NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Study information

Title	Comparative Clinical and Economic Outcomes Among Venous Thromboembolism Patients Who Initiated Apixaban or Warfarin in the United States Medicare Population
Protocol number	B0661113
Version identifier of the final study report	1.0
Date	August 30, 2019
EU Post Authorization Study (PAS) register number	NEUPAS24902
Medicinal product	Apixaban
Product reference	Not applicable
Procedure number	Not applicable
Marketing Authorization Holder (MAH)	Bristol-Myers Squibb Company

Research question and objectives	**Clinical Perspective:** **Aim 1:** Compare the demographic and clinical characteristics of patients prescribed apixaban or warfarin. **Aim: 2**: Compare both the incidence rates and the risk of MB between patients who received apixaban versus warfarin. **Aim 3:** Compare both the incidence rates and the risk of clinically relevant non-major (CRNM) bleeding between patients who received apixaban versus warfarin. **Aim 4:** Compare both the incidence rates and the risk of recurrent VTE events between patients who received apixaban versus warfarin. **Economic Perspective:** **Aim 1:** Compare MB-related medical costs patients who received apixaban versus warfarin. **Aim 2:** Compare recurrent venous thromboembolism (VTE)-related medical costs patients who received apixaban versus warfarin. **Aim 3:** Compare all-cause health care resource use (HCRU) and costs patients who received apixaban versus warfarin.
Country of study	USA
Authors	Allison Keshishian Email : akeshishian@statinmed.com Patrick Hlavacek Email: patrick.hlavacek@pfizer.com

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

1. ABSTRACT (STAND-ALONE DOCUMENT)

Title: Comparative Clinical and Economic Outcomes Among Venous Thromboembolism Patients Who Initiated Apixaban or Warfarin Therapies in the United States Medicare Population

Rationale and background: Venous thromboembolism (VTE) is a major cause of morbidity and mortality for hospitalized patients, the prevalence of which increases with age. Each year in the United States, the incidence of VTE is 1 case per 1000 patients, with >600,000 hospitalizations, up to 100,000 deaths, and an economic burden ranging from $13.5-$27.2 billion. Vitamin K antagonists (VKAs) such as warfarin have been the treatment of choice for anticoagulation. However, direct oral anticoagulants (DOACs) have emerged to treat VTE and have efficacy equal to warfarin and less complex pharmacodynamics, with limited need for routine monitoring. These include apixaban, which is an oral factor Xa inhibitor that eliminates the need for an initial parenteral anticoagulant, thus simplifying VTE treatment. The AMPLIFY randomized clinical trial program demonstrated that a fixed-dose regimen of apixaban alone was associated with significantly less bleeding compared to the conventional therapy for VTE (subcutaneous enoxaparin, followed by warfarin). In VTE patients who had completed 6-12 months of anticoagulation therapy, an additional 12 months of apixaban administration was found to significantly reduce the rate of recurrent VTE compared to placebo; thus, it was shown to be efficacious for the prevention of recurrent VTE.

This study evaluated the patient profiles, current antithrombotic patterns, and real-world clinical and economic outcomes among patients with VTE in the Medicare population.

Objectives:

Clinical Perspective:

Aim 1: Compare the demographic and clinical characteristics of patients who were prescribed apixaban or warfarin.

Aim: 2: Compare both the incidence rates and the risk (using hazard ratios) of major bleeding (MB) between patients who received apixaban versus warfarin.

Aim 3: Compare both the incidence rates and the risk of clinically relevant non-major (CRNM) bleeding between patients who received apixaban versus warfarin.

Aim 4: Compare both the incidence rates and the risk of recurrent VTE events between patients who received apixaban versus warfarin.

Economic Perspective:

Aim 1: Compare MB-related medical costs between patients who received apixaban versus warfarin.

Aim 2: Compare recurrent VTE-related medical costs between patients who received apixaban

versus warfarin.

Aim 3: Compare all-cause health care resource utilization (HCRU) and costs between patients who received apixaban versus warfarin.

Study design: The study was a longitudinal retrospective cohort analysis using the CMS fee-for-service (FFS) Medicare database. The study period was from 01MAR2014-31DEC2016 and allowed for a 6-month baseline period prior to the index date in the identification period (from 01SEP2014 through 31DEC2016, or until the last date of the data cut available for the study). Patients were required to have a VTE diagnosis in the primary or secondary position in inpatient or ambulatory settings and an apixaban or warfarin prescription claim within 30 days of the VTE event. Patients were followed from the day after the index date until the earliest of treatment discontinuation, treatment switch, death, disenrollment, 6-months after the index date, or study end.

Population: Elderly patients (aged ≥65 years) in the Medicare population who were diagnosed with VTE, were prescribed apixaban or warfarin (bridging to warfarin) between 01SEP2014-31 DEC2016 and had continuous health plan enrolment for 6 months prior to the prescription.

Variables: Demographic and clinical characteristics; clinical treatment patterns; economic outcomes; and clinical outcomes including MB, CRNM, recurrent VTE, all-cause HCRU, and costs were compared between VTE patients who were prescribed apixaban or warfarin.

Data sources: The study was conducted using member enrollment as well as medical and pharmacy claims from the Medicare database, a large national FFS claims database.

Study size: All eligible patients available for analysis were included. Based on the AMPLIFY clinical trial, the rate of MB is 0.6% corresponding to 6 months of follow-up for apixaban users and 1.8% corresponding to 6 months of follow-up for warfarin users. Therefore, a survival analysis of MB would need 1,926 patients in each group. The sample size calculation used the assumptions of an alpha of 0.05, power of 80%, an accrual period (i.e., the time period when patients are identified until study end [01SEPT2014-31DEC2016]) of 1.3 years, and a loss of follow-up of 15% for both the warfarin and apixaban cohorts. This calculation assumed a uniform accrual and loss to follow-up during the identification period.

