | 106 (12.1%) | 2.52 | 1,156 (12.2%) | 648 (12.3%) | 0.21 | 337 (13.8%) | 178 (13.1%) | 2.09 | 346 (15.1%) | 166 (13.0%) | 5.62 | 419 (12.4%) | 252 (13.4%) | 2.87 |
| **Statins** | 846 (53.9%) | 485 (55.2%) | 2.60 | 5,505 (58.3%) | 3,029 (57.5%) | 1.59 | 1,471 (60.2%) | 835 (61.2%) | 2.06 | 1,258 (54.9%) | 710 (55.6%) | 1.23 | 1,747 (51.8%) | 983 (52.2%) | 0.79 |
| **Anti-platelets** | 185 (11.8%) | 96 (10.9%) | 2.84 | 1,296 (13.7%) | 729 (13.8%) | 0.38 | 411 (16.8%) | 238 (17.4%) | 1.66 | 419 (18.3%) | 211 (16.6%) | 4.34 | 454 (13.5%) | 254 (13.5%) | 0.15 |
| **Aromatase Inhibitors** | <11 | <11 | 8.66 | 20 (0.2%) | <11 | 1.61 | <11 | <11 | 0.76 | <11 | <11 | 5.95 | <11 | <11 | 7.57 |
| **Beta Blockers** | 725 (46.2%) | 409 (46.5%) | 0.65 | 5,199 (55.0%) | 2,879 (54.7%) | 0.79 | 1,586 (64.9%) | 873 (64.0%) | 1.67 | 1,577 (68.8%) | 877 (68.7%) | 0.32 | 1,743 (51.7%) | 1,005 (53.4%) | 3.34 |
| **Gastroprotective Agents** | 544 (34.6%) | 317 (36.0%) | 2.96 | 3,502 (37.1%) | 1,932 (36.7%) | 0.86 | 967 (39.6%) | 586 (43.0%) | 6.82 | 972 (42.4%) | 536 (41.9%) | 0.96 | 1,296 (38.4%) | 692 (36.8%) | 3.46 |
| **SERMS** | <11 | <11 | 0.97 | 57 (0.6%) | 32 (0.6%) | 0.11 | 16 (0.7%) | <11 | 1.74 | <11 | <11 | 1.49 | <11 | <11 | 1.67 |
| **NSAIDs** | 425 (27.1%) | 239 (27.2%) | 0.42 | 1,934 (20.5%) | 1,112 (21.1%) | 1.57 | 401 (16.4%) | 207 (15.2%) | 3.27 | 370 (16.2%) | 172 (13.5%) | 7.12 | 809 (24.0%) | 467 (24.8%) | 1.82 |
| **Hormone Therapy (estrogen)** | 32 (2.0%) | 20 (2.3%) | 1.76 | 175 (1.9%) | 94 (1.8%) | 0.61 | 42 (1.7%) | 19 (1.4%) | 2.49 | 33 (1.4%) | 25 (1.9%) | 3.54 | 70 (2.1%) | 37 (2.0%) | 0.79 |
| **Apixaban Index Dose, n(%)** | | | | | | | | | | | | | | | |
| **On Standard Dose (Apixaban 5mg)** | | 805 (91.6%) | | | 4,644 (88.2%) | | | 992 (72.8%) | | | 906 (70.9%) | | | 1,650 (87.7%) | |
| **Lower Dose (Apixaban 2.5mg)** | | 74 (8.4%) | | | 624 (11.8%) | | | 371 (27.2%) | | | 371 (29.1%) | | | 232 (12.3%) | |

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

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

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

**Figure 11. Risk of Recurrent VTE, MB and CRNM Bleeding by CKD Stage**




### 9.2.4. Findings for High Risk of Bleeding Subgroup Analysis

After applying the selection criteria, a total of 155,119 VTE patients were identified including 60,786 (39.2%) who initiated apixaban and 94,333 (60.8%) who initiated warfarin. Of the total VTE patients, 88,281 (56.9%) were categorized as having a high risk of bleeding and 66,838 (43.1%) patients not having a high risk of bleeding (Figure 12). After applying IPTW but before stratification by high risk of bleeding, patient characteristics were generally balanced. For both treatment cohorts, most patients were aged 65-79 years (apixaban: 62.6%; warfarin: 62.6%), followed by ≥80 years (apixaban: 37.4%; warfarin: 37.4%) with mean ages of about 67 years for both cohorts (**Table 7**). A majority of patients across the two cohorts were female (54.9% for both cohorts), and the average CCI was 2.2 (**Table 7**).

Table 22 shows the baseline characteristics of VTE patients with or without a high risk of bleeding before IPTW. Patients with a high risk of bleeding were older (mean age: 74.2 vs 56.7), sicker (mean CCI: 3.0 vs 1.2), and more likely to be females (60.2% vs 47.6%) compared to VTE patients not at a high risk of bleeding. Additionally, patients with a high

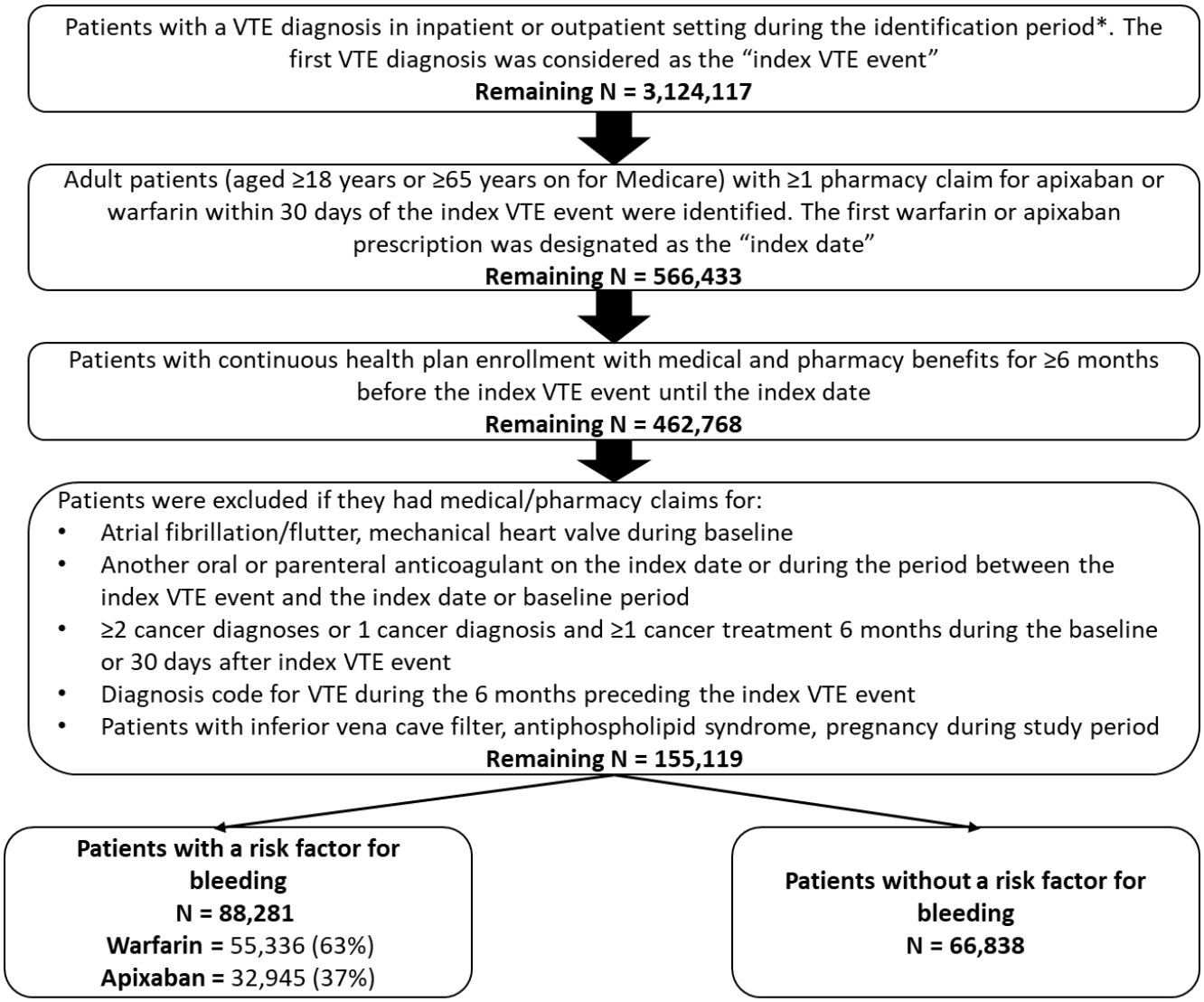
risk of bleeding were more likely to have an inpatient VTE diagnosis (61.2% vs 44.5%) and a provoked VTE (63.2% vs 47.0%) for the index VTE event compared to patients not at a high risk of bleeding. Patients with a high risk of bleeding were also more likely to have comorbidities such as hypertension (81.5% vs 52.2%), history of bleed (25.9% vs 13.6%), and hematologic disorders associated with bleeding (9.5% vs 6.0%).

The risk factors that defined high risk of bleeding were evaluated. Among patients with a high risk of bleeding, 58.9% were aged ≥75 years, 35.4% had concomitant medications that may increase the risk of bleeding, 25.1% had a prior GI condition, and 25.0% had CKD during baseline period. Additionally, 63.7% patients had only 1 risk factor, 28.8% had 2 risk factors, 6.8% had 3 risk factors, and 0.7% had all 4 risk factors.

Table 23 represents the pre- and post-IPTW baseline characteristics among VTE patients with a high risk of bleeding who initiated apixaban vs warfarin: 32,945 (37.3%) patients initiated apixaban and 55,336 (62.7%) initiated warfarin. After applying IPTW among patients with a high risk of bleeding, the baseline patient characteristics were balanced between apixaban and warfarin cohorts. Among VTE patients with a high risk of bleeding, apixaban was associated with a significantly lower risk of recurrent VTE (HR: 0.78; 95% CI: 0.70-0.87), overall MB (HR: 0.75; 95% CI: 0.67-0.83), gastrointestinal MB (HR: 0.77; 95% CI: 0.67-0.88), intracranial MB (HR: 0.56; 95% CI: 0.42-0.76), other MB (HR:0.78; 95% CI: 0.65-0.93), and CRNM bleeding (HR: 089; 95% CI: 0.85-0.93) compared to warfarin. No significant difference was observed between apixaban and warfarin for the risk of GI CRNM bleeding (HR:1.02; 95% CI: 0.94-1.10; (Figure 13).

Tables 24 and 25 include baseline characteristics of VTE patients at high risk of bleed stratified by the number of bleeding risk factors and type of bleeding risk factor, respectively. When stratified by number of bleeding risk factors, no significant interactions were observed between treatment and the number of risk factors on MB (interaction p=0.143) and CRNM bleeding (interaction p=0.246; Figure 14). One significant interaction was observed between treatment and number of risk factors on recurrent VTE (interaction p=0.049): apixaban showed a lower risk of recurrent VTE compared to warfarin in patients with 1 or 2 risk factors, whereas there was a trend toward a higher risk in the ~8% of patients with 3 or more risk factors. When stratified by type of bleeding risk factor, no significant interactions were observed between treatment and type of risk factors on recurrent VTE (interaction p=0.180), MB (interaction p=0.144), and CRNM bleeding (interaction p=0.699; Figure 14).

**Figure 12. Selection of Patients with a High Risk of Bleeding**



## Table 22. Baseline Characteristics Among VTE Patients At or Not At High Risk of Bleeding

| | Patients at a high risk of bleeding | Patients not at a high risk of bleeding | STD[a] |
|---|---|---|---|
| **Sample Size** | **88,281** | **66,838** | |
| **Age in years, Mean (SD)** | 74.2 (13.6) | 56.7 (13.2) | 130.51 |
| **Gender, n (%)** | | | |
| Male | 35,099 (39.8%) | 35,012 (52.4%) | 25.53 |
| Female | 53,182 (60.2%) | 31,826 (47.6%) | 25.53 |
| **Setting of Index VTE Event, n (%)** | | | |
| Inpatient | 54,066 (61.2%) | 29,756 (44.5%) | 33.98 |
| Outpatient | 34,215 (38.8%) | 37,082 (55.5%) | 33.98 |
| **Index VTE Diagnosis, n (%)** | | | |
| Deep-vein thrombosis only | 49,577 (56.2%) | 38,039 (56.9%) | 1.52 |
| Pulmonary embolism with deep-vein thrombosis | 12,337 (14.0%) | 9,638 (14.4%) | 1.28 |
| Pulmonary embolism without deep-vein thrombosis | 26,367 (30.0% ) | 19161 (28.7%) | 2.64 |
| **Index VTE Etiology, n (%)** | | | |
| Provoked | 55,801 (63.2%) | 31,404 (47.0%) | 33.06 |
| Unprovoked | 32,480 (36.8%) | 35,434 (53.0%) | 33.06 |
| **Deyo-Charlson Comorbidity Index, Mean (SD)** | 3.0 (2.5) | 1.2 (1.6) | 85.97 |
| **Baseline Comorbidity, n (%)** | | | |
| Alcohol abuse | 2,409 (2.7%) | 2,474 (3.7%) | 5.52 |
| Anemia | 33,729 (38.2%) | 11,734 (17.6%) | 47.32 |
| Central venous Catheter | 8,768 (9.9%) | 3,794 (5.7%) | 15.91 |
| Hematologic disorders associated with bleeding[b] | 8,380 (9.5%) | 4,041 (6.0%) | 12.90 |
| Ischemic heart/ coronary artery disease | 30,025 (34.0%) | 9,225 (13.8%) | 48.77 |
| Dyspepsia or stomach discomfort | 23,764 (26.9%) | 11,582 (17.3%) | 23.26 |
| Hyperlipidemia | 51,210 (58.0%) | 23,348 (34.9%) | 47.56 |
| Obesity | 23,893 (27.1%) | 19,202 (28.7%) | 3.71 |
| Pneumonia | 15,578 (17.6%) | 6,780 (10.1%) | 21.82 |
| Rheumatologic disease | 5,817 (6.6%) | 1,454 (2.2%) | 21.69 |
| Sleep apnea | 12,174 (13.8%) | 8,616 (12.9%) | 2.64 |
| Spinal cord injury | 212 (0.2%) | 203 (0.3%) | 1.22 |
| Thrombophilia[c] | 2,880 (3.3%) | 3,210 (4.8%) | 7.84 |
| Varicose Veins | 3,719 (4.2%) | 2,852 (4.3%) | 0.27 |
| Hypertension | 71,945 (81.5%) | 34,864 (52.2%) | 65.56 |
| Non-ESRD Renal Disease - Stage I & II | 3,501 (4.0%) | 825 (1.2%) | 17.23 |
| Inflammatory Bowel Disease | 2,045 (2.3%) | 857 (1.3%) | 7.79 |
| History of Bleed | 22,844 (25.9%) | 9,084 (13.6%) | 31.24 |
| **Risk Factors for GI Bleed, n (%)** | | | |
| **Age ≥75 years (on index date)** | 52,001 (58.9%) | n/a | n/a |
| **Concurrent medications (on index date)** | 31,253 (35.4%) | n/a | n/a |
| Antiplatelets | 7,932 (9.0%) | n/a | n/a |
| Nonsteroidal anti-inflammatory drug | 14,247 (16.1%) | n/a | n/a |
| Corticosteroids | 11,473 (13.0%) | n/a | n/a |
| **Prior GI conditions** | 22,201 (25.1%) | n/a | n/a |
| Peptic ulcer | 3,177 (3.6%) | n/a | n/a |
| Prior GI bleeding | 8,340 (9.4%) | n/a | n/a |
| Helicobacter pylori | 522 (0.6%) | n/a | n/a |
| Diverticulosis | 13,810 (15.6%) | n/a | n/a |
| Angiodysplasias | 257 (0.3%) | n/a | n/a |
| GI cancer | 365 (0.4%) | n/a | n/a |
| Other GI lesions | 1,260 (1.4%) | n/a | n/a |
| **Chronic Kidney Disease** | 22,100 (25.0%) | n/a | n/a |
| Stage III | 18,365 (20.8%) | n/a | n/a |
| Stage IV | 5,080 (5.8%) | n/a | n/a |
| End Stage Renal Disease & Stage V | 3,570 (4.0%) | n/a | n/a |
| **Number of Risk Factors for GI Bleed, n (%)** | | | |
| Only 1 risk factor | 56,219 (63.7%) | n/a | n/a |
| 2 risk factors | 25,434 (28.8%) | n/a | n/a |
| 3 risk factors | 6,044 (6.8%) | n/a | n/a |
| 4 risk factors | 584 (0.7%) | n/a | n/a |
| **Index Medication** | | | |
| Apixaban | 32,945 (37.3%) | 27,841 (41.7%) | 8.88 |
| Warfarin | 55,336 (62.7%) | 38,997 (58.3%) | 8.88 |

ESRD: end stage renal disease; GI: Gastrointestinal; IPTW: inverse probability treatment weighting; SD: Standard deviation; STD: standardized difference; VTE: venous thromboembolism

[a] Standardized Difference=100*|actual standardized difference|. Standardized Difference greater than 10 was considered significant.

[b] Hematologic disorders associated with bleeding: conditions that hinder mediation of blood clotting and increase bleeding risk, e.g., Von Willebrand's disease, the defibrination syndrome, acquired coagulation factor deficiency, unspecified coagulation defects, allergic purpura, qualitative platelet defects, nonthrombocytopenic purpuras, thrombocytopenia, and thrombotic microangiopathy.

[c] Thrombophilia: conditions that increase the risk of blood clot development, e.g., diseases of blood and blood-forming organs, thalassemia, polycythemia vera, prothrombin gene mutation, and lupus anticoagulant syndrome.

