NON-INTERVENTIONAL STUDY PROTOCOL

Study information

Title	Post-Discharge Treatment Patterns and Outcomes in Patients with Venous Thromboembolism
Protocol number	*B0661190*
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Research question and objectives	The purpose of this study is to evaluate the post-discharge treatment patterns including persistence, recurrent venous thromboembolism (VTE) and bleeding among hospitalized adult VTE patients treated with apixaban or warfarin. The study objectives are as to: 1. Describe the proportion of patients with VTE treated with apixaban or warfarin in the hospital 2. Understand the post-discharge treatment patterns (including persistence, switch, and discontinuation) among patients who started on apixaban or warfarin in the hospital The secondary objective is to: 3. Assess recurrent VTE, major bleeding, and clinically relevant non-major (CRNM) bleeding among patients who continue on apixaban or warfarin in the outpatient setting, while persistent on index therapy

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
AIDS	Acquired Immune Deficiency Syndrome
ARB	Angiotensin Receptor Blockers
CCI	Charlson Comorbidity Index
CDM	Hospital Charge Data Master
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease 2019
CPT-4	Current Procedural Terminology version 4
CRF	Case Report Form
CRNM	Clinically-relevant non-major
DOAC	Direct Oral Anticoagulant
DCT	Data Collection Tools
DVT	Deep Vein Thrombosis
Dx	Professional Fee/ Medical Claims
ER	Emergency Room
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
ICD-9-CM	International Classification of Diseases, ninth revision, clinical modification
ICD-10-CM	International Classification of Diseases, tenth revision, clinical modification
ID	Identifier
IEC	Independent Ethics Committee

IQR	Interquartile Range
IRB	Institutional Review Board
LMWH	Low molecular weight heparin
LRx	Longitudinal prescription claims database
NSAID	Nonsteroidal anti-inflammatory drugs
OAC	Oral Anticoagulant
PAC	Parenteral Anticoagulant
PCP	Primary Care Provider
PE	Pulmonary Embolism
SAS	Statistical Analysis System
SD	Standard Deviation
SERM	Selective Estrogen Receptor Modulators
US	United States
VTE	Venous Thromboembolism

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title

Post-Discharge Treatment Patterns and Outcomes in Patients with Venous Thromboembolism
Version: 1.0
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Primary author:
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Pfizer, Inc.

Rationale and background

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major health concern associated with significant mortality and morbidity. There are >330,000 hospital admissions for VTE every year in the United States (US).[3] Historical data suggests that the rate of hospitalization for VTE increased from 7.0 to 8.4 per 1,000 discharges in the US.[4]

Management of VTE during an acute hospital encounter involves rapid anticoagulation. Current guidelines recommend continuing anticoagulation therapy post-discharge with warfarin, a vitamin K antagonist, or one of the newer direct oral anticoagulants (DOACs) which do not require Parental Anticoagulant (PAC) bridging therapy.[5] Over the past decade, the use of DOACs, particularly apixaban, to treat VTE has increased dramatically.[6]

There are some gaps in real world evidence (RWE) regarding oral anticoagulant (OAC) use among patients hospitalized with VTE. First, there is a need for RWE regarding the proportion of patients treated with particular OACs during the VTE hospitalization. Second, there needs to be a better understanding of the OAC-related treatment patterns post-discharge following the VTE hospitalizations. There is evidence that a large proportion of patients treated in both inpatient and observational hospital settings do not fill an anticoagulant prescription post-discharge.[7] Research shows that the choice of treatment regimen and/or setting could influence the likelihood of post-discharge continuation of OAC medication.[7] This study will investigate the initial treatment patterns during VTE hospitalization and further investigate the treatment patterns post-discharge and factors associated with poor outcomes among these patients.

Research question and objectives

The purpose of this study is to evaluate the post-discharge treatment patterns including persistence and outcomes such as recurrent VTE and bleeding among hospitalized adults with VTE treated with apixaban or warfarin.

The study objectives are to:

1. Describe the proportion of patients with VTE treated with apixaban or warfarin in the hospital

2. Understand the post-discharge treatment patterns (including persistence, switch, and discontinuation) among patients who started on apixaban or warfarin in the hospital

The secondary objective is to:

3. Assess recurrent VTE, major bleeding, and clinically relevant non-major (CRNM) bleeding among patients who continue on apixaban or warfarin in the outpatient setting while persistent on index therapy

Study design

A retrospective database analysis will be conducted among patients hospitalized with a primary diagnosis of VTE. This study will utilize linked data from IQVIA's hospital charge master data (CDM), professional fee claims (Dx) and prescription claims (LRx) from 01 July 2017 through 31 December 2022 or the latest available data at the time of extraction (i.e., the *study period*), including 6-month pre-hospitalization period (starting the day before the admit date of hospitalization and a minimum 1-month post-hospitalization (starting a day after discharge date of hospitalization) period. The first apixaban or warfarin treatment during the index hospitalization will be flagged. Following discharge, patients who continue apixaban or warfarin, respectively, in the outpatient setting (with outpatient treatment claim occurng on or within 30-days following the discharge date) will be identified. The date of the first apixaban or warfarin claim will serve as the treatment index date. The baseline period will be 6 months prior to the treatment index.

