NON-INTERVENTIONAL (NI) STUDY REPORT

Study Information

Title	Real-world Evidence of Prolonged Apixaban Treatment of Unprovoked Venous Thromboembolism
Protocol number	B0661127
Version identifier of the final study report	1.0
Date of last version of the final study report	July 08, 2019
Medicinal product	Apixaban
Research question and objectives	The objectives of this study were to describe patient characteristics, treatment patterns, and outcomes among unprovoked venous thromboembolism (VTE) patients who received apixaban treatment and either continued or discontinued apixaban after 6 months: **Aim 1:** Describe demographic and clinical characteristics. **Aim 2:** Describe treatment patterns. **Aim 3:** Evaluate the rate of recurrent VTE events. **Aim 4:** Evaluate the rate of major bleeding and clinically-relevant non-major bleeding.
Country of study	USA
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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

Annex 1. List of stand-alone documents

1. ABSTRACT (STAND-ALONE DOCUMENT)

BACKGROUND: Current CHEST guidelines recommend extended anticoagulation therapy without a scheduled stop in patients with unprovoked venous thromboembolism (VTE) and low bleeding risk following initial anticoagulation treatment of 3 months. The AMPLIFY-EXT study, an extension of the AMPLIFY randomized clinical trial, suggests that extended treatment with apixaban beyond 6 months reduces the risk of recurrent VTE without increasing major bleeding rates. This study evaluated patient characteristics, patterns of extended apixaban treatment, and clinical outcomes (major bleeding [MB], clinically relevant non-major [CRNM] bleeding, and recurrent VTE) among unprovoked VTE patients in a real-world setting.

METHODS: Utilizing 4 commercial claims databases, this retrospective study assessed unprovoked VTE patients (VTE events that were not preceded by a provoking risk factor or event) who initiated apixaban within 30 days from the VTE event (identification period: 01SEPT2014–31MAR2018). Patients were required to have ≥6 months of continuous apixaban treatment (without a gap of >30 days) at identification. Patient characteristics and clinical outcomes of patients treated beyond 6 months and those who discontinued at 6 months were evaluated descriptively. An additional analysis was conducted to assess the treatment pattern and clinical outcomes of patients with apixaban treatment for ≥3 months.

RESULTS: A total of 763,170 patients with an unprovoked VTE event during the identification period were identified from the pooled datasets. Among these unprovoked VTE patients, 60.8% and 34.6% had apixaban treatment for ≥3 and ≥6 months, respectively. After applying all eligibility criteria, only 3,015 patients with ≥6 months of apixaban treatment were selected and included in the primary analysis of this study. Of those treated for ≥6 months, 75.6% (2,280) continued treatment beyond 6 months and 24.4% (735) discontinued at 6 months. Compared to patients who discontinued apixaban treatment at 6 months, continued cohort patients were significantly younger (61.7 vs 63 years, p=0.037) and more likely to have thrombophilia in the baseline (12.9% vs 7.4%, p<0.001). Among patients with treatment beyond 6 months, 7.5% switched from apixaban 5mg to 2.5mg, 36.5% discontinued therapy, and 1.1% switched to another oral anticoagulant. The descriptive analysis of outcomes shows similar rates of major bleeding, CRNM bleeding, and recurrent VTE between patients who continued treatment beyond 6 months and patients who discontinued at 6 months. Additionally, a total of 5,243 patients were found to have ≥3 months of apixaban treatment after applying all eligibility criteria, 83.4% (4,372) continued the treatment beyond 3 months and 16.6% (871) discontinued the treatment at 3 months. Patients who continued apixaban beyond 3 months were older, had a higher CCI score, more likely to have baseline comorbidities, more likely to have index VTE in the inpatient setting and as PE with or without DVT compared to patients who discontinued treatment at the 3 months. The rates of major bleeding, CRNM bleeding, and recurrent VTE were similar between the 2 cohorts in the descriptive analysis.

CONCLUSION: Among unprovoked VTE patients treated with apixaban, a large proportion did not receive ≥3 months of treatment. Although the AMPLIFY-EXT study showed beneficial effects of extended apixaban treatment beyond 6 months, the percentage of patients with ≥6 months of apixaban treatment was very low in this study. Some patient characteristics have been found to be associated with a higher likelihood of continuing apixaban treatment beyond

3 months or beyond 6 months. Additional studies are needed to fully understand factors that drive physicians' and patients' decisions about extended treatment of VTE. Future studies with a larger sample size and statistical analyses to address differences in patient characteristics are needed to thoroughly evaluate the safety and effectiveness of extended apixaban treatment in routine clinical practice.

2. 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
CRNM	Clinically Relevant Non-Major
DVT	Deep Vein Thrombosis
ER	Emergency Room
HCFA	Health Care Financing Agency
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
LMWH	Low-molecular-weight Heparin
OAC	Oral Anticoagulant
PE	Pulmonary Embolism
UFH	Unfractionated Heparin
VTE	Venous Thromboembolism

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

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4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Study progress report I (Protocol)	April 2018	August 2018	
Descriptive results	May 2018	February 2019	The delay was due to the wait for refresh data
Final report of study results	July 2018	June 2019	

6. RATIONALE AND BACKGROUND

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) or pulmonary embolism (PE), is the third most common cause of death related to vascular diseases.[1] The annual incidence of VTE in the United States is 1 case per 1000 patients.[1] Each year in the United States, >600,000 hospitalizations and >100,000 deaths are attributed to VTE.[2] The total per patient VTE treatment cost exceeds $20,000 during the first year following a VTE event,[2] and the economic burden of VTE ranges between $13.5 and $27.2 billion per year.[3]

An episode of VTE can either be provoked or unprovoked by an environmental risk factor. The provoking risk factor may be transient (including acute immobilization, surgery, trauma, pregnancy, or estrogen use) or persistent as in active cancer. VTE should generally be treated for a minimum of 3 months or indefinitely.[4,5] For many years, the prevailing practice for treating an unprovoked VTE was 6 months of anticoagulation.[5,6] It can be challenging to extend the anticoagulation treatment due to major bleeding risks. The decision to extend treatment is based on the balance between the risk of recurrence after stopping the treatment and the risk of major bleeding from continuing.[5]

The risk of recurrent VTE depends on several factors such as VTE event type, age, sex, previous surgery, trauma, and cancer.[7] The risk of recurrent VTE is high after an acute VTE episode, but it decreases with time.[8] Recurrent VTE prevalence is 15% in patients with an unprovoked VTE event and 5% in patients with a VTE event provoked by non-surgical factors within 1 year of the index event.[7]

The American College of Chest Physicians and European Society of Cardiology recommend using anticoagulants beyond 3 months in patients with unprovoked DVT who do not have a high risk of bleeding.[9,10] However, clinical practices have reported inconsistencies in the duration of anticoagulant treatment for unprovoked DVT patients.[9] A meta-analysis of 6 randomized controlled trials reported that a longer duration of anticoagulation (mean duration=18.6 months) was associated with significantly lower all-cause mortality in VTE patients who were at an intermediate risk of VTE recurrence (without transient risk factors or cancer and exposed to shorter or longer anticoagulation) compared to a shorter duration of anticoagulation (mean duration=7.5 months).[11] The study also reported that major bleeding was not significantly higher in the longer anticoagulation arm (RR 2.26; 95% confidence interval [CI] 1.52-3.37) compared to the shorter duration.[12]