## Table 23. Pre-/Post-IPTW Baseline Characteristics Among VTE Patients With a High Risk of Bleeding

| | Pre-IPTW | | | Post-IPTW[c] | | |
|---|---|---|---|---|---|---|
| Sample Size | Warfarin Cohort 55,336 | Apixaban Cohort 32,945 | STD[a] | Warfarin Cohort 55,336 | Apixaban Cohort 32,945 | STD[a] |
| **Age in years, Mean (SD)** | 74.5 (13.3) | 73.6 (14.0) | 6.12 | 74.6 (13.2) | 73.4 (14.1) | 8.39 |
| **Age in years[b], n (%)** | | | | | | |
| 18-54 | 4,785 (8.6%) | 3,319 (10.1%) | 4.90 | 4,636 (8.4%) | 3,459 (10.5%) | 7.26 |
| 55-64 | 4,830 (8.7%) | 3,820 (11.6%) | 9.50 | 4,943 (8.9%) | 3,702 (11.2%) | 7.65 |
| 65-74 | 12,622 (22.8%) | 6,904 (21.0%) | 4.48 | 12,407 (22.4%) | 7,128 (21.6%) | 1.90 |
| 75-79 | 12,064 (21.8%) | 6,853 (20.8%) | 2.44 | 12,052 (21.8%) | 6,847 (20.8%) | 2.43 |
| ≥80 | 21,035 (38.0%) | 12,049 (36.6%) | 2.98 | 21,298 (38.5%) | 11,809 (35.8%) | 5.47 |
| **Gender[b], n (%)** | | | | | | |
| Male | 21,756 (39.3%) | 13,343 (40.5%) | 2.42 | 21,721 (39.3%) | 13,308 (40.4%) | 2.33 |
| Female | 33,580 (60.7%) | 19,602 (59.5%) | 2.42 | 33,615 (60.7%) | 19,637 (59.6%) | 2.33 |
| **Geographic Region[b], n (%)** | | | | | | |
| Northeast | 8,882 (16.1%) | 4,882 (14.8%) | 3.41 | 8,789 (15.9%) | 4,950 (15.0%) | 2.38 |
| North Central | 17,058 (30.8%) | 7,054 (21.4%) | 21.56 | 15,236 (27.5%) | 8,886 (27.0%) | 1.27 |
| South | 18,593 (33.6%) | 16,320 (49.5%) | 32.77 | 21,603 (39.0%) | 13,246 (40.2%) | 2.38 |
| West | 10,696 (19.3%) | 4,649 (14.1%) | 14.02 | 9,614 (17.4%) | 5,811 (17.6%) | 0.70 |
| Other | 107 (0.2%) | 40 (0.1%) | 1.82 | 94 (0.2%) | 53 (0.2%) | 0.20 |
| **Setting of Index VTE Event[b], n (%)** | | | | | | |
| Inpatient | 34,940 (63.1%) | 19,126 (58.1%) | 10.42 | 34,169 (61.7%) | 19,839 (60.2%) | 3.14 |
| Outpatient | 20,396 (36.9%) | 13,819 (41.9%) | 10.42 | 21,167 (38.3%) | 13,106 (39.8%) | 3.14 |
| **Index VTE Diagnosis[b], n (%)** | | | | | | |
| Deep-vein thrombosis only | 31,308 (56.6%) | 18,269 (55.5%) | 2.27 | 31,003 (56.0%) | 18,655 (56.6%) | 1.20 |
| Pulmonary embolism with deep-vein thrombosis | 7,774 (14.0%) | 4,563 (13.9%) | 0.57 | 7,812 (14.1%) | 4,522 (13.7%) | 1.13 |
| Pulmonary embolism without deep-vein thrombosis | 16,254 (29.4%) | 10,113 (30.7%) | 2.89 | 16,521 (29.9%) | 9,768 (29.6%) | 0.45 |
| **Index VTE Etiology[b], n (%)** | | | | | | |
| Provoked | 36,214 (65.4%) | 19,587 (59.5%) | 12.39 | 35,494 (64.1%) | 20,416 (62.0%) | 4.50 |
| Unprovoked | 19,122 (34.6%) | 13,358 (40.5%) | 12.39 | 19,842 (35.9%) | 12,529 (38.0%) | 4.50 |
| **Deyo-Charlson Comorbidity Index[b], Mean (SD)** | 3.0 (2.5) | 2.9 (2.5) | 4.41 | 3.0 (2.5) | 3.0 (2.5) | 1.68 |
| **Baseline Comorbidity[b], n (%)** | | | | | | |
| Alcohol abuse | 1,539 (2.8%) | 870 (2.6%) | 0.86 | 1,491 (2.7%) | 945 (2.9%) | 1.07 |
| Anemia | 22,087 (39.9%) | 11,642 (35.3%) | 9.46 | 21,345 (38.6%) | 12,477 (37.9%) | 1.44 |
| Central venous Catheter | 5,927 (10.7%) | 2,841 (8.6%) | 7.07 | 5,443 (9.8%) | 3,344 (10.2%) | 1.05 |
| Hematologic disorders associated with bleeding[d] | 5,647 (10.2%) | 2,733 (8.3%) | 6.59 | 5,278 (9.5%) | 3,177 (9.6%) | 0.36 |
| Ischemic heart/ coronary artery disease | 18,773 (33.9%) | 11,252 (34.2%) | 0.48 | 19,023 (34.4%) | 10,982 (33.3%) | 2.20 |
| Dyspepsia or stomach discomfort | 15,066 (27.2%) | 8,698 (26.4%) | 1.86 | 14,865 (26.9%) | 8,970 (27.2%) | 0.82 |
| Hyperlipidemia | 31,883 (57.6%) | 19,327 (58.7%) | 2.12 | 32,345 (58.5%) | 18,824 (57.1%) | 2.66 |
| Obesity | 14,512 (26.2%) | 9,381 (28.5%) | 5.05 | 14,808 (26.8%) | 9,048 (27.5%) | 1.58 |
| Pneumonia | 9,817 (17.7%) | 5,761 (17.5%) | 0.67 | 9,830 (17.8%) | 5,769 (17.5%) | 0.67 |
| Rheumatologic disease | 3,714 (6.7%) | 2,103 (6.4%) | 1.33 | 3,688 (6.7%) | 2,114 (6.4%) | 1.01 |
| Sleep apnea | 7,577 (13.7%) | 4,597 (14.0%) | 0.76 | 7,601 (13.7%) | 4,526 (13.7%) | 0.01 |
| Spinal cord injury | 141 (0.3%) | 71 (0.2%) | 0.81 | 134 (0.2%) | 82 (0.2%) | 0.11 |
| Thrombophilia[e] | 1,877 (3.4%) | 1,003 (3.0%) | 1.97 | 1,785 (3.2%) | 1,095 (3.3%) | 0.55 |
| Varicose Veins | 2,192 (4.0%) | 1,527 (4.6%) | 3.32 | 2,329 (4.2%) | 1,364 (4.1%) | 0.34 |
| Hypertension | 45,334 (81.9%) | 26,611 (80.8%) | 2.96 | 45,364 (82.0%) | 26,616 (80.8%) | 3.06 |
| Non-ESRD Renal Disease - Stage I & II | 2,093 (3.8%) | 1,408 (4.3%) | 2.50 | 2,210 (4.0%) | 1,322 (4.0%) | 0.10 |
| Inflammatory Bowel Disease | 1,333 (2.4%) | 712 (2.2%) | 1.66 | 1,266 (2.3%) | 777 (2.4%) | 0.48 |
| History of Bleed | 15,398 (27.8%) | 7,446 (22.6%) | 12.05 | 14,307 (25.9%) | 8,615 (26.2%) | 0.67 |
| **Recent History of Falls[b], n (%)** | 5,183 (9.4%) | 3,003 (9.1%) | 0.87 | 5,209 (9.4%) | 2,995 (9.1%) | 1.11 |
| **Fracture/trauma involving Lower Extremities[b], n (%)** | 8,519 (15.4%) | 5,368 (16.3%) | 2.46 | 8,761 (15.8%) | 5,183 (15.7%) | 0.28 |
| **Selected Surgeries[b], n (%)** | 16,413 (29.7%) | 9,073 (27.5%) | 4.69 | 15,915 (28.8%) | 9,633 (29.2%) | 1.05 |
| **Baseline Medication Use[b], n (%)** | | | | | | |
| Antiarrhythmic | 6,412 (11.6%) | 3,790 (11.5%) | 0.26 | 6,367 (11.5%) | 3,790 (11.5%) | 0.01 |
| Statins | 25,860 (46.7%) | 15,643 (47.5%) | 1.50 | 26,148 (47.3%) | 15,318 (46.5%) | 1.52 |
| Anti-platelets | 6,675 (12.1%) | 4,152 (12.6%) | 1.64 | 6,813 (12.3%) | 3,993 (12.1%) | 0.59 |
| Aromatase Inhibitors | 127 (0.2%) | 67 (0.2%) | 0.56 | 122 (0.2%) | 69 (0.2%) | 0.26 |
| Beta Blockers | 24,374 (44.0%) | 13,894 (42.2%) | 3.78 | 24,159 (43.7%) | 14,177 (43.0%) | 1.27 |
| Gastroprotective Agents | 19,670 (35.5%) | 11,403 (34.6%) | 1.96 | 19,550 (35.3%) | 11,525 (35.0%) | 0.72 |
| Selective Estrogen Receptor Modulator | 398 (0.7%) | 260 (0.8%) | 0.81 | 423 (0.8%) | 232 (0.7%) | 0.71 |
| Nonsteroidal Anti-inflammatory Drug | 15,717 (28.4%) | 10,748 (32.6%) | 9.18 | 16,296 (29.4%) | 10,130 (30.7%) | 2.83 |
| Hormone Therapy | 1,735 (3.1%) | 1,207 (3.7%) | 2.92 | 1,805 (3.3%) | 1,138 (3.5%) | 1.06 |
| **Risk Factors for GI Bleed, n (%)** | | | | | | |
| **Age ≥75 years (on index date)** | 33,099 (59.8%) | 18,902 (57.4%) | 4.96 | 33,349 (60.3%) | 18,657 (56.6%) | 7.39 |
| **Concurrent medications (on index date)[b]** | 18,843 (34.1%) | 12,410 (37.7%) | 7.55 | 19,285 (34.9%) | 11,947 (36.3%) | 2.95 |
| Antiplatelets | 4,858 (8.8%) | 3,074 (9.3%) | 1.92 | 4,958 (9.0%) | 2,949 (9.0%) | 0.03 |
| Nonsteroidal anti-inflammatory drug | 8,303 (15.0%) | 5,944 (18.0%) | 8.19 | 8,659 (15.6%) | 5,572 (16.9%) | 3.43 |
| Corticosteroids | 7,063 (12.8%) | 4,410 (13.4%) | 1.85 | 7,127 (12.9%) | 4,369 (13.3%) | 1.13 |
| **Prior GI conditions[b]** | 14,160 (25.6%) | 8,041 (24.4%) | 2.73 | 13,842 (25.0%) | 8,386 (25.5%) | 1.01 |
| Peptic ulcer | 2,092 (3.8%) | 1,085 (3.3%) | 2.64 | 1,982 (3.6%) | 1,185 (3.6%) | 0.09 |
| Prior GI bleeding | 5,564 (10.1%) | 2,776 (8.4%) | 5.63 | 5,173 (9.3%) | 3,186 (9.7%) | 1.10 |
| Helicobacter pylori | 338 (0.6%) | 184 (0.6%) | 0.69 | 323 (0.6%) | 196 (0.6%) | 0.15 |
| Diverticulosis | 8,728 (15.8%) | 5,082 (15.4%) | 0.96 | 8,659 (15.6%) | 5,164 (15.7%) | 0.07 |
| Angiodysplasias | 183 (0.3%) | 74 (0.2%) | 2.02 | 161 (0.3%) | 98 (0.3%) | 0.15 |
| GI cancer (Stomach, colon, esophageal, and rectal cancer) | 242 (0.4%) | 123 (0.4%) | 1.01 | 232 (0.4%) | 131 (0.4%) | 0.35 |
| Other GI lesions | 696 (1.3%) | 564 (1.7%) | 3.76 | 784 (1.4%) | 478 (1.5%) | 0.28 |
| **Chronic Kidney Disease[b]** | | | | | | |
| Stage III | 11,572 (20.9%) | 6,793 (20.6%) | 0.72 | 11,573 (20.9%) | 6,856 (20.8%) | 0.25 |
| Stage IV | 3,570 (6.5%) | 1,510 (4.6%) | 8.19 | 3,208 (5.8%) | 1,912 (5.8%) | 0.02 |
| End Stage Renal Disease & Stage V | 2,666 (4.8%) | 904 (2.7%) | 10.89 | 2,236 (4.0%) | 1,379 (4.2%) | 0.74 |
| **Number of Risk Factors for GI Bleed, n (%)** | | | | | | |
| Only 1 risk factor | 34,855 (63.0%) | 21,364 (64.8%) | 3.87 | 34,832 (62.9%) | 21,282 (64.6%) | 3.44 |
| 2 risk factors | 16,233 (29.3%) | 9,201 (27.9%) | 3.11 | 16,270 (29.4%) | 9,285 (28.2%) | 2.69 |
| 3 risk factors | 3,882 (7.0%) | 2,162 (6.6%) | 1.80 | 3,866 (7.0%) | 2,167 (6.6%) | 1.62 |
| 4 risk factors | 366 (0.7%) | 218 (0.7%) | 0.00 | 369 (0.7%) | 210 (0.6%) | 0.34 |

ESRD: end stage renal disease; GI: Gastrointestinal; IPTW: inverse probability treatment weighting; SD: Standard deviation; STD: standardized difference; VTE:

[a] Standardized Difference=100*|actual standardized difference|. Standardized Difference greater than 10 was considered significant.

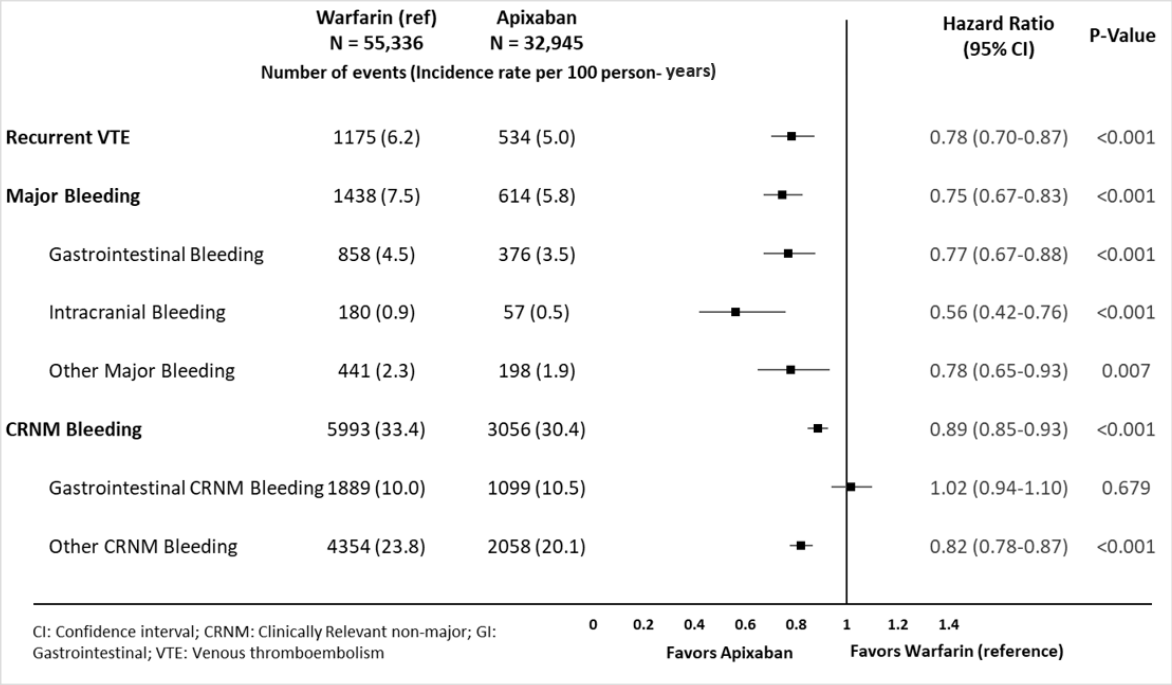
[b] Variables that were adjusted in inverse probability of treatment weighting

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

[d] Hematologic disorders associated with bleeding: conditions that hinder mediation of blood clotting and increase bleeding risk, e.g., Von Willebrand's disease

[e] Thrombophilia: conditions that increase the risk of blood clot development, e.g., diseases of blood and blood-forming organs, thalassemia, polycythemia ver