Population

The study cohorts will be identified during the selection window from 01 January 2018 to 30 November 2022. Based on the treatment (apixaban or warfarin) received during the VTE hospitalization, patients will be classified into apixaban and warfarin cohorts. Patients will be required to have medical and pharmacy activity during the 6 month pre-hospitalization period and 1-month post-hospitalization period i.e. post-discharge. Following discharge, patients will be indexed to either apixaban or warfarin based on the first observed outpatient pharmacy claim for the respective therapy, and will have a 6-month baseline period prior to the treatment index date and a variable follow-up period after the treatment index date. Treatment patterns and clinical outcomes will be evaluated during the variable follow-up period.

Variables

Exposures and explanatory variables on the treatment index date and 6-months prior to the treatment index period (which includes the hospitalization)

- Demographic characteristics
- Clinical characteristics

Characteristics of hospitalization

- Hospital characteristics

Outcomes

- Apixaban and warfarin treatment rates during hospitalization

- Post-discharge continuity (i.e. persistence of hospitalization treatment/treatment discontinuation or switch)
- Post-discharge treatment patterns among those who continue the same treatment provided during hospitalization (persistent days, discontinuation, switching)
- Post treatment-index recurrent VTE and bleeding hospitalizations

Data sources

IQVIA's CDM database linked with Dx and LRx will be utilized for this analysis. IQVIA's CDM is comprised of hospital-based data which are sourced from hospital CDM files. CDM covers more than 450 hospitals per month and approximately 8 million inpatient visits and 105 million outpatient visits per year. Dx database includes outpatient medical claims which will be necessary for describing baseline clinical characteristics. Dx database captures over one billion pre-adjudicated claims and three billion records obtained annually from approximately 800,000 office-based physicians and specialists. LRx database captures information on dispensed prescriptions sourced from retail, mail, long-term care, and specialty pharmacies. IQVIA has industry-leading coverage in the following channels: 92% coverage of the retail channel, 72% coverage of standard mail service, and 76% of long-term care facilities. LRx will be necessary for describing baseline treatment history and reporting post-index treatment patterns.

Study size

All eligible patients will be included in the study.

Data analysis

Descriptive analysis will be conducted for all relevant study measures for the two cohorts of interest. No comparisons will be conducted in this analysis. Four multivariable regression models or Cox proportional hazards model will be conducted to evaluate factors associated with outcomes of interest. All analyses will be based on observed, not projected data. Analyses will be conducted using Statistical Analysis System® (SAS) Release 9.4 (SAS Institute Inc., Cary, NC), and the results will be reported in Excel tables.

Milestones (tentative)

Protocol approval:	17 February, 2023
Start of data analysis:	27 February , 2023
Final results:	05 May, 2023
Final study report:	09 June, 2023

5. AMENDMENTS AND UPDATES

None

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1				
2				

6. MILESTONES

Milestone	Planned date
Protocol approval	17 February, 2023
Start of analysis	27 February, 2023
Analysis completion	05 May, 2023
Final study report	09 June, 2023

7. RATIONALE AND BACKGROUND

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major health concern associated with significant mortality and morbidity. It is the third most common cause of vascular disease-related death and poses a substantial economic burden to the healthcare system. In the United States (US), approximately 1 million people develop symptomatic VTE each year.[1,2] There are >330,000 hospital admissions for VTE every year in the United States (US).[3] Historical data suggests that the rate of hospitalizations for VTE increased from 7.0 to 8.4 per 1,000 discharges in the US.[4]

Management of VTE during an acute hospital encounter involves rapid anticoagulation. Current guidelines recommend continuing anticoagulation therapy post-discharge with vitamin K antagonists such as warfarin, or one of the newer direct oral anticoagulants (DOAC) which do not require PAC bridging therapy.[5] Over the past decade, the use of DOACs, particularly apixaban to treat VTE has increased dramatically.[6]

There are some gaps in RWE regarding OAC use among patients hospitalized with VTE. First, there is need for RWE regarding the proportion of patients treated with particular OAC during the VTE hospitalization. Second, there needs to be a better understanding of the OAC-related treatment patterns post-discharge following VTE hospitalizations. There is evidence that a large proportion of patients treated in inpatient and observational hospital settings do not fill an anticoagulant prescription post-discharge[7]. Research shows that the choice of treatment regimen and/or setting could influence the likelihood of post-discharge continuation of OAC medication.[7] This study will investigate the initial treatment patterns during VTE hospitalization and further investigate the treatment patterns and factors associated with poor outcomes among these patients.

The study team, comprised of members from Pfizer and Bristol Myers Squibb (hereon referred to as the 'Alliance'), is collaborating with IQVIA in conducting a study to assess treatment patterns and health outcomes post hospital discharge for VTE.

8. RESEARCH QUESTION AND OBJECTIVES

The purpose of this study is to evaluate the post-discharge treatment patterns including persistence and outcomes such as recurrent VTE and bleeding among hospitalized adults with VTE treated with apixaban or warfarin.