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. Appropriate tests (e.g., t-test, chi-square test) were used based on the distribution of the measure. The cumulative incidence rate for clinical outcomes (MB, CRNM, and recurrent VTE) were calculated. Propensity score matching (PSM) was used to balance patient characteristics of the cohorts. Cox regression models were used to evaluate the risk of clinical outcomes. Generalized linear models and two-part models were used to compare health care costs between the apixaban and warfarin cohorts. Data analysis was executed using statistical software SAS version 9.3/9.4.

Results: Before matching 37,799 patients, 66.9% had initiated warfarin and 33.1% had initiated apixaban (25,284 and 12,515, respectively). Post-PSM, 11,363 matched pairs of apixaban-warfarin patients were identified with a mean follow-up period of 4.0 and 4.4 months, respectively. The mean age was 78 years, and about 37% of patients were male, with a mean Charlson Comorbidity Index score of 2.9. Warfarin was associated with a higher risk of MB (Hazard ratio [HR]: 1.31; 95% confidence interval [CI]: 1.10, 1.57) and CRNM bleeding (HR: 1.31; 95% CI: 1.19, 1.43) vs apixaban. The risks of recurrent VTE (HR: 0.96; 95% CI: 0.70, 1.33) and all-cause hospitalization (HR: 1.05; 95% CI: 0.99, 1.12) were similar among warfarin and apixaban patients. Patients who had initiated warfarin had significantly higher all-cause ($3,267 vs $3,033; p<0.001) and MB-related costs ($147 vs $75; p<0.001) compared to apixaban patients. These results were generally consistent across various subgroups including those defined by index VTE encounter, type of VTE diagnosis, VTE etiology, sex, frailty, and active cancer.

Conclusions: Among elderly patients with VTE, apixaban was associated with a lower risk of MB and CRNM bleeding. These results may be helpful in evaluating the risk-benefit ratio of apixaban for elderly VTE patients.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
BMS	Bristol-Myers Squibb
COPD	Chronic Obstructive Pulmonary Disease
CRNM	Clinically Relevant Non-Major
DOAC	Direct Oral Anticoagulant
DME	Durable Medical Equipment
DVT	Deep Vein Thrombosis
EDB	Enrollment Database
GHP	Group Health Plan
GLM	Generalized Linear Models
GPP	Good Pharmacoepidemiology Practices
HHA	Home Health Agency
HCRU	Health Care Resource Utilization
HIPAA	Health Insurance Portability and Accountability Act
ICD-9-CM	International Classification of Disease, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Disease, Tenth Revision, Clinical Modification
ICH	Intracranial Hemorrhage
INR	International Normalized Ratio
ISPE	International Society for Pharmacoepidemiology
IVC	Inferior Vena Cava

NDC	National Drug Codes
OAC	Oral Anticoagulant
PAC	Parenteral Anticoagulant
PE	Pulmonary Embolism
PPPM	Per Patient Per Month
PSM	Propensity Score Matching
SNF	Skilled Nursing Facility
US	United States
VTE	Venous Thromboembolism

3. 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
Allison Keshishian, MPH	Sr. Project Manager	STATinMED Research
Patrick Hlavacek, MPH	Director, HEOR	Pfizer, Inc

4. OTHER RESPONSIBLE PARTIES

Not applicable

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Draft study protocol	23 January 2018	23 January 2018	
Final study protocol	10 August 2018	10 August 2018	
Registration in the EU PAS register	10 August 2018	10 August 2018	
Start of data analysis	10 August 2018	10 August 2018	
End of data analysis	15 May 2019	15 May 2019	
Final study report	29 August 2019	30 August 2019	

6. RATIONALE AND BACKGROUND

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE) and is a major cause of morbidity and mortality in hospitalized patients.[1,2] Major surgical procedures including hip and knee replacement are the highest risk factors for VTE,[3] and it is the third most common cause of vascular-related death, following myocardial infarction (MI) and stroke.[4]

Each year, the incidence rate of VTE is 1 case per 1000 patients,[4] with >600,000 hospitalizations and >100,000 deaths overall**Error! Bookmark not defined.** and a total per patient t reatment cost over $20,000 during the first year following a VTE event.[5] These factors contribute to VTE's overall economic burden, which ranges from $13.5-$27.2 billion per year.[6] Prevalence increases with age, as older adults are more prone to VTE, and patients with comorbid conditions such as extremity trauma, cancer, surgery, prolonged immobilization, and hormone therapy are also at a greater risk.[7,8,9,10,11,12]

Vitamin K antagonists (VKAs) such as warfarin have been the treatment of choice for anticoagulation. However, to maximize benefits and minimize complications (such as bleeding), warfarin therapy should be monitored and adjusted within a narrow therapeutic index of international normalized ratio (INR) results.[13,14] Moreover, the pharmacokinetic profile of warfarin is complex due to several drug-drug and drug-food interactions.[15] Further, it is difficult to achieve long-term stability in some warfarin patients due to fluctuating INR values, which may be caused by diet, seasonal variation, or alcohol consumption, among other factors.[16] Ultimately, the need for regular monitoring, risk of hemorrhage, and poor control of INR levels may lead to medication non-adherence.[17,18]

According to the American College of Chest Physicians (ACCP) guidelines, DVT and PE patients who do not have cancer should be initiated on anticoagulation therapy with a non-vitamin K antagonist oral anticoagulant (dabigatran, rivaroxaban, apixaban, or edoxaban) rather than a VKA.[19] Direct oral anticoagulants (DOACs)—including dabigatran, apixaban, edoxaban, and rivaroxaban—were approved in the United States for treatment of VTE and prevention of recurrence among VTE patients and have emerged as a viable alternative to warfarin, with comparable efficacy, less complex pharmacodynamics, and lower monitoring needs.

