NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Outcomes among Venous Thromboembolism Patients Who were Admitted into the Emergency Department and Treated with Apixaban or Warfarin in the U.S.
Protocol number	B0661138
Protocol version identifier	1
Date of last version of protocol	April 3, 2019
EU Post Authorisation Study (PASS) Register Number	
Medicinal Product	Apixaban
Research question and objectives	Primary research question: What are the outcomes of venous thromboembolism (VTE) patients admitted into the emergency department (ED) and treated with either apixaban or warfarin? Primary objective: • To evaluate the ED discharge status, hospital healthcare resource utilization and costs of VTE patients admitted into the ED and treated with warfarin vs. apixaban Secondary objectives: • To evaluate 1-month all-cause, major bleeding (MB)-related, any bleeding-related, and VTE-related readmission rates of VTE patients admitted into the ED and treated with warfarin vs. apixaban • To determine hospital length of stay (LOS) and costs associated with all-cause, MB-related, any bleeding-related, and VTE-related readmissions occurring within 1 month after the index date of VTE patients treated with warfarin vs.

	apixaban
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TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AF	Atrial Fibrillation
AFL	Atrial Flutter
CCI	Charlson Comorbidity Index
DOAC	Direct Oral Anticoagulant
DVT	Deep Vein Thrombosis
HIPAA	Health Insurance Portability and Accountability Act
ICD-9 CM	International Classification of Diseases, 9th Revision
ICD-10 CM	International Classification of Diseases, 10th Revision
IVCF	Inferior Vena Cava Filter
LMWH	Low-Molecular-Weight Heparin
LOS	Length of Stay
MB	Major Bleeding
OAC	Oral Anticoagulant
PE	Pulmonary Embolism
UFH	Unfractionated Heparin
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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3. ABSTRACT

Title: Outcomes among Venous Thromboembolism Patients Who were Admitted into the Emergency Department and Treated with Apixaban or Warfarin in the U.S.

Version: 1
Date of Protocol: April 3, 2019
Author: Jay Lin, PhD, MBA, Novosys Health; Patrick Hlavacek, MPH, Pfizer

Rationale and background:
Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cause of vascular disease-related deaths. Direct oral anticoagulants (DOAC) have allowed for the initial use of single drug therapy in place of traditional parenteral anticoagulant and oral vitamin K antagonist combination therapy. Treatment guidelines now recommend initial DOAC therapy for the long-term treatment of VTE and suggest that patients presenting with acute DVT of the leg or low-risk PE in the emergency department (ED) be discharged home for outpatient treatment rather than be admitted to the hospital. However, while the clinical and economic outcomes of hospitalized VTE patients has been studied, little is known regarding the outcomes of patients who initiate VTE treatment in the ED, particularly those patients who are subsequently discharged from the ED for outpatient VTE treatment. This study will evaluate the outcomes of VTE patients who are admitted to the ED and treated with the DOAC, apixaban, or warfarin. In addition to the ED discharge status, hospital healthcare resource utilization and costs associated with the initial VTE-related ED admission, and 1-month readmission outcomes will be evaluated.

Research question: What are the outcomes of VTE patients admitted into the ED and treated with either apixaban or warfarin?

Objectives:

Primary objective:
- To evaluate the ED discharge status, hospital healthcare resource utilization and costs of VTE patients admitted into the ED and treated with warfarin vs. apixaban. The ED discharge status is defined as whether the ED admitted patients were discharged from ED or further admitted into the inpatient hospitalizations.

Secondary objectives:
- To evaluate 1-month all-cause, MB-related, any bleeding-related, and VTE-related readmission rates of VTE patients admitted into the ED and treated with warfarin vs. apixaban
- To determine hospital length of stay (LOS) and costs associated with all-cause, MB-related, any bleeding-related, and VTE-related readmissions occurring within 1 month after the index date of VTE patients treated with warfarin vs. apixaban

Study design: The study will be a retrospective cohort analysis using the Premier Hospital database. The overall study period will be from August 1, 2013 through June 30, 2018, including a 1-month follow-up period for observation of readmissions and a 1-year baseline observation period.