Apixaban is an oral factor Xa inhibitor administered in fixed doses to prevent recurrent VTE and major bleeding in patients with VTE.[13] In the AMPLIFY-EXT (Apixaban after the initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-line Therapy–Extended Treatment) study, extended treatment (≥6 months) with 5mg and 2.5mg apixaban in patients who had already received 6-12 months of anticoagulation treatment was associated with a significantly reduced risk of recurrent VTE without increasing the risk of major bleeding when compared to a placebo.[12] The rates of major bleeding were 0.2% among 2.5mg apixaban patients, 0.1% among 5mg apixaban patients, and 0.5% among placebo patients.[14] The rates of clinically-relevant non-major (CRNM) bleeding were 3.0% and 4.2% among patients prescribed 2.5mg and 5mg apixaban, respectively, compared with 2.3% for those on a placebo.[14]

There is insufficient real-world evidence regarding the optimal duration of apixaban treatment for unprovoked VTE. This study aims to describe patient characteristics, treatment patterns,

and outcomes among unprovoked VTE patients who received apixaban treatment and either continued or discontinued apixaban after 6 months.

This was not a PASS study nor a commitment or requirement to any regulatory agency.

7. RESEARCH QUESTION AND OBJECTIVES

Aim 1: Describe the clinical and demographic characteristics of unprovoked VTE patients who received apixaban treatment and continued versus discontinued apixaban after 6 months.

Aim 2: Describe the treatment patterns of patients who received apixaban treatment and continued versus discontinued apixaban after 6 months.

Aim 3: Evaluate the rate of recurrent VTE events among patients who received apixaban treatment and continued versus discontinued apixaban after 6 months.

Aim 4: Evaluate the rate of major bleeding and CRNM bleeding among patients who received apixaban treatment and continued versus discontinued apixaban after 6 months.

8. AMENDMENTS AND UPDATES

None.

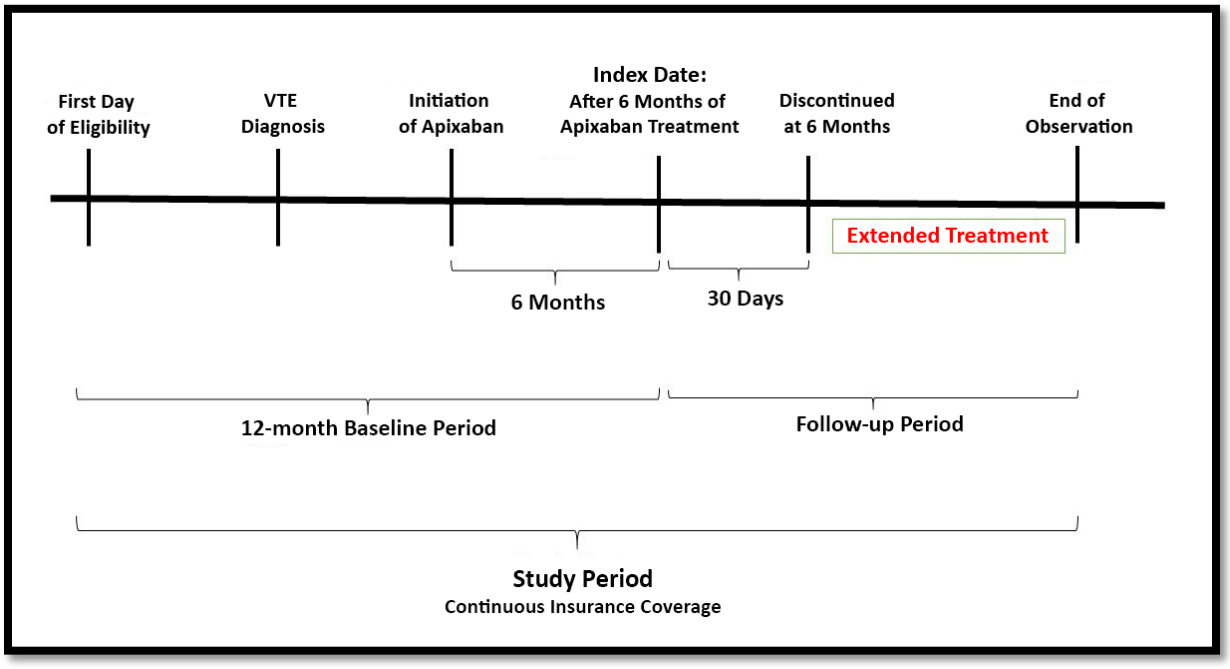
9. RESEARCH METHODS

9.1. Study design

The study was a longitudinal retrospective cohort analysis using a pooled dataset (Humana, IMS PharMetrics, Optum, and MarketScan). The study and identification periods varied by dataset and were determined by the last date available at the time of study initiation. The study period for the Truven MarketScan database was March 1, 2014 through June 30, 2017; for the Optum and Humana database, these were March 1, 2014 through December 31, 2017; for the IMS PharMetrics database, these was March 1, 2014 through March 31, 2018. The identification period ranged from September 1, 2014 through the last available date in each database.

The index date was designated as the end date of the initial 6 months of apixaban treatment following the first VTE diagnosis date (index VTE event). Patients whose continuous apixaban treatment ended within the 30-day window after the index date were assigned to the discontinued cohort. Patients whose continuous apixaban treatment continued for ≥30 days after the index date were assigned to the continued cohort. The study period allowed for a 12-month baseline period prior to the index date. Patient data were assessed until the earliest of health plan disenrollment, death, initiation of anticoagulants, or the end of the study period.

Figure 1. Study design figure (for illustration purposes; may not be proportional)



9.2. Setting

Adult patients prescribed apixaban within 30 days of an unprovoked VTE event were selected between September 1, 2014 and June 30, 2017 in MarketScan; September 1, 2014 and December 31, 2017 in Optum and Humana; and September 1, 2014 and March 31, 2018 in IMS PharMetrics. The end of the initial 6 months of continuous apixaban treatment without a gap of >30 days was designated as the index date. Patients were required to have continuous health plan enrollment for 12 months prior to and on the index date to ensure the patients' complete medical history is available.

9.3. Subjects

Inclusion criteria

Patients must have met all the following criteria to be eligible for inclusion in the study:

a) had ≥1 medical claim with a primary or secondary unprovoked VTE diagnosis (index VTE event) in the inpatient or ambulatory setting during the identification period (between September 1, 2014 and June 30, 2017 in MarketScan; September 1, 2014 and December 31, 2017 in Optum and Humana; and September 1, 2014 and March 31, 2018 in PharMetrics). The first VTE diagnosis was designated as the index VTE event;

   Unprovoked VTE was defined as all events not classified as provoked. Provoked VTE was defined as events preceded during the 3-month pre-index VTE period by hormone therapy, fracture/trauma involving lower extremities, pelvic/orthopedic surgery, active cancer (≥2 medical diagnoses for cancer or 1 medical diagnosis for cancer and ≥1 claim for cancer-related treatment [chemotherapy, radiation therapy, or cancer-related surgery]), or hospitalization for any reason for ≥3 days.

b) had ≥1 pharmacy claim for apixaban during the 30-day period following the index VTE event during the identification period (so that all patients had the opportunity to have 6 months of use). Patients were required to have continuous apixaban use for ≥6 months without a >30-day gap. The end of the initial 6 months of apixaban treatment following the index VTE event was designated as the index date;

c) were aged ≥18 years on the index date; and

d) had continuous health plan enrollment for ≥12 months prior to the index date; patient data were assessed until the earliest of death, end of continuous enrollment, initiation of anticoagulants, or study end (follow-up period).