The study objectives are to:

1. Describe the proportion of patients with VTE treated with apixaban or warfarin in the hospital
2. Understand the post-discharge treatment patterns (including persistence, switch, and discontinuation) among patients who started on apixaban or warfarin in the hospital

The secondary objective is to:

3. Assess recurrent VTE, major bleeding, and clinically relevant non-major (CRNM) bleeding among patients who continue on apixaban or warfarin in the outpatient setting while persistent on index therapy

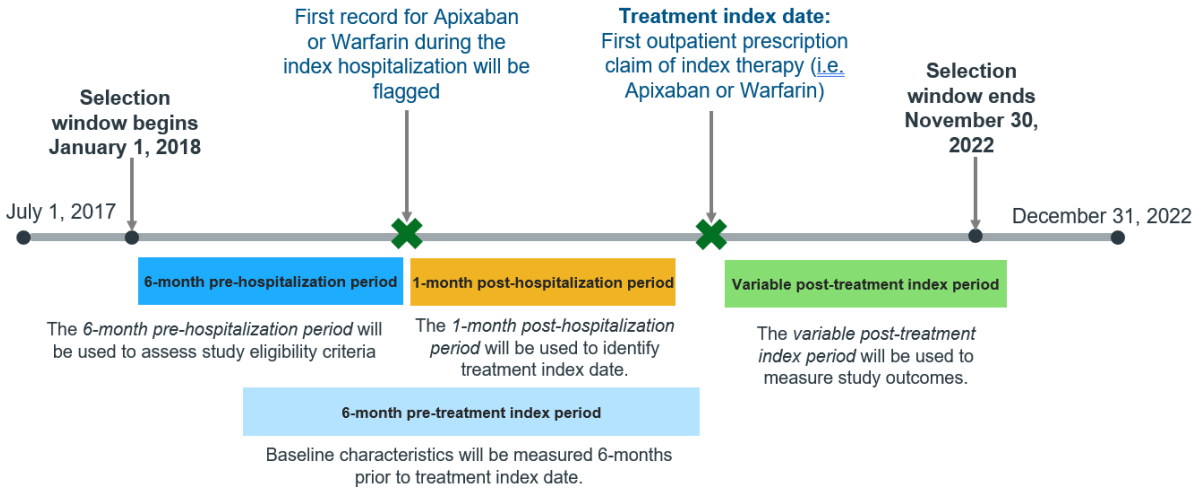
9. RESEARCH METHODS

A retrospective database analysis will be conducted among patients hospitalized with a primary diagnosis of VTE. This study will utilize linked data from IQVIA's hospital charge data master (CDM), professional fee claims (Dx) and longitudinal prescription claims (LRx) using data from 01 July 2017 through 31 December 2022 or the latest available data at the time of extraction (i.e., the study period), including a 6-month pre-hospitalization period (to confirm study eligibility) and minimum 1-month post-hospitalization period (to identify post-discharge treatment). Following discharge, patients will be indexed to the apixaban or warfarin cohort, based on the first observed outpatient pharmacy claim for the respective therapy. A 6-month pre-treatment index period (baseline) will be applied to capture demographic and clinical characteristics, and a variable follow-up period will be used to capture post- treatment index patterns and clinical outcomes.

9.1. Study period and study design

The analysis will be conducted using data from 01 July 2017 through 31 December 2022 or the latest available data at the time of extraction (i.e., the *study period*). Figure 1 illustrates the study schematic for this project. The study cohorts will be identified during a selection window from 01 January 2018 to 30 November 2022. The date of the first treatment with apixaban or warfarin during the hospitalization will be flagged. Based on this treatment during the VTE hospitalization, patients will be classified into the apixaban and warfarin cohorts. Patients will be required to have medical and pharmacy activity during the 6 months prior to the admit date of the hospitalization (pre hospitalization period) and 1-month (minimum) from the discharge date of the hospitalization (post hospitalization period). The date of the first outpatient prescription for apixaban or warfarin on or within 30 days after discharge date from the hospitalization will be termed as 'treatment index date'.

Figure 1. Study Period



*Latest available data at the time of extraction will be utilized for this study

9.1.1. Inclusion criteria

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

1. Patients with an inpatient hospitalization with admit date and discharge date between 01 January 2018 and 30 November 2022 (selection window) in CDM with a primary diagnosis of VTE

   Note: The admit date of the first hospitalization with primary diagnosis of VTE during the selection window will be flagged. Only patients with overnight stays with discharge date after the admit date (to confirm inpatient stay with overnight admission) will be included in the study.

   Note: Number of patients who died during hospitalization (identified from discharge disposition measure) will be reported and these patients will be excluded from the study.

2. With evidence of receiving apixaban or warfarin during the hospitalization

   Note: The date of the record with first apixaban or warfarin administration during the hospitalization will be flagged as the start of apixaban or warfarin treatment. Patients will be assigned to the apixaban or warfarin cohort based on this treatment received during hospitalization.

3. With linkage to LRx between 01 July 2017 and 31 December 2022 (i.e. study period)
4. With linkage to Dx during the study period
5. With activity in the 6 months prior to the admit date of hospitalization, defined as ≥1 claim in Dx and ≥1 prescription claim in LRx (pre hospitalization period)
6. With activity in the 1-month after the discharge date of hospitalization, defined as ≥1 claim in Dx and ≥1 prescription claim in LRx (variable post hospitalization period)

   Note: Patients will have a minimum 1-month post discharge period (to capture outpatient treatment)

7. With age ≥18 years on apixaban or warfarin administration date during index hospitalization

9.1.2. Exclusion criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Patients with hospitalization with a primary diagnosis of VTE in the 6-month pre hospitalization period
2. Patients with any OAC administration other than apixban for apixaban cohort (except warfarin use before apixaban) or warfarin for warfarin cohort during hospitalization

   Note: Apixaban cohort patients will be allowed to have warfarin prior to apixaban administration. At this step, we will also report the number of patients that have both apixaban and warfarin use during the hospitalization.