**Figure 13. Risk of Recurrent VTE, MB and CRNM Bleed among VTE patients with a high risk of bleeding**



## Table 24. Post IPTW Baseline Characteristics Among VTE Patients with a High Risk of Bleeding Stratified by Number of Risk Factors

| | Patients with one risk factor | | | Patients with two risk factors | | | Patients with three or more risk factors | | |
|---|---|---|---|---|---|---|---|---|---|
| | Warfarin Cohort | Apixaban | | Warfarin | Apixaban | | Warfarin | Apixaban | |
| **Sample Size** | 34,832 | 21,282 | STD[a] | 16,270 | 9,285 | STD[a] | 4,234 | 2,378 | STD[a] |
| **Age in years, Mean (SD)** | 71.8 (14.0) | 70.4 (14.7) | 9.70 | 78.8 (10.5) | 78.3 (11.2) | 4.49 | 81.5 (7.8) | 81.8 (8.4) | 3.40 |
| **Age in years, n (%)** | | | | | | | | | |
| 18-54 | 4,129 (11.9%) | 3,076 (14.5%) | 7.71 | 479 (2.9%) | 364 (3.9%) | 5.37 | 29 (0.7%) | 19 (0.8%) | 1.38 |
| 55-64 | 4,174 (12.0%) | 3,117 (14.6%) | 7.85 | 699 (4.3%) | 546 (5.9%) | 7.18 | 70 (1.6%) | 39 (1.6%) | 0.16 |
| 65-74 | 9,687 (27.8%) | 5,638 (26.5%) | 2.97 | 2,472 (15.2%) | 1,353 (14.6%) | 1.75 | 248 (5.9%) | 137 (5.7%) | 0.50 |
| 75-79 | 6,180 (17.7%) | 3,519 (16.5%) | 3.21 | 4,500 (27.7%) | 2,550 (27.5%) | 0.43 | 1,371 (32.4%) | 778 (32.7%) | 0.69 |
| ≥80 | 10,661 (30.6%) | 5,932 (27.9%) | 6.03 | 8,120 (49.9%) | 4,472 (48.2%) | 3.48 | 2,516 (59.4%) | 1,406 (59.1%) | 0.62 |
| **Gender, n (%)** | | | | | | | | | |
| Male | 14,259 (40.9%) | 8,997 (42.3%) | 2.72 | 5,905 (36.3%) | 3,416 (36.8%) | 1.01 | 1,557 (36.8%) | 896 (37.7%) | 1.88 |
| Female | 20,573 (59.1%) | 12,285 (57.7%) | 2.72 | 10,365 (63.7%) | 5,870 (63.2%) | 1.01 | 2,677 (63.2%) | 1,482 (62.3%) | 1.88 |
| **Setting of Index VTE Event, n (%)** | | | | | | | | | |
| Inpatient | 20,063 (57.6%) | 12,075 (56.7%) | 1.74 | 10,911 (67.1%) | 6,054 (65.2%) | 3.91 | 3,195 (75.5%) | 1,709 (71.9%) | 8.08 |
| Outpatient | 14,769 (42.4%) | 9,207 (43.3%) | 1.74 | 5,359 (32.9%) | 3,231 (34.8%) | 3.91 | 1,039 (24.5%) | 668 (28.1%) | 8.08 |
| **Index VTE Diagnosis, n (%)** | | | | | | | | | |
| Deep-vein thrombosis only | 19,529 (56.1%) | 11,932 (56.1%) | 0.00 | 9,022 (55.5%) | 5,357 (57.7%) | 4.50 | 2,452 (57.9%) | 1,365 (57.4%) | 0.96 |
| Pulmonary embolism with deep-vein thrombosis | 4,829 (13.9%) | 2,924 (13.7%) | 0.36 | 2,351 (14.5%) | 1,252 (13.5%) | 2.79 | 632 (14.9%) | 346 (14.6%) | 1.01 |
| Pulmonary embolism without deep-vein thrombosis | 10,474 (30.1%) | 6,425 (30.2%) | 0.27 | 4,897 (30.1%) | 2,677 (28.8%) | 2.77 | 1,151 (27.2%) | 666 (28.0%) | 1.86 |
| **Index VTE Etiology, n (%)** | | | | | | | | | |
| Provoked | 20,805 (59.7%) | 12,310 (57.8%) | 3.84 | 11,322 (69.6%) | 6,305 (67.9%) | 3.63 | 3,367 (79.5%) | 1,802 (75.8%) | 9.02 |
| Unprovoked | 14,027 (40.3%) | 8,972 (42.2%) | 3.84 | 4,948 (30.4%) | 2,981 (32.1%) | 3.63 | 867 (20.5%) | 576 (24.2%) | 9.02 |
| **Deyo-Charlson Comorbidity Index, Mean (SD)** | 2.4 (2.2) | 2.3 (2.2) | 2.40 | 3.8 (2.6) | 3.9 (2.6) | 3.27 | 5.3 (2.5) | 5.3 (2.5) | 0.52 |
| **Baseline Comorbidity, n (%)** | | | | | | | | | |
| Alcohol abuse | 1,033 (3.0%) | 678 (3.2%) | 1.28 | 378 (2.3%) | 228 (2.5%) | 0.86 | 80 (1.9%) | 39 (1.7%) | 1.76 |
| Anemia | 11,100 (31.9%) | 6,651 (31.2%) | 1.33 | 7,552 (46.4%) | 4,393 (47.3%) | 1.79 | 2,692 (63.6%) | 1,434 (60.3%) | 6.78 |
| Central venous Catheter | 2,977 (8.5%) | 1,889 (8.9%) | 1.17 | 1,834 (11.3%) | 1,092 (11.8%) | 1.51 | 632 (14.9%) | 363 (15.3%) | 0.97 |
| Hematologic disorders associated with bleeding[b] | 2,977 (8.5%) | 1,750 (8.2%) | 1.17 | 1,719 (10.6%) | 1,058 (11.4%) | 2.67 | 583 (13.8%) | 369 (15.5%) | 4.98 |
| Ischemic heart/ coronary artery disease | 9,872 (28.3%) | 5,877 (27.6%) | 1.62 | 6,799 (41.8%) | 3,829 (41.2%) | 1.13 | 2,352 (55.5%) | 1,276 (53.7%) | 3.74 |
| Dyspepsia or stomach discomfort | 8,190 (23.5%) | 5,091 (23.9%) | 0.97 | 4,936 (30.3%) | 2,905 (31.3%) | 2.05 | 1,739 (41.1%) | 973 (40.9%) | 0.29 |
| Hyperlipidemia | 18,522 (53.2%) | 11,060 (52.0%) | 2.42 | 10,672 (65.6%) | 6,048 (65.1%) | 0.96 | 3,152 (74.4%) | 1,716 (72.2%) | 5.07 |
| Obesity | 9,318 (26.8%) | 5,870 (27.6%) | 1.87 | 4,335 (26.6%) | 2,470 (26.6%) | 0.11 | 1,155 (27.3%) | 708 (29.8%) | 5.56 |
| Pneumonia | 5,374 (15.4%) | 3,274 (15.4%) | 0.13 | 3,381 (20.8%) | 1,918 (20.7%) | 0.31 | 1,075 (25.4%) | 577 (24.3%) | 2.58 |
| Rheumatologic disease | 1,799 (5.2%) | 1,068 (5.0%) | 0.67 | 1,356 (8.3%) | 770 (8.3%) | 0.14 | 533 (12.6%) | 276 (11.6%) | 3.08 |
| Sleep apnea | 4,734 (13.6%) | 2,907 (13.7%) | 0.20 | 2,230 (13.7%) | 1,225 (13.2%) | 1.51 | 637 (15.0%) | 394 (16.6%) | 4.20 |
| Spinal cord injury | 87 (0.3%) | 55 (0.3%) | 0.13 | 32 (0.2%) | 21 (0.2%) | 0.65 | 14 (0.3%) | 6 (0.2%) | 1.90 |
| Thrombophilia[c] | 1,149 (3.3%) | 733 (3.4%) | 0.80 | 510 (3.1%) | 280 (3.0%) | 0.68 | 126 (3.0%) | 82 (3.4%) | 2.72 |
| Varicose Veins | 1,449 (4.2%) | 878 (4.1%) | 0.17 | 700 (4.3%) | 382 (4.1%) | 0.97 | 180 (4.3%) | 105 (4.4%) | 0.73 |
| Hypertension | 26,726 (76.7%) | 15,983 (75.1%) | 3.81 | 14,587 (89.7%) | 8,368 (90.1%) | 1.56 | 4,051 (95.7%) | 2,264 (95.2%) | 2.09 |
| Non-ESRD Renal Disease - Stage I & II | 1,043 (3.0%) | 631 (3.0%) | 0.16 | 816 (5.0%) | 501 (5.4%) | 1.68 | 350 (8.3%) | 190 (8.0%) | 0.97 |
| Inflammatory Bowel Disease | 665 (1.9%) | 417 (2.0%) | 0.35 | 457 (2.8%) | 284 (3.1%) | 1.49 | 144 (3.4%) | 77 (3.2%) | 1.02 |
| History of Bleed | 7,663 (22.0%) | 4,724 (22.2%) | 0.47 | 4,833 (29.7%) | 2,915 (31.4%) | 3.66 | 1,811 (42.8%) | 977 (41.1%) | 3.42 |
| **Risk Factors for GI Bleed, n (%)** | | | | | | | | | |
| **Age ≥75 years (on index date)** | 16,842 (48.4%) | 9,451 (44.4%) | 7.92 | 12,620 (77.6%) | 7,022 (75.6%) | 4.57 | 3,887 (91.8%) | 2,183 (91.8%) | 0.06 |
| **Concurrent medications (on index date)** | 9,081 (26.1%) | 6,086 (28.6%) | 5.67 | 7,184 (44.2%) | 4,130 (44.5%) | 0.64 | 3,020 (71.3%) | 1,732 (72.9%) | 3.42 |
| Antiplatelets | 1,604 (4.6%) | 1,042 (4.9%) | 1.37 | 2,128 (13.1%) | 1,246 (13.4%) | 1.01 | 1,226 (29.0%) | 661 (27.8%) | 2.54 |
| Nonsteroidal anti-inflammatory drug | 5,206 (14.9%) | 3,559 (16.7%) | 4.87 | 2,726 (16.8%) | 1,538 (16.6%) | 0.50 | 726 (17.2%) | 475 (20.0%) | 7.27 |
| Corticosteroids | 2,899 (8.3%) | 1,913 (9.0%) | 2.38 | 2,914 (17.9%) | 1,704 (18.4%) | 1.14 | 1,314 (31.0%) | 751 (31.6%) | 1.21 |
| **Prior GI conditions** | 5,276 (15.1%) | 3,476 (16.3%) | 3.27 | 5,710 (35.1%) | 3,339 (36.0%) | 1.79 | 2,856 (67.4%) | 1,570 (66.1%) | 2.95 |
| Peptic ulcer | 709 (2.0%) | 477 (2.2%) | 1.43 | 838 (5.2%) | 480 (5.2%) | 0.10 | 435 (10.3%) | 228 (9.6%) | 2.31 |
| Prior GI bleeding | 1,942 (5.6%) | 1,311 (6.2%) | 2.48 | 2,126 (13.1%) | 1,284 (13.8%) | 2.22 | 1,104 (26.1%) | 591 (24.8%) | 2.83 |
| Helicobacter pylori | 130 (0.4%) | 85 (0.4%) | 0.40 | 127 (0.8%) | 79 (0.9%) | 0.77 | 65 (1.5%) | 32 (1.4%) | 1.61 |
| Diverticulosis | 3,189 (9.2%) | 2,068 (9.7%) | 1.93 | 3,639 (22.4%) | 2,061 (22.2%) | 0.40 | 1,831 (43.2%) | 1,034 (43.5%) | 0.52 |
| Angiodysplasias | 48 (0.1%) | 29 (0.1%) | 0.11 | 73 (0.5%) | 47 (0.5%) | 0.77 | 39 (0.9%) | 23 (1.0%) | 0.39 |
| GI cancer | 82 (0.2%) | 42 (0.2%) | 0.80 | 101 (0.6%) | 56 (0.6%) | 0.22 | 49 (1.2%) | 33 (1.4%) | 1.89 |
| Other GI lesions | 360 (1.0%) | 228 (1.1%) | 0.38 | 296 (1.8%) | 185 (2.0%) | 1.31 | 129 (3.0%) | 65 (2.7%) | 1.96 |
| **Chronic Kidney Disease** | 3,633 (10.4%) | 2,269 (10.7%) | 0.76 | 7,025 (43.2%) | 4,080 (43.9%) | 1.53 | 3,308 (78.1%) | 1,857 (78.1%) | 0.03 |
| Stage III | 2,861 (8.2%) | 1,823 (8.6%) | 1.26 | 5,859 (36.0%) | 3,443 (37.1%) | 2.20 | 2,853 (67.4%) | 1,591 (66.9%) | 0.95 |
| Stage IV | 773 (2.2%) | 524 (2.5%) | 1.60 | 1,615 (9.9%) | 935 (10.1%) | 0.46 | 820 (19.4%) | 453 (19.1%) | 0.75 |
| End Stage Renal Disease & Stage V | 816 (2.3%) | 497 (2.3%) | 0.06 | 1,020 (6.3%) | 617 (6.6%) | 1.54 | 400 (9.5%) | 266 (11.2%) | 5.64 |

ESRD: end stage renal disease; GI: Gastrointestinal; IPTW: inverse probability treatment weighting; SD: Standard deviation; STD: standardized difference; VTE: venous thromboembolism

[a] Standardized Difference=100*|actual standardized difference|. Standardized Difference greater than 10 was considered significant.

[b] Hematologic disorders associated with bleeding: conditions that hinder mediation of blood clotting and increase bleeding risk, e.g., Von Willebrand's disease, the defibrination syndrome, acquir

[c] Thrombophilia: conditions that increase the risk of blood clot development, e.g., diseases of blood and blood-forming organs, thalassemia, polycythemia vera, prothrombin gene mutation, and lu