Exclusion criteria

Patients with evidence of any of the following criteria were not included in the study:

a) VTE (unprovoked or provoked) during the 6-month period preceding the index VTE event unless the index VTE encounter occurred in the inpatient setting and was preceded by an outpatient VTE event within 7 days of the index VTE event;

b) atrial fibrillation/flutter or mechanical heart valve during the study period;

c) evidence of a prescription claim for another anticoagulant on the index date or during the period between the index VTE event and the index date;

d) evidence of a prescription claim for another anticoagulant during the 6-month period preceding the index VTE event;

e) a recurrent VTE event between the index VTE event and index date;

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

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

Treatment/cohort labels

a. **Discontinued cohort:** Patients whose continuous apixaban treatment ended within the 30-day window after the index date were placed in the discontinued cohort. Patient data was assessed from the day after the index date until disenrollment, death, initiation of anticoagulants, or the end of the study period.

b. **Continued cohort:** Patients whose continuous apixaban treatment continued for ≥30 days after the index date were placed in the continued cohort. Patient data was assessed from the day after the index date until the earliest of disenrollment, death, discontinuation of apixaban, switch to another anticoagulant, or the end of the study period.

9.4. Variables

Table 1. Endpoints

Variable	Operational Definition
Major bleeding	A major bleeding event observed during follow-up was identified using hospital records with a major bleeding diagnosis as the first listed diagnosis as listed by the ICD-9-CM or ICD-10 diagnosis or procedure code. Major bleeding event was a dichotomous variable that equaled 1 if there was ≥1 bleeding event during the follow-up period. The time to the first major bleeding event was calculated. Major bleeding was stratified by gastrointestinal (GI) bleeding, intracranial hemorrhage (ICH), and other bleeding.
CRNM bleeding	A CRNM bleeding event was defined as a bleeding event not considered to be major bleeding (without a principal diagnosis code for GI/ICH/other bleeding or a procedure code for bleeding treatment). This includes: • 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 • 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). CRNM bleeding events that followed major bleeding events were not considered in the analysis of CRNM bleeding.
Recurrent VTE	A recurrent VTE event was identified as an acute-care inpatient admission with a corresponding first listed diagnosis; admissions occurring within 7 days of the qualifying VTE event, irrespective of care setting, were considered.
Discontinuation	Discontinuation was defined as no evidence of apixaban for 30 days from the last days' supply of the last filled prescription. The date of discontinuation was the last days' supply of the last filled prescription.
Time-to-discontinuation	Time from the index date to discontinuation date was evaluated among patients that discontinued index therapy.
Switch among anticoagulants	Patients who received a prescription for another anticoagulation other than apixaban (dabigatran, edoxaban, rivaroxaban, warfarin, UFH, LMWHs, fondaparinux, danaparoid, hirudin, bivalirudin, and argatroban) during the follow-up period were considered switchers if the above occurred within ±30 days of the last days' supply.
Dose change	Patients who had a different dose of apixaban after the index date during the follow-up period; the number and percentage of patients who switched from 5mg to 2.5mg apixaban or vice versa after the index date were calculated.
Time-to-dose change	The mean time from the index date to the first dose change was calculated in days.

Table 2. Baseline Variables

Variable	Operational Definition
Age	Age was defined as of the index date and used to assign patients to the following age groups: 18-54, 55-64, 65-74, 75-79, and ≥80 years.
Sex	A flag was created for female beneficiaries and reported as a percentage.
US geographic region	The United States was divided into 5 regions: Northeast, South, Midwest, West, and Other. Geographic region was captured from enrollment data.
Setting of index VTE event	Flags were created for patients with index VTE event in inpatient or ambulatory settings. Qualifying outpatient encounters followed by qualifying inpatient encounters within 7 days were considered an inpatient episode (unless warfarin, LMWH, or apixaban was initiated between encounters, in which case it was classified as an outpatient encounter).
Position of VTE diagnosis	Flags were created for the position of VTE diagnosis, including primary (principle diagnosis or first listed) or secondary position.
VTE diagnosis	Flags were created for the type of VTE diagnosis including DVT only, PE with DVT, or PE without DVT.
AIDS	A flag was created for patients with claims for AIDS.
Alcohol abuse	A flag was created for patients with claims for alcohol abuse.
Anemia	A flag was created for patients with claims for anemia.
Central venous catheter	A flag was created for patients with claims for central venous catheter.
Cerebrovascular disease	A flag was created for patients with claims for cerebrovascular disease.
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.

Variable	Operational Definition
Congestive heart failure	A flag was created for patients with claims for congestive heart failure.
Diabetes	A flag was created for patients with claims for diabetes.
Hypertension	A flag was created for patients with claims for hypertension.
Renal disease	A flag was created for patients with claims for renal disease. A flag for chronic kidney disease stage V, end-stage renal disease, or dialysis was created.
Liver disease	A flag was created for patients with claims for liver disease.
COPD	A flag was created for patients with claims for chronic obstructive pulmonary disease.
Peptic ulcer disease	A flag was created for patients with claims for peptic 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.
Recent history of falls	A flag was created for patients with a fall history and reported as a percentage.
Fracture/trauma involving the lower extremities	A flag was created for patients having a fracture or a trauma and reported as a percentage.
Selected surgeries	A flag was created for patients having a surgery and reported as a percentage.
Baseline Deyo-Charlson comorbidity index score	The Deyo-Charlson comorbidity index score was created.
Other baseline medications	Flags were created for patients with prescription fills for antiarrhythmic, statin, antiplatelet, aromatase inhibitors, beta blockers, gastroprotective agents, SERMs, NSAIDs, and hormone therapy.
Apixaban initial dose	Flags were created based on initial dose of apixaban (2.5mg or 5mg).
Dose change during baseline period	The number of patients with different apixaban doses during the baseline period were evaluated. The number and percentage of patients who switched from 5mg to 2.5mg apixaban and vice versa were calculated.
Time-to-dose change during baseline period	The mean time from the initial apixaban prescription date to the first dose change was calculated in days.
Apixaban index dose	Flags were created for the index dose based on the dose of the index prescription of apixaban (2.5mg, 5mg, or 10mg). Apixaban index dose was based on the apixaban prescription claim date closest to the index date.
Baseline major bleeding	A major bleeding event was identified using hospital records which had a major bleeding diagnosis as the first listed or principle diagnosis as listed by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or ICD-10 diagnosis or procedure code. Major bleeding event was a dichotomous variable that equaled 1 if there was ≥1 bleeding event during the follow-up period. The time to the first major bleeding event was calculated.

9.5. Data sources and measurement

MarketScan

The Truven 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 consisting of Medicare-eligible retirees with employer-sponsored Medicare Supplemental plans. This database contains predominantly fee-for-service plan data. The Medicare Supplemental and Coordination of Benefits database may not accurately represent the US Medicare population.

Optum

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. Underlying information is geographically diverse across the United States and updated frequently.