3. Patients with unfractioned heparin or low molecular weight heparin (LMWH) administration after apixaban (for apixaban cohort) or warfarin (for warfarin cohort) administration during hospitalization.

Note: that unfractionated heparin or LMWH prior to apixaban or warfarin will be allowed.

4. With ≥1 claim/record with a diagnosis code for atrial fibrillation/flutter in Dx or CDM during the hospitalization and in the 6-month pre hospitalization period
5. With ≥1 claim with a procedure code for mechanical heart valve in Dx or CDM during the hospitalization and in the 6-month pre hospitalization period
6. With ≥1 claim with a procedure code for inferior vena cava filter in Dx or CDM during the study period
7. With ≥1 claim with a diagnosis code or procedure code of pregnancy in Dx or CDM during the study period
8. With use of OAC or PAC (in LRx or Dx) (unless prophylactic) during the 6-month pre-hospitalization period

   Note: The OAC or PAC prescription claim will be considered prophylactic if duration of the prescription is ≤ 42 days AND the start date of OAC or PAC occurs within 2 days before or 7 days after knee/hip replacement surgery

   OR

   Start date of OAC or PAC occurred within 7 days after the admission of a hospitalization associated with 'medically ill' (primary discharge diagnosis; codes provided separately) AND with a ≥ 3-day length of stay of the hospitalization.
9. With data quality issues (invalid/missing enrollment dates, gender and payer type)

A preliminary attrition table will be provided to the Alliance for review, at which time modifications to the inclusion and exclusion criteria may be considered.

9.2. Variables

From the final sample, the following measures will be reported (Figure 2):

1. Patients with a claim for the respective treatment (apixaban for apixaban cohort or warfarin for warfarin cohort; using NDC from LRx) as their first post-discharge outpatient treatment (on or within 30 days following discharge i.e. discharge date or ≤30 days after discharge date) (n, %). These patients will comprise the analytic cohort for outcomes assessment.

a. The date of the first post-discharge outpatient prescription claim in LRx (apixaban or warfarin) will be defined as the 'treatment index date' for patients in both cohorts respectively.

b. Patients will be required to have pharmacy stability during the 6-month period preceding the treatment index date, defined as consistent reporting of data in each month from the pharmacy associated with the treatment index date in LRx to ensure continuous visibility within LRx. The number of patients excluded due to lack of stability will be reported (n, %)

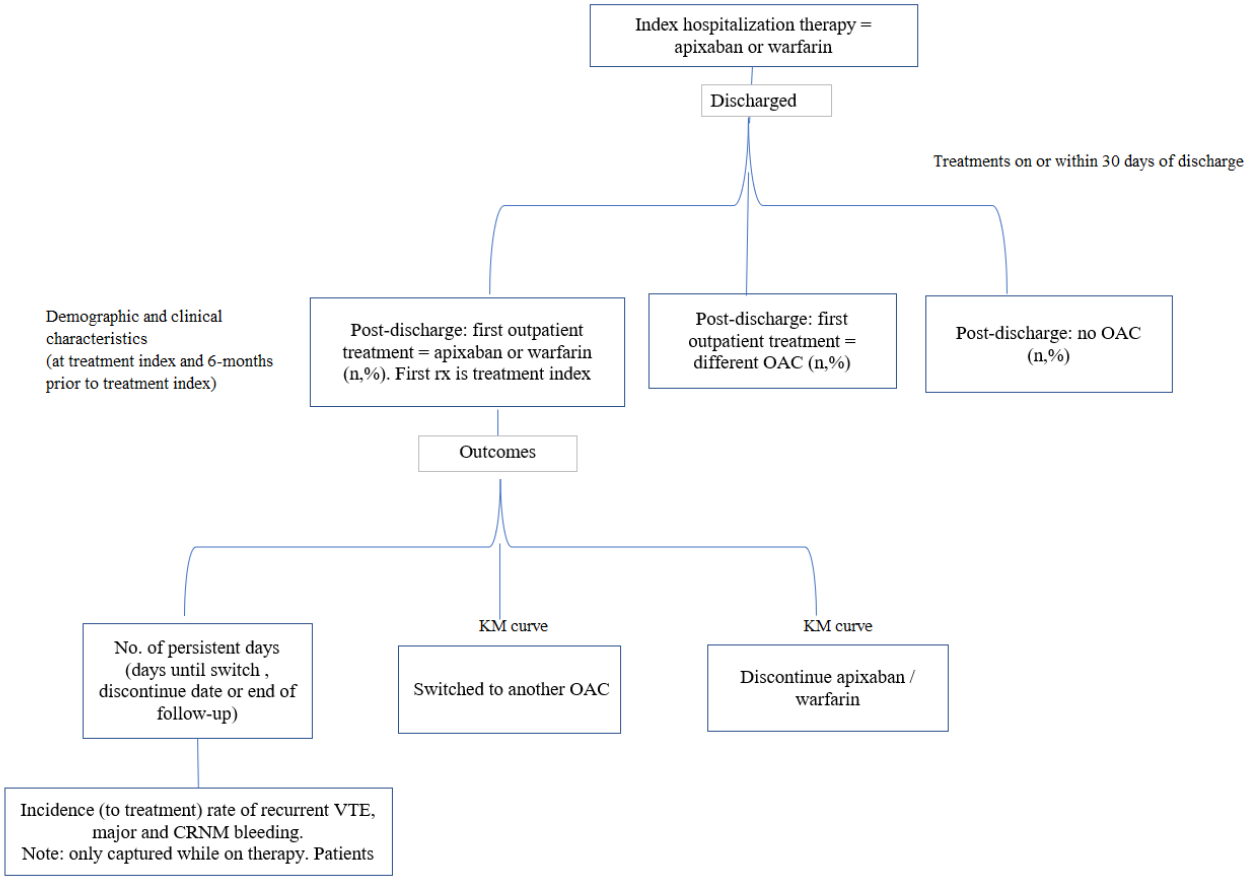
c. Patients with recurrent VTE, major bleeding, or CRNM bleeding between the discharge date and the treatment index date will be excluded. The number of patients excluded due to these reasons will be reported (n, %).

