NON-INTERVENTIONAL STUDY PROTOCOL

Study information

Title	Cost comparison between apixaban and low molecular weight heparin (LMWH) among venous thromboembolism (VTE) cancer patients
Protocol number	B0661183
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Date	29 July 2022
Research question and objectives	To evaluate the costs and healthcare resource utilization (HCRU) associated with treating VTE cancer patients with apixaban compared to LMWH To compare costs and HCRU associated with recurrent VTE, major bleeding, and clinically relevant non-major (CRNM) bleeding among VTE cancer patients treated with apixaban vs LMWH
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ACE	Angiotensin-converting enzyme
AIDS	acquired immune deficiency syndrome
APS	antiphospholipid syndrome
ARB	Angiotensin receptor blockers
ASH	American Society of Hematology
BMS	Bristol Myers Squibb
CCI	Charlson comorbidity index
COPD	chronic obstructive pulmonary disease
CRNM	clinically relevant non-major bleeding
DCTs	data collection tools
DVT	deep vein thrombosis
ER	emergency room
ESA	Erythropoiesis stimulating agents
GI	gastrointestinal
GLM	generalized linear models
HCPCS	healthcare common procedure coding system
HCRU	healthcare resource utilization
HIPAA	health insurance portability and accountability act
HMO	health maintenance organization

ICD-10-CM	international classification of diseases, tenth revision, clinical modification
ICH	intracranial hemorrhage
ID	identifier
IEC	independent ethics committee
IPTW	inverse probability of treatment weighting
IQR	Interquartile range
IRB	institutional review board
LMWH	low molecular weight heparin
LOS	Length of stay
NDC	National Drug Codes
NSAID	Nonsteroidal anti-inflammatory drugs
OAC	oral anticoagulant
PAC	parenteral anticoagulant
PCP	primary care provider
PE	pulmonary embolism
PPO	preferred provider organization
SAS	statistical analysis system
SCHIP	State Children's Health Insurance Program
SD	standard deviation
SERM	Selective estrogen receptor modulators
SMD	standardized mean difference
US	United States

USD	United States dollars
VTE	venous thromboembolism

3. RESPONSIBLE PARTIES

Principal Investigators of the Protocol

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4. ABSTRACT

Title

Cost comparison between apixaban and low molecular weight heparin (LMWH) among venous thromboembolism (VTE) cancer patients

Version: 2.0
Date: 29 July 2022

Primary author:
PPD
Pfizer, Inc.

Rationale and background

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in patients with cancer. The risk of developing VTE in these patients is four to seven times higher compared to patients without cancer, with a reported incidence of up to 15% per year.[1,2] American Society of Hematology (ASH) guidelines recommend direct-acting oral anticoagulants (OAC) or low molecular weight heparin (LMWH) in ambulatory patients with cancer at high risk for VTE or for initial treatment of VTE.[4]

The risk of recurrent VTE, despite anticoagulant therapy, and bleeding complications is higher among patients with cancer compared to those without cancer.[5] Apixaban, an oral factor Xa inhibitor has been previously shown to be efficacious in treating cancer-associated VTE without increased risk of major bleeding.[7] There is a lack of evidence comparing the direct medical cost of using LMWH with direct-acting OAC's such as apixaban which has been previously demonstrated to decrease the risk of recurrent VTE and major bleeding in cancer patients with VTE.[8,9] Therefore, this study will evaluate the costs and healthcare resource utilization (HCRU) associated with treating VTE cancer patients with apixaban compared to LMWH.

Research question and objectives

The purpose of this study is to evaluate the costs and HCRU associated with treating VTE cancer patients with apixaban compared to LMWH (dalteparin or enoxaparin).