Population: This retrospective cohort study will evaluate the ED discharge status, hospital LOS and costs among ED admitted adult patients with VTE in the USA. The more detailed patient selection is described below:

Adult patients (age ≥18 years) admitted into the ED with a primary discharge diagnosis code indicating VTE will be identified from the Premier Hospital database between August 1, 2014 and May 31, 2018. Patients who received apixaban or warfarin during the ED admissions will be identified and grouped into study cohorts based on the oral anticoagulant (OAC) used. Patients receiving warfarin will be further required to have received at least one of the injectable anticoagulants, including unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) or fondaparinux during the ED admissions. The overall study population will also be stratified based on whether patients were discharged home or were admitted into the inpatient setting following their ED admission. The first of such VTE ED admissions will be defined as the index event, with the corresponding ED or hospital discharge date as the index date. Patients who received both apixaban and warfarin or any other DOAC (rivaroxaban, dabigatran, edoxaban, betrixaban) during their index ED admission or were diagnosed with atrial fibrillation/atrial flutter (AF), pregnancy, or had inferior vena cava filter (IVCF) usage during the baseline period or during the index ED admission will be excluded from the study.

Variables: Demographic, patient clinical characteristics, hospital characteristics, and key anticoagulant treatment-related information will be measured during the index ED admission. Other clinical characteristics (e.g. prior bleeding) of VTE patients will be measured during a 12-month baseline period. The discharge status, LOS, and costs during the index ED admission will be determined and compared between the apixaban and warfarin cohorts. The proportion of patients treated with apixaban and warfarin that have all-cause, MB-related, any bleeding-related and VTE-related readmissions that occur within 1 month after the index date will be evaluated and compared between the apixaban and warfarin cohorts. Hospital LOS and associated costs of have all-cause, MB-related, any bleeding-related and VTE-related readmissions will be determined and compared between the apixaban and warfarin cohorts. The event rate, hospital LOS and cost associated with 1-month VTE-any-diagnosis readmissions, defined as readmissions with VTE as either primary or secondary diagnosis, will be evaluated as the sensitivity analysis. Hospital cost data from the Premier database will reflect the hospital perspective (cost occurred to hospitals).

Data sources: The study will be conducted using the Premier Hospital database which is a nationally representative inpatient hospitalization records database that captures more than 45 million hospital discharges from greater than 600 acute care hospitals, representing approximately 20% of all hospital admissions in the U.S.

Study size: The preliminary data evaluation of the Premier database indicated that there are at least 10,000 patients for each OAC cohort during the study period described for this study. It is assumed that for the ED discharge status, the percentages of ED Only patients among the patients treated with warfarin and apixaban are 30% and 40% respectively. With a two-sided test, an alpha-level of 0.05, we have estimated the following power calculation.

Power Calculation		
Nominal Power	**Actual Power**	**N Total-One Arm**
0.70	0.701	562
0.75	0.750	630
0.80	0.800	712
0.85	0.850	814
0.90	0.901	954
0.95	0.950	1178

Thus, the study is expected to have sufficient sample sizes for the study measurements.

Data analysis: Means ± standard deviations, and medians will be provided for continuous variables. Numbers and percentages will be provided for dichotomous and polychotomous variables. Bivariate comparisons of baseline patient demographics, clinical characteristics, hospital characteristics and unadjusted readmission rates and costs will be provided, with appropriate tests (e.g., ANOVA test, chi-square test) used based on the distribution of the measure. A multivariable logistic regression analysis will be carried out to assess the potential impact of treatment with warfarin compared to treatment with apixaban on index ED discharge status as well as 1-month all-cause, MB-related, any bleeding-related, major bleeding-related and VTE-related readmission risks, separately. The independent covariates in the regression analyses will include key patient demographics and hospital characteristics. A generalized linear model with log transformation and gamma distribution or a two-part model analysis will be used examine the impact of treatment with warfarin vs. apixaban on index event costs or hospital readmission costs. Sensitivity analyses will be used to evaluate 1-month VTE-any-diagnosis readmission rates of VTE patients admitted into the ED and treated with warfarin vs. apixaban. The sensitivity analyses will also be used to determine hospital length of stay (LOS) and costs associated with VTE-any-diagnosis readmissions occurring within 1 month after the index date of VTE patients treated with warfarin vs. apixaban. A critical value of 0.05 will be used to determine statistical significance. All data analysis will be executed using statistical software SAS version 9.4.