## Table 25. Post IPTW Baseline Characteristics Among VTE Patients with a High Risk of Bleeding by Risk Factor Type

| | Among patients with one risk factor for bleeding | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Age ≥75 years | | | Concurrent medications | | | Prior GI conditions | | | Chronic Kidney Disease | | |
| Sample Size | Warfarin Cohort 16,842 | Apixaban 9,451 | STD[a] | Warfarin 9,081 | Apixaban 6,086 | STD[a] | Warfarin Cohort 5,276 | Apixaban 3,476 | STD[a] | Warfarin Cohort 3,633 | Apixaban Cohort 2,269 | STD[a] |
| **Age in years, Mean (SD)** | 82.7 (6.3) | 82.8 (6.6) | 1.42 | 60.0 (12.1) | 58.8 (11.7) | 9.61 | 61.8 (11.0) | 60.5 (11.9) | 10.85 | 65.2 (8.8) | 64.9 (9.5) | 4.23 |
| **Gender, n (%)** | | | | | | | | | | | | |
| Male | 5,500 (32.7%) | 3,164 (33.5%) | 1.76 | 4,323 (47.6%) | 2,940 (48.3%) | 1.41 | 2,598 (49.2%) | 1,668 (48.0%) | 2.51 | 1,838 (50.6%) | 1,225 (54.0%) | 6.72 |
| Female | 11,342 (67.3%) | 6,287 (66.5%) | 1.76 | 4,758 (52.4%) | 3,146 (51.7%) | 1.41 | 2,678 (50.8%) | 1,809 (52.0%) | 2.51 | 1,794 (49.4%) | 1,044 (46.0%) | 6.72 |
| **Setting of Index VTE Event, n (%)** | | | | | | | | | | | | |
| Inpatient | 9,581 (56.9%) | 5,309 (56.2%) | 1.44 | 4,694 (51.7%) | 3,137 (51.5%) | 0.29 | 3,286 (62.3%) | 2,166 (62.3%) | 0.07 | 2,502 (68.9%) | 1,463 (64.5%) | 9.22 |
| Outpatient | 7,261 (43.1%) | 4,142 (43.8%) | 1.44 | 4,387 (48.3%) | 2,949 (48.5%) | 0.29 | 1,990 (37.7%) | 1,310 (37.7%) | 0.07 | 1,131 (31.1%) | 806 (35.5%) | 9.22 |
| **Index VTE Diagnosis, n (%)** | | | | | | | | | | | | |
| Deep-vein thrombosis only | 9,650 (57.3%) | 5,428 (57.4%) | 0.27 | 5,053 (55.6%) | 3,324 (54.6%) | 2.04 | 2,700 (51.2%) | 1,775 (51.1%) | 0.22 | 2,126 (58.5%) | 1,405 (61.9%) | 6.80 |
| Pulmonary embolism with deep-vein thrombosis | 2,269 (13.5%) | 1,288 (13.6%) | 0.46 | 1,155 (12.7%) | 813 (13.4%) | 1.93 | 865 (16.4%) | 542 (15.6%) | 2.14 | 541 (14.9%) | 281 (12.4%) | 7.25 |
| Pulmonary embolism without deep-vein thrombosis | 4,923 (29.2%) | 2,735 (28.9%) | 0.64 | 2,874 (31.7%) | 1,948 (32.0%) | 0.78 | 1,712 (32.4%) | 1,159 (33.3%) | 1.90 | 965 (26.6%) | 583 (25.7%) | 1.92 |
| **Index VTE Etiology, n (%)** | | | | | | | | | | | | |
| Provoked | 10,063 (59.7%) | 5,496 (58.2%) | 3.24 | 5,016 (55.2%) | 3,254 (53.5%) | 3.55 | 3,309 (62.7%) | 2,129 (61.3%) | 3.00 | 2,417 (66.5%) | 1,430 (63.0%) | 7.28 |
| Unprovoked | 6,779 (40.3%) | 3,954 (41.8%) | 3.24 | 4,065 (44.8%) | 2,832 (46.5%) | 3.55 | 1,967 (37.3%) | 1,347 (38.7%) | 3.00 | 1,215 (33.5%) | 839 (37.0%) | 7.28 |
| **Deyo-Charlson Comorbidity Index, Mean (SD)** | 2.1 (2.0) | 2.1 (2.0) | 0.35 | 1.8 (2.0) | 1.7 (1.9) | 5.51 | 2.0 (2.1) | 2.0 (2.2) | 2.55 | 5.2 (2.2) | 5.0 (2.4) | 6.59 |
| **Baseline Comorbidity, n (%)** | | | | | | | | | | | | |
| Alcohol abuse | 226 (1.3%) | 164 (1.7%) | 3.16 | 309 (3.4%) | 199 (3.3%) | 0.72 | 379 (7.2%) | 236 (6.8%) | 1.59 | 118 (3.2%) | 79 (3.5%) | 1.30 |
| Anemia | 4,954 (29.4%) | 2,759 (29.2%) | 0.49 | 2,141 (23.6%) | 1,395 (22.9%) | 1.56 | 2,101 (39.8%) | 1,374 (39.5%) | 0.61 | 1,903 (52.4%) | 1,122 (49.5%) | 5.80 |
| Central venous Catheter | 665 (3.9%) | 391 (4.1%) | 0.97 | 699 (7.7%) | 506 (8.3%) | 2.27 | 854 (16.2%) | 550 (15.8%) | 1.03 | 759 (20.9%) | 443 (19.5%) | 3.40 |
| Hematologic disorders associated with bleeding[b] | 1,218 (7.2%) | 684 (7.2%) | 0.03 | 657 (7.2%) | 418 (6.9%) | 1.44 | 618 (11.7%) | 350 (10.1%) | 5.26 | 483 (13.3%) | 297 (13.1%) | 0.59 |
| Ischemic heart/ coronary artery disease | 4,957 (29.4%) | 2,796 (29.6%) | 0.35 | 2,348 (25.9%) | 1,540 (25.3%) | 1.28 | 1,196 (22.7%) | 722 (20.8%) | 4.60 | 1,371 (37.7%) | 819 (36.1%) | 3.37 |
| Dyspepsia or stomach discomfort | 2,892 (17.2%) | 1,599 (16.9%) | 0.66 | 1,683 (18.5%) | 1,124 (18.5%) | 0.16 | 2,778 (52.6%) | 1,831 (52.7%) | 0.05 | 837 (23.0%) | 537 (23.6%) | 1.44 |
| Hyperlipidemia | 9,225 (54.8%) | 5,231 (55.4%) | 1.17 | 4,304 (47.4%) | 2,823 (46.4%) | 2.02 | 2,504 (47.5%) | 1,535 (44.1%) | 6.64 | 2,489 (68.5%) | 1,471 (64.8%) | 7.75 |
| Obesity | 2,715 (16.1%) | 1,541 (16.3%) | 0.51 | 3,125 (34.4%) | 2,131 (35.0%) | 1.27 | 1,836 (34.8%) | 1,191 (34.3%) | 1.10 | 1,642 (45.2%) | 1,007 (44.4%) | 1.67 |
| Pneumonia | 2,469 (14.7%) | 1,347 (14.3%) | 1.16 | 1,387 (15.3%) | 955 (15.7%) | 1.18 | 826 (15.6%) | 565 (16.3%) | 1.64 | 692 (19.1%) | 406 (17.9%) | 2.94 |
| Rheumatologic disease | 680 (4.0%) | 335 (3.5%) | 2.62 | 799 (8.8%) | 497 (8.2%) | 2.28 | 194 (3.7%) | 143 (4.1%) | 2.33 | 126 (3.5%) | 93 (4.1%) | 3.26 |
| Sleep apnea | 1,351 (8.0%) | 738 (7.8%) | 0.78 | 1,618 (17.8%) | 1,071 (17.6%) | 0.55 | 907 (17.2%) | 597 (17.2%) | 0.06 | 859 (23.6%) | 501 (22.1%) | 3.68 |
| Spinal cord injury | 32 (0.2%) | 19 (0.2%) | 0.32 | 27 (0.3%) | 13 (0.2%) | 1.65 | 14 (0.3%) | 16 (0.5%) | 3.10 | 14 (0.4%) | 7 (0.3%) | 1.80 |
| Thrombophilia[c] | 349 (2.1%) | 218 (2.3%) | 1.61 | 380 (4.2%) | 248 (4.1%) | 0.54 | 273 (5.2%) | 170 (4.9%) | 1.28 | 147 (4.0%) | 96 (4.2%) | 0.97 |
| Varicose Veins | 732 (4.3%) | 415 (4.4%) | 0.25 | 379 (4.2%) | 256 (4.2%) | 0.14 | 194 (3.7%) | 128 (3.7%) | 0.04 | 144 (4.0%) | 79 (3.5%) | 2.53 |
| Hypertension | 13,615 (80.8%) | 7,635 (80.8%) | 0.13 | 6,105 (67.2%) | 3,984 (65.5%) | 3.75 | 3,570 (67.7%) | 2,248 (64.7%) | 6.33 | 3,436 (94.6%) | 2,116 (93.3%) | 5.50 |
| Non-ESRD Renal Disease - Stage I & II | 464 (2.8%) | 250 (2.6%) | 0.69 | 152 (1.7%) | 99 (1.6%) | 0.37 | 97 (1.8%) | 77 (2.2%) | 2.65 | 330 (9.1%) | 206 (9.1%) | 0.09 |
| Inflammatory Bowel Disease | 158 (0.9%) | 78 (0.8%) | 1.19 | 189 (2.1%) | 130 (2.1%) | 0.36 | 261 (4.9%) | 172 (5.0%) | 0.07 | 57 (1.6%) | 36 (1.6%) | 0.21 |
| History of Bleed | 2,721 (16.2%) | 1,465 (15.5%) | 1.80 | 1,462 (16.1%) | 974 (16.0%) | 0.26 | 2,696 (51.1%) | 1,769 (50.9%) | 0.43 | 784 (21.6%) | 516 (22.7%) | 2.69 |

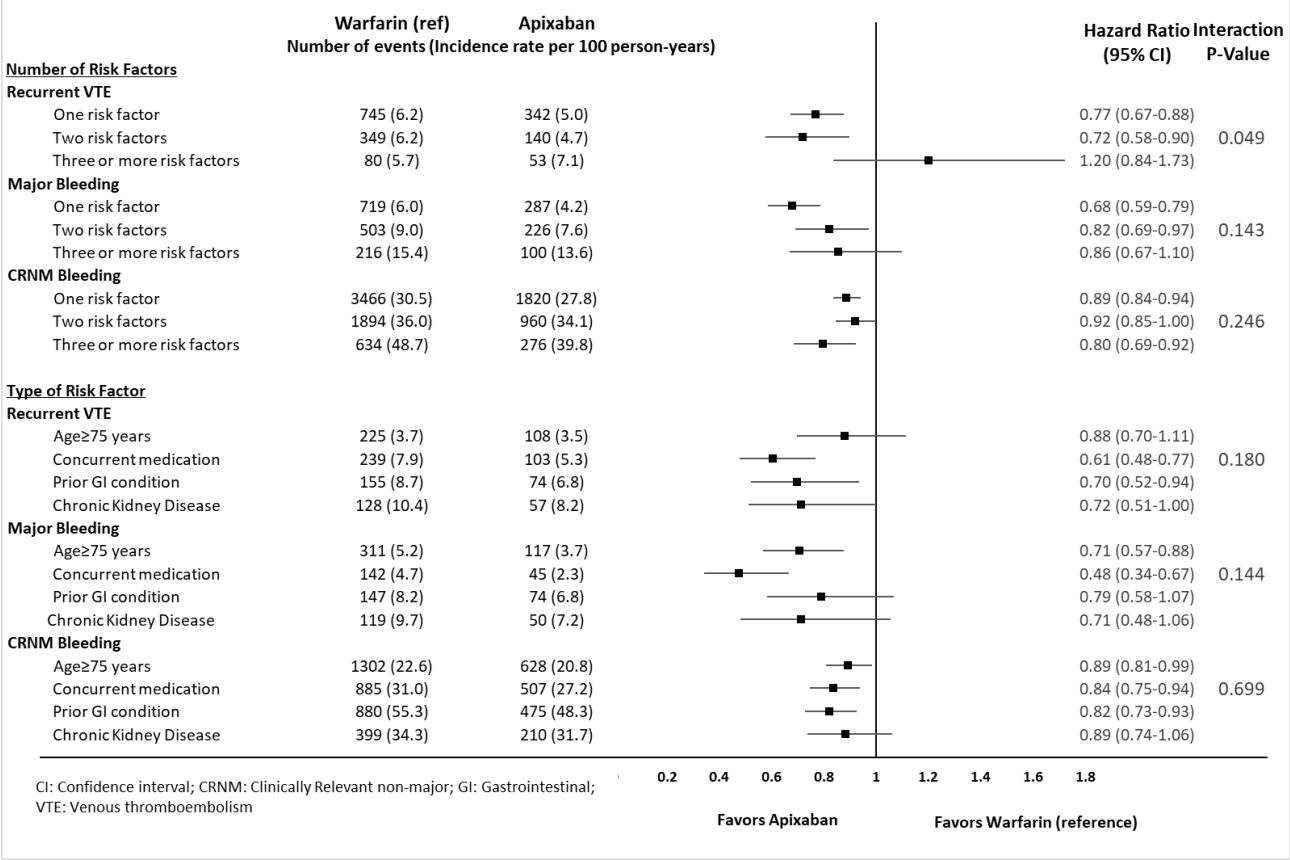
ESRD: end stage renal disease; GI: Gastrointestinal; IPTW: inverse probability treatment weighting; SD: Standard deviation; STD: standardized difference; VTE: venous thromboembolism

[a]Standardized Difference=100*|actual standardized difference|. Standardized Difference greater than 10 was considered significant.

[b]Hematologic disorders associated with bleeding: conditions that hinder mediation of blood clotting and increase bleeding risk, e.g., Von Willebrand's disease, the defibrination syndrome, acquired coagulation factor deficiency, unspecified coagulation defects, allergic purpura, qualitative platelet defects, nonthrombocytopenic purpuras, thrombocytopenia, and thrombotic microangiopathy.

[c]Thrombophilia: conditions that increase the risk of blood clot development, e.g., diseases of blood and blood-forming organs, thalassemia, polycythemia vera, prothrombin gene mutation, and lupus anticoagulant syndrome.

**Figure 14. Risk of Recurrent VTE, MB and CRNM Bleed among VTE patients with a high risk of bleeding stratified by number and type of risk factors**




### 9.2.5. Findings from Bleeding and VTE Recurrence Risk Factor Subgroup Analysis

After applying the inclusion and exclusion criteria, a total of 155,119 patients with VTE, including 60,786 (39.2%) who initiated apixaban and 94,333 (60.8%) who initiated warfarin, were identified in the pooled databases (Figure 15). The baseline characteristics of patients with VTE receiving apixaban or warfarin before and after IPTW are shown in Table 26.

Post-IPTW baseline characteristics were well balanced (Tables 27 and 28). For the two treatment cohorts, 20.7% of patients had a history of bleed whereas 5.4% had thrombocytopenia, ~4.0% had thrombophilia, 6.7% (warfarin) to 7.8% (apixaban) had chronic liver disease, and 5.3% (apixaban) to 7.0% (warfarin) had immune mediated disorders during the baseline period. During follow-up, apixaban was associated with a significantly lower risk of recurrent VTE (hazard ratio [HR]: 0.72; 95% confidence interval [CI]: 0.67-0.78), MB (HR: 0.70; 95% CI: 0.64-0.76), and CRNM bleeding (HR:0.83; 95% CI:0.80-0.86) compared to warfarin.

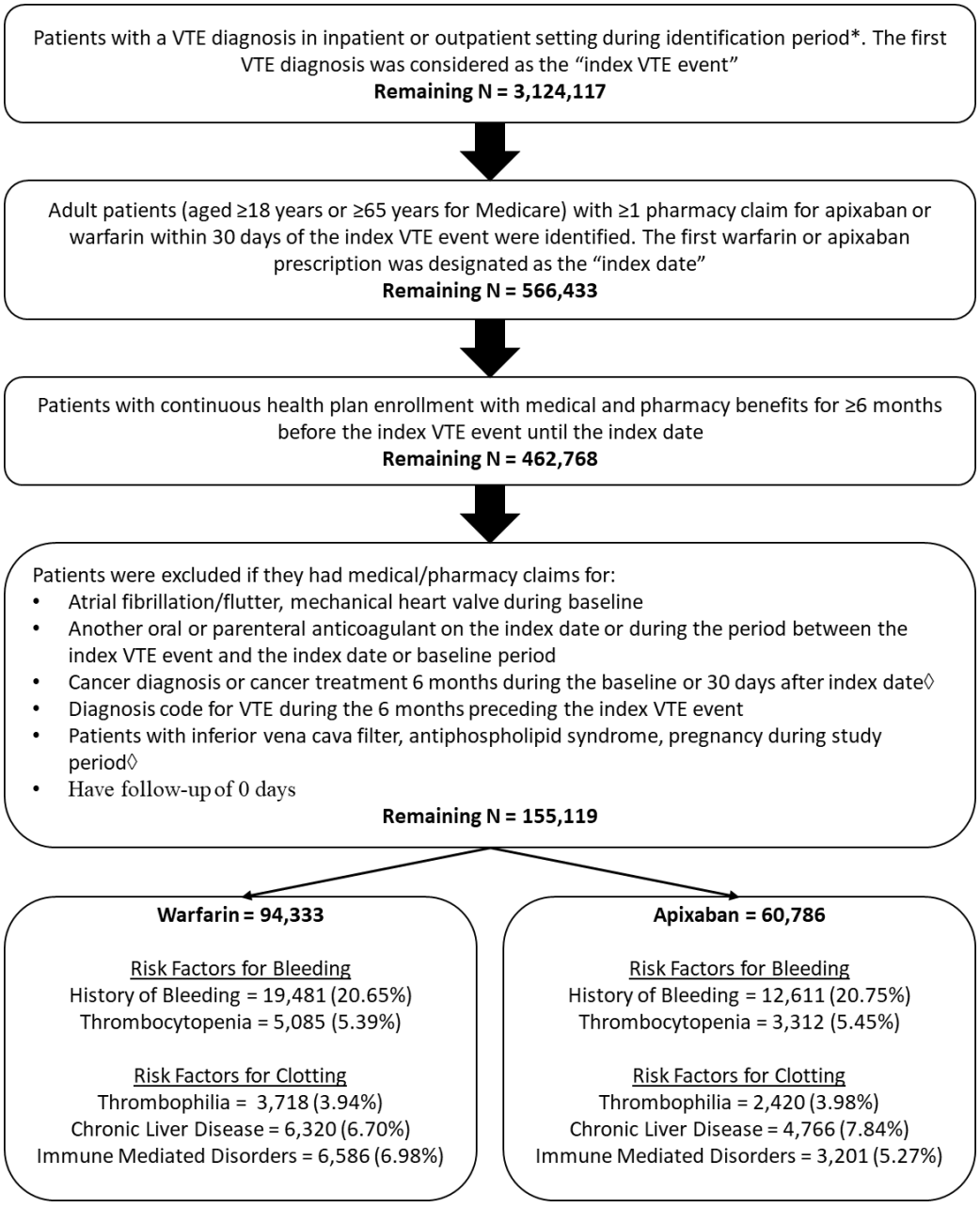
Table 27 shows patient characteristics stratified by history of bleeding and thrombocytopenia. Patients with a history of bleeding were more likely to have an inpatient

VTE diagnosis, provoked VTE, and higher mean Deyo-Charlson comorbidity index (Deyo-CCI) score compared to patients without a history of bleeding. Similar differences were observed for patients with thrombocytopenia vs. those without thrombocytopenia. Patient characteristics by thrombophilia, chronic liver disease and immune mediated disorders were presented in Table 3. Patients with each of the conditions were also more likely to have inpatient VTE diagnosis than those without the condition. The mean Deyo-CCI score was also higher for patients with chronic liver disease and patients with immune mediated disorders.

Figures 16-18 show incidence rates and hazard ratios of recurrent VTE, MB, and CRNM bleeding for apixaban vs. warfarin stratified by history of bleed, thrombocytopenia, thrombophilia, chronic liver disease and immune mediated disorders. No significant interaction was observed between treatment and history of bleed for recurrent VTE (interaction p=0.309); however, significant interactions were observed between treatment and history of bleed for MB (interaction p=0.001) and CRNM bleeding (interaction p<0.001). Apixaban patients had a lower risk of MB and CRNM bleeding among patients with or without a history of bleed, but the magnitude of the treatment effects was larger for patients without a history of bleeding. When stratified by diagnosis of thrombocytopenia, no significant interaction was observed between treatment and thrombocytopenia for recurrent VTE (interaction p=0.349) or CRNM bleeding (interaction p=0.628). A significant interaction was observed between treatment and thrombocytopenia for MB (interaction p=0.006): apixaban had a lower risk among patients without thrombocytopenia and similar risk among patients with thrombocytopenia compared to warfarin.

When stratified by the presence and absence of thrombophilia, no significant interaction was observed between treatment and thrombophilia for recurrent VTE (interaction p=0.598) or MB (interaction p=0.500). A significant interaction was observed between treatment and thrombophilia for CRNM bleeding (interaction p=0.078). Apixaban was associated with a lower risk of CRNM bleeding across patients with or without thrombophilia compared to warfarin, but treatment effects were larger for patients with thrombophilia. No significant interaction was observed between treatment and chronic liver disease for recurrent VTE (interaction p=0.853), MB (interaction p=0.389), or CRNM bleeding (interaction p=0.652). Similarly, no significant interaction was observed between treatment and immune mediated disorders for recurrent VTE (interaction p=0.692), MB (interaction p=0.211), or CRNM bleeding (interaction p=0.906).