d. Patients will be followed from the treatment index date until the earliest of last prescription, last patient medical claim, end of pharmacy stability, or end of study period using the Dx/Rx databases.

2. Patients with OAC (warfarin, apixaban, rivaroxabn, dabigatran, or edoxaban) other than the respective inpatient treatment as their first outpatient prescription claim (on discharge date or within 30 days of discharge) (NDC codes from LRx; n, %). These patients will be captured as having switched from inpatient therapy and will not be further evaluated for outcomes.
3. Patients with no post-discharge outpatient prescription claim for any OAC (on or within 30 days of discharge) (NDC from LRx; n, %)

All study outcomes will be evaluated for the apixaban and warfarin cohorts.

Figure 2. Study Flow



9.2.1. Baseline Measures

Baseline demographic, hospitalization and clinical characteristics will be assessed for the apixaban and warfarin cohorts, specifically among patients with their first outpatient index prescription (i.e. treatment index date) and with pharmacy stability. Demographic features will be measured on the patient's treatment index date. Clinical characteristics will be assessed during the 6-months prior to the treatment-index date. Index hospitalization characteristics will also be assessed and reported for the apixaban and warfarin cohorts.

Baseline demographic characteristics (using LRx data)

- Age (years; mean, standard deviation [SD], median, interquartile range (IQR), min, max)
- Age group (18-34, 35-44, 45-54, 55-64, ≥65 years; n, %)
- Gender (male, female; n, %)
- Payer type (Third party, Medicaid, Medicare, Medicare part D, cash, other; n, %)
- Index date year (2018, 2019, 2020, 2021, 2022; n, %)

- Follow-up duration (mean, SD, median, IQR, min, max)

Hospitalization characteristics (using CDM data)

- Hospital geographic region (Northeast, Midwest, South, West)
- Number of hospital beds (1-99 beds, 100-199 beds, 200-299 beds, 300-499 beds, 500+ beds)
- Hospital location (Rural, Urban)
- Teaching status (Teaching, Non-teaching)
- Admitting source (ER, referral and transfer, routine admission, other, unspecified)
- Discharge disposition (Alive – Home, Left Against Medical Advice or Discontinued Care [LAMA], Transferred – Long Term Care, Transferred – Other Institution, Transferred – Short-Term Hospital, Unknown/Other)
- Index VTE type (DVT only, PE only, DVT and PE; n, %).
- VTE etiology: (Provoked: VTE preceded by hormone therapy, fracture/trauma involving lower extremities, pelvic/orthopedic surgery, or hospitalization for any reason for ≥3 days during 3 months prior to index VTE event. Unprovoked: VTE events not classified as provoked)

Baseline clinical characteristics

- Prescribing provider specialty associated with the treatment index prescription in LRx (primary care [general practice/family practice/internal medicine/physician assistant/nurse practitioner], cardiologist, other, unknown; n, %) (Frequency table will be provided with details on provider specialty counts within 'other' category)
- Charlson Comorbidity Index (CCI, Dartmouth-Manitoba adaptation; mean, SD, median, IQR, min, max)
- CCI (categorical [0-1, 2, 3, 4+]); n, %)
- Comorbidities of interest (ICD-10 diagnosis codes in Dx or CDM; n, %)
  - Acquired immune deficiency syndrome (AIDS)
  - Alcohol/drug abuse
  - Anemia
  - Cerebrovascular disease
  - Coronary heart disease/ischemic heart disease
  - Congestive heart failure
  - Chronic obstructive pulmonary disease (COPD)
  - Coronavirus disease 2019 (COVID-19)