Milestones:

Milestone	Planned date
Draft study protocol	April 3, 2019
Final study protocol	
Registration in the EU PAS register	
Start of data analysis	
End of data analysis	
Final study report	

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason

5. MILESTONES

Milestone	Planned date
Draft study protocol	April 3, 2019
Final study protocol	
Registration in the EU PAS register	
Start of data analysis	
End of data analysis	
Final study report	

6. RATIONALE AND BACKGROUND

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cause of vascular disease-related deaths.[1,2] With an annual incidence rate of approximately 1 to 2 per 1,000 person-years, the estimated number of people affected by VTE in the United States (US) may be as high as 900,000.[3,4] Studies have estimated the annual cost of incident VTE to be from $7-$10 billion and the total cost of VTE to range from $13.5-$27.2 billion annually.[5,6] Since VTE is primarily a disease of older age and taking into consideration the growing elderly population in the US, the number of persons with VTE is estimated to more than double by 2050.[7] Consequently, the economic burden of VTE, largely related to hospitalizations, is also predicted to significantly increase by 2050.

Traditional standard-of-care therapy for acute VTE is comprised of initial parenteral therapy with a low-molecular-weight heparin (LMWH), fondaparinux or unfractionated heparin as a bridging agent, overlapping with and followed by an oral vitamin K antagonist (VKA) such as warfarin.[8] However, the introduction of direct oral anticoagulants (DOAC) such as apixaban, dabigatran, rivaroxaban, and edoxaban, has allowed for the initial use of single drug therapy in place of traditional combination therapy. Furthermore, updated treatment guidelines now recommend DOAC therapy over both VKA and LMWH therapy for the long-term treatment VTE.[9,10] With fixed-dose regimens, fast onset of action, and no requirement for routine coagulation monitoring, these oral anticoagulants (OAC) have also facilitated the treatment of VTE on an outpatient basis. Clinical practice guidelines suggest that patients presenting with acute DVT of the leg or low-risk PE in the emergency department (ED) be discharged home for outpatient treatment rather than be admitted to the hospital.[8,9,11]

VTE is commonly diagnosed and treated in the ED and emergency physicians are often responsible for the initial diagnosis of acute DVT and PE, and subsequent treatment decisions. However, while the clinical and economic outcomes of hospitalized VTE patients

has been studied, little is known regarding the outcomes of patients who initiate VTE treatment in the ED, particularly those patients who are subsequently discharged from the ED for outpatient VTE treatment. In addition, while the efficacy and safety of DOACs in comparison to traditional warfarin therapy has been evaluated in clinical trials, there is limited real-world evidence regarding their use for the outpatient treatment of VTE.[12-17] For this study, patients admitted to the ED for VTE and treated with apixaban and warfarin will be identified from August 1, 2014 through May 31, 2018. In addition to the ED discharge status, hospital healthcare resource utilization and costs associated with the initial VTE-related ED admission, and 1-month readmission outcomes will be evaluated.

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The study will address the following primary research question: What are the outcomes of venous thromboembolism (VTE) patients admitted into the emergency department (ED) and treated with either apixaban or warfarin?

- The primary objective of the study is to evaluate the ED discharge status, hospital healthcare resource utilization and costs of VTE patients admitted into the ED and treated with warfarin vs. apixaban. The ED discharge status is defined as whether the ED admitted patients were discharged from ED or further admitted into the inpatient hospitalizations.
- The secondary objectives are:
    - To evaluate 1-month all-cause, major bleeding (MB)-related, any bleeding-related, and VTE-related readmission rates of VTE patients admitted into the ED and treated with warfarin vs. apixaban.
    - To determine average hospital length of stay (LOS) and costs associated with all-cause, MB-related, any bleeding-related, and VTE-related readmissions occurring within 1 month after the index date of VTE patients treated with warfarin vs. apixaban.

8. RESEARCH METHODS

8.1. Study design

The study will be a retrospective cohort analysis using the Premier Hospital database. The overall study period will be from August 1, 2013 through June 30, 2018, including a 1-month follow-up period for observation of readmissions and a 1-year baseline observation period.