**Figure 15. Patient Selection Risk of Bleed and Clot**



# Table 26. Patient Characteristics Stratified by Bleeding Risk Factors

| | Patients at risk of bleeding | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | History of Bleed - No | | | | | History of Bleed - Yes | | | | | Thrombocytopenia - No | | | | | Thrombocytopenia - Yes | | | | |
| | Warfarin Cohort | | Apixaban Cohort | | | Warfarin Cohort | | Apixaban Cohort | | | Warfarin Cohort | | Apixaban Cohort | | | Warfarin Cohort | | Apixaban Cohort | | |
| | N/Mean | %/SD | N/Mean | %/SD | STD* | N/Mean | %/SD | N/Mean | %/SD | STD* | N/Mean | %/SD | N/Mean | %/SD | STD* | N/Mean | %/SD | N/Mean | %/SD | STD* |
| **Sample Size** | **74,852** | **1** | **48,175** | **1** | **0** | **19,481** | **1** | **12,611** | **1** | **0** | **89,248** | **1** | **57,474** | **1** | **0** | **5,085** | **1** | **3,312** | **1** | **0** |
| **Age** | 66.40 | 16.15 | 66.35 | 15.68 | 0.27 | 67.66 | 15.15 | 68.43 | 17.14 | 4.76 | 67.34 | 15.85 | 65.13 | 16.16 | 13.80 | 70.31 | 13.56 | 68.67 | 16.28 | 10.94 |
| **18-54** | 16,632 | 22.22% | 10,790 | 22.40% | 0.43 | 3,817 | 19.59% | 2,308 | 18.31% | 3.21 | 18141.68 | 0.203273 | 14,403 | 25.06% | 11.33 | 649 | 12.76% | 519 | 15.68% | 8.09 |
| **55-64** | 12,687 | 16.95% | 8,259 | 17.14% | 0.52 | 2,743 | 14.08% | 1,649 | 13.08% | 2.86 | 13,568 | 15.20% | 10,738 | 18.68% | 9.30 | 635 | 12.49% | 562 | 16.96% | 12.20 |
| **65-74** | 20,863 | 27.87% | 13,325 | 27.66% | 0.48 | 5,846 | 30.01% | 3,894 | 30.88% | 1.84 | 26,037 | 29.17% | 15,001 | 26.10% | 6.88 | 1,773 | 34.86% | 1,000 | 30.20% | 9.71 |
| **75-79** | 8,991 | 12.01% | 5,752 | 11.94% | 0.22 | 2,555 | 13.11% | 1,720 | 13.64% | 1.49 | 11,369 | 12.74% | 6,366 | 11.08% | 5.14 | 742 | 14.59% | 457 | 13.79% | 2.24 |
| **≥80** | 15,680 | 20.95% | 10,049 | 20.86% | 0.22 | 4,520 | 23.20% | 3,040 | 24.10% | 2.06 | 20,132 | 22.56% | 10,966 | 19.08% | 8.58 | 1,286 | 25.30% | 774 | 23.37% | 4.39 |
| **Gender** | | | | | | | | | | | | | | | | | | | | |
| **Male** | 34,411 | 45.97% | 22,214 | 46.11% | 0.28 | 8,179 | 41.99% | 5,196 | 41.20% | 1.55 | 39,253 | 43.98% | 26,267 | 45.70% | 3.46 | 2,708 | 53.25% | 1,792 | 54.12% | 1.70 |
| **Female** | 40,441 | 54.03% | 25,961 | 53.89% | 0.28 | 11,302 | 58.01% | 7,415 | 58.80% | 1.55 | 49,995 | 56.02% | 31,207 | 54.30% | 3.46 | 2,377 | 46.75% | 1,519 | 45.88% | 1.70 |
| **Type of Index Encounter** | | | | | | | | | | | | | | | | | | | | |
| **Inpatient** | 37,495 | 50.09% | 24,276 | 50.39% | 0.60 | 13,602 | 69.82% | 8,754 | 69.41% | 0.87 | 47,946 | 53.72% | 29,524 | 51.37% | 4.72 | 3,870 | 76.10% | 2,520 | 76.10% | 0.00 |
| **Outpatient** | 37,358 | 49.91% | 23,898 | 49.61% | 0.60 | 5,878 | 30.18% | 3,857 | 30.59% | 0.87 | 41,302 | 46.28% | 27,950 | 48.63% | 4.72 | 1,215 | 23.90% | 792 | 23.90% | 0.00 |
| **VTE Diagnosis** | | | | | | | | | | | | | | | | | | | | |
| **DVT only** | 42,924 | 57.34% | 27,511 | 57.11% | 0.48 | 10,356 | 53.16% | 6,857 | 54.37% | 2.37 | 50,292 | 56.35% | 32,741 | 56.97% | 1.24 | 2,781 | 54.70% | 1,894 | 57.19% | 4.90 |
| **PE with DVT** | 10,584 | 14.14% | 6,871 | 14.26% | 0.35 | 2,809 | 14.42% | 1,764 | 13.98% | 1.22 | 12,547 | 14.06% | 7,908 | 13.76% | 0.86 | 958 | 18.83% | 585 | 17.66% | 2.97 |
| **PE without DVT** | 21,344 | 28.52% | 13,793 | 28.63% | 0.26 | 6,315 | 32.42% | 3,991 | 31.65% | 1.61 | 26,409 | 29.59% | 16,824 | 29.27% | 0.70 | 1,346 | 26.47% | 833 | 25.15% | 2.93 |
| **VTE Etiology** | | | | | | | | | | | | | | | | | | | | |
| **Provoked** | 38,528 | 51.47% | 24,840 | 51.56% | 0.18 | 14,548 | 74.68% | 9,424 | 74.73% | 0.11 | 50,321 | 56.38% | 30,762 | 53.52% | 5.76 | 3,814 | 74.99% | 2,478 | 74.82% | 0.39 |
| **Unprovoked** | 36,324 | 48.53% | 23,335 | 48.44% | 0.18 | 4,933 | 25.32% | 3,187 | 25.27% | 0.11 | 38,927 | 43.62% | 26,712 | 46.48% | 5.76 | 1,272 | 25.01% | 834 | 25.18% | 0.39 |
| **Baseline Comorbidity** | | | | | | | | | | | | | | | | | | | | |
| **Deyo-Charlson Comorbidity Index** | 2.00 | 2.28 | 2.00 | 2.22 | 0.07 | 3.00 | 2.52 | 3.07 | 2.98 | 2.57 | 2.18 | 2.35 | 2.04 | 2.29 | 6.21 | 3.64 | 2.69 | 3.60 | 3.14 | 1.58 |
| **AIDS** | 321 | 0.43% | 183 | 0.38% | 0.78 | 81 | 0.42% | 50 | 0.40% | 0.25 | 335 | 0.38% | 222 | 0.39% | 0.16 | 43 | 0.84% | 34 | 1.04% | 1.96 |
| **Alcohol abuse** | 2,072 | 2.77% | 1,345 | 2.79% | 0.14 | 915 | 4.70% | 592 | 4.70% | 0.00 | 2,520 | 2.82% | 1,699 | 2.96% | 0.79 | 409 | 8.05% | 298 | 9.00% | 3.30 |
| **Anemia** | 15,675 | 20.94% | 10,332 | 21.45% | 1.24 | 12,076 | 61.99% | 7,653 | 60.69% | 2.61 | 25,455 | 28.52% | 15,317 | 26.65% | 4.19 | 2,911 | 57.24% | 1,946 | 58.76% | 3.01 |
| **Central venous Catheter** | 3,967 | 5.30% | 2,663 | 5.53% | 1.02 | 3,705 | 19.02% | 2,313 | 18.34% | 1.69 | 6,494 | 7.28% | 4,149 | 7.22% | 0.22 | 1,166 | 22.93% | 791 | 23.87% | 2.15 |
| **Cerebrovascular disease** | 7,919 | 10.58% | 4,756 | 9.87% | 2.34 | 4,243 | 21.78% | 2,538 | 20.12% | 3.98 | 11,414 | 12.79% | 6,245 | 10.87% | 5.96 | 1,068 | 21.01% | 601 | 18.16% | 7.02 |
| **Coagulation defects** | 4,860 | 6.49% | 3,186 | 6.61% | 0.49 | 2,751 | 14.12% | 1,814 | 14.38% | 0.73 | 2,610 | 2.92% | 1,549 | 2.70% | 1.39 | 5,085 | 100.00% | 3,312 | 100.00% | 0.00 |
| **Ischemic heart/ coronary artery disease** | 17,426 | 23.28% | 11,232 | 23.32% | 0.08 | 6,525 | 33.49% | 4,259 | 33.77% | 0.57 | 22,646 | 25.37% | 13,328 | 23.19% | 5.10 | 2,002 | 39.38% | 1,298 | 39.20% | 0.36 |
| **Dementia** | 4,208 | 5.62% | 3,322 | 6.90% | 5.29 | 1,467 | 7.53% | 1,279 | 10.14% | 8.89 | 5,621 | 6.30% | 3,747 | 6.52% | 0.90 | 408 | 8.02% | 348 | 10.50% | 8.30 |
| **Dyspepsia or stomach discomfort** | 14,296 | 19.10% | 9,268 | 19.24% | 0.36 | 7,256 | 37.25% | 4,692 | 37.20% | 0.09 | 19,967 | 22.37% | 12,678 | 22.06% | 0.76 | 1,675 | 32.93% | 1,138 | 34.37% | 2.96 |
| **Hemiplegia or Paraplegia** | 1,225 | 1.64% | 773 | 1.60% | 0.26 | 810 | 4.16% | 524 | 4.16% | 0.01 | 1,883 | 2.11% | 1,146 | 1.99% | 0.82 | 168 | 3.30% | 123 | 3.71% | 2.15 |
| **Hyperlipidemia** | 34,704 | 46.36% | 22,366 | 46.43% | 0.13 | 10,740 | 55.13% | 6,967 | 55.24% | 0.22 | 43,436 | 48.67% | 26,268 | 45.70% | 5.95 | 2,984 | 58.69% | 1,885 | 56.93% | 3.46 |
| **Obesity** | 20,258 | 27.06% | 12,978 | 26.94% | 0.28 | 5,960 | 30.60% | 3,919 | 31.07% | 1.01 | 24,408 | 27.35% | 16,043 | 27.91% | 1.26 | 1,603 | 31.53% | 1,005 | 30.35% | 2.49 |
| **Pneumonia** | 9,404 | 12.56% | 6,053 | 12.56% | 0.00 | 4,237 | 21.75% | 2,766 | 21.93% | 0.42 | 12,587 | 14.10% | 7,690 | 13.38% | 2.10 | 1,255 | 24.68% | 867 | 26.17% | 3.33 |
| **Rheumatologic disease** | 3,303 | 4.41% | 2,139 | 4.44% | 0.13 | 1,127 | 5.78% | 715 | 5.67% | 0.49 | 4,290 | 4.81% | 2,503 | 4.35% | 2.16 | 289 | 5.68% | 184 | 5.57% | 0.49 |
| **Sleep apnea** | 9,677 | 12.93% | 6,231 | 12.93% | 0.02 | 2,957 | 15.18% | 1,887 | 14.96% | 0.59 | 11,887 | 13.32% | 7,580 | 13.19% | 0.39 | 783 | 15.39% | 480 | 14.48% | 2.50 |
| **Spinal cord injury** | 132 | 0.18% | 99 | 0.20% | 0.64 | 121 | 0.62% | 69 | 0.55% | 0.92 | 238 | 0.27% | 150 | 0.26% | 0.12 | 15 | 0.30% | 20 | 0.61% | 4.46 |
| **Thrombophilia** | 2,865 | 3.83% | 1,876 | 3.89% | 0.34 | 853 | 4.38% | 545 | 4.32% | 0.28 | 3,319 | 3.72% | 2,259 | 3.93% | 1.11 | 327 | 6.43% | 208 | 6.28% | 0.61 |
| **Varicose Veins** | 3,305 | 4.42% | 2,111 | 4.38% | 0.16 | 683 | 3.51% | 449 | 3.56% | 0.27 | 3,834 | 4.30% | 2,446 | 4.26% | 0.20 | 188 | 3.71% | 101 | 3.06% | 3.53 |
| **Congestive Heart Failure** | 11,350 | 15.16% | 7,212 | 14.97% | 0.54 | 4,551 | 23.36% | 3,108 | 24.64% | 2.92 | 14,852 | 16.64% | 8,663 | 15.07% | 4.30 | 1,529 | 30.07% | 1,006 | 30.37% | 0.64 |
| **Diabetes** | 22,713 | 30.34% | 13,444 | 27.91% | 5.38 | 6,995 | 35.91% | 4,344 | 34.45% | 2.98 | 28,084 | 31.47% | 15,922 | 27.70% | 8.26 | 2,157 | 42.41% | 1,253 | 37.83% | 9.13 |
| **Hypertension** | 50,066 | 66.89% | 32,177 | 66.79% | 0.20 | 15,000 | 77.00% | 9,837 | 78.00% | 2.33 | 62,041 | 69.52% | 38,072 | 66.24% | 7.02 | 4,143 | 81.47% | 2,658 | 80.24% | 3.02 |
| **Non-ESRD Renal Disease** | 9,677 | 12.93% | 6,131 | 12.73% | 0.61 | 3,160 | 16.22% | 2,166 | 17.18% | 2.50 | 12,122 | 13.58% | 7,121 | 12.39% | 3.55 | 1,119 | 22.00% | 704 | 21.27% | 1.71 |
| **End Stage Renal Disease** | 1,311 | 1.75% | 834 | 1.73% | 0.15 | 868 | 4.46% | 600 | 4.76% | 1.41 | 1,894 | 2.12% | 1,125 | 1.96% | 1.17 | 339 | 6.66% | 259 | 7.81% | 4.29 |
| **Chronic Liver Disease** | 4,245 | 5.67% | 3,263 | 6.77% | 4.58 | 2,075 | 10.65% | 1,503 | 11.92% | 3.89 | 5,312 | 5.95% | 4,139 | 7.20% | 5.05 | 953 | 18.74% | 687 | 20.74% | 4.89 |
| **COPD** | 12,863 | 17.18% | 8,208 | 17.04% | 0.39 | 4,602 | 23.62% | 3,069 | 24.33% | 1.62 | 16,592 | 18.59% | 9,781 | 17.02% | 4.12 | 1,388 | 27.30% | 869 | 26.24% | 2.34 |
| **Peptic Ulcer Disease** | 806 | 1.08% | 510 | 1.06% | 0.17 | 1,164 | 5.98% | 760 | 6.02% | 0.20 | 1,843 | 2.06% | 1,102 | 1.92% | 1.05 | 184 | 3.61% | 111 | 3.34% | 1.43 |
| **Inflammatory Bowel Disease** | 1,054 | 1.41% | 683 | 1.42% | 0.08 | 715 | 3.67% | 449 | 3.56% | 0.59 | 1,618 | 1.81% | 1,067 | 1.86% | 0.32 | 147 | 2.88% | 81 | 2.44% | 2.72 |
| **Peripheral vascular disease** | 13,162 | 17.58% | 8,304 | 17.24% | 0.92 | 5,049 | 25.92% | 3,301 | 26.18% | 0.57 | 17,207 | 19.28% | 10,032 | 17.45% | 4.72 | 1,513 | 29.74% | 935 | 28.23% | 3.26 |
| **Baseline bleed** | 0 | 0.00% | 0 | 0.00% | 0.00 | 19,481 | 100.00% | 12,611 | 100.00% | 0.00 | 17,718 | 19.85% | 11,155 | 19.41% | 1.12 | 1,941 | 38.17% | 1,254 | 37.86% | 0.62 |
| **Recent History of Falls** | 4,528 | 6.05% | 2,894 | 6.01% | 0.17 | 2,325 | 11.93% | 1,532 | 12.15% | 0.63 | 6,544 | 7.33% | 3,872 | 6.74% | 2.33 | 509 | 10.02% | 345 | 10.42% | 1.31 |
| **Fracture/trauma involving Lower Extremities** | 10,459 | 13.97% | 6,796 | 14.11% | 0.39 | 4,056 | 20.82% | 2,549 | 20.21% | 1.47 | 13,720 | 15.37% | 8,867 | 15.43% | 0.15 | 852 | 16.75% | 513 | 15.50% | 3.30 |
| **Selected Surgeries** | 13,391 | 17.89% | 8,819 | 18.31% | 1.09 | 9,962 | 51.14% | 6,290 | 49.87% | 2.47 | 21,099 | 23.64% | 13,363 | 23.25% | 0.92 | 2,320 | 45.63% | 1,557 | 47.00% | 2.68 |
| **Baseline Medication Use** | | | | | | | | | | | | | | | | | | | | |
| **Antiarrhythmic** | 6,722 | 8.98% | 4,385 | 9.10% | 0.42 | 2,322 | 11.92% | 1,456 | 11.55% | 1.13 | 8,548 | 9.58% | 5,383 | 9.37% | 0.72 | 561 | 11.03% | 380 | 11.48% | 1.38 |
| **Statins** | 27,875 | 37.24% | 17,991 | 37.34% | 0.22 | 8,418 | 43.21% | 5,446 | 43.18% | 0.06 | 34,653 | 38.83% | 21,058 | 36.64% | 4.52 | 2,352 | 46.24% | 1,473 | 44.48% | 3.45 |
| **Anti-platelets** | 5,042 | 6.74% | 3,240 | 6.73% | 0.05 | 2,097 | 10.77% | 1,374 | 10.89% | 0.39 | 6,827 | 7.65% | 3,974 | 6.91% | 2.83 | 533 | 10.49% | 375 | 11.32% | 2.61 |
| **Aromatase Inhibitors (Anastrozole, exemestabe, letrozole)** | 182 | 0.24% | 115 | 0.24% | 0.09 | 25 | 0.13% | 16 | 0.13% | 0.06 | 197 | 0.22% | 127 | 0.22% | 0.02 | 12 | 0.25% | 7 | 0.20% | 1.02 |
| **Beta Blockers** | 24,201 | 32.33% | 15,576 | 32.33% | 0.00 | 7,907 | 40.59% | 5,208 | 41.29% | 1.40 | 30,393 | 34.06% | 18,341 | 31.91% | 4.57 | 2,415 | 47.49% | 1,613 | 48.71% | 2.37 |
| **Gastroprotective Agents** | 19,186 | 25.63% | 12,349 | 25.63% | 0.00 | 7,555 | 38.78% | 4,926 | 39.06% | 0.55 | 25,291 | 28.34% | 15,497 | 26.96% | 3.08 | 1,893 | 37.22% | 1,215 | 36.70% | 1.06 |
| **SERMS** | 450 | 0.60% | 294 | 0.61% | 0.11 | 117 | 0.60% | 70 | 0.55% | 0.61 | 575 | 0.64% | 320 | 0.56% | 1.13 | 20 | 0.39% | 20 | 0.59% | 2.72 |
| **NSAIDs** | 19,389 | 25.90% | 12,403 | 25.75% | 0.36 | 5,382 | 27.63% | 3,548 | 28.14% | 1.11 | 23,355 | 26.17% | 15,465 | 26.91% | 1.68 | 1,142 | 22.46% | 793 | 23.93% | 3.40 |
| **Hormone Therapy (estrogen)** | 4,053 | 5.41% | 2,665 | 5.53% | 0.51 | 1,154 | 5.92% | 679 | 5.39% | 2.28 | 4,875 | 5.46% | 3,524 | 6.13% | 2.87 | 125 | 2.46% | 83 | 2.50% | 0.30 |