DOACs have emerged with two main drug classes: the factor Xa inhibitors and the direct thrombin inhibitors. Apixaban is an oral factor Xa inhibitor, which eliminates the need for an initial parenteral anticoagulant, thus simplifying VTE treatment.[20] The AMPLIFY randomized clinical trial program demonstrated that a 5mg twice-daily fixed-dose oral regimen of apixaban alone (after administering 10mg twice daily for 7 days) was associated with significantly less bleeding compared to conventional VTE therapy (subcutaneous enoxaparin, overlapped and followed by warfarin).[21] Furthermore, among VTE patients who completed 6-12 months of anticoagulation therapy, apixaban administered for an additional 12 months was found to significantly reduce the rate of recurrent VTE compared to placebo and was thus shown to be efficacious for the prevention of recurrent VTE.**Error! Bookmark not defined.**[21]

A comparative effectiveness study on VTE patients who were treated with apixaban versus warfarin is important to identify more effective treatment regimens for VTE. Toward that end, this study examined the rate of MB, CRNM bleeding, recurrent VTE, corresponding costs associated with each of the events, health care resource utilization (HCRU), and all-cause costs among Medicare enrollees diagnosed with VTE and prescribed warfarin or apixaban.

This was not a commitment or requirement to any regulatory agency.

7. RESEARCH QUESTION AND OBJECTIVES

The following aims were addressed:

Clinical perspective:

Aim 1: Compare the demographic and clinical characteristics of patients who were prescribed apixaban or warfarin.

Aim 2: Compare both the incidence rates and the risk of MB between these cohorts.

Aim 3: Compare both the incidence rates and the risk of CRNM bleeding between these cohorts.

Aim 4: Compare both the incidence rates and the risk of recurrent VTE events between these cohorts.

Economic perspective:

Aim 1: Compare MB-related medical costs between these cohorts.

Aim 2: Compare recurrent VTE-related medical costs between these cohorts.

Aim 3: Compare all-cause HCRU and costs between these cohorts.

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1.0	01/07/2019	Substantial	9.9.4	Sensitivity and subgroup analysis were updated	Depending on the descriptive results the team decided to conduct additional sensitivity and subgroup analysis to generate evidence for VTE patients on treatment

9. RESEARCH METHODS

9.1. Study Design

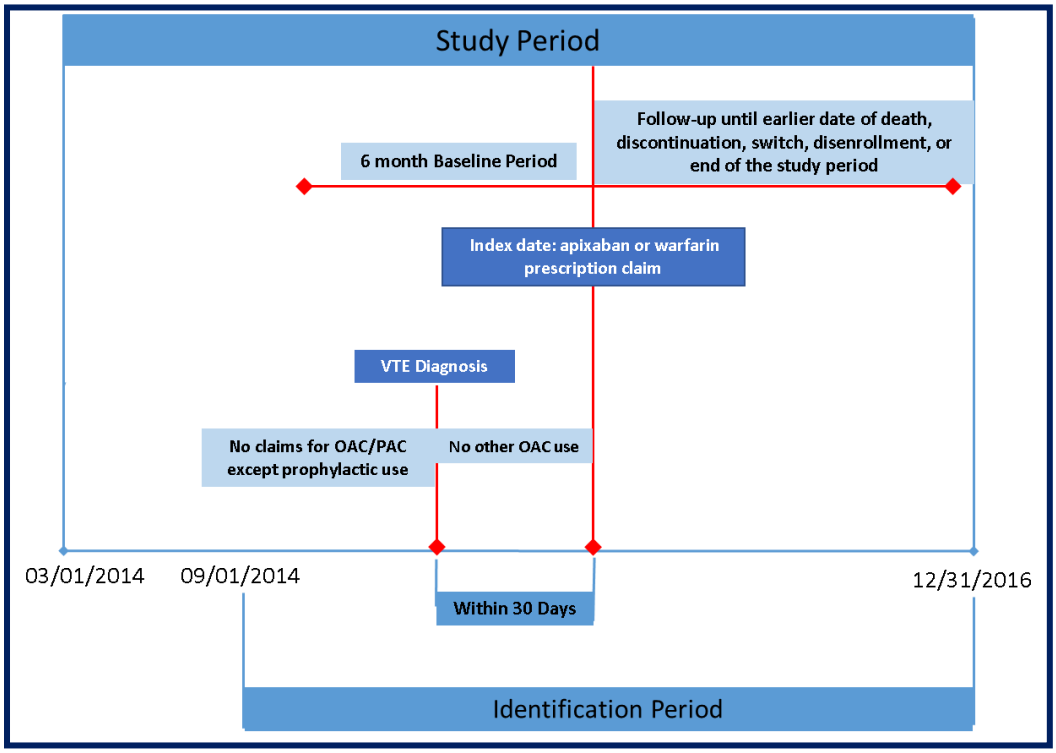
9.1.1. Key Index Period Definitions

- **Study period:** 01MAR2014-31DEC2016
- **Patient identification period:** 01SEP2014-31DEC2016
- **Baseline period:** 6 months prior to the index date
- **Follow-up period:** a maximum of 6 months after the index date or until the earliest of treatment discontinuation, treatment switch, death, health plan disenrollment, or study end

9.1.2. Key Index Point Definitions

- **Index encounter:** the first evidence of a VTE diagnosis in the primary or secondary position during the identification period for each patient
- **Index therapy:** the first apixaban or warfarin treatment prescribed within 30 days from the index encounter
- **Index date:** the first prescription claim date for the index therapy

Figure 1. Study Design Figure (for illustration purposes only, may not be proportionate)



9.2. Setting

Adult patients who were prescribed apixaban or warfarin were selected from the Medicare database from 01SEP2014-31DEC2016. Patients were required to have a VTE diagnosis in the primary or secondary position in the inpatient or ambulatory setting and an apixaban or warfarin prescription claim within 30 days of the VTE event. Patients were required to have had health plan enrollment for 6 months prior to and on the index date to ensure that the patients' complete medical history was available. Patients were required to be aged ≥18 years on the index date.