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

Medical claims or encounter data are collected from all available health care sites (inpatient hospital, outpatient hospital, emergency room [ER], physician's office, surgery center, etc) for virtually all types of provided services, including specialty, preventive, and office-based treatments. Medical claims and coding conform to insurance industry standards. Claims for ambulatory services submitted by individual providers (eg, physicians) use the Health Care Financing Agency (HCFA)-1500 format. Claims for facility services submitted by institutions (eg, hospitals) use the uniform bill (UB)-82 or UB-92 format. Medical claims include multiple diagnosis codes recorded with the ICD-9-CM diagnosis codes; procedures recorded with ICD-9-CM procedure codes, Current Procedural Terminology, or HCFA Common Procedure Coding System codes; site of service codes; provider specialty codes; revenue codes (for

facilities); paid amounts; and other information. Typically, facility claims do not include any drugs administered in hospital. Approximately 6 months following the delivery of services is required for complete medical data. Medical claims identify patients that used United Health Group for their health care services.

IMS PharMetrics Plus

The IMS PharMetrics Plus claims database includes claims for medical (provider and institutional) and pharmacy services in the United States, with claim paid and allowed amounts as well as all-patient payment amounts. The database reflects ~40 million lives in any given recent year. IMS PharMetrics Plus is the product of a strategic partnership between IMS and Blue Health Intelligence (BHI) and incorporates a number of Blue Cross Blue Shield plans. Complete data from a large number of commercial health plans, covering all 50 states, are available. The population aged ≥65 years consists of enrollees in managed care plans for seniors, the working elderly, and others in commercial plans; BHI Medicare Advantage members are not included.

Humana

The Humana database includes >11.3 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 the 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 stays. Pharmacy data includes information on prescription fills for each member, days of supply, payment amounts per insurers, and beneficiaries and dates of services.

9.6. Bias

While claims data are extremely valuable for the efficient and effective examination of health care outcomes, treatment patterns, health care resource utilization, and costs, claims data are collected for payment and not research. Therefore, certain limitations are associated with claims data use.

For example, the presence of a claim for a filled prescription does not indicate that the medication was consumed or taken as prescribed. In addition, medications filled over-the-counter or provided as samples by the physician cannot be observed in the claims data. Moreover, the presence of a diagnosis code on a medical claim is not positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. And certain information is not readily available in claims data that could influence study outcomes, such as certain clinical and disease-specific parameters.

9.7. Study size

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

9.8. Data transformation

Not applicable.

9.9. Statistical methods

9.9.1. Main summary measures

Continuous and categorical study variables were analyzed descriptively. All outcome variables and baseline variables, including demographic and clinical characteristics, were compared between the cohorts. Descriptive analysis was performed comparing the discontinued apixaban cohort (reference) to the continued apixaban cohort.

The cumulative incidence rate for clinical outcomes (major bleeding, CRNM bleeding, recurrent VTE) was calculated. The incidence rate was calculated as the number of patients who experience the event divided by the observed time at risk.

9.9.2. Main statistical methods

Descriptive analysis:

- **Analysis of continuous data:** Means, medians, and standard deviations (SDs) were provided for continuous variables when performing descriptive analysis.
- **Analysis of categorical data:** Numbers and percentages were provided for dichotomous and polychotomous variables when performing descriptive analysis.

Bivariate comparisons of baseline characteristics and outcomes measures were provided. Appropriate tests (eg, t-test, Mann Whitney-U test, chi-square test) were used based on the distribution of the measure. P-values and 95% CIs were provided.

Numbers and percentages were provided for dichotomous and polychotomous variables. Continuous variables were summarized by providing the number of observations, mean, and SD. Statistical tests of significance for distribution differences between the cohorts were conducted. Chi-square tests were used to evaluate the statistical significance of differences in categorical variables; student t-tests were used for the means of continuous variables. Non-parametric tests can be applied if there was a deviation from asymptotical assumptions. The incidence rate was calculated as the number of patients who experienced the event divided by the observed time at risk.

For all objectives, comparisons were made between the discontinued and continued apixaban cohorts.

In addition to p-values, standardized differences were calculated for each variable. These differences are important to distinguish practical versus statistical significance. For example,

some variables may be statistically significant (as indicated by p-values) due to large sample sizes, although the practical significance is small (as indicated by standardized differences). Following are the thresholds, set by Cohen for statistical significance (SS),[15] based on SD: trivial (SS < 0.20), small (0.20 ≤ SD < 0.50), moderate (0.50 ≤ SD < 0.80) or large (SD ≥ 0.80).

9.9.3. Missing values

None.

9.9.4. Sensitivity analyses

A sensitivity analysis was conducted using 3 months of continued apixaban use to evaluate the robustness of findings.

9.9.5. Amendments to the statistical analysis plan

None.

9.10. Quality control

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

- Design and review: STATinMED Research incorporates sound scientific design and clinically rigorous review into its studies. To address important research questions, STATinMED Research develops a detailed study protocol that includes definitions, codes, analyses, and table shells for the study. A member of the STATinMED Research clinical team is involved in reviewing the appropriateness and validity of the coding strategy and in identifying any issues that may be relevant but were not discussed during the proposal phase of the project. The protocol further provides STATinMED Research and Pfizer an opportunity to solidify the research questions and address any potential gaps in information.
- Data collection: STATinMED Research believes that a study is only as good as the dataset created for analysis. Therefore, we generate the most accurate datasets by incorporating rigorous quality assurance checks during dataset construction. Several checks are used, including record-level verification of all data elements, double-programming of certain portions of the dataset, programming data edit checks, visually reviewing raw claims data against the constructed data elements, and reviewing the analysis to assess the validity of results. Twenty percent of a randomly-selected sample is subjected to such checks.
- Analysis review: STATinMED Research analysis is performed by a statistician or senior analyst under the supervision of the project director. The project director reviews output for consistency with the analysis plan for quality and accuracy. Further, results were reviewed with Pfizer to establish that the results meet Pfizer's expectations.
- Final review: The final deliverables produced by STATinMED Research receive internal review by a clinical consultant and/or another senior researcher for quality and completeness.