# Table 27. Patient Characteristics Stratified by VTE Recurrence Risk Factors

| | Patients at risk of clotting | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Thrombophilia - No | | | | | Thrombophilia - Yes | | | | | Chronic Liver Disease - No | | | | | Chronic Liver Disease - Yes | | | | | Immune mediated disorder - No | | | | | Immune mediated disorder - Yes | | | | |
| | Warfarin Cohort | | Apixaban Cohort | | | Warfarin Cohort | | Apixaban Cohort | | | Warfarin Cohort | | Apixaban Cohort | | | Warfarin Cohort | | Apixaban Cohort | | | Warfarin Cohort | | Apixaban Cohort | | | Warfarin Cohort | | Apixaban Cohort | | |
| | N/Mean | %/SD | N/Mean | %/SD | STD* | N/Mean | %/SD | N/Mean | %/SD | STD* | N/Mean | %/SD | N/Mean | %/SD | STD* | N/Mean | %/SD | N/Mean | %/SD | STD* | N/Mean | %/SD | N/Mean | %/SD | STD* | N/Mean | %/SD | N/Mean | %/SD | STD* |
| **Sample Size** | **90,615** | **1** | **58,366** | **1** | **0** | **3,718** | **1** | **2,420** | **1** | **0** | **88,013** | **1** | **56,020** | **1** | **0** | **6,320** | **1** | **4,766** | **1** | **0** | 87,747 | **1** | 57,585 | **1** | **0** | 6,586 | **1** | 3,201 | **1** | **0** |
| **Age** | 66.92 | 15.88 | 67.00 | 15.87 | 0.51 | 60.32 | 16.14 | 61.62 | 17.66 | 7.70 | 66.85 | 16.05 | 66.92 | 16.05 | 0.48 | 64.04 | 14.18 | 65.16 | 14.88 | 7.67 | 67.36 | 15.82 | 65.24 | 16.18 | 13.29 | 69.38 | 14.56 | 66.96 | 16.23 | 15.69 |
| **18-54** | 19,151 | 21.13% | 12,333 | 21.13% | 0.01 | 1,298 | 34.90% | 765 | 31.62% | 6.86 | 18,947 | 21.53% | 12,073 | 21.55% | 0.06 | 1,502 | 23.76% | 1,025 | 21.52% | 5.32 | 17785.33 | 0.202688 | 14,282 | 24.80% | 10.87 | 1,005 | 15.27% | 640 | 19.99% | 12.27 |
| **55-64** | 14,712 | 16.24% | 9,474 | 16.23% | 0.01 | 718 | 19.30% | 435 | 17.96% | 3.41 | 14,130 | 16.05% | 9,002 | 16.07% | 0.04 | 1,300 | 20.57% | 906 | 19.02% | 3.85 | 13,400 | 15.27% | 10,744 | 18.66% | 9.04 | 804 | 12.20% | 556 | 17.37% | 14.40 |
| **65-74** | 25,749 | 28.42% | 16,553 | 28.36% | 0.12 | 959 | 25.80% | 666 | 27.51% | 3.82 | 24,631 | 27.99% | 15,588 | 27.83% | 0.36 | 2,078 | 32.87% | 1,631 | 34.22% | 2.83 | 25,623 | 29.20% | 15,069 | 26.17% | 6.78 | 2,187 | 33.20% | 932 | 29.12% | 8.74 |
| **75-79** | 11,227 | 12.39% | 7,225 | 12.38% | 0.03 | 318 | 8.55% | 246 | 10.16% | 5.41 | 10,893 | 12.38% | 6,921 | 12.35% | 0.07 | 652 | 10.31% | 550 | 11.54% | 3.91 | 11,148 | 12.70% | 6,427 | 11.16% | 4.77 | 963 | 14.62% | 396 | 12.36% | 6.57 |
| **≥80** | 19,775 | 21.82% | 12,780 | 21.90% | 0.18 | 425 | 11.44% | 308 | 12.74% | 3.93 | 19,411 | 22.05% | 12,436 | 22.20% | 0.35 | 789 | 12.49% | 653 | 13.70% | 3.56 | 19,791 | 22.55% | 11,063 | 19.21% | 8.23 | 1,627 | 24.71% | 677 | 21.16% | 8.36 |
| **Gender** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Male** | 40,798 | 45.02% | 26,221 | 44.92% | 0.20 | 1,792 | 48.21% | 1,189 | 49.13% | 1.83 | 39,427 | 44.80% | 25,114 | 44.83% | 0.07 | 3,163 | 50.05% | 2,296 | 48.18% | 3.72 | 39,936 | 45.51% | 26,998 | 46.88% | 2.75 | 2,024 | 30.74% | 1,062 | 33.18% | 5.17 |
| **Female** | 49,817 | 54.98% | 32,145 | 55.08% | 0.20 | 1,926 | 51.79% | 1,231 | 50.87% | 1.83 | 48,586 | 55.20% | 30,907 | 55.17% | 0.07 | 3,157 | 49.95% | 2,470 | 51.82% | 3.72 | 47,811 | 54.49% | 30,588 | 53.12% | 2.75 | 4,561 | 69.26% | 2,139 | 66.82% | 5.17 |
| **Type of Index Encounter** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Inpatient** | 48,750 | 53.80% | 31,413 | 53.82% | 0.04 | 2,347 | 63.11% | 1,617 | 66.82% | 7.66 | 46,810 | 53.19% | 29,717 | 53.05% | 0.28 | 4,287 | 67.83% | 3,313 | 69.52% | 3.60 | 47,633 | 54.28% | 30,113 | 52.29% | 4.00 | 4,183 | 63.51% | 1,932 | 60.35% | 6.44 |
| **Outpatient** | 41,865 | 46.20% | 26,953 | 46.18% | 0.04 | 1,372 | 36.89% | 803 | 33.18% | 7.66 | 41,203 | 46.81% | 26,303 | 46.95% | 0.28 | 2,033 | 32.17% | 1,453 | 30.48% | 3.60 | 40,114 | 45.72% | 27,473 | 47.71% | 4.00 | 2,403 | 36.49% | 1,269 | 39.65% | 6.44 |
| **VTE Diagnosis** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **DVT only** | 51,491 | 56.82% | 33,220 | 56.92% | 0.19 | 1,788 | 48.10% | 1,147 | 47.41% | 1.36 | 50,067 | 56.89% | 32,052 | 57.21% | 0.66 | 3,213 | 50.83% | 2,316 | 48.59% | 4.46 | 49,463 | 56.37% | 32,783 | 56.93% | 1.13 | 3,611 | 54.82% | 1,852 | 57.87% | 6.09 |
| **PE with DVT** | 12,588 | 13.89% | 8,096 | 13.87% | 0.06 | 806 | 21.67% | 539 | 22.26% | 1.41 | 12,381 | 14.07% | 7,891 | 14.09% | 0.05 | 1,013 | 16.02% | 744 | 15.61% | 1.11 | 12,459 | 14.20% | 8,060 | 14.00% | 0.58 | 1,046 | 15.88% | 433 | 13.52% | 6.61 |
| **PE without DVT** | 26,536 | 29.28% | 17,050 | 29.21% | 0.16 | 1,124 | 30.23% | 734 | 30.33% | 0.21 | 25,565 | 29.05% | 16,078 | 28.70% | 0.77 | 2,095 | 33.14% | 1,706 | 35.80% | 5.55 | 25,825 | 29.43% | 16,742 | 29.07% | 0.79 | 1,929 | 29.30% | 916 | 28.61% | 1.51 |
| **VTE Etiology** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Provoked** | 51,034 | 56.32% | 32,825 | 56.24% | 0.16 | 2,042 | 54.92% | 1,439 | 59.46% | 9.05 | 48,891 | 55.55% | 31,033 | 55.40% | 0.31 | 4,185 | 66.22% | 3,231 | 67.79% | 3.33 | 49,744 | 56.69% | 31,190 | 54.16% | 5.09 | 4,391 | 66.67% | 2,050 | 64.07% | 5.42 |
| **Unprovoked** | 39,581 | 43.68% | 25,541 | 43.76% | 0.16 | 1,676 | 45.08% | 981 | 40.54% | 9.05 | 39,122 | 44.45% | 24,987 | 44.60% | 0.31 | 2,135 | 33.78% | 1,535 | 32.21% | 3.33 | 38,003 | 43.31% | 26,396 | 45.84% | 5.09 | 2,195 | 33.33% | 1,150 | 35.93% | 5.42 |
| **Baseline Comorbidity** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Deyo-Charlson Comorbidity Index** | 2.21 | 2.37 | 2.23 | 2.40 | 0.58 | 2.05 | 2.21 | 2.15 | 2.59 | 3.84 | 2.09 | 2.29 | 2.09 | 2.33 | 0.24 | 3.86 | 2.72 | 3.75 | 2.76 | 3.97 | 2.20 | 2.38 | 2.07 | 2.34 | 5.17 | 3.09 | 2.44 | 2.96 | 2.56 | 5.16 |
| **AIDS** | 391 | 0.43% | 219 | 0.38% | 0.88 | 11 | 0.29% | 14 | 0.57% | 4.12 | 330 | 0.37% | 185 | 0.33% | 0.75 | 72 | 1.13% | 48 | 1.01% | 1.23 | 361 | 0.41% | 243 | 0.42% | 0.16 | 17 | 0.25% | 13 | 0.41% | 2.64 |
| **Alcohol abuse** | 2,852 | 3.15% | 1,840 | 3.15% | 0.03 | 135 | 3.64% | 98 | 4.03% | 2.01 | 2,136 | 2.43% | 1,382 | 2.47% | 0.26 | 851 | 13.47% | 556 | 11.66% | 5.43 | 2,756 | 3.14% | 1,920 | 3.33% | 1.09 | 173 | 2.63% | 77 | 2.41% | 1.42 |
| **Anemia** | 26,655 | 29.42% | 17,203 | 29.47% | 0.13 | 1,096 | 29.48% | 782 | 32.30% | 6.00 | 25,130 | 28.55% | 15,967 | 28.50% | 0.11 | 2,621 | 41.47% | 2,018 | 42.34% | 1.76 | 25,353 | 28.89% | 15,757 | 27.36% | 3.41 | 3,012 | 45.74% | 1,506 | 47.06% | 2.62 |
| **Central venous Catheter** | 7,362 | 8.12% | 4,761 | 8.16% | 0.12 | 310 | 8.33% | 216 | 8.91% | 2.02 | 6,519 | 7.41% | 4,114 | 7.34% | 0.24 | 1,153 | 18.24% | 863 | 18.10% | 0.35 | 6,818 | 7.77% | 4,430 | 7.69% | 0.29 | 842 | 12.79% | 510 | 15.92% | 8.83 |
| **Cerebrovascular disease** | 11,612 | 12.81% | 7,008 | 12.01% | 2.45 | 550 | 14.80% | 285 | 11.78% | 8.79 | 11,232 | 12.76% | 6,645 | 11.86% | 2.74 | 930 | 14.71% | 648 | 13.61% | 3.15 | 11,478 | 13.08% | 6,403 | 11.12% | 6.02 | 1,005 | 15.26% | 443 | 13.85% | 3.96 |
| **Coagulation defects** | 6,923 | 7.64% | 4,526 | 7.75% | 0.43 | 689 | 18.52% | 474 | 19.60% | 2.71 | 6,397 | 7.27% | 4,162 | 7.43% | 0.62 | 1,214 | 19.22% | 838 | 17.58% | 4.18 | 6,747 | 7.69% | 4,362 | 7.58% | 0.43 | 948 | 14.40% | 499 | 15.58% | 3.27 |
| **Ischemic heart/ coronary artery disease** | 23,093 | 25.48% | 14,919 | 25.56% | 0.18 | 858 | 23.07% | 572 | 23.62% | 1.29 | 22,036 | 25.04% | 14,077 | 25.13% | 0.21 | 1,915 | 30.30% | 1,414 | 29.66% | 1.39 | 22,758 | 25.94% | 13,741 | 23.86% | 4.80 | 1,891 | 28.71% | 885 | 27.64% | 2.34 |
| **Dementia** | 5,563 | 6.14% | 4,498 | 7.71% | 6.18 | 113 | 3.03% | 103 | 4.26% | 6.40 | 5,343 | 6.07% | 4,290 | 7.66% | 6.28 | 332 | 5.26% | 311 | 6.53% | 5.35 | 5,704 | 6.50% | 3,915 | 6.80% | 1.20 | 325 | 4.94% | 180 | 5.62% | 3.04 |
| **Dyspepsia or stomach discomfort** | 20,598 | 22.73% | 13,374 | 22.91% | 0.43 | 953 | 25.65% | 586 | 24.22% | 3.24 | 18,357 | 20.86% | 11,637 | 20.77% | 0.21 | 3,195 | 50.55% | 2,323 | 48.75% | 3.58 | 19,355 | 22.06% | 12,558 | 21.81% | 0.60 | 2,287 | 34.72% | 1,258 | 39.30% | 9.39 |
| **Hemiplegia or Paraplegia** | 1,940 | 2.14% | 1,229 | 2.11% | 0.25 | 95 | 2.55% | 68 | 2.80% | 1.51 | 1,871 | 2.13% | 1,184 | 2.11% | 0.09 | 163 | 2.58% | 112 | 2.36% | 1.44 | 1,936 | 2.21% | 1,193 | 2.07% | 0.93 | 115 | 1.75% | 76 | 2.36% | 4.26 |
| **Hyperlipidemia** | 43,799 | 48.33% | 28,244 | 48.39% | 0.11 | 1,645 | 44.25% | 1,089 | 44.99% | 1.46 | 42,257 | 48.01% | 26,848 | 47.93% | 0.17 | 3,187 | 50.43% | 2,485 | 52.14% | 3.41 | 42,991 | 48.99% | 26,594 | 46.18% | 5.64 | 3,429 | 52.07% | 1,560 | 48.74% | 6.60 |
| **Obesity** | 25,070 | 27.67% | 16,140 | 27.65% | 0.03 | 1,149 | 30.90% | 756 | 31.25% | 0.74 | 23,794 | 27.04% | 15,209 | 27.15% | 0.26 | 2,424 | 38.36% | 1,687 | 35.39% | 6.10 | 24,172 | 27.55% | 16,200 | 28.13% | 1.31 | 1,840 | 27.94% | 848 | 26.49% | 3.22 |
| **Pneumonia** | 13,102 | 14.46% | 8,443 | 14.47% | 0.02 | 539 | 14.50% | 376 | 15.53% | 2.81 | 12,248 | 13.92% | 7,778 | 13.88% | 0.09 | 1,393 | 22.04% | 1,041 | 21.84% | 0.48 | 12,552 | 14.30% | 7,947 | 13.80% | 1.45 | 1,290 | 19.59% | 611 | 19.08% | 1.27 |
| **Rheumatologic disease** | 4,268 | 4.71% | 2,734 | 4.68% | 0.12 | 162 | 4.35% | 119 | 4.93% | 2.70 | 4,066 | 4.62% | 2,608 | 4.66% | 0.17 | 363 | 5.75% | 246 | 5.16% | 2.59 | 1,427 | 1.63% | 1,474 | 2.56% | 6.52 | 3,151 | 47.85% | 1,213 | 37.91% | 19.99 |
| **Sleep apnea** | 12,112 | 13.37% | 7,749 | 13.28% | 0.26 | 523 | 14.06% | 369 | 15.25% | 3.30 | 11,467 | 13.03% | 7,321 | 13.07% | 0.12 | 1,168 | 18.47% | 797 | 16.73% | 4.56 | 11,682 | 13.31% | 7,615 | 13.22% | 0.26 | 988 | 15.01% | 444 | 13.89% | 3.16 |
| **Spinal cord injury** | 243 | 0.27% | 162 | 0.28% | 0.19 | 10 | 0.28% | 6 | 0.23% | 0.94 | 230 | 0.26% | 145 | 0.26% | 0.05 | 23 | 0.37% | 23 | 0.48% | 1.74 | 238 | 0.27% | 161 | 0.28% | 0.16 | 15 | 0.22% | 9 | 0.28% | 1.01 |
| **Thrombophilia** | | | | | | 3,718 | 100.00% | 2,420 | 100.00% | | 3,373 | 3.83% | 2,175 | 3.88% | 0.26 | 345 | 5.45% | 245 | 5.14% | 1.37 | 3,341 | 3.81% | 2,285 | 3.97% | 0.83 | 305 | 4.63% | 182 | 5.69% | 4.73 |
| **Varicose Veins** | 3,821 | 4.22% | 2,472 | 4.24% | 0.09 | 167 | 4.50% | 88 | 3.63% | 4.36 | 3,740 | 4.25% | 2,392 | 4.27% | 0.10 | 248 | 3.93% | 168 | 3.52% | 2.15 | 3,748 | 4.27% | 2,425 | 4.21% | 0.30 | 275 | 4.17% | 122 | 3.81% | 1.80 |
| **Congestive Heart Failure** | 15,368 | 16.96% | 9,947 | 17.04% | 0.22 | 533 | 14.32% | 372 | 15.39% | 2.95 | 14,518 | 16.49% | 9,248 | 16.51% | 0.04 | 1,383 | 21.88% | 1,071 | 22.48% | 1.42 | 14,978 | 17.07% | 9,061 | 15.73% | 3.61 | 1,403 | 21.31% | 608 | 19.00% | 5.70 |
| **Diabetes** | 28,711 | 31.68% | 17,186 | 29.45% | 4.86 | 997 | 26.83% | 603 | 24.91% | 4.32 | 27,267 | 30.98% | 16,056 | 28.66% | 5.08 | 2,441 | 38.62% | 1,733 | 36.36% | 4.63 | 28,016 | 31.93% | 16,199 | 28.13% | 8.29 | 2,225 | 33.78% | 975 | 30.47% | 7.03 |
| **Hypertension** | 62,755 | 69.25% | 40,460 | 69.32% | 0.15 | 2,312 | 62.19% | 1,554 | 64.21% | 4.13 | 60,272 | 68.48% | 38,373 | 68.50% | 0.04 | 4,794 | 75.86% | 3,640 | 76.39% | 1.24 | 61,168 | 69.71% | 38,404 | 66.69% | 6.49 | 5,016 | 76.16% | 2,325 | 72.65% | 7.96 |
| **Non-ESRD Renal Disease** | 13,525 | 14.93% | 8,735 | 14.97% | 0.11 | 449 | 12.07% | 334 | 13.82% | 5.12 | 12,928 | 14.69% | 8,273 | 14.77% | 0.22 | 1,045 | 16.54% | 796 | 16.71% | 0.47 | 12,092 | 13.78% | 7,304 | 12.68% | 3.24 | 1,149 | 17.45% | 521 | 16.28% | 3.08 |
| **End Stage Renal Disease** | 2,105 | 2.32% | 1,365 | 2.34% | 0.10 | 74 | 1.98% | 69 | 2.87% | 5.65 | 1,887 | 2.14% | 1,226 | 2.19% | 0.30 | 291 | 4.61% | 208 | 4.37% | 1.14 | 2,044 | 2.33% | 1,274 | 2.21% | 0.79 | 188 | 2.86% | 110 | 3.43% | 3.26 |
| **Chronic Liver Disease** | 5,976 | 6.59% | 4,521 | 7.75% | 4.46 | 345 | 9.27% | 245 | 10.12% | 2.85 | | | | | | 6,320 | 100.00% | 4,766 | 100.00% | | 5,674 | 6.47% | 4,416 | 7.67% | 4.70 | 591 | 8.98% | 410 | 12.80% | 12.13 |
| **COPD** | 16,822 | 18.56% | 10,867 | 18.62% | 0.14 | 642 | 17.28% | 410 | 16.93% | 0.91 | 15,915 | 18.08% | 10,118 | 18.06% | 0.05 | 1,550 | 24.52% | 1,159 | 24.31% | 0.49 | 16,279 | 18.55% | 9,928 | 17.24% | 3.43 | 1,701 | 25.83% | 723 | 22.59% | 7.52 |
| **Peptic Ulcer Disease** | 1,889 | 2.08% | 1,211 | 2.08% | 0.06 | 81 | 2.19% | 59 | 2.43% | 1.55 | 1,673 | 1.90% | 1,054 | 1.88% | 0.14 | 297 | 4.70% | 216 | 4.52% | 0.85 | 1,793 | 2.04% | 1,097 | 1.90% | 1.00 | 233 | 3.54% | 116 | 3.62% | 0.42 |
| **Inflammatory Bowel Disease** | 1,681 | 1.85% | 1,069 | 1.83% | 0.18 | 89 | 2.38% | 63 | 2.61% | 1.42 | 1,548 | 1.76% | 939 | 1.68% | 0.63 | 222 | 3.51% | 192 | 4.04% | 2.76 | 0 | 0.00% | 0 | 0.00% | 0.00 | 1,765 | 26.80% | 1,148 | 35.86% | 19.38 |
| **Peripheral vascular disease** | 17,480 | 19.29% | 11,120 | 19.05% | 0.60 | 732 | 19.68% | 484 | 20.02% | 0.83 | 16,678 | 18.95% | 10,497 | 18.74% | 0.54 | 1,533 | 24.26% | 1,107 | 23.24% | 2.39 | 17,113 | 19.50% | 10,217 | 17.74% | 4.52 | 1,606 | 24.39% | 750 | 23.42% | 2.26 |
| **Baseline bleed** | 18,628 | 20.56% | 12,067 | 20.67% | 0.29 | 853 | 22.93% | 545 | 22.50% | 1.02 | 17,406 | 19.78% | 11,108 | 19.83% | 0.13 | 2,075 | 32.83% | 1,503 | 31.54% | 2.75 | 17,694 | 20.16% | 11,400 | 19.80% | 0.92 | 1,965 | 29.84% | 1,009 | 31.52% | 3.61 |
| **Recent History of Falls** | 6,684 | 7.38% | 4,293 | 7.36% | 0.08 | 168 | 4.53% | 133 | 5.48% | 4.25 | 6,383 | 7.25% | 4,062 | 7.25% | 0.01 | 470 | 7.43% | 364 | 7.64% | 0.81 | 6,491 | 7.40% | 3,964 | 6.88% | 1.99 | 562 | 8.54% | 253 | 7.92% | 2.22 |
| **Fracture/trauma involving Lower Extremities** | 14,144 | 15.61% | 9,078 | 15.55% | 0.15 | 372 | 10.00% | 268 | 11.06% | 3.39 | 13,577 | 15.43% | 8,717 | 15.56% | 0.37 | 938 | 14.84% | 629 | 13.19% | 4.73 | 13,548 | 15.44% | 8,877 | 15.42% | 0.07 | 1,023 | 15.54% | 503 | 15.72% | 0.50 |
| **Selected Surgeries** | 22,442 | 24.77% | 14,471 | 24.79% | 0.06 | 910 | 24.49% | 638 | 26.35% | 4.21 | 20,799 | 23.63% | 13,250 | 23.65% | 0.05 | 2,554 | 40.41% | 1,859 | 39.00% | 2.86 | 21,296 | 24.27% | 13,792 | 23.95% | 0.75 | 2,123 | 32.24% | 1,127 | 35.22% | 6.24 |
| **Baseline Medication Use** | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Antiarrhythmic** | 8,749 | 9.65% | 5,605 | 9.60% | 0.18 | 295 | 7.94% | 236 | 9.75% | 6.27 | 8,352 | 9.49% | 5,275 | 9.42% | 0.25 | 692 | 10.94% | 566 | 11.87% | 2.88 | 8,175 | 9.32% | 5,270 | 9.15% | 0.57 | 935 | 14.19% | 493 | 15.41% | 3.38 |
| **Statins** | 35,043 | 38.67% | 22,652 | 38.81% | 0.28 | 1,250 | 33.62% | 785 | 32.42% | 2.53 | 34,039 | 38.68% | 21,625 | 38.60% | 0.15 | 2,254 | 35.66% | 1,812 | 38.02% | 4.86 | 34,520 | 39.34% | 21,393 | 37.15% | 4.51 | 2,484 | 37.72% | 1,137 | 35.54% | 4.49 |
| **Anti-platelets** | 6,889 | 7.60% | 4,436 | 7.60% | 0.00 | 251 | 6.75% | 177 | 7.31% | 2.18 | 6,670 | 7.58% | 4,262 | 7.61% | 0.11 | 470 | 7.43% | 351 | 7.37% | 0.22 | 6,826 | 7.78% | 4,110 | 7.14% | 2.45 | 534 | 8.11% | 239 | 7.47% | 2.36 |
| **Aromatase Inhibitors (Anastrozole, exemestabe, letrozole)** | 194 | 0.21% | 123 | 0.21% | 0.08 | 12 | 0.34% | 9 | 0.35% | 0.28 | 189 | 0.21% | 123 | 0.22% | 0.10 | 18 | 0.28% | 9 | 0.18% | 2.18 | 200 | 0.23% | 128 | 0.22% | 0.10 | 10 | 0.16% | 5 | 0.16% | 0.03 |
| **Beta Blockers** | 31,034 | 34.25% | 20,050 | 34.35% | 0.22 | 1,074 | 28.90% | 735 | 30.35% | 3.13 | 29,606 | 33.64% | 18,842 | 33.64% | 0.01 | 2,502 | 39.58% | 1,942 | 40.75% | 2.36 | 30,225 | 34.44% | 18,743 | 32.55% | 4.02 | 2,584 | 39.23% | 1,211 | 37.83% | 2.85 |
| **Gastroprotective Agents** | 25,763 | 28.43% | 16,649 | 28.52% | 0.21 | 978 | 26.30% | 626 | 25.85% | 1.02 | 24,157 | 27.45% | 15,336 | 27.37% | 0.16 | 2,584 | 40.89% | 1,939 | 40.68% | 0.42 | 24,376 | 27.78% | 15,347 | 26.65% | 2.54 | 2,808 | 42.64% | 1,365 | 42.65% | 0.02 |
| **SERMS** | 553 | 0.61% | 356 | 0.61% | 0.01 | 14 | 0.37% | 8 | 0.32% | 0.88 | 541 | 0.61% | 345 | 0.62% | 0.03 | 26 | 0.42% | 18 | 0.38% | 0.53 | 558 | 0.64% | 322 | 0.56% | 1.01 | 37 | 0.56% | 18 | 0.56% | 0.09 |
| **NSAIDs** | 23,849 | 26.32% | 15,339 | 26.28% | 0.09 | 921 | 24.77% | 612 | 25.29% | 1.19 | 23,009 | 26.14% | 14,642 | 26.14% | 0.01 | 1,762 | 27.87% | 1,309 | 27.47% | 0.88 | 22,498 | 25.64% | 15,363 | 26.68% | 2.36 | 1,999 | 30.35% | 895 | 27.97% | 5.18 |
| **Hormone Therapy (estrogen)** | 4,985 | 5.50% | 3,197 | 5.48% | 0.11 | 222 | 5.97% | 147 | 6.08% | 0.45 | 4,973 | 5.65% | 3,157 | 5.63% | 0.07 | 234 | 3.70% | 187 | 3.93% | 1.17 | 4,563 | 5.20% | 3,390 | 5.89% | 3.01 | 437 | 6.64% | 217 | 6.77% | 0.51 |