Follow-up Period:

The follow-up period was defined as the period between the day after the index date and study end (31DEC2016). Study outcomes were assessed from the day after therapy initiation through the earliest of the subsequent 6-month period, health plan disenrollment, death, index therapy discontinuation, switch to another OAC, initiation of (new) parenteral anticoagulant (PAC) treatment, or study end.

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

Episodes of PAC treatment were differentiated based on a gap in therapy of ≥2 days that occurred after 14 days post-index date.

9.3. Subjects

9.3.1. Selection Criteria

Patients were included in the study if they:

a) had a medical claim with a primary or secondary VTE diagnosis in an inpatient or ambulatory setting during the identification period;

- If occurring in the outpatient setting: the index encounter date was defined as the service date.
- In the inpatient setting: the discharge date was designated as the index encounter date.
- Qualifying outpatient encounters followed by qualifying inpatient encounters within 7 days were considered an inpatient episode (unless warfarin or apixaban was initiated between encounters, in which case it was classified as an outpatient encounter).

b) had ≥1 pharmacy claim for apixaban or warfarin during the 30-day period following the index encounter;

- The first warfarin or apixaban prescription date was designated as the index date.

c) were aged ≥65 years as of the index date; and

d) had continuous medical and pharmacy health plan enrollment (Part A, B, and D) for ≥6 months prior to the index encounter until the index date.

9.3.2. Exclusion Criteria

Patients were excluded if they:

a) had evidence of atrial fibrillation (AF)/flutter during the 6-month period preceding the index date;

- Patients with AF were excluded so that the OAC use was associated only with VTE diagnosis.

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

c) had evidence of another OAC on the index date (or during the period between the index encounter and the index date);

d) had a pharmacy claim for OAC/PAC use during the 6-month period preceding the index encounter, unless it was determined that such therapy was administered prophylactically;

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

e) had ≥2 medical claims for a cancer diagnosis or 1 claim for a cancer diagnosis and ≥1 claim for cancer treatment (e.g., chemotherapy, radiation, cancer-related surgery), 6 months before the index VTE date or 30 days after index VTE diagnosis;

f) had a medical claim indicating a diagnosis code for VTE during the 6-months preceding the index VTE encounter (unless the index VTE encounter occurred in the inpatient setting and was preceded by an outpatient VTE encounter within 7 days of the index encounter);

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

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

i) were warfarin patients with an index encounter requiring outpatient care only, who did not have evidence of PAC use from 14 days pre- to 14 days post-index date; or

j) were warfarin patients with evidence of PAC use during this period and received it beyond the 14-day period following the index date.

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

9.4. Variables

Baseline variables were measured during the 6 months prior to and on the index date. Baseline variables were evaluated using codes in primary or secondary position unless noted otherwise. Outcome variables were measured from the day after the index date.

Table 2. Baseline Demographic and Clinical Characteristic Variables

Variable	Operational Definition
Age	Age was defined as of the index date and used to assign patients to the following age groups: 65-74, 75-79, and ≥80 years.
Sex	A flag was created for female beneficiaries and reported as a percentage.
Race	Flags were created for patients of different races: White, African American, Hispanic, and Other.
US Geographic Region	The United States was divided into five regions: Northeast, South, North Central, West, and Other. Geographic region was captured from enrollment data.
Medicare/Medicaid Dual Eligibility	A flag was created for patients with Medicare/Medicaid dual eligibility and reported as a percentage.
Part D Low-income Subsidy	A flag was created for patients with a Part D low-income subsidy and reported as a percentage.
Type of Index Encounter	Flags were created for patients diagnosed with VTE in inpatient or ambulatory settings. Qualifying outpatient encounters followed by qualifying inpatient encounters within 7 days were considered an inpatient episode (unless warfarin or apixaban was initiated between encounters, in which case it would be classified as an outpatient encounter).
Position of VTE Diagnosis	Flags were created for the position of VTE diagnosis including primary (principle diagnosis) 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. Provoked VTE was defined as events that were preceded during the 3-month pre-index-encounter period by hormone therapy, fracture/trauma involving the lower extremities, pelvic/orthopedic surgery, or hospitalization for any reason for ≥3 days. Unprovoked VTE was defined as all events not classified as provoked. (See Table 5 Appendix 1 for codes.)
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.
Coagulopathy	A flag was created for patients with claims for coagulopathy.
Ischemic Heart/Coronary Artery Disease	A flag was created for patients with claims for ischemic heart/coronary artery disease.

Variable	Operational Definition
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.
Thrombocytopenia	A flag was created for patients with claims for thrombocytopenia.
Thrombophilia	A flag was created for patients with claims for thrombophilia.
Varicose Veins	A flag was created for patients with claims for varicose veins.
Congestive Heart Failure	A flag was created for patients with claims for congestive heart failure.
Diabetes	A flag was created for patients with claims for diabetes.
Hypertension	A flag was created for patients with claims for hypertension.
Renal Disease	A flag was created for patients with claims for renal disease. Flags for chronic kidney disease stage V, end-stage renal disease, or dialysis were also 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.
Recent History of Falls	A flag was created for patients who suffered a fall and was reported as a percentage.
Fracture/Trauma (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 calculated.

Variable	Operational Definition
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.
Health Care Resource Utilization	All-cause utilization variables were computed for inpatient, outpatient, ER, office, skilled nursing facility (SNF), durable medical equipment (DME), home health agency (HHA), hospice, and part D pharmacy claims.
Health Care Costs	Health care costs included total baseline all-cause costs and the following components: inpatient, outpatient, ER, office, SNF, DME, HHA, hospice, and part D pharmacy.
Apixaban Index Dose	Standard dose (apixaban 5 mg) and lower dose (apixaban 2.5 mg) was based on the dose of the initial apixaban prescription.