9.11. Protection of human subjects

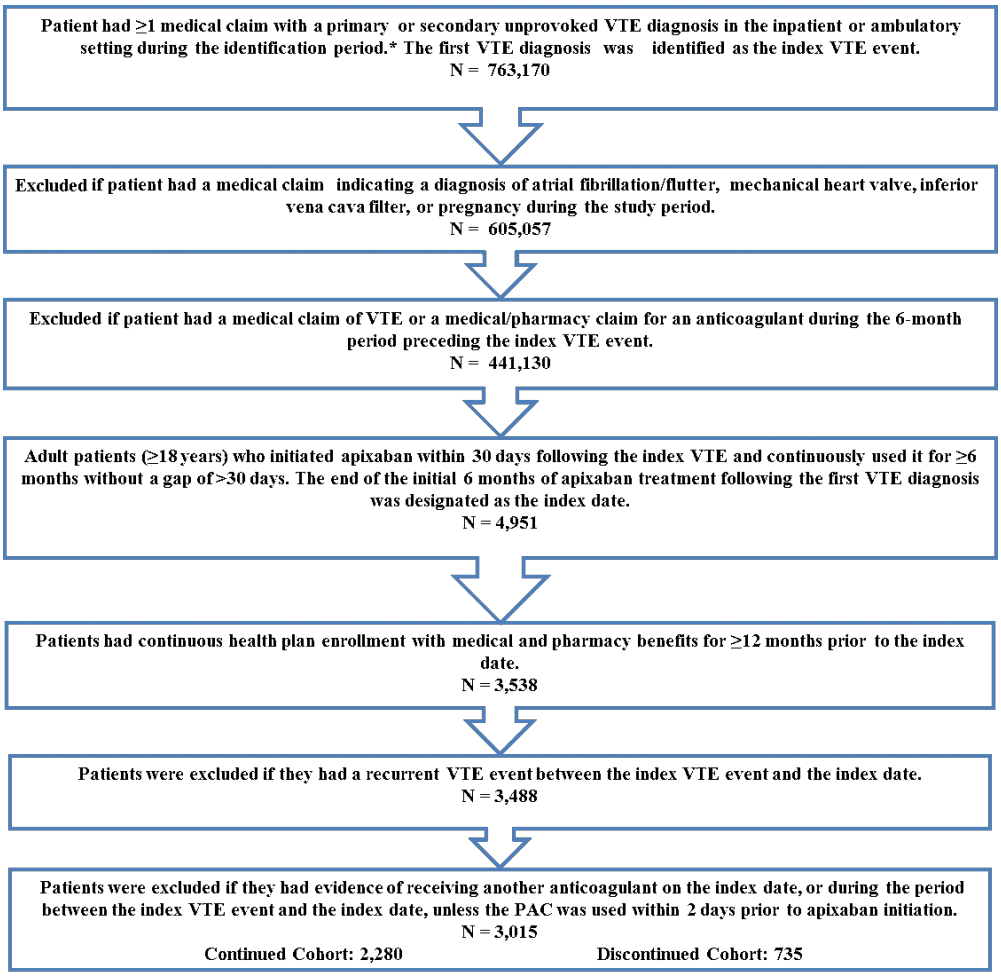
Not applicable.

10. RESULTS

10.1. Participants

A total of 763,170 patients with an unprovoked VTE event during the identification period were identified from the pooled datasets. Among unprovoked VTE patients, 60.8% and 36.4% had apixaban treatment for ≥3 months and ≥6 months, respectively. After applying all exclusion criteria (excluding patients with atrial fibrillation or mechanical heart valve, inferior vena cava filter, pregnancy, evidence of VTE during the 6 months prior to the index encounter, ≥1 claim for an OAC any time prior to the index date, recurrent VTE between the index VTE event and index date, or evidence of receipt of another OAC on the index date), a total of 3,015 patients with ≥6 months of apixaban treatment were selected and included in the primary analysis of this study (Figure 2).

Figure 2. Patient selection flow chart



*Identification Period: MarketScan (September 1, 2014 and June 30, 2017), Optum and Humana (September 1, 2014 and December 31, 2017), PharMetrics (September 1, 2014 and March 31, 2018)

10.2. Descriptive data

10.2.1. Patients with ≥6 months of apixaban therapy

Among the 3,015 patients who received ≥6 months of apixaban therapy, 2,280 (75.6%) continued the treatment beyond 6 months and were included in the continued cohort. Only 735 (24.4%) discontinued the apixaban therapy at 6 months and were included in the discontinued cohort. Among those in the continued cohort, 919 (40.3%) had an additional 6 months of continuous apixaban use without a gap of >30 days after the index date, and 328 (14.4%) had 12 months of continuous apixaban use without a gap of >30 days after the index date.

Table 3 shows patient characteristic comparisons for continued versus discontinued patients. Compared to patients who discontinued apixaban treatment at 6 months, continued cohort patients were significantly younger (61.7 vs 63 years, p=0.037). Patients in the continued cohort were also more likely to have thrombophilia in the baseline compared to the discontinued cohort (13% vs 7.4%, p<0.001). Discontinued and continued cohorts were not statistically different in terms of Charlson comorbidity index (CCI), other baseline comorbidities, and baseline medication use. Approximately one-third of patients had PE with or without DVT and 80% of patients had their index VTE in the ambulatory setting.

Table 3. Baseline characteristics for the continued vs discontinued apixaban cohorts

	Discontinuous Cohort (Reference)		Continuous Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	STD*
Sample size	**735**		**2,280**			
Age	63.02	15.20	61.69	14.29	0.0366	9.01
18-54	202	27.48%	671	29.43%	0.3116	4.31
55-64	200	27.21%	736	32.28%	0.0098	11.10
65-74	161	21.90%	452	19.82%	0.2230	5.12
75-79	79	10.75%	153	6.71%	0.0004	14.33
≥80	93	12.65%	268	11.75%	0.5140	2.74
Sex						
Male	428	58.23%	1,388	60.88%	0.2025	5.39
Female	307	41.77%	892	39.12%	0.2025	5.39
Geographic region						
Northeast	107	14.56%	339	14.87%	0.8366	0.88
South	336	45.71%	1,073	47.06%	0.5244	2.70
Midwest	161	21.90%	520	22.81%	0.6110	2.16
West	125	17.01%	341	14.96%	0.1811	5.60
Other	6	1.10%	7	0.41%	0.0644	7.95
Setting of index VTE event						
Inpatient	143	19.46%	446	19.56%	0.9499	0.27
Ambulatory	592	80.54%	1,834	80.44%	0.9499	0.27
Position of VTE diagnosis						
Primary (principal or first listed)	663	90.20%	2,045	89.69%	0.6903	1.70
Secondary	72	9.80%	235	10.31%	0.6903	1.70

	Discontinuous Cohort (Reference)		Continuous Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	STD*
Sample size	**735**		**2,280**			
VTE diagnosis						
DVT only	494	67.21%	1,498	65.70%	0.4524	3.20
PE with DVT	75	10.20%	241	10.57%	0.7781	1.20
PE without DVT	166	22.59%	541	23.73%	0.5247	2.71
Baseline comorbidity						
Deyo-Charlson comorbidity index	1.33	1.90	1.25	1.81	0.3046	4.30
AIDS	4	0.54%	9	0.39%	0.5907	2.19
Alcohol abuse	14	1.90%	26	1.14%	0.1152	6.24
Anemia	101	13.74%	275	12.06%	0.2306	5.01
Central venous catheter	8	1.09%	13	0.57%	0.1418	5.71
Cerebrovascular disease	33	4.49%	115	5.04%	0.5454	2.60
Coagulation defects	38	5.17%	153	6.71%	0.1360	6.52
Ischemic heart/ coronary artery disease	100	13.61%	285	12.50%	0.4349	3.28
Dementia	19	2.59%	46	2.02%	0.3570	3.78
Dyspepsia or stomach discomfort	70	9.52%	247	10.83%	0.3142	4.33
Hemiplegia or paraplegia	1	0.14%	8	0.35%	0.3532	4.36
Hyperlipidemia	272	37.01%	806	35.35%	0.4153	3.45
Obesity	114	15.51%	358	15.70%	0.9011	0.53
Pneumonia	22	2.99%	83	3.64%	0.4053	3.61
Rheumatologic disease	27	3.67%	82	3.60%	0.9226	0.41
Sleep apnea	84	11.43%	283	12.41%	0.4781	3.03
Spinal cord injury	0	0.00%	2	0.09%	0.4218	4.19
Thrombophilia	54	7.35%	296	12.98%	<.0001	18.72
Varicose veins	45	6.12%	114	5.00%	0.2364	4.90
Congestive heart failure	36	4.90%	109	4.78%	0.8972	0.55
Diabetes	141	19.18%	445	19.52%	0.8423	0.84
Hypertension	378	51.43%	1199	52.59%	0.5843	2.32
Renal disease	103	14.01%	290	12.72%	0.3648	3.80
Liver disease	39	5.31%	107	4.69%	0.5007	2.81
COPD	62	8.44%	179	7.85%	0.6114	2.14
Peptic ulcer disease	4	0.54%	14	0.61%	0.8308	0.92
Inflammatory bowel disease	7	0.95%	35	1.54%	0.2411	5.26
Peripheral vascular disease	87	11.84%	246	10.79%	0.4309	3.31
Recent history of falls	10	1.36%	43	1.89%	0.3459	4.16
Fracture/trauma involving lower extremities	51	6.94%	121	5.31%	0.0972	6.81
Selected surgeries	26	3.54%	60	2.63%	0.1995	5.24
Baseline medication use						
Antiarrhythmic	50	6.80%	154	6.75%	0.9638	0.19
Statins	252	34.29%	774	33.95%	0.8663	0.71
Anti-platelets	28	3.81%	64	2.81%	0.1694	5.60
Aromatase inhibitors	1	0.14%	14	0.61%	0.1092	7.82
Beta blockers	194	26.39%	547	23.99%	0.1882	5.54
Gastroprotective agents	151	20.54%	453	19.87%	0.6906	1.68
SERMS	4	0.54%	7	0.31%	0.3537	3.64
NSAIDs	104	14.15%	304	13.33%	0.5737	2.37
Hormone therapy	3	0.41%	14	0.61%	0.5169	2.89