# Table 28. Patient Characteristics Pre/Post IPTW

| | Pre-IPTW | | | | | Post-IPTW | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Warfarin Cohort (Reference) | | Apixaban Cohort | | | Warfarin Cohort (Reference) | | Apixaban Cohort | | |
| | N/Mean | %/SD | N/Mean | %/SD | STD* | N/Mean | %/SD | N/Mean | %/SD | STD* |
| **Sample Size** | **94,333** | | **60,786** | | **0** | **94,333** | **1** | **60,786** | **1** | **0** |
| **Age** | 67.4 | 15.71 | 65.4 | 16.26 | 12.76 | 66.66 | 15.94 | 66.79 | 15.97 | 0.80 |
| **18-54** | 18,924 | 20.06% | 14,876 | 24.47% | 10.62 | 20,449 | 21.68% | 13,098 | 21.55% | 0.31 |
| **55-64** | 13,976 | 14.82% | 11,517 | 18.95% | 11.05 | 15,430 | 16.36% | 9,908 | 16.30% | 0.15 |
| **65-74** | 28,334 | 30.04% | 15,491 | 25.48% | 10.18 | 26,709 | 28.31% | 17,219 | 28.33% | 0.03 |
| **75-79** | 12,064 | 12.79% | 6,853 | 11.27% | 4.66 | 11,545 | 12.24% | 7,471 | 12.29% | 0.16 |
| **≥80** | 21,035 | 22.30% | 12,049 | 19.82% | 6.08 | 20,200 | 21.41% | 13,089 | 21.53% | 0.29 |
| **Gender** | | | | | | | | | | |
| **Male** | 41,850 | 44.36% | 28,261 | 46.49% | 4.28 | 42,590 | 45.15% | 27,410 | 45.09% | 0.11 |
| **Female** | 52,483 | 55.64% | 32,525 | 53.51% | 4.28 | 51,743 | 54.85% | 33,376 | 54.91% | 0.11 |
| **Type of Index Encounter** | | | | | | | | | | |
| **Inpatient** | 53,019 | 56.20% | 30,803 | 50.67% | 11.10 | 51,097 | 54.17% | 33,030 | 54.34% | 0.35 |
| **Outpatient** | 41,314 | 43.80% | 29,983 | 49.33% | 11.10 | 43,236 | 45.83% | 27,756 | 45.66% | 0.35 |
| **VTE Diagnosis** | | | | | | | | | | |
| **DVT only** | 53,645 | 56.87% | 33,971 | 55.89% | 1.98 | 53,279 | 56.48% | 34,367 | 56.54% | 0.12 |
| **PE with DVT** | 13,268 | 14.07% | 8,707 | 14.32% | 0.74 | 13,394 | 14.20% | 8,635 | 14.21% | 0.02 |
| **PE without DVT** | 27,420 | 29.07% | 18,108 | 29.79% | 1.59 | 27,660 | 29.32% | 17,784 | 29.26% | 0.14 |
| **VTE Etiology** | | | | | | | | | | |
| **Provoked** | 55,058 | 58.37% | 32,147 | 52.89% | 11.05 | 53,076 | 56.26% | 34,264 | 56.37% | 0.21 |
| **Unprovoked** | 39,275 | 41.63% | 28,639 | 47.11% | 11.05 | 41,257 | 43.74% | 26,522 | 43.63% | 0.21 |
| **Deyo-Charlson Comorbidity Index** | 2.3 | 2.40 | 2.1 | 2.33 | 9.33 | 2.21 | 2.37 | 2.22 | 2.41 | 0.71 |
| **Baseline Comorbidity** | | | | | | | | | | |
| **Alcohol abuse** | 3,115 | 3.30% | 1,768 | 2.91% | 2.27 | 2,987 | 3.17% | 1,937 | 3.19% | 0.12 |
| **Anemia** | 29,504 | 31.28% | 15,959 | 26.25% | 11.11 | 27,751 | 29.42% | 17,985 | 29.59% | 0.37 |
| **Central venous Catheter** | 8,428 | 8.93% | 4,134 | 6.80% | 7.93 | 7,672 | 8.13% | 4,977 | 8.19% | 0.20 |
| **Coagulation defects** | 8,318 | 8.82% | 4,103 | 6.75% | 7.72 | 7,611 | 8.07% | 5,000 | 8.23% | 0.58 |
| **Ischemic heart/ coronary artery disease** | 24,298 | 25.76% | 14,952 | 24.60% | 2.67 | 23,951 | 25.39% | 15,491 | 25.48% | 0.22 |
| **Dyspepsia or stomach discomfort** | 21,891 | 23.21% | 13,455 | 22.14% | 2.56 | 21,551 | 22.85% | 13,960 | 22.97% | 0.28 |
| **Hyperlipidemia** | 45,702 | 48.45% | 28,856 | 47.47% | 1.95 | 45,444 | 48.17% | 29,333 | 48.26% | 0.16 |
| **Obesity** | 25,602 | 27.14% | 17,493 | 28.78% | 3.65 | 26,218 | 27.79% | 16,896 | 27.80% | 0.01 |
| **Pneumonia** | 13,782 | 14.61% | 8,576 | 14.11% | 1.43 | 13,641 | 14.46% | 8,819 | 14.51% | 0.13 |
| **Rheumatologic disease** | 4,620 | 4.90% | 2,651 | 4.36% | 2.55 | 4,430 | 4.70% | 2,854 | 4.69% | 0.01 |
| **Sleep apnea** | 12,725 | 13.49% | 8,065 | 13.27% | 0.65 | 12,634 | 13.39% | 8,118 | 13.35% | 0.11 |
| **Spinal cord injury** | 279 | 0.30% | 136 | 0.22% | 1.42 | 253 | 0.27% | 168 | 0.28% | 0.15 |
| **Thrombophilia** | 3,924 | 4.16% | 2,166 | 3.56% | 3.10 | 3,718 | 3.94% | 2,420 | 3.98% | 0.21 |
| **Varicose Veins** | 3,754 | 3.98% | 2,817 | 4.63% | 3.23 | 3,988 | 4.23% | 2,560 | 4.21% | 0.08 |
| **Hypertension** | 66,061 | 70.03% | 40,748 | 67.04% | 6.45 | 65,067 | 68.98% | 42,014 | 69.12% | 0.31 |
| **Non-ESRD Renal Disease** | 14,449 | 15.32% | 8,399 | 13.82% | 4.25 | 12,837 | 13.61% | 8,297 | 13.65% | 0.12 |
| **End Stage Renal Disease** | 2,666 | 2.83% | 904 | 1.49% | 9.23 | 2,179 | 2.31% | 1,434 | 2.36% | 0.33 |
| **Inflammatory Bowel Disease** | 1,850 | 1.96% | 1,052 | 1.73% | 1.71 | 1,769 | 1.88% | 1,132 | 1.86% | 0.10 |
| **Baseline bleed** | 21,339 | 22.62% | 10,589 | 17.42% | 13.02 | 19,481 | 20.65% | 12,611 | 20.75% | 0.24 |
| **Recent History of Falls** | 7,007 | 7.43% | 4,204 | 6.92% | 1.98 | 6,853 | 7.26% | 4,426 | 7.28% | 0.06 |
| **Fracture/trauma involving Lower Extremities** | 14,141 | 14.99% | 9,720 | 15.99% | 2.76 | 14,515 | 15.39% | 9,346 | 15.37% | 0.03 |
| **Selected Surgeries** | 24,184 | 25.64% | 14,052 | 23.12% | 5.87 | 23,353 | 24.76% | 15,109 | 24.86% | 0.23 |
| **Baseline Medication Use** | | | | | | | | | | |
| **Antiarrhythmic** | 9,111 | 9.66% | 5,747 | 9.45% | 0.69 | 9,044 | 9.59% | 5,841 | 9.61% | 0.07 |
| **Statins** | 36,673 | 38.88% | 22,842 | 37.58% | 2.67 | 36,293 | 38.47% | 23,437 | 38.56% | 0.17 |
| **Anti-platelets** | 7,201 | 7.63% | 4,497 | 7.40% | 0.89 | 7,140 | 7.57% | 4,613 | 7.59% | 0.08 |
| **Aromatase Inhibitors** | 189 | 0.20% | 158 | 0.26% | 1.24 | 207 | 0.22% | 131 | 0.22% | 0.06 |
| **Beta Blockers** | 33,151 | 35.14% | 19,486 | 32.06% | 6.54 | 32,108 | 34.04% | 20,784 | 34.19% | 0.33 |
| **Gastroprotective Agents** | 27,400 | 29.05% | 16,487 | 27.12% | 4.28 | 26,741 | 28.35% | 17,274 | 28.42% | 0.16 |
| **SERMS** | 539 | 0.57% | 398 | 0.65% | 1.07 | 567 | 0.60% | 364 | 0.60% | 0.04 |
| **NSAIDs** | 23,751 | 25.18% | 17,052 | 28.05% | 6.51 | 24,770 | 26.26% | 15,951 | 26.24% | 0.04 |
| **Hormone Therapy** | 4,652 | 4.93% | 3,970 | 6.53% | 6.89 | 5,207 | 5.52% | 3,344 | 5.50% | 0.08 |