Table 3. Clinical and Outcome Variables

Variable	Operational Definition
Major Bleeding	MB events observed during follow-up were identified as a hospitalization with a MB ICD-9-CM or ICD-10 diagnosis or procedure code as the principle diagnosis. MB event was a dichotomous variable that equaled 1 if there was ≥1 bleeding event during the follow-up period. Time to the first MB event was calculated. MB was stratified by gastrointestinal bleeding, intracranial hemorrhage, and other bleeding.
CRNM Bleeding	A CRNM bleeding event was defined as: • an acute-care inpatient admission with a secondary diagnosis code for "non-critical site" for GI bleeding, ICH bleeding, or other selected types/sites of bleeding (without a principal diagnosis code for GI/ICH/other bleeding, or a procedure code for bleeding treatment); or • an ambulatory-care encounter with a diagnosis code for GI bleeding, ICH bleeding, or other selected types/sites of bleeding (without a diagnosis code for ICH bleeding).
Recurrent VTE	A recurrent VTE event was identified as an acute-care inpatient admission with a corresponding principal diagnosis; admissions occurring within 7 days of the qualifying VTE event (irrespective of care setting) were not considered in identifying new events. Secondary recurrent VTE: A recurrent VTE event was identified as an acute-care inpatient admission with a corresponding principal diagnosis for DVT, PE, or atypical DVT (DVT at hepatic, portal, mesenteric, renal, cerebral, and multi-segmental).
Major-bleeding-related Costs	Follow-up major-bleeding medical costs included the first major-bleeding hospitalization costs in the primary position plus costs related to all major-bleeding events (primary and secondary position) in the inpatient or outpatient setting after the first major bleed.
Recurrent VTE-related Costs	Follow-up recurrent VTE medical costs included the first recurrent VTE hospitalization costs in the primary position plus costs related to all recurrent VTE events (primary and secondary position) in the inpatient or outpatient setting after the recurrent VTE event.
Follow-up All-cause Health Care Utilization	All-cause health care utilization in the follow-up period was computed for inpatient, length of stay (LOS), outpatient, ER, office, SNF, DME, HHA, hospice, and part D pharmacy claims.
Follow-up All-cause Health Care Costs	All-cause health care costs in the follow-up period were computed for inpatient, outpatient, ER, office, SNF, DME, HHA, hospice, and part D pharmacy costs. Costs were adjusted to 2016 US dollars using the medical care component of the Consumer Price Index. Total medical and total health care costs were calculated per patient per month (PPPM).
All-cause Death	All-cause death in the follow-up period was evaluated and verified by Social Security records including date of death.

9.5. Data Sources and Measurement

This analysis used 100% CMS Medicare data, including the following files:

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 diagnoses (International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification [ICD-9-CM and ICD-10-CM] diagnosis code, procedure (ICD-9 and ICD-10 procedure code), diagnosis-related groups, dates of service, reimbursement amounts, hospital providers, and beneficiary demographic information. The file contains claims-level observations.

Medicare Outpatient Data

The outpatient claim file contains final action claims data submitted by institutional outpatient providers, including hospital outpatient departments, rural health clinics, renal dialysis facilities, outpatient rehabilitation facilities, comprehensive outpatient rehabilitation facilities, and community mental health centers. Some information contained in this file includes diagnosis and procedure codes (ICD-9-CM diagnosis, ICD-9 procedure, ICD-10 diagnosis, ICD-10 procedure, Centers for Medicare and Medicaid Service [CMS] Healthcare Common Procedure Coding System [HCPCS] codes), dates of service, reimbursement amounts, outpatient provider numbers, revenue center codes, and beneficiary demographic information. Each observation in this file is at the claim level.

Medicare Part D Drug Events Data

The Part D Drug Events (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; rather, they are summary extracts using CMS-defined standard fields.

Skilled Nursing Facility Research Identifiable File

The skilled nursing facility (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 Research Identifiable File

The home health agency (HHA) file contains final action, FFS claims submitted by HHA providers. This file includes: number of visits, type of visit (skilled nursing care, home health

aides, physical therapy, speech therapy, occupational therapy, and medical social services), diagnoses (ICD-9-CM and ICD-10-CM diagnoses), dates of visit, reimbursement amounts, HHA provider numbers, and beneficiary demographic information.

Hospice Research Identifiable File

The hospice file contains final action claims submitted by hospice providers. Once a beneficiary elects hospice care, all hospice-related claims are found in this file, regardless of whether 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 diagnoses (ICD-9-CM and ICD-10-CM diagnoses), dates of service, reimbursement amounts, hospice provider numbers, and beneficiary demographic information.

Durable Medical Equipment Research Identifiable File

The durable medical equipment (DME) file contains a final action, FFS claims submitted by DME suppliers. This file includes diagnoses (ICD-9-CM and ICD-10-CM diagnoses), services provided (CMS HCPCS codes), dates of service, reimbursement amounts, DME provider numbers, 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 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).

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 the files constructed and available annually in May of the current year, for the previous year. The files do not contain data on all beneficiaries ever entitled to Medicare, only those entitled during the year of the data.

9.6. Bias

Propensity score matching (PSM) was used to control for potential confounders when comparing the cohorts.[23] Covariates in the logistic regression model included the following variables: age, geographic region, CCI score, comorbidities, and other clinical characteristics such as bleeding history and renal disease. The final lists of variables used in the model were discussed and determined during analysis development, after reviewing the pre-matched descriptive tables. Each subject in the reference cohort was matched to a subject in the comparator cohort with the closest propensity score. The nearest neighbor method (without replacement and with a caliper of 0.01) was used to select the matched samples. The balance of covariates between treatment groups was determined using the absolute standardized difference of the mean ≤ 0.10. After PSM, no significant differences were observed among all pre-index measures between the patient cohorts.

9.7. Study Size

The sample size was calculated for survival analysis comparing the MB rates between apixaban and warfarin patients using an alpha of 0.05, power of 80%, an accrual period (identification period when patients are selected into the study until end of study [01SEPT2014-31DEC2016]) of 1.3 years, and a loss of follow-up of 15% for both the warfarin and apixaban cohorts. This calculation assumed a uniform accrual and loss to follow-up during the identification period. Using the AMPLIFY clinical trial, with a MB rate of 0.6% per year for the apixaban cohort and 1.9% per year in the warfarin cohort, a Cox proportional hazards analysis of MB would require 1,926 patients in each group. The sample size and event rates were evaluated prior to proceeding with the analysis to determine that there was sufficient power.