Patient Populations:

This retrospective cohort study will evaluate the ED discharge status, hospital LOS and costs among ED admitted adult patients with VTE in the USA. The more detailed patient selection is described below:

Adult patients (age ≥18 years) admitted into the ED with a primary discharge diagnosis code indicating VTE will be identified from the Premier Hospital database between August 1, 2014 and May 31, 2018. Patients who received apixaban or warfarin prior to their discharge from the ED will be identified and grouped into study cohorts based on the oral anticoagulant initiated. Patients receiving warfarin will be further required to have received at least one of the injectable anticoagulants, including unfractionated heparin (UFH), LMWH or fondaparinux during the ED admissions. The overall study population will also be stratified based on whether patients were discharged home or were admitted into the inpatient setting following their ED admission. The first of such VTE ED admissions will be defined as the index event, with the corresponding ED or hospital discharge date as the index date. Patients who received both apixaban and warfarin or any other direct OAC (rivaroxaban, dabigatran, edoxaban, betrixaban) during their index ED admission, were diagnosed with atrial fibrillation/atrial flutter or pregnancy during the baseline period or during the index ED admission, or had inferior vena cava filter usage during the baseline period or index ED admission will be excluded from the study.

Demographic, patient clinical characteristics, hospital characteristics, and key anticoagulant treatment-related information will be measured during the index ED admission. Other clinical characteristics (e.g. prior bleeding) of VTE patients will be measured during a 12-month baseline period. The discharge status, LOS, and costs during the index ED admission will be determined and compared between the apixaban and warfarin cohorts. In this study, readmissions will be evaluated as either ED or inpatient readmissions as recorded in the Premier database. The proportion of patients treated with apixaban and warfarin that have all-cause, MB-related, any bleeding-related and VTE-related readmissions that occur within 1 month after the index date will be evaluated and compared between the apixaban and warfarin cohorts. Hospital LOS and associated costs of have all-cause, MB-related, any bleeding-related and VTE-related readmissions will be determined and compared between the apixaban and warfarin cohorts. In the analysis, MB-related and VTE-related readmissions will be defined as either ED or inpatient readmissions with MB or VTE as the primary discharge diagnosis code, respectively. Any bleeding-related readmissions will be defined as

either ED or inpatient readmission with MB as either the primary or non-primary (secondary) discharge diagnosis codes.

The proportion of patients treated with apixaban and warfarin that have VTE-any-diagnosis readmissions that occur within 1 month after the index date will be evaluated and compared between the apixaban and warfarin cohorts. Hospital LOS and associated costs of VTE-any-diagnosis readmissions will be determined and compared between the apixaban and warfarin cohorts. VTE-any-diagnosis readmissions will be defined as either ED or inpatient readmissions with VTE as either the primary or non-primary (secondary) discharge diagnosis codes.

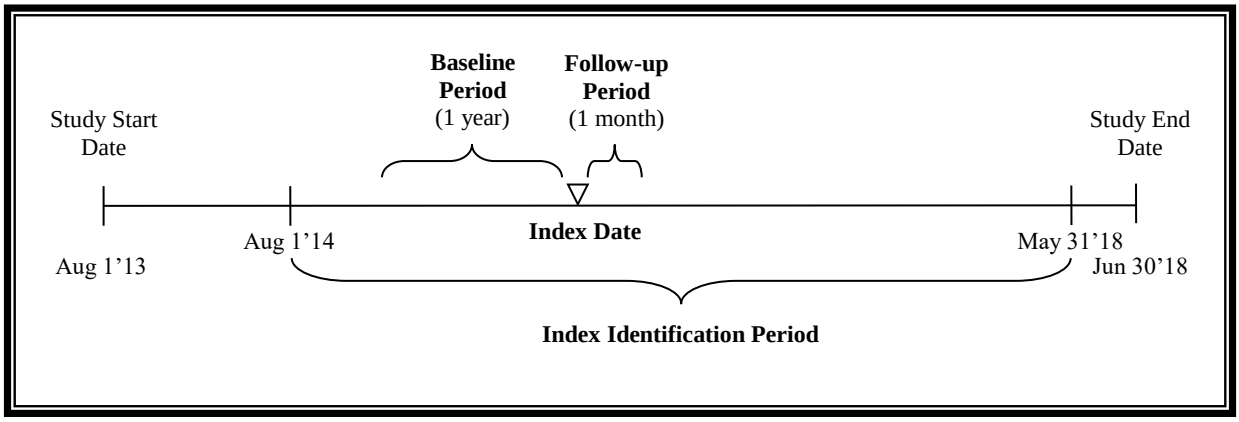
Key Study Periods:

1. **Index Identification Period:** the time period between August 1, 2014 and May 31, 2018, during which the index event will be identified. The first ED visit for patients with VTE as the primary discharge diagnosis will be identified as the index event from the Premier Hospital database during the index identification period. The corresponding discharge date for the index event is defined as the index date.