**Figure 16. Risk of Recurrent VTE Stratified by Risk of Bleeding and Clotting**

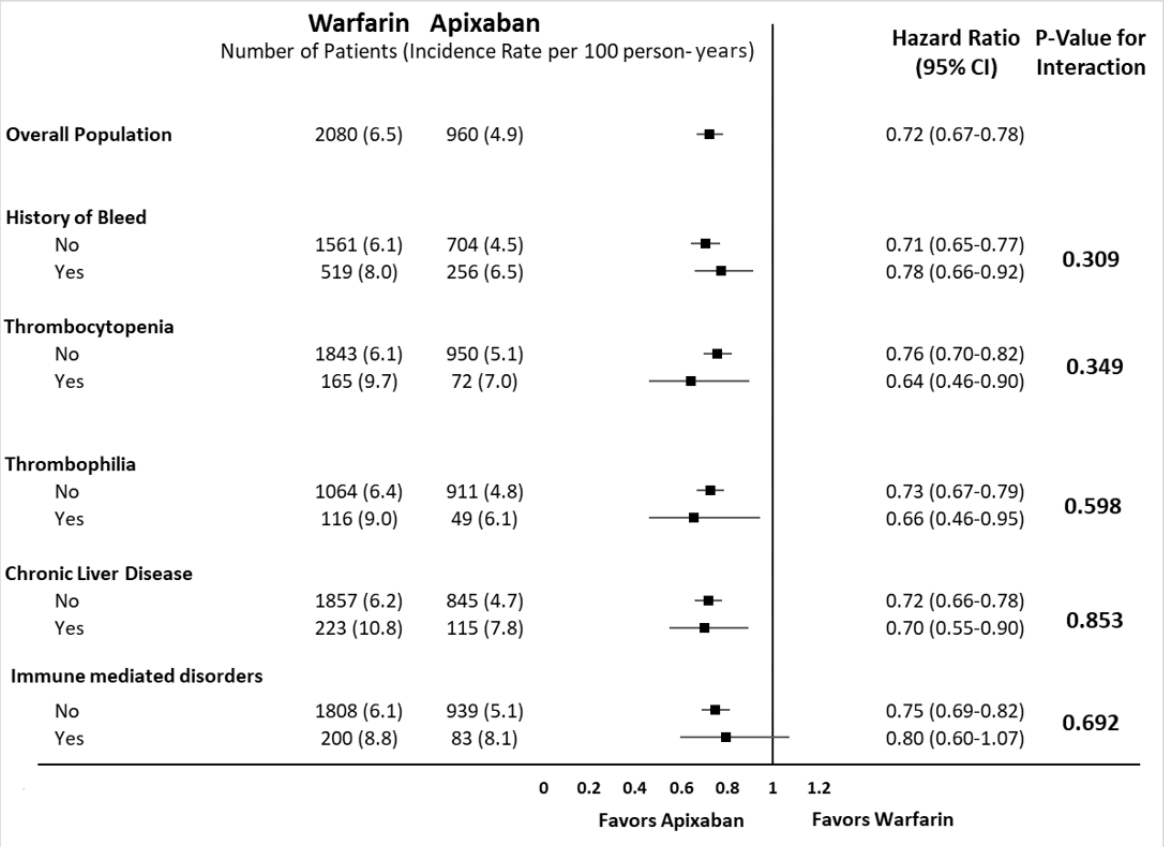


**Figure 17. Risk of MB Stratified by Risk of Bleeding and Clotting**

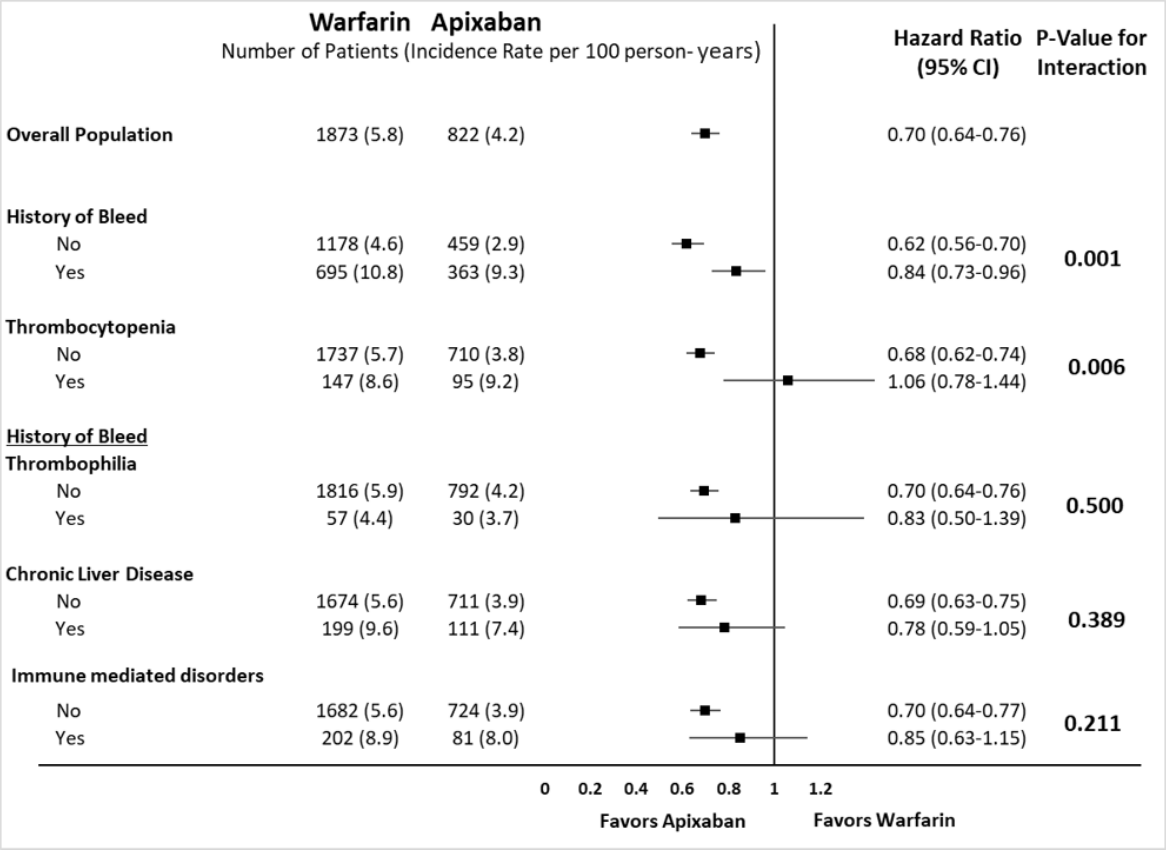
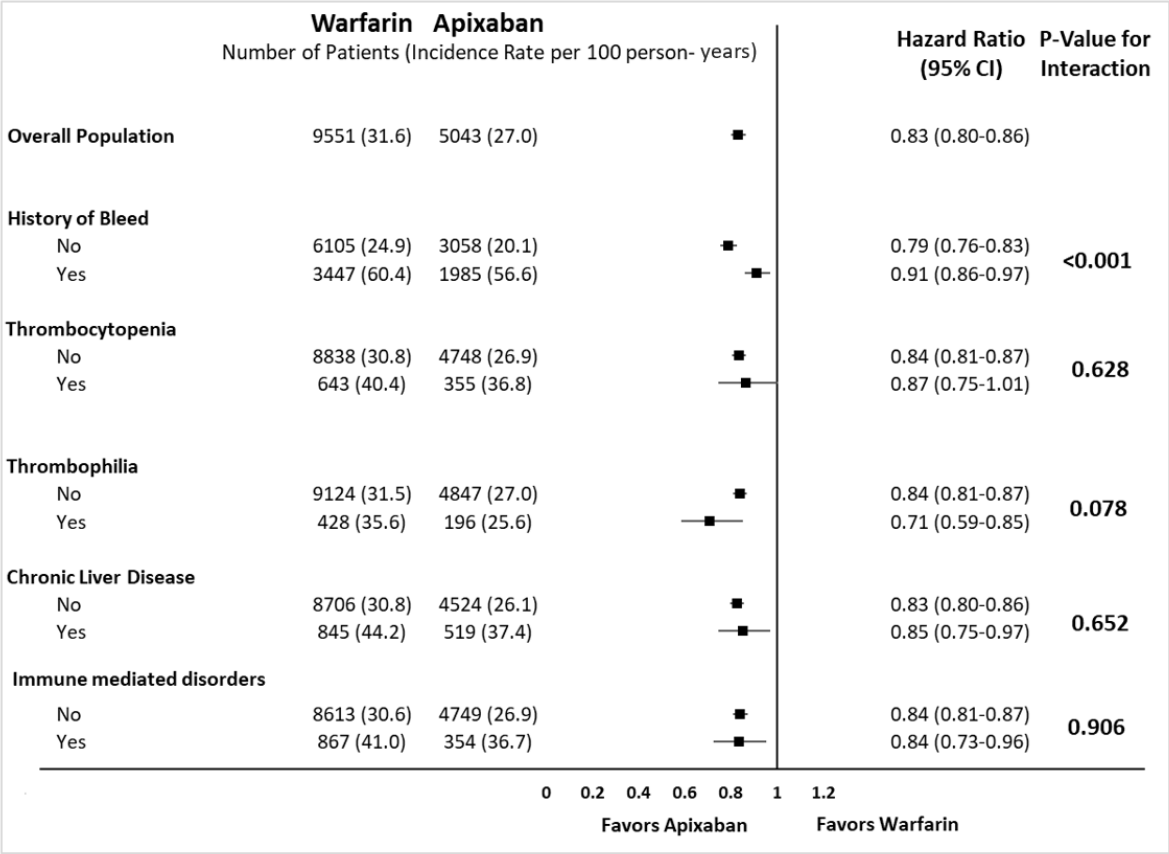


**Figure 18. Risk of CRNM Bleed Stratified by Risk of Bleeding and Clotting**




## 9.3. Other Analyses

None

## 9.4. Adverse Events/Reactions

This study only includes structured data in an electronic database which are limited in clinical detail. In these data sources, it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available, and AEs are not reportable as individual AE designations.

# DISCUSSION

## 10.1. Key Results

Of the 155,119 patients eligible for analysis, 94,333 (60.8%) were prescribed warfarin and 60,786 (39.2%) were prescribed apixaban. After IPTW, patient characteristics were generally balanced. Apixaban patients had a lower risk of MB, CRNMB, and recurrent VTE compared to warfarin patients in the overall population. Lower risk of MB, CRNMB and recurrent VTE

for apixaban vs. warfarin was also observed in the subgroup of patients with obesity, morbid obesity, CKD and high risk of bleeding, respectively. Subgroup interaction analyses showed that treatment effects were generally consistent across subgroups of patients with different demographic and socioeconomic characteristics, different CKD stages, whether or not having a bleeding risk factor (thrombocytopenia and history of bleed) or a recurrent VTE risk factor (thrombophilia, chronic liver disease, and immune mediated disorders). In summary, VTE patients who initiated apixaban had a significantly lower risk of MB, CRNMB, and recurrent VTE compared to warfarin patients in the overall and some specific high-risk subgroups of patients. Treatment outcomes of apixaban were generally consistent across various subgroups of patients.

## 10.2. Strengths and Limitations

A key strength of this study is to pool five databases together to increase study sample size and improve generalizability of study findings. The large sample size allows the evaluation of specific subgroups of patients. Additionally, this study provides a better understanding about the study population in real-world clinical practice and offers complementary information to controlled clinical trials. Some subgroups of patients are often under-represented in clinical trials, such as those with comorbidities and the elderly. A comprehensive analysis of various high risk subgroups provides additional information for health care providers to better manage these patients.

There are certain limitations associated with the use of claims data, however. For instance, the presence of a claim for a filled prescription does not indicate whether the medication was actually consumed or taken as prescribed. The presence of a diagnosis code on a medical claim does 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. Certain information is not readily available in claims data that could influence study outcomes, such as INR tests. Retrospective observational claims studies can only demonstrate association and not causality.

Specific to this study, obesity and renal subgroups were identified based on diagnosis codes—not on actual weight and renal function. There may have been misclassifications for the diagnosis codes. Duplicates were not excluded across the databases. However, prior literature has reported only 0.5% duplicates between two databases.[32] Hence, duplicates should not have impacted our study results.

## 10.3. Interpretation

This real-world study integrated patient information from Medicare and 4 major national commercial databases to construct a large and highly representative sample of VTE patients initiating apixaban or warfarin in the United States. The study found that apixaban patients had a lower risk of MB, CRNMB, and recurrent VTE compared to warfarin patients in the overall population. Lower risk of MB, CRNMB and recurrent VTE for apixaban vs. warfarin was also observed in the subgroup of patients with obesity, morbid obesity, CKD and high risk of bleeding respectively. Subgroup interaction analyses showed that results were generally consistent across subgroups of patients with different demographic and socioeconomic

characteristics, different CKD stages, whether or not having a bleeding risk factor (thrombocytopenia and history of bleed) or a recurrent VTE risk factor (thrombophilia, chronic liver disease, and immune mediated disorders).

The findings of this study are generally consistent with the AMPLIFY main analysis and subgroup analyses[10]. In the age and gender subgroup analysis of AMPLIFY, there was no significant interaction between treatment of apixaban vs. warfarin and age subgroups (65 years, 65–74 years, and 75 years, interaction p = 0.3427) as well as between the treatment and gender (interaction p = 0.4514) with regards to recurrent VTE or VTE-related death[10]. There was also no significant interaction between treatment and age (interaction p = 0.8174) or between treatment and gender (interaction p = 0.4168) with regards to MB[10]. In the obesity subgroup analysis of AMPLIFY, no significant interaction was observed between treatment of apixaban vs. warfarin and obesity status for recurrent VTE and MB[10]. The renal subgroup analysis of AMPLIFY showed no significant interaction between the level of renal function and treatment effects of apixaban vs. warfarin on recurrent VTE (interaction p = 0.8757) or MB (interaction p = 0.3606)[10]. Consistently, our study showed generally consistent treatment effects across different age, gender, obesity status and CKD stages.

The current study expands upon the subgroup analyses from AMPLIFY. First, we evaluated some subgroups of patients who were excluded or under-represented in the AMPLIFY. For example, the AMPLIFY trial excluded VTE patients at a high risk of bleeding[10]. There was no information about treatment effects in different racial and socioeconomic subgroups in the AMPLIFY trial. The AMPLIFY trial included a very small percentage of patients with VTE risk factor like thrombophilia (2%). Second, we were able to identify large sample of patients for some specific subgroups such as patients with obesity, morbid obesity, CKD and high risk of bleeding. The large sample size allowed us to compare the risk of recurrent VTE, MB and CRNMB between apixaban and warfarin within each specific subgroup.

## OTHER INFORMATION

Not Applicable

## CONCLUSIONS

In this study of a large and highly representative sample of VTE patients initiating apixaban or warfarin in the United States, apixaban was associated with a significantly lower risk of MB, CRNMB, and recurrent VTE compared to warfarin in the overall and some specific high-risk subgroups of patients. Findings associated with apixaban were generally consistent across various subgroups of patients. The current study findings add to the limited evidence about effects of apixaban in various high-risk subgroups and provide additional information to help inform oral anticoagulant decision for VTE patients.

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