9.8. Data Transformation

This study used secondary data collected in the Medicare Database, which is de-identified and HIPAA compliant.

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), are documented in the statistical analysis plan, which is dated, filed, and maintained by the sponsor (Appendix 4).

9.9. Statistical Methods

9.9.1. Main Summary Measures

Means, medians, and standard deviations were provided for continuous variables in the descriptive analysis of continuous data. Numbers and percentages were provided for dichotomous and polychotomous variables in the descriptive analysis of categorical data.

Bivariate comparisons of baseline characteristics and outcomes measures were provided. Appropriate tests (e.g., t-test, chi-square test) were used based on the distribution of the measure. The cumulative incidence rates for clinical outcomes (MB, CRNM, recurrent VTE) were calculated. The incidence rates were calculated as the number of patients who experienced the event divided by the observed time at risk. An unadjusted Kaplan-Meier curve was drawn to illustrate time-to-event analysis.

9.9.2. Main Statistical Methods

Cox proportional models were fit to compare MB, CRNM, recurrent VTE, and other clinical outcomes among the apixaban and warfarin cohorts. This model tests proportional hazards models on survival (or time-to-event) data via maximum likelihood with consideration of exponential, Weibull, and Gompertz distributions.

A generalized linear model (GLM) was applied for the multivariable analysis of health care costs among the warfarin and apixaban cohorts. Since a large proportion of zeros existed in the health care cost variables (e.g., MB costs, inpatient, or emergency department [ER] costs), two-part models were implemented, in which the first part was a logistic regression of event and the second part a GLM regression of costs. Bootstrapping with the two-part model was conducted to generate the 95% confidence interval.

All data analysis was executed using statistical software SAS version 9.3/9.4

9.9.3. Missing Values

None

9.9.4. Sensitivity Analyses

The following analyses were conducted to evaluate the robustness of findings with respect to changes in the definitions of the following key variables and assumptions:

- Recurrent VTE including 7 days
- Recurrent VTE including hospitalization and ER
- Recurrent VTE including 7 days in hospitalization or ER

Subgroup analysis: The following subgroup analyses were conducted:

- VTE encounter—inpatient vs ambulatory
- VTE diagnosis—DVT only vs PE with or without DVT
- VTE etiology—provoked vs unprovoked
- Sex—male vs female

- Frailty—frail vs non-frail patients
- Active Cancer—active vs non-active cancer patients

9.9.5. Amendments to the Statistical Analysis Plan

None

9.10. Quality Control

Data in Medicare databases are collected periodically in an electronic format. Medicare employs a number of subsequent quality assurance procedures and undertakes routine audits to ensure the quality of information. The data analysis followed our best practices, which have been validated through many past studies and publications. The analysis was also inspected by two independent researchers for quality control purposes.

9.11. 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, and 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.

10. RESULTS

10.1. Participants

Of 37,799 patients eligible for analysis before PSM, 25,284 (66.9%) were prescribed warfarin and 12,515 (33.1%) were prescribed apixaban. Patients who had initiated warfarin had significantly higher baseline CCI compared to the apixaban cohort (Supplemental Table 1). After 1:1 PSM, there were 11,363 apixaban-warfarin matched pairs (Figure 1).

10.2. Descriptive Data

The pre-PSM matched descriptive baseline characteristics appear in Table 1. The mean ages were 77.5 and 77.7 years for warfarin and apixaban, respectively. More than 36% of patients were males and 37% of the patients were residing in the South region of the United States. Warfarin patients had significantly higher Medicare/Medicaid dual eligibility (29.3 vs 26.3%; p<0.001) and part D low-income subsidies (32.0% vs 29.3%; p<0.001) compared to apixaban. More than 50% of the patients had DVT only. Warfarin patients had unprovoked VTE rates of 64.1% vs 68.4% among apixaban patients. Warfarin patients had a higher CCI compared to apixaban (3.0 vs 2.9; p=0.002). Anemia (36-42%), ischemic heart/coronary artery disease (36-38%), diabetes (38-42%), and hypertension (47-66%%) were the most common comorbidities prevalent in VTE patients. 88.2% of the apixaban patients had a standard dose of apixaban. The baseline total health care costs were higher for warfarin than apixaban ($5,082 vs $3,976; p<0.001).

10.3. Outcome Data

The pre-PSM matches results for outcomes appear in Table 2. Before PSM, warfarin patients had a longer follow-up length compared to apixaban (135 days vs 119 days; p<0.001). Compared to apixaban, warfarin was associated with higher incidence rates of MB (7.62 vs 5.74) and CRNM bleeding (27.87 vs 22.0). The incidence rate for recurrent VTE was similar between the two cohorts (2.22 vs 1.99). Compared to apixaban, a significantly larger proportion of warfarin patients discontinued (63.2% vs 49.1%; p<0.001) and switched (8.6 vs 3.7%; p<0.003).

10.4. Main Results

10.4.1. Post-PSM Baseline Characteristics

The descriptive baseline characteristics post-PSM matching are shown in Table 3. After PSM, comparisons of baseline characteristics between matched cohorts did not show significant differences, except for baseline HCRU and costs; warfarin-apixaban matched patients had a mean age of 78 years and mean CCI score of 2.9. About 32% of the matched patients had a provoked VTE, and 54% of patients had DVT only. Standard dose apixaban was prescribed to 88.2% of matched patients.