	Discontinuous Cohort (Reference)		Continuous Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	STD*
Sample size	**735**		**2,280**			
Apixaban initial dose						
Standard dose (apixaban 5mg)	701	95.37%	2,190	96.05%	0.4205	3.35
Lower dose (apixaban 2.5mg)	34	4.63%	90	3.95%	0.4205	3.35
Dose change during the baseline period						
Standard (5mg) to lower (2.5mg) dose	28	3.81%	136	5.96%	0.0251	10.01
Lower (2.5mg) to standard (5mg) dose	5	0.68%	17	0.75%	0.8564	0.78
Time-to-dose change	75.45	61.94	100.14	62.99	0.0420	39.51
Apixaban index dose**						
Standard dose (apixaban 5mg)	681	92.65%	2,050	89.91%	0.0270	9.72
Lower dose (apixaban 2.5mg)	54	7.35%	230	10.09%	0.0270	9.72
Baseline any bleed	77	10.48%	210	9.21%	0.3093	4.25

Std Difference=100(actual std diff). Std Difference >10 is considered significant.

**Apixaban index dose is based on the apixaban prescription claim date closest to the index date.

The descriptive analysis of the outcomes are shown in Table 4. Among patients who continued apixaban beyond 6 months, 7.5% switched from 5mg apixaban to 2.5 mg, 36.5% discontinued treatment during follow-up, and 1.1% of patients switched to another anticoagulant during the follow-up period. Major bleeding (1.28 vs 1.50, p=0.761), CRNM bleeding (14.74 vs 11.72, p=0.161), and recurrent VTE rates (1.38 vs 2.41, p=0.207) were similar among patients in the continued and discontinued cohorts.

Table 4. Descriptive outcome table for continued vs discontinued apixaban cohorts

	Discontinuous Cohort (Reference)		Continuous Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	STD*
Sample size	**735**		**2,280**			
Follow-up time (in days)	211.15	207.92	208.77	166.51	0.7776	1.26
Minimum	1		4			
Q1	41		89			
Median	137		154			
Q3	333		276			
Maximum	955		992			
Major bleeding	8	1.09%	18	0.79%	0.4459	3.10
GI bleeding	4	0.54%	8	0.35%	0.4691	2.90
Intracranial hemorrhage	0	0.00%	2	0.09%	0.4218	4.19
Other bleeding	5	0.68%	9	0.39%	0.3221	3.90
Time to major bleeding	47.38	69.79	216.28	235.53	0.0108	97.24
Major bleeding incidence rate (per 100 person-years)	1.50		1.28		0.7610	
GI bleeding	0.90		0.59		0.5515	
Intracranial hemorrhage	0.00		0.20			
Other bleeding	0.89		0.49		0.4130	
CRNM bleeding (excluding CRNM followed by MB)	47	6.39%	182	7.98%	0.1576	6.15
GI bleeding	11	1.50%	58	2.54%	0.0987	7.45
Other bleeding	38	5.17%	124	5.44%	0.7789	1.20
Time to CRNM bleeding	149.98	152.92	142.94	140.48	0.7639	4.79
CRNM bleeding incidence rate (per 100 person-years)	11.72		14.74		0.1612	

	Discontinuous Cohort (Reference)		Continuous Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	STD*
Sample size	**735**		**2,280**			
GI bleeding	2.60		4.49		0.0964	
Other bleeding	9.33		9.81		0.7845	
Recurrent VTE	9	1.22%	20	0.88%	0.4015	3.40
DVT	4	0.54%	13	0.57%	0.9349	0.35
PE	6	0.82%	9	0.39%	0.1578	5.43
Time to recurrent VTE	137.33		166.40	139.38		
Recurrent VTE incidence rate (per 100 person-years)	2.41		1.38		0.2068	
Discontinuation			832	36.49%		
Time-to-discontinuation			141.57	108.92		
Switch			26	1.14%		
Time-to-switch			149.38	121.11		
Apixaban dose change from index date till end of follow-up period						
Standard (5mg) to lower (2.5mg) dose			170	7.46%		
Lower (2.5mg) to standard (5mg) dose			14	0.61%		
Time-to-dose change			143.47	134.99		

Std Difference=100(actual std diff). Std Difference >10 is considered significant.

10.2.2. Sensitivity analysis of patients with ≥ 3 months of continuous apixaban use

Sensitivity analysis was conducted to evaluate the demographic and clinical characteristics and outcomes among patients who used apixaban for at least 3 months. A total of 5,243 patients were found to have ≥3 months of apixaban treatment after applying all eligibility criteria, 83.4% continued the treatment beyond 3 months and 16.6% discontinued the treatment at 3 months. Patients who continued apixaban beyond 3 months were older (61.4 years vs 58.1 years, p<0.001) and had a higher CCI score (1.3 vs 1.1, p<0.001) compared to patients who discontinued at the 3 months. Additionally, patients who continued beyond 3 months were more likely to have baseline comorbidities such as coronary artery disease (13.4% vs 10.5%, p=0.017), hyperlipidemia (38.6% vs 29.6%, p<0.001), and hypertension (56.1% vs 46.2%, p<0.001) when compared to patients who discontinued at 3 months. Continuous cohort patients were more likely to have index VTE in the inpatient setting (18.8% vs 11.6%, p<0.001) and have the index VTE events as PE with or without DVT (33.1% vs 23.4%, p<0.001) compared to patients who discontinued treatment at the 3 months.