2. **Baseline Period:** the 12-month period prior to the admission of the index event is defined as the baseline period.

3. **Follow-up Period:** the 1-month period after the discharge of the index event is defined as the follow-up period.

Figure 1. Study Time Periods (for illustration purposes, may not be proportional)



8.2. Patient Selection

This retrospective cohort study will evaluate the ED discharge status, hospital LOS and costs among ED admitted adult patients with VTE in the USA. The more detailed patient selection is described below:

Adult patients (age ≥18 years) admitted to the ED for VTE, based on a primary discharge diagnosis code indicating VTE, will be identified from the Premier Hospital database

between August 1, 2014 and May 31, 2018. Patients who received apixaban or warfarin prior to being discharged from the ED will be identified and grouped into study cohorts based on the OAC initiated. The first of such ED admissions will be defined as the index event. The overall study population will be stratified based on whether patients were discharged home or were admitted into the inpatient setting with the corresponding ED or hospital discharge date as the index date.

8.2.1. Inclusion criteria

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

- Have a primary diagnosis of VTE identified by the following ICD-9-CM or ICD-10 codes from the Premier Hospital database between August 1, 2014 and May 31, 2018 (see Annex 2 for all codes used in the study)
    - Pulmonary embolism (PE)
    - Deep vein thrombosis (DVT)
- Received either apixaban or warfarin prior to discharge from the ED
    - Patients receiving warfarin will be further required to have received at least one of the injectable anticoagulants, including UFH, LMWH or fondaparinux during their ED admission.
- Have an age ≥18 years as of the index ED admission for VTE

8.2.2. Exclusion criteria

Patients meeting any of the following criteria within the records for the index hospitalizations will not be included in the study:

- Received both apixaban and warfarin during the index ED admission. This exclusion criterion will allow for a clean grouping of patients into the apixaban and warfarin usage cohorts.
- Received any other DOAC including rivaroxaban, dabigatran edoxaban and betrixaban during the index ED admissions.
- Had medical claims indicating one of the following conditions or procedures during the index ED admission or within 12 months prior to the index date, consistent with exclusion criteria that were used in previous studies:
    1. Atrial fibrillation (AF)/ Atrial flutter (AFL)
    2. Pregnancy
    3. Inferior vena cava filter (IVCF) usage:
- Patients transferred from other facilities.
- Patients who died during the index ED admission.

These inclusion and exclusion criteria are consistent with other previous apixaban retrospective database studies of patients with VTE.

8.2.3. Study Cohorts

After applying the inclusion and exclusion criteria, eligible patients will be grouped into the following study populations:

- **All ED**: All eligible VTE patients who were admitted to the ED
    - **ED Only**: Eligible VTE patients who were discharged home from their index ED admission
    - **ED Inpatient**: Eligible VTE patients who were admitted into the inpatient setting from their index ED admission

Among all study patients, the proportion of patients with ED Inpatient status is defined as the primary endpoint.

The All ED patient group will be further evaluated for the secondary and sensitivity analyses as appropriate.

Descriptive study measurements will be provided for the stratified patient cohorts: a) ED Only and b) ED Inpatient.

Within each study population, patients will be assigned to the following cohorts based on the OAC treatment received during index ED admission.

- **Apixaban Cohort**: VTE patients who received apixaban during the index ED admission
- **Warfarin Cohort**: VTE patients who received warfarin during the index ED admission

8.3. Study Variables

All data will be extracted from the Premier Hospital database described in section 8.4. Hospital cost data used in this study will be from the hospital perspective reflecting cost incurred to hospitals.

Table 1. Demographic Variables, Patient Clinical Characteristic Variables, and Hospital Characteristic Variables (Covariates)

Variable	Role	Operational definition
Age	Patient characteristic and potential confounder	Age will be defined as of the index date and used to assign patients to age groups: 18-34, 35-44, 45-54, 55-64, 65-74 and >75 years, reported as count and