10.4.2. Post-PSM Outcomes Characteristics

The follow-up characteristics for the matched cohort appears in Table 4. The incidence rates of MB, CRNM bleeding, and recurrent VTE appear in Figure 2. Warfarin was associated with

significantly higher rates MB (hazard ratio [HR]: 1.31; 95% confidence interval [CI]: 1.10, 1.57) and CRNM bleeding (HR: 1.31; 95% CI: 1.19, 1.43) compared to apixaban. Recurrent VTE rates were similar between warfarin and apixaban (HR: 0.96; 95% CI: 0.70, 1.33).

Compared to apixaban, warfarin had significantly higher MB-related PPPM medical costs ($147 vs $75; difference: $72; 95% CI: $32, $121; p=0.003). The recurrent VTE-related costs were similar between warfarin and apixaban patients ($30 vs $36; difference: -$6; 95% CI: --$24, $13, p=0.516) (Table 5). Warfarin patients had significantly higher total all-cause health care costs compared to apixaban ($3,267 vs $3,033; difference: $234, 95% CI: $230, $239; p<0.001) (Table 5).

When warfarin was used as a reference, apixaban was associated with a significantly lower risk of MB (hazard ratio [HR]:0.76; 95% CI: 0.64-0.91) and CRNM bleeding (HR: 0.77; 95% CI: 0.70-0.84) compared with warfarin. Recurrent VTE rates were similar between apixaban and warfarin patients (HR: 1.04; 95% CI: 0.75-1.43) (Figure 3).

10.5. Sensitivity analysis

The results of the sensitivity analysis were generally consistent with those of the main analysis. When the 7 days post-index encounter were included in the definition of recurrent VTE, the risk of recurrent VTE was similar across apixaban and warfarin patients (HR: 1.01; 95% CI: 0.75, 1.35; p=0.918). However, warfarin patients had a significantly higher risk of recurrent VTE compared to apixaban when the definition of recurrent VTE included ER visits (HR: 1.47; 95% CI: 1.16, 1.85; p=0.001) or ER visits and 7 days post-index encounter (HR: 1.56; 95% CI: 1.25, 1.92; p<0.001 [Table 6]). Results for cost outcomes when applying these definitions for recurrent VTE were consistent with the main analysis (Table 5b).

10.6. Subgroup analysis

The subgroup analyses were generally consistent with the main analysis (the descriptive variables for the subgroups can be found in Tables 7-13).

No significant interaction was observed between treatment and VTE encounter for MB (p=0.451), CRNM bleeding (p=0.734), and recurrent VTE (p=0.460; Figures 4A-C).

No significant interaction was observed between treatment and type of VTE diagnosis for MB (p=0.619), CRNM bleeding (p=0.480), and recurrent VTE (p=0.113).

No significant interaction was observed between treatment and VTE etiology for MB (p=0.718) or CRNM bleeding (p=0.684). A significant interaction was found between treatment and VTE etiology for recurrent VTE (p=0.053). Provoked VTE apixaban patients trended toward a higher risk of recurrent VTE (HR: 1.68, 95% CI: 0.93-3.01), while apixaban patients with unprovoked VTE trended toward a lower risk (HR: 0.83, 95% CI: 0.56-1.23).

No significant interaction was observed between treatment and gender for MB (p=0.784), CRNM bleeding (p=0.411), and recurrent VTE (p=0.789).

No significant interaction was found between treatment and frailty for MB (p=0.440) and recurrent VTE (p=0.752), however, there was a significant interaction was found between treatment and frailty for CRNM bleeding (p=0.015). Compared with their warfarin counterparts, frail apixaban patients were associated with a 15% lower risk of CRNM bleeding (HR: 0.85, 95% CI: 0.75-0.97), while non-frail apixaban patients were associated with a 32% lower risk (HR: 0.68, 95% CI: 0.59-0.78).

10.6.1. Cancer Subgroup Analysis

In the main analysis, active cancer patients (defined as ≥2 medical claims for 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 date or 30 days after index VTE diagnosis) were excluded from the study. For the cancer subgroup analysis, the active cancer patients were included in the analysis. Of 47,219 patients eligible for analysis before PSM, 31,431 (66.6%) were prescribed warfarin and 15,788 (33.4%) were prescribed apixaban. About 20% of patients had active cancer. Patients that initiated apixaban had similar age and CCI compared to warfarin. After 1:1 PSM, there were 14,363 apixaban-warfarin matched pairs.

No significant interaction was observed between treatment and active cancer for MB (p=0.984), CRNM bleeding (p=0.296), and recurrent VTE (p=0.3414). There was a 24%, 26%, and 29% reduction in MB (HR: 0.76, 95% CI: 0.57-1.00), CRNM bleeding (HR: 0.74, 95% CI: 0.63-0.87), and recurrent VTE (HR: 0.71, 95% CI: 0.42-1.18) among apixaban patients with active cancer. Similarly, there was a reduction in MB (HR: 0.75, 95% CI: 0.63-0.90), CRNM bleeding (HR: 0.81, 95% CI: 0.74-0.90), and recurrent VTE (HR: 0.94, 95% CI: 0.69-1.29) among apixaban patients with non-active cancer.

10.7. Other Analyses

None

10.8. Adverse Events/Reactions

This study includes unstructured data (e.g., narrative fields in the database) that were converted to structured (i.e., coded) data solely by a computer using automated/algorithmic methods and data that already exist as structured data in an electronic database. 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.

11. DISCUSSION

11.1. Key Results

In the pre-matched cohort, 25,284 patients-initiated warfarin (66.9%) and 12,515 patients-initiated apixaban (33.1%). After 1:1 PSM, 11,363 matched pairs of apixaban-warfarin patient data were assessed for means of 4.0 and 4.4 months, respectively. In the matched cohorts, the mean age was 78 years, and the mean CCI score was 2.9. Compared to apixaban, warfarin was associated with significantly higher MB (HR: 1.31; 95% CI: 1.10, 1.57) and CRNM bleeding (HR: 1.31; 95% CI: 1.19, 1.43). Recurrent VTE was similar between warfarin and apixaban (HR: 0.96; 95% CI: 0.70, 1.33). Patients initiating warfarin had significantly higher all-cause ($3,267 vs $3,033; p<0.001) and MB-related costs ($147 vs $75; p=0.003) but lower recurrent VTE-related medical costs PPPM ($30 vs $36; p=0.516). These results were generally consistent across various subgroups including those defined by index VTE encounter, type of VTE diagnosis, VTE etiology, sex, frailty, and active cancer.