Table 5. Baseline characteristics for continued vs discontinued apixaban cohorts – 3-month sensitivity analysis

	Discontinuous Cohort (Reference)		Continuous Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	STD*
Sample size	**871**		**4,372**			
Age	58.11	14.89	61.35	14.64	<.0001	21.94
18-54	350	40.18%	1,354	30.97%	<.0001	19.33
55-64	251	28.82%	1,374	31.43%	0.1283	5.69
65-74	153	17.57%	816	18.66%	0.4458	2.85
75-79	41	4.71%	322	7.37%	0.0048	11.17
≥80	76	8.73%	506	11.57%	0.0146	9.44
Sex						

	Discontinuous Cohort (Reference)		Continuous Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	STD*
Male	522	59.93%	2,604	59.56%	0.8388	0.75
Female	349	40.07%	1,767	40.42%	0.8487	0.71
Geographic region						
Northeast	142	16.30%	660	15.10%	0.3661	3.32
South	362	41.56%	2,021	46.23%	0.0116	9.41
Midwest	215	24.68%	1,008	23.06%	0.2994	3.82
West	147	16.88%	653	14.94%	0.1457	5.31
Other	5	0.75%	30	0.90%	0.7075	1.64
Setting of index VTE event						
Inpatient	101	11.60%	820	18.76%	<.0001	20.05
Ambulatory	770	88.40%	3,552	81.24%	<.0001	20.05
Position of VTE diagnosis						
Primary (principal or first listed)	778	89.32%	3,931	89.91%	0.5988	1.94
Secondary	93	10.68%	441	10.09%	0.5988	1.94
VTE diagnosis						
DVT only	667	76.58%	2,929	66.99%	<.0001	21.41
PE with DVT	51	5.86%	438	10.02%	0.0001	15.44
PE without DVT	153	17.57%	1,005	22.99%	0.0004	13.51
Baseline comorbidity						
Deyo-Charlson comorbidity index	1.07	1.63	1.31	1.81	<.0001	14.38
AIDS	0	0.00%	14	0.32%	0.0945	8.01
Alcohol abuse	14	1.61%	63	1.44%	0.7094	1.36
Anemia	101	11.60%	564	12.90%	0.2908	3.98
Central venous catheter	9	1.03%	42	0.96%	0.8419	0.73
Cerebrovascular disease	34	3.90%	218	4.99%	0.1725	5.25
Coagulation defects	47	5.40%	266	6.08%	0.4338	2.96
Ischemic heart/ coronary artery disease	91	10.45%	587	13.43%	0.0167	9.19
Dementia	14	1.61%	94	2.15%	0.3031	4.00
Dyspepsia or stomach discomfort	120	13.78%	618	14.14%	0.7814	1.03
Hemiplegia or paraplegia	4	0.46%	18	0.41%	0.8429	0.72
Hyperlipidemia	258	29.62%	1,688	38.61%	<.0001	19.04
Obesity	144	16.53%	767	17.54%	0.4722	2.69
Pneumonia	37	4.25%	268	6.13%	0.0303	8.49
Rheumatologic disease	28	3.21%	164	3.75%	0.4415	2.93
Sleep apnea	90	10.33%	481	11.00%	0.5628	2.17
Spinal cord injury	1	0.11%	3	0.07%	0.6521	1.53
Thrombophilia	47	5.40%	433	9.90%	<.0001	17.02
Varicose veins	67	7.69%	261	5.97%	0.0553	6.83
Congestive heart failure	40	4.59%	239	5.47%	0.2939	4.00
Diabetes	153	17.57%	864	19.76%	0.1344	5.64
Hypertension	402	46.15%	2451	56.06%	<.0001	19.91
Renal disease	96	11.02%	585	13.38%	0.0586	7.21
Liver disease	45	5.17%	267	6.11%	0.2840	4.08
COPD	65	7.46%	386	8.83%	0.1891	4.99
Peptic ulcer disease	9	1.03%	42	0.96%	0.8419	0.73
Inflammatory bowel disease	14	1.61%	53	1.21%	0.3431	3.35
Peripheral vascular disease	81	9.30%	540	12.35%	0.0109	9.83
Recent history of falls	27	3.10%	82	1.88%	0.0207	7.86
Fracture/trauma involving lower extremities	75	8.61%	265	6.06%	0.0053	9.79
Selected surgeries	52	5.97%	217	4.96%	0.2188	4.43
Baseline medication use						
Antiarrhythmic	62	7.12%	315	7.20%	0.9279	0.34
Statins	252	28.93%	1,422	32.53%	0.0378	7.79

	Discontinuous Cohort (Reference)		Continuous Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	STD*
Anti-platelets	27	3.10%	180	4.12%	0.1592	5.45
Aromatase inhibitors	2	0.23%	18	0.41%	0.4260	3.22
Beta blockers	170	19.52%	1,033	23.63%	0.0084	10.00
Gastroprotective agents	162	18.60%	900	20.59%	0.1829	5.00
SERMS	6	0.69%	21	0.48%	0.4324	2.73
NSAIDs	214	24.57%	1,020	23.33%	0.4312	2.90
Hormone therapy	3	0.34%	13	0.30%	0.8180	0.83
Apixaban initial dose						
Standard dose (apixaban 5mg)	848	97.36%	4,196	95.97%	0.0508	7.72
Lower dose (apixaban 2.5mg)	23	2.64%	176	4.03%	0.0508	7.72
Dose change during the baseline period						
Standard (5mg) to lower (2.5mg) dose	17	1.95%	87	1.99%	0.9412	0.27
Lower (2.5mg) to standard (5mg) dose	3	0.34%	31	0.71%	0.2209	5.04
Time-to-dose change	34.25	26.31	27.78	27.22	0.3251	24.17
Apixaban index dose**						
Standard dose (apixaban 5mg)	836	95.98%	4,141	94.72%	0.1202	6.01
Lower dose (apixaban 2.5mg)	35	4.02%	231	5.28%	0.1202	6.01
Baseline any bleed	88	10.10%	424	9.70%	0.7129	1.36

Std Difference=100(actual std diff). Std Difference >10 is considered significant.

**Apixaban index dose is based on the apixaban prescription claim date closest to the index date.

The descriptive outcomes in the sensitivity analysis are shown in Table 6. Among patients who continued apixaban beyond 3 months, 52.9% discontinued apixaban treatment during follow-up, 1.8% of patients switched to another anticoagulant during follow-up, and 8.1% of patients switched from a standard dose (5mg) to a lower dose (2.5mg). The incidence of major bleeding (1.51 vs 1.28), CRNM bleeding (16.07 vs 12.88), and recurrent VTE (1.74 vs 1.29) were similar between the continued and discontinued cohorts (Table 6).