Variable	Role	Operational definition
		percentages, evaluated on the index date.
Gender	Patient characteristic and potential confounder	Distribution of female and male patients and reported as count and percentage, evaluated on the index date.
Race	Patient characteristic and potential confounder	Patients with white, black, and other/unknown race and reported as count and percentages, evaluated on the index date.
Payer Type	Patient characteristic and potential confounder	Patients with Medicare, Medicaid, commercial, and other/unknown insurance coverage and reported as counts and percentages, evaluated on the index date.
Index ED Admission Deyo-Charlson Comorbidity Index	Patient characteristic and potential confounder	The Deyo-Charlson Comorbidity Index will be calculated for the index ED admission.
Baseline Prior Bleed	Patient characteristic and potential confounder	Patients with a bleeding diagnosis on hospital records during the baseline period and reported as count and percentage. Bleeding diagnoses will have a breakdown of any, gastrointestinal, and intracranial.
Baseline Prior VTE	Patient characteristic and potential confounder	Patients with a VTE diagnosis on hospital records during the baseline period and reported as count and percentage. VTE diagnoses will have a breakdown of any, DVT, PE, and DVT/PE.
Index ED Admission Comorbid Conditions	Patient characteristic and potential confounder	Patients with a diagnosis on hospital records for the following comorbidities at the index date and reported as count and percentage: congestive heart failure, diabetes, hypertension, myocardial infarction, peripheral vascular disease, coronary artery disease, inflammatory bowel disease, cancer/malignancy (excluding non-melanoma skin cancer), pneumonia, rheumatologic disease, thrombocytopenia, thrombophilia. The count of index events with primary diagnosis of DVT vs. PE will be measured too.
Index ED Admission Apixaban Dose Strength	Patient characteristic and potential confounder	Patients with apixaban dose strengths of high, low, and unknown during the index ED admission and reported as count and percentage.

Variable	Role	Operational definition
Other Anticoagulants During Index ED Admission	Patient characteristic and potential confounder	Patients who receive enoxaparin, dalteparin, tinzaparin, heparin, and fondaparinux during the index ED admission and reported as count and percentage.
Index Hospital Geographic Region	Patient characteristic and potential confounder	East North Central, East South Central, Middle Atlantic, Mountain, New England, Pacific, South Atlantic, West North Central, West South Central. Reported as count and percentage
Index Hospital Urban/Rural Status	Patient characteristic and potential confounder	Rural, urban- reported as count and percentage
Index Hospital Teaching Status	Patient characteristic and potential confounder	Yes/No- reported as count and percentage
Index Hospital Bed Size	Patient characteristic and potential confounder	0-99, 100-199, 200-200, 300-399, 400-499, and ≥500- reported as count and percentage

Table 2. Outcome Measurements for Primary and Secondary Objectives

Variable	Role	Operational definition
Index ED Discharge status	Primary Objective: Outcome	Number and percentage of patients discharged from the ED or admitted into the inpatient setting. The proportion of patients with each discharge status will be compared between the warfarin and apixaban cohorts of the overall study population.
Index ED Resource Utilization	Primary Objective: Outcome	Associated LOS, hospital charges and hospital costs for the index ED admission will be determined. LOS for ED Only admissions (patients discharged home from their index ED admission) will be set to 0. LOS and hospital cost/charge per patient will be compared between the warfarin and apixaban cohorts of each study population.
All-cause Readmission	Secondary Objective: Outcome	Number and percentage of patients with all-cause readmissions within 1 month after the index date in study cohorts will be reported. Associated LOS, hospital charges and hospital cost for all-cause readmissions will be determined.
Major Bleeding (MB)-related Readmission	Secondary Objective: Outcome	Defined as readmissions with a major bleeding (MB) diagnosis at the first position of the hospital discharge diagnosis codes. Number and percentage of patients with MB-related readmissions within 1 month after the index date in study cohorts will be reported. Associated LOS, hospital charges and hospital cost for MB-related readmissions will be determined. The number and percentage of patients with sub-types of MB-related readmissions (GI, ICH and other MB) within 1 month after the index date in study cohorts will be reported.
VTE-related Readmission	Secondary Objective: Outcome	Defined as readmissions with a VTE diagnosis at the first position of the hospital discharge diagnosis codes. Number and percentage of patients with VTE-related readmissions within 1 month after the index date in study cohorts will be reported. Associated LOS, hospital charges and hospital cost for VTE-related readmissions will be determined. The number and percentage of patients with sub-types of VTE-related readmissions (DVT or PE) within 1 month after the index date in study cohorts will be reported.