11.2. Limitations

Claims data are extremely valuable for the efficient and effective examination of health care outcomes, treatment patterns, HCRU, and costs. Moreover, this particular study offers unique insight into longitudinal parameters of a nationally representative population, a relatively new drug, patients often overlooked in clinical trials, and other important aspects of real-world clinical practice.

However, as with all retrospective observational claims studies, the data were collected for administrative purposes, not research, and engender certain limitations. For instance, the presence of a claim for a filled prescription does not indicate that the medication was taken as prescribed or at all. Moreover, medications filled over the counter or provided as samples by the physician cannot be captured in the claims data. In addition, the presence of a diagnosis code on a medical claim does not indicate the positive presence of disease, as the diagnosis code may have been incorrectly coded or included as rule-out criteria rather than actual disease.

This study also has some particular limitations. For instance, the Medicare databases do not uniformly capture over-the-counter medications, such as aspirin, which have also been used for stroke prevention in AF patients and could have an impact on the treatment outcomes of the anticoagulants being studied. Also, the Medicare databases include only FFS patients and thus yield results that may not be generalizable to broader populations.

11.3. Interpretation

12. OTHER INFORMATION

Not Applicable

13. CONCLUSIONS

Among elderly OAC-naïve patients with VTE, apixaban was associated with a lower risk of MB and CRNM bleeding and incurred significantly lower all-cause and MB-related medical costs, compared to those prescribed warfarin. These results may be helpful in evaluating the risk-benefit ratio of apixaban for elderly VTE patients.

14. REFER

[1] Clagett GP, Anderson FA, Gaerts W, et al. Prevention of venous thromboembolism. *Chest.* 1998;114(5 suppl):531S-560S.

[2] Haake DA, Berkman SA. Venous disease after hip surgery. Risk factors, prophylaxis, and diagnosis. *Clin Orthop.* 1989;242:212-231.

[3] Oster G, Ollendorf DA, Vera-Llonch M, Hagiwara M, Berger A, Edelsberg J. Economic consequences of venous thromboembolism following major orthopedic surgery. *Ann Pharmacother*. 2004;38(3):377-382.

[4] Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet.* 2012(9828);379:1835-1846.

[5] Coleman CI, Baugh C, Crivera C, et al. Healthcare costs associated with rivaroxaban or warfarin use for the treatment of venous thromboembolism. *J Med Econ*. 2017;20(2):200–203.

[6] Mahan CE, Borrego ME, Woersching AL, et al. Venous thromboembolism: Annualised United States models for total, hospital-acquired and preventable costs utilising long-term attack rates. *Thromb Haemost.* 2012;108(2):291–302.

[7] Lehmann R, Luxembourg B, Miesbach W, et al. Idiopathic (unexplained) pulmonary embolism is associated with an impaired prognosis compared to other entities of pulmonary embolism. *Blood Coagul Fibrinolysis*. 2010;21(1):70–76.

[8] Kim DY, Kobayashi L, Barmparas G, et al. Venous thromboembolism in the elderly: the result of comorbid conditions or a consequence of injury? *J Trauma Acute Care Surg.* 2012;72(5):1286–1291.

[9] Velmahos GC, Konstantinos S, Tabbara M, et al. Pulmonary embolism and deep venous thrombosis in trauma are they related? *Arch Surg*. 2009;144(10):928–932.

[10] Wilasrusmee C, Kiranantawat K, Horsirimanont S, et al. Deep venous thrombosis in surgical intensive care unit: prevalence and risk factors. *Asian J Surg*. 2009;32(2):85–88.

[11] Darze ES, Latado AL, Guimaraes AG. Incidence and clinical predictors of pulmonary embolism in severe heart failure patients admitted to a coronary care unit. *Chest.* 2005;128(4):2576–2580.

[12] Cushman M, Kuller LH, Prentice R, et al. Estrogen plus progestin and risk of venous thrombosis. *JAMA.* 2004;292(13):1573-1580.

[13] Melamed OC, Horowitz G, Elhayany A, Vinker S. Quality of anticoagulation control among patients with atrial fibrillation. *Am J Manag Care.* 2011;17(3)232-237.

[14] Connolly SJ, Pogue J, Eikelboom J, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of International Normalized Ratio control achieved by centers and countries as measured by time in therapeutic range. *Circulation*. 2008;118(20):2029-2037.

[15] Finks SW, Trujillo TC, Dobesh PP. Management of venous thromboembolism: Recent advances in oral anticoagulation therapy. *Annal Pharmacother.* 2016;50(6):486–501.

[16] Limone BL, Hernandez AV, Michalak D, et al. Timing of recurrent venous thromboembolism early after the index event: a meta-analysis of randomized controlled trials. *Thromb Res*. 2013;132:420–426.

[17] Helgason CM, Do MA, Nutescu E. Warfarin in patients with stroke and reasons for discontinuation. *J Stroke Cerebrovasc Dis*. 2004;13(2):70-73.

[18] Fang MC, Go AS, Chang Y, et al. Warfarin discontinuation after starting warfarin for atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2010;3(6):624-631.

[19] Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest.* 2016;149(2):315–352.

[20] The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010;363(26):2499-2510.

[21] Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808.

[22] Pan X, Kachroo S, Liu JXC, et al. Real-world discontinuation among early users of apixaban, dabigatran, rivaroxaban or warfarin among atrial fibrillation patients newly initiated on anticoagulation therapy: Tell of first 200 days. *Eur Heart J.* 2014;35(Abstract Supplement):897.

[23] Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983;70(1):41-55.