Table 6. Outcomes for continued vs discontinued apixaban cohorts – 3-month sensitivity analysis

	Discontinuous Cohort (Reference)		Continuous Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	STD*
Sample size	871		4,372			
Follow-up time (in days)	251.65	209.12	193.17	149.31	<.0001	32.18
Minimum	1		1			
Q1	93		99			
Median	191		142			
Q3	375		239			
Maximum	980		1,005			
Major bleeding	8	0.92%	32	0.73%	0.5634	2.06
GI bleeding	5	0.57%	14	0.32%	0.2549	3.80
Intracranial hemorrhage	1	0.11%	5	0.11%	0.9972	0.01
Other bleeding	2	0.23%	15	0.34%	0.5906	2.12
Time to major bleeding	139.88	233.51	157.16	147.61	0.7946	8.85
Major bleeding incidence rate (per 100 person-years)	1.28		1.51		0.7148	
GI bleeding	0.64		0.73		0.8441	
Intracranial hemorrhage	0.21		0.22		0.966	

Other bleeding	0.43		0.67		0.5522	
CRNM bleeding (excluding CRNM after major bleeding)	73	8.38%	352	8.05%	0.7446	1.20
GI bleeding	23	2.64%	104	2.38%	0.6462	1.67
Other bleeding	51	5.86%	251	5.74%	0.8949	0.49
Time to CRNM bleeding	135.78	135.71	116.78	126.35	0.2490	14.49
CRNM bleeding incidence rate (per 100 person-years)	12.88		16.07		0.0847	
GI bleeding	3.84		4.53		0.4786	
Other bleeding	8.83		11.22		0.1198	
Recurrent VTE	10	1.15%	42	0.96%	0.6102	1.83
DVT	5	0.57%	25	0.57%	0.9936	0.03
PE	5	0.57%	20	0.46%	0.6483	1.63
Time to recurrent VTE	135.00	118.72	149.81	118.58	0.7242	12.48
Recurrent VTE incidence rate (per 100 person-years)	1.29		1.74		0.5037	
Discontinuation			2,311	52.86%		
Time-to-discontinuation			133.94	100.29		
Switch			78	1.78%		
Time-to-switch			135.38	100.80		
Apixaban dose change from index date till end of follow-up period						
Standard (5mg) to lower (2.5mg) dose	26	2.99%	355	8.12%	<.0001	22.56

Std Difference=100 (actual std diff). Std Difference >10 is considered significant.

10.3. Other analyses

None.

10.4. Adverse events / adverse reactions

Not applicable.

11. DISCUSSION

11.1. Key results

This retrospective study describes patient characteristics, treatment patterns, and outcomes among unprovoked VTE patients who received extended apixaban treatment. Among this patient population, 60.8% and 36.4% had apixaban treatment for ≥3 months and ≥6 months, respectively. Current CHEST guidelines recommend extended anticoagulation therapy without a scheduled stop in patients with unprovoked VTE and low bleeding risk following initial anticoagulation treatment of 3 months.[5] The AMPLIFY-EXT study suggests that extended treatment with apixaban beyond 6 months reduces the risk of recurrent VTE without increasing major bleeding rates.[12] However, in the current study of unprovoked VTE patients treated with apixaban in routine clinical practice, we found a large proportion of patients did not receive ≥3 months of treatment and the percentage of patients with ≥6 months of treatment was very low.

Among patients who did receive ≥6 months of apixaban therapy, the majority (75.6%) continued the treatment beyond 6 months and only a small percentage (24.4%) discontinued the therapy at 6 months. Of patients treated with apixaban beyond 6 months, 7.5% switched from a 5mg dose of apixaban to a 2.5mg dose of apixaban, 36.5% discontinued therapy, and 1.1% switched to another oral anticoagulant. Patients who continued apixaban treatment

beyond 6 months tended to be younger and more likely to have thrombophilia in the baseline compared to patients who discontinued at 6 months. The descriptive analysis of outcomes shows similar rates of major bleeding, CRNM bleeding, and recurrent VTE between patients who continued treatment beyond 6 months and patients who discontinued at 6 months. Of particular importance is the small number of patients who discontinued at 6 months (<800).

In the sensitivity analysis of patients who received ≥3 months of apixaban treatment, a large proportion (83.4%) continued the treatment beyond 3 months and only a small proportion (16.6%) discontinued at 3 months. The continued and discontinued cohorts had many differences in patient characteristics. Compared to the discontinued cohort, continued cohort patients tended to be older, had higher CCI scores, had more comorbidities in the baseline, and were more likely to have the index VTE event in the inpatient setting, presenting as PE with or without DVT. The rates of major bleeding, CRNM bleeding, and recurrent VTE were similar between the 2 cohorts in the descriptive analysis. As with the 6-month cohorts, the number of patients who discontinued apixaban treatment at 3 months was small (<900).

11.2. Limitations

As with all observational retrospective analysis, this study could only examine associations rather than causal relationships (between clinical factors and treatment patterns of interest). Claims data is also limited by the potential for missing data, coding errors, and lack of evidence of medication administration.

Specifically, differences in patient characteristics were not taken into consideration when evaluating clinical outcomes, and results on clinical outcomes should be interpreted cautiously. Moreover, the relatively small sample size for patients who discontinued apixaban treatment at 3 or 6 months prevents a meaningful and rigorous evaluation of the clinical outcomes. A larger sample size for these patients is needed for future investigations. In addition, the results may not be generalizable to the entire US VTE population, as only commercially insured patients were evaluated. Finally, it should be noted we did not exclude duplicates from the database; however, prior literature has reported duplicates of only 0.5% between 2 databases,[14] hence the duplicates were not likely to significantly affect the results.

11.3 Interpretation

Current CHEST guidelines recommend extended anticoagulation therapy without a scheduled stop in patients with unprovoked VTE and low bleeding risk following initial anticoagulation treatment of 3 months.[5] The AMPLIFY-EXT study which compared an additional 12 months of apixaban treatment (at either a standard or lowered dose) with no treatment among VTE patients who had completed 6-12 months of anticoagulant therapy found reduced rates of recurrent VTE or death from VTE without increasing the risk of major bleeding.[12] A meta-analysis of the efficacy and safety of DOACs for the extended treatment of VTE by Sardar et al (2013) showed that all the direct anticoagulants, including apixaban, reduced the risk of recurrent VTE without increasing the risk of major bleeding. Additionally, DOACs reduce the risk of all-cause mortality compared to placebo.[16] Nonetheless, despite the guidelines and existing evidence, in this study the percentage of patients receiving ≥3 months of apixaban

treatment was relatively low, and that of patients with ≥6 months of apixaban therapy was considerably low.

Some patient characteristics have been found to be associated with a higher likelihood of continuing apixaban treatment beyond 3 months or beyond 6 months. Additional studies are needed to fully understand factors that drive physicians' and patients' decisions about extended treatment of VTE. Rates of clinical outcomes were found to be similar between patients who received extended apixaban treatment and patients who did not receive extended treatment. However, due to a restricted sample size for patients who discontinued apixaban treatment at 3 months or at 6 months and the descriptive nature of the analysis, this study did not offer rigorous evaluations about the safety and effectiveness of extended apixaban treatment in routine clinical practice. Future studies with a larger sample size and appropriate statistical technical are needed to address this important question.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

Among unprovoked VTE patients treated with apixaban, a large proportion did not receive ≥3 months of treatment. Although AMPLIFY-EXT study showed beneficial effects of extended apixaban treatment beyond 6 months, the percentage of patients with ≥6 months of apixaban treatment was very low in this study. Some patient characteristics have been found to be associated with a higher likelihood of continuing apixaban treatment beyond 3 months or beyond 6 months. Additional studies are needed to fully understand factors that drive physicians' and patients' decisions about extended treatment of VTE. Rates of clinical outcomes were found to be similar between patients who received extended apixaban treatment or not. However, this study did not provide rigorous evaluations of the clinical outcomes due to a relatively small sample size for patients who discontinued apixaban treatment at 3 months or at 6 months and the descriptive nature of the analysis. Future studies with a larger sample size are needed to evaluate the safety and effectiveness of extended apixaban treatment in routine clinical practice.

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