Variable	Role	Operational definition
Any-bleeding-related Readmission	Secondary Objective: Outcome	Defined as readmissions with a major bleeding diagnosis at any position of the hospital discharge diagnosis codes. Number and percentage of patients with bleeding-related readmissions within 1 month after the index date in study cohorts will be reported. Associated LOS, hospital charges and hospital cost for bleeding-related readmissions will be determined. The number and percentage of patients with sub-types of Any-bleeding-related readmissions (GI, ICH and other bleeding) within 1 month after the index date in study cohorts will be reported.
VTE-any-diagnosis Readmission	Sensitivity Analysis: Outcome	Defined as readmissions with a VTE diagnosis at any position of the hospital discharge diagnosis codes. Number and percentage of patients with VTE-any-diagnosis readmissions within 1 month after the index date in study cohorts will be reported. Associated LOS, hospital charges and hospital cost for VTE-any-diagnosis readmissions will be determined. The number and percentage of patients with sub-types of VTE-any-diagnosis readmissions (DVT or PE) within 1 month after the index date in study cohorts will be reported.

Sensitivity and Sub-Population Analyses: The following measurements will be carried out as the sensitivity or sub-population analysis:

- To descriptively evaluate 1-month VTE-any-diagnosis (as either primary or secondary diagnosis) readmission rates of VTE patients admitted into the ED and treated with warfarin vs. apixaban
- To descriptively evaluate hospital length of stay (LOS) and costs associated with VTE-any-diagnosis readmissions occurring within 1 month after the index date of VTE patients treated with warfarin vs. apixaban
- To descriptively evaluate the primary objective (the ED discharge status, hospital healthcare resource utilization and costs of VTE patients admitted into the ED and treated with warfarin vs. apixaban) with stratification by the primary index VTE diagnosis type: DVT vs. PE.

8.4. Data sources

The data source is the Premier Hospital database, which provides hospital billing information on a patient's hospital stay as well as information on ICD-9 and ICD-10 codes and current procedural terminology codes. Specifically, the database contains a date-stamped log of all billed items, including medications, laboratory, diagnostic, and therapeutic services, and

primary and secondary diagnoses for each patient's hospitalization. Identifier-linked files provide demographic and payer information. Detailed service-level information for each hospital day is recorded and this includes details on medication received. Billed items are standardized by the database vendor after the hospital both reviews and consents to the items.

8.5. Study size

The preliminary data evaluation of the Premier database indicated that there are at least 10,000 patients for each OAC cohort during the study period described for this study. It is assumed that for the ED discharge status, the percentages of ED Only patients among the patients treated with warfarin and apixaban are 30% and 40% respectively. With a two-sided test, an alpha-level of 0.05, we have estimated the following power calculation.

Power Calculation		
Nominal Power	**Actual Power**	**N Total-One Arm**
0.70	0.701	562
0.75	0.750	630
0.80	0.800	712
0.85	0.850	814
0.90	0.901	954
0.95	0.950	1178

Thus, the study is expected to have sufficient sample sizes for the study measurements.

8.6. Data management

This study will use secondary data collected in the Premier database, which is de-identified and HIPAA compliant.

8.7. Data analysis

Bivariate descriptive statistics will be utilized to describe demographics, clinical characteristics, readmission rates, and unadjusted resource utilization and costs among each patient cohort. Means, medians, and standard deviations will be provided for continuous variables when performing descriptive analysis of continuous data. Counts and percentages will be provided for dichotomous and polychotomous variables when performing descriptive analysis of categorical data. ANOVA-tests and chi-square tests will be used to detect statistically significant differences in continuous and categorical variables, respectively.

A multivariable logistic regression analysis will be carried out to assess the potential impact of treatment with warfarin compared to treatment with apixaban on index ED discharge status as well as 1-month all-cause, MB-related, any bleeding-related and VTE-related readmission risks, separately. Independent variables in the regressions may include age, gender, region, race, payer type, CCI, apixaban dosage level (standard/low) at index date, prior bleeding, prior VTE, select comorbidities, hospital teaching status, urban/rural, hospital bed-size categories.