  - Dementia/Alzheimer's disease
  - Dyspepsia or stomach discomfort
  - Diabetes mellitus
  - Hemiplegia/Paraplegia
  - Hematologic disorders associated with bleeding (thrombocytopenia)
  - Hyperlipidemia
  - Hypertension
  - Inflammatory bowel disease
  - Liver/Gall bladder/Pancreatic disease
  - Obesity
  - Peptic ulcer
  - Peripheral vascular disease
  - Pneumonia
  - Renal disease
  - Rheumatologic disease
  - Sleep apnea
  - Spinal cord injury
  - Thrombocytopenia
  - Thrombophilia
  - Varicose veins
- Procedures of interest (ICD-10 diagnosis or procedure codes, CPT Codes, HCPCS codes in Dx or CDM; n, %)
  - Orthopedic surgery
  - Central Venous Catheter
- Baseline bleeds (ICD-10 diagnosis or procedure codes, CPT Codes, HCPCS codes in Dx or CDM; n, %)
  - Gastrointestinal
  - Intracranial
  - Others
- History of falls (ICD-10 diagnosis codes in Dx or CDM; n, %)
- Fracture/trauma involving lower extremities (ICD-10 diagnosis codes in Dx or CDM; n, %)

- Medications of interest (NDC or HCPCS codes in LRx or Dx; n, %)
    - Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARB)
    - Antiarrhythmic agents
    - Antiplatelet agents
    - Aromatase inhibitors
    - Beta blockers
    - Erythropoiesis stimulating agents (ESA)
    - Gastroprotective agents
    - Nonsteroidal anti-inflammatory drugs (NSAID)
    - Selective estrogen receptor modulators (SERM)
    - Statins

9.2.2. Outcome measures

The following outcome measures are assessed post-discharge, and will be measured during the variable post-index period starting on the treatment index date for the apixaban and warfarin cohorts.

Treatment patterns

- Persistent days (mean, SD, median, IQR, min, max) will be reported for patients until they discontinue, switch or end of follow-up based on definitions below
- Patients discontinuing outpatient treatment of apixaban or warfarin, respectively (NDC codes from LRx; n, %)

Note: Discontinuation will be defined as the occurrence of a ≥ 30 day gap from the run-out of days' supply of the treatment (post-discharge) index prescription (i.e. apixaban or warfarin) to the date of the next claim for the respective therapy or with no other claims for the respective therapy. The date of the discontinuation will be defined as the last day of the days' supply of the last filled prescription.

    - Time (in days) from treatment index date to discontinuation date (mean, SD, median, IQR, min, max)

Note: Kaplan-Meier (KM) curves will be generated to measure median time (and 95 % CI) to discontinuation.

- Patients switching to an OAC other than apixaban or warfarin, respectively (switched) (NDC codes from LRx; n, %)

Note: Patients will be considered to have switched if they filled a prescription for OAC other than apixaban or warfarin, respectively (identified through NDC codes in LRx) or for PAC within 30 days before or after the run out date of index treatment. The date of the switch will be defined as date of the prescription of such a therapy (OAC or PAC).

- Time (in days) from treatment index date to switch date, defined as the date of the first claim for the new OAC or PAC (mean, SD, median, IQR, min, max)

Note: KM curves will be generated to measure median time (and 95 % CI) to switching

Clinical Outcomes

The following clinical outcomes will be assessed during the time patients are persistent with their respective index apixaban or warfarin treatment (treatment index):

- Patients with ≥1 hospitalization for recurrent VTE (ICD-10 codes in CDM; n, %)
- Incidence rate (IR) of recurrent VTE (per 100 patient years)
    - The date of the first observed event will be flagged. The numerator for IR will be the number of patients with the event of interest and denominator will be the 'at risk' period i.e. the time to first event. The 95% confidence intervals (CI) will also be reported.

Note: Recurrent VTE will be defined as inpatient hospitalization with a primary diagnosis of VTE occurring 7 or more days after the first hospitalization discharge date.

    - Time (days) from first hospitalization discharge date to first recurrent VTE hospitalization (mean, SD, median, IQR, min, max)
    - Time (days) from treatment index date to first recurrent VTE hospitalization (mean, SD, median, IQR, min, max)
- Patients with ≥1 hospitalization for major bleeding (ICD-10 codes in CDM; n, %)
- IR of major bleeding (per 100 patient years)

Note: Major bleeding will be defined as inpatient hospitalization with primary diagnosis of gastro-intestinal bleeding, intracranial hemorrhage (ICH) or other major bleeding

    - Time (days) from first hospitalization discharge date to first major bleeding episode (mean, SD, median, IQR, min, max)
    - Time (days) from treatment index date to first major bleeding episode (mean, SD, median, IQR, min, max)
- Patients with ≥1 CRNM bleeding event (n, %)
- IR of CRNM bleeding (per 100 patient years)

Note: CRNM bleeding will be defined as inpatient hospitalization with a secondary diagnosis code for bleeding (without a major bleeding code in the primary position) or an outpatient encounter with a diagnosis code in any position for CRNM GI bleeding or other non-critical types of bleeding. Specifically, it is defined as:

(1) An inpatient admission with a secondary diagnosis for "noncritical site" bleeding such as GI bleeding or other selected noncritical types/sites of bleeding (excluded if major bleeding occurred during the same hospitalization), OR

(2) An outpatient encounter with a diagnosis code for GI bleeding and other selected noncritical types/sites of bleeding.

Any CRNM bleeding events (as described above) that follow a major bleeding event (described above) will not be included in the analysis of CRNM bleeding

- Time (days) from first hospitalization discharge date to first CRNM bleeding episode (mean, SD, median, IQR, min, max)
- Time (days) from treatment index date to first CRNM bleeding episode (mean, SD, median, IQR, min, max)

9.3. Data sources

IQVIA's CDM database will be linked to Dx and LRx for this analysis.