A generalized linear model (GLM) will be used examine the impact of treatment with warfarin vs. apixaban on index event LOS and hospital readmission LOS. A generalized linear model (GLM) with log transformation and gamma distribution will be used examine the impact of treatment with warfarin vs. apixaban on index event costs or all-cause hospital readmission costs. A two-part model analysis will be used examine the impact of treatment with warfarin vs. apixaban on 1-month MB-related and VTE-related readmission costs. The GLM and two-part regression models will adjust for key patient characteristics, as appropriate. Independent variables in the regressions may include age, gender, region, race, payer type, CCI, apixaban dosage level (standard/low) at index date, prior bleeding, prior VTE, select comorbidities, hospital teaching status, urban/rural, hospital bed-size categories. In the two-part model, the first part will consist of a multivariable logistic regression which will be used to evaluate the impact of warfarin vs. apixaban treatment on the risk of 1-month MB-related and VTE-related readmissions. The second part will consist of a multivariable GLM with log transformation and gamma distribution which will be applied to the 1-month MB-related and VTE-related readmission cost data. For example, with the MB-related cost evaluation, the incremental MB-related cost will be evaluated among patients with such MB events. Then, the odds ratio estimated from the first part is combined with the incremental MB-related costs estimated from the second part to estimate the incremental MB-related cost among all patients. Such two-part calculations will be carried out in 1,000 cycles of random bootstrapping resampling to generate 1,000 such estimates. The univariate statistics of the 1,000 incremental MB-related costs among all patients will be used to evaluate the MB-related cost distribution. The 2.5-percentile and 97.5-percentile of the incremental MB-related costs estimated from the 1,000 cycles of bootstrapping will be used to represent the lower and upper levels of the 95% confidence interval.

These regression analysis approaches are consistent with the methods approved for previous Eliquis alliance retrospective database analyses.

The summary of the statistical analyses with the study objectives is listed below:

SUMMARY OF ANALYSES

Outcome	Supports Protocol Objective Number	Statistical Method	Covariates
ED discharge status, index hospital LOS and costs	1	Descriptive statistics and multivariable regressions	Demographic and clinical characteristics
1-month all-cause, major bleeding (MB)-related, any bleeding-related, and VTE-related readmission rates	2	Descriptive statistics and multivariable regressions	Demographic and clinical characteristics
Readmission LOS and cost associated with 1-month all-cause, major bleeding (MB)-related, any bleeding-related, and VTE-related readmission rates	2	Descriptive statistics and multivariable regressions	Demographic, clinical characteristics, and index event costs

1-month VTE-any-diagnosis readmission rate	Sensitivity and Sub-population	Descriptive statistics	N/A
Readmission LOS and cost associated with 1-month VTE-any-diagnosis readmission rate	Sensitivity and Sub-population	Descriptive statistics	N/A
ED discharge status, index hospital LOS and costs, with breakdown by index primary VTE diagnosis type	Sensitivity and Sub-population	Descriptive statistics	N/A

An alpha value of 0.05 will be used to determine statistical significance. As in other previous approved HEOR studies, no adjustment on the p-value will be made for multiple testing. It is important to point out that the p-values obtained for the bivariate statistics for non-hypothesis testing purpose can only be considered as nominal p-values for descriptive purposes. Thus, such nominal p-values may not indicate the statistical significance of the differences between the comparison groups. Such a limitation will be described in future potential publications.

All data analysis will be executed using statistical software SAS version 9.4.

8.8. Quality control

Data in Premier database are collected periodically in an electronic format. Premier database employs a number of subsequent quality assurance procedures and undertakes routine audits to ensure the quality of information. The data analysis follows our good data analysis practices which have been demonstrated in many past research studies and publications. The analysis is also inspected with at least two independent researchers to for quality control purpose.

8.9. Strengths and limitations of the research methods

A key strength is that retrospective analyses provide a better understanding of the study population in real-world clinical practice as compared to the controlled conditions of a clinical trial. Retrospective database studies allow observation of patients who are often under-represented in clinical trials, such as those with comorbidities and the elderly.

Patient data in the Premier Hospital database are only representative of hospital costs and exclude outpatient healthcare utilization and costs not received in a hospital. While the Premier Hospital database contains information from a large number of hospitals across the U.S., it is possible that it may not be representative of the entire U.S. population of VTE patients. Additionally, patient treatment information and history in the outpatient settings are not available in the Premier Hospital database. Also, hospital readmissions are only captured when patients are readmitted to the same Premier database hospitals. Lastly, billing and coding errors and missing data could potentially occur on database records.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

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

9.2. Patient withdrawal

Not applicable.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

IRB/IEC review is not required.

9.4. Ethical Conduct of the Study

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

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves unstructured data: data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.
In these data sources, individual patient data are not retrieved or validated, and 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) cannot be met.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final study report detailing the final study protocol and the analysis results will be provided when the study is complete.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

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13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Diagnosis and procedure codes used in the study:


Study Codes.xls