Hospital Charge Data Master (CDM)

IQVIA's Hospital CDM is comprised of hospital-based data which are sourced from hospital CDM files that roll up to the UB-04 files which are submitted for payment. Data covers non-federal, acute-care short-stay hospitals, covering inpatient and outpatient services, including emergency room (ER) utilization with information on diagnoses, procedures, treatment and daily un-adjudicated charge details. Limited patient and hospital characteristics are also available. Data is available from 2001, with a data lag of approximately 6 weeks. The data cover more than 450 hospitals per month and approximately 8 million inpatient visits and 105 million outpatient visits per year. Charge details during a stay are provided on a daily basis (and lack a time stamp). Diagnoses lack a time or day stamp.

It is important to note some limitations of this dataset. Firstly, because this is an open-source database, there is a loss of visibility to healthcare activity and consumption outside of hospitals that participate in/contribute to the database. Secondly, unlike administrative health plan claims data, it is not possible to apply continuous enrollment (CE) requirements. Proxies for CE must be implemented based on hospital reporting to provide greater assurance that patient healthcare activity within this database is captured during the study period. Socioeconomic details, such as race/ethnicity or income, are unavailable in the data. Clinical detail is also limited. Due to patient privacy reasons, a subject who is 85 years or older will only have the recorded age of "85". And finally, only charges are available in CDM, thus a national cost to charge ratio must be applied to charges.

Medical claims (Dx) database

IQVIA's Dx database captures over one billion pre-adjudicated claims and three billion records obtained annually from approximately 800,000 office-based physicians and specialists. Dx database is updated on a weekly basis with approximately a 30-60 day lag for data completeness. Key information includes International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) and International Classification of Diseases, tenth revision, clinical modification (ICD-10-CM) diagnoses, CPT/procedure/Healthcare Common Procedure Coding System (HCPCS) for medical conditions and procedures, date of service, location of care, (pre-adjudicated) charged amount for service, payer types (commercial, Medicaid, Medicare, cash payment), patient age and sex. Note that inpatient data is limited.

Longitudinal Prescription Claims (LRx)

IQVIA LRx database captures information on dispensed prescriptions sourced from retail, mail, long-term care, and specialty pharmacies. These suppliers have direct, long-standing relationships with IQVIA, with many providing data on a daily basis, and all suppliers support weekly data feeds with an ability to provide insight within ten days of the end of each week. This enables IQVIA to ensure that the LRx database has good longitudinal, representative, and current data from consistent and stable suppliers. IQVIA has industry-leading coverage in the following channels: 92% coverage of the retail channel, 72% coverage of standard mail service, and 76% of long-term care facilities. IQVIA receives specialty data directly from the pharmacy resulting in near census data coverage, contributing to greater precision for longitudinal analysis. Additionally, diagnosis is included directly on the majority of specialty pharmacy transactions from the specialty pharmacy providers. An important strength of the LRx database for this analysis is the longitudinal capture of adjudicated and cash prescriptions for all age categories, regardless of insurance type.

Linkage Methodology

A proposed dataset will be constructed utilizing patient data from LRx, Dx and CDM, with the appropriate dataset being selected based upon proportion of linked patients. This process which is compliant with The Health Insurance Portability and Accountability Act of 1996 (HIPAA) is described below:

- IQVIA has developed a patented and proprietary encryption algorithm that utilizes actual patient-level information to create a unique Patient identifier (ID)[8]
    - First Name
    - Last Name
    - Date of Birth
    - Gender
    - Street Address
    - ZIP Code (5-digit)
- IQVIA deploys this encryption tool across its data suppliers to de-identify patient data at the source
- Once IQVIA brings the encrypted and de-identified data in house, the data undergoes a deterministic matching process to be assigned a unique and persistent IQVIA patient ID; we are then able to match the Patient ID across our portfolio of databases

It is important to note that IQVIA uses a deterministic matching algorithm to link patients across databases.[9] This type of algorithm uses actual patient information, rather than statistical probability based on patient age, number of visits, etc. to ensure continuity of patient records across datasets. Source data is passed through an encryption engine and a one-way hash algorithm results in "tokens" that cannot be decrypted. The resulting output is de-identified patient records that can be linked to other assets in the IQVIA patient data warehouse. Patient Tokens as well as other attributes (e.g., gender) are used for matching to the IQVIA Patient Master to assign an existing or new IQVIA Patient ID which can be used as available across data sources. The IQVIA matching algorithm achieves a balance between false positives

(~2%) and false negative (~3%) rates, optimizing the size of the linked sample that can be obtained.

9.4. Study size

An earlier feasibility assessment estimated that there were 139,061 hospitalized patients with a primary diagnosis of VTE in CDM between 01 January 2017 and 30 August 2022. Among these, 53,918 patients received apixaban and 18,035 received warfarin during the hospitalization. Among the patients receiving apixaban during first VTE hospitalization, 47,029 patients had linked data in Dx and LRx between 01 January 2017 and 30 August 2022. These counts were for informational purposes only and will not represent the actual number of patients to be utilized in the study. Application of other inclusion and exclusion criteria or other factors will reduce the sample size. All eligible participants will be included in the study.

9.5. Data management

Data contributions are subjected to a series of quality checks to ensure a standardized format and to minimize error rates. IQVIA standardizes a limited number of fields, such as gender, place of service and state, for which the standard is easy to define and widely agreed upon. For every active health plan, IQVIA compares the current submission to the previous submission. The frequency distributions of key fields are compared. In addition, basic statistical analyses are generated for key fields to check for trend breaks and data gaps. Data management, calculations and analyses will be performed using SAS, version 9.4 or later (SAS Institute Inc., Cary, NC, USA). Please refer to section 8.7 for details regarding quality control.

9.5.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

Not applicable.

9.5.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, IQVIA agrees to keep all study-related records, including study documentation, archived analytic datasets, and adequate documentation of relevant correspondence. The records should be retained by IQVIA according to local regulations or as specified in the study protocol, whichever is longer. IQVIA must ensure that the records continue to be stored securely for so long as they are retained.

If IQVIA becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless IQVIA and Pfizer have expressly agreed to a different period of retention via

a separate written agreement. Record must be retained for longer than 15 years or as required by applicable local regulations.

IQVIA must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.6. Data analysis

Descriptive statistics will be produced for all relevant study measures previously described, for the overall cohort and for each treatment (apixaban and warfarin). Categorical measures will be presented using frequency (number of patients [n]) and percentage (%) of total study patients observed in each category. Continuous and count variables will be presented as the mean, SD, median, minimum, maximum and IQR. As relevant, continuous variables will also be categorized into intervals. Univariate statistics will be calculated for each measure of interest. No comparisons will be made between the two cohorts..

Four multivariable regression models will be developed for this study. Cox proportional hazards models will be conducted to evaluate both the risk (expressed as hazard ratios with corresponding 95% confidence intervals) of discontinung or switching from the index treatment as well as the risk of experiencing a clinical event (i.e., recurrent VTE, major bleeding, or CRNM bleeding).. The main effect variable will be the treatment cohort (apixaban vs. warfarin, with warfarin as the reference group). Covariates to be considered for inclusion into the models will include demographic and clinical characteristics of interest. A backward elimination of independent variables least associated with the dependent variable may be used. Clinically relevant covariates that are not retained during backward elimination may also be forced into the model. Collinearity among the variables of interest will be evaluated during model development.

Kaplan-Meier analyses will also be utilized to report the time to an event of interest (e.g., switch, discontinuation). Kaplan-Meier is a method for estimating the probability of the proportion of individuals remaining in the sample at a particular time from an initiation point. It takes into account patients lost or censored before the study endpoint. All analyses will be based on observed, not projected, data. Analyses will be conducted using SAS® Release 9.4 (SAS Institute Inc., Cary, NC), and the results will be reported in Excel tables.

Any major modifications of primary endpoint definitions (treatment patterns) or their analyses would be reflected in a protocol amendment.

9.7. Quality control

Data management for this study will be conducted using standard IQVIA processes. The process will take into consideration any data governance imposed on the data source. All patient-level data is de-identified and fully HIPAA-compliant. After study specific data extraction from the databases, anonymized patient-level linked data extract will be securely transferred to IQVIA's secure server compliant with US data protection laws. Only aggregated, anonymous, cohort-level data are provided to the study sponsor.

The IQVIA Advanced Analytics team employs a two-programmer approach to ensure accuracy and reproducibility of coding, including a multi-point quality control checklist for retrospective database studies. All data are stored on secure servers and are auto-archived and password-protected for any future access requirements. Study documents are retained in a minimum of two secure locations and are only removed or deleted upon written request from the sponsor.

9.8. Limitations of the research methods

This study will have limitations inherent to observational studies involving claims and hospital charge data, as well as limitations related to the study design. Results from retrospective studies must be interpreted with caution and can only establish associations and not cause-and-effect relationships.

Claims data do not provide as much clinical detail as medical records as they are primarily collected for the purposes of payment. Therefore, there is a potential for miscoding or misclassification (e.g., identification of newly treated VTE patients). There is also the potential for under-coding if they are not captured for billing purposes.

Because these are open-source databases, there is a loss of visibility to healthcare activity/consumption at pharmacies, offices and hospitals that do not participate/contribute to the databases. Pharmacy stability requirements will be applied to the index prescription pharmacy at the patient level. Nevertheless, LRx has high prescription coverage (e.g., 63% of retail pharmacies in the US). Over-the-counter products will not be captured.

Unlike administrative health plan claims data, it is not possible to define periods of continuous enrollment (CE). Only proxies can be implemented based on patient activity and pharmacy stability to provide greater assurance that patient healthcare activity within these databases is captured during the study period. The data also lack information on mortality.

Only patients with a hospitalization or outpatient visit to a hospital in the CDM database are present in the CDM database, therefore potentially representing a more severe population.

9.9. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information.

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by the Alliance is not required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

Not applicable.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start.

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.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Tables of study results will be shared with the Alliance throughout the analytic phase of the study. The draft and final study report will be provided to the Alliance upon completion of the analytic phase.

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 IQVIA is aware of any new information which might influence the evaluation of the benefits and risks of an Alliance product, Alliance should be informed immediately.

13. REFERENCES

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9. Huse DM, Russo PA, Vasey J. Expanding the evidence base in outcomes research: linking electronic medical records and claims data. ISPOR Connections Vol 19 No 3. May-June 2013.

14. LIST OF TABLES

Not applicable

15. LIST OF FIGURES