The objectives of the study are as follows:

Primary objectives:

- To compare all-cause healthcare costs among VTE patients with cancer treated with apixaban vs LMWH

- To compare costs associated with recurrent VTE, major bleeding, and clinically relevant non-major (CRNM) bleeding among VTE patients with cancer treated with apixaban vs LMWH

Secondary objectives:

- To compare all-cause HCRU among VTE patients with cancer treated with apixaban vs LMWH
- To compare HCRU associated with recurrent VTE, major bleeding, and CRNM bleeding among VTE patients with cancer treated with apixaban vs LMWH

Study design

A retrospective database analysis will be conducted using IQVIA's PharMetrics® Plus database among newly diagnosed VTE patients with active cancer who received apixaban or a LMWH on or within 30 days following the VTE diagnosis. The analysis will be conducted using data from 01 January 2016 through 31 December 2021 (i.e., the *study period*), including a 12-month pre-index period and 1-month post-index period and patients will be followed through the earliest of the following: health plan disenrollment, index therapy discontinuation, switch to another anticoagulant or end of study period.

Population

Adult patients with evidence of cancer and newly diagnosed VTE, followed by a claim of apixaban or LMWH will be identified. The date of the first apixaban or LMWH prescription will be termed as the index date and two cohorts will be identified based on this index prescription. Patient will be continuously enrolled during the 12-month pre-index period and with a variable post-index period. Other exclusion criteria will also be applied such as patients with evidence of atrial fibrillation, mechanical heart valve, inferior vena cava filter, antiphospholipid syndrome, pregnancy and with any data quality issues.

Variables

Exposures and explanatory variables in the pre-index period or on index date:

- Demographic characteristics
- Clinical characteristics
- Baseline HCRU and costs

Outcomes

- All-cause HCRU and costs
- Recurrent VTE related HCRU and costs
- Major bleeding related HCRU and costs
- CRNM bleeding related HCRU and costs

Data sources

IQVIA's PharMetrics® Plus database comprises adjudicated claims for more than 190 million unique enrollees across the United States (US). Enrollees with both medical and pharmacy coverage in 2020 represented 40 million lives. PharMetrics Plus has diverse representation of

geography, employers, payers, providers and therapy areas. Patients in each zip code and every Metropolitan Statistical Area of the US are included, with coverage of data from 90% of US hospitals, 80% of all US doctors, and representation from 85% of the Fortune 100 companies. In addition to standard fields such as inpatient and outpatient diagnosis and procedures, retail and mail-order prescription records, PharMetrics Plus has detailed information on the pharmacy and medical benefit (copayment, deductible), the inpatient stay (admission type and source, discharge status) and provider details (specialty, provider identifier [ID]). Payment amounts include the negotiated rate between the plan and providers (allowed) and the actual amount paid by health plans to the provider for all services rendered. Charge amount is also available for a subset of claims. Other data elements include dates of service, demographic variables (age, gender, and geographic region), product type (e.g., health maintenance organization [HMO], preferred provider organization [PPO]), payer type (e.g., commercial, self-insured), and start and stop dates of health-plan enrollment.

Study size

An earlier feasibility study estimated that there were 4,972 VTE patients with cancer with evidence of apixaban in PharMetrics® Plus.

A minimum sample of 1,867 patients in each cohort is required to achieve 80% power at a 5% level of significane (two-sided) using recurrent VTE event rates from Agneli at al.[7] of 5.6% in apixaban cohort and 7.9% in dalteparin cohort. Using recurrent VTE rates 4.362% in apixaban cohort and 6.483% in LMWH cohort from Cohen et al.,[8] we require a minimum sample of 1,788 patients in each cohort to achieve 80% power. Based on the sample size calculations, for the current study we need a minimum sample in the range of 1,788-1,867 patients in each cohort.

Data analysis

Descriptive statistics will be produced for all relevant study measures, for the 2 therapy cohorts. Stabilized inverse probability treatment weighting (IPTW) will be used to balance patient characteristics between apixaban and LMWH cohorts. Post-IPTW, comparisons will be conducted using weighted chi-square tests for categorical variables and weighted t-tests (mean) for continuous variables. Comparisons between independent samples (e.g., among patients with ≥1 hospitalization) and pre-IPTW samples will be conducted using the parametric t-test (mean) and non-parametric Wilcoxon rank-sum test (median) for continuous variables. A p value of ≤ 0.05 will be considered significant.

Up to 4 regression models will be developed and these may include weighted generalized linear models (GLM) with log transformation and gamma distribution to estimate adjusted (all-cause) cost ratio between the two cohorts or a negative binomial distribution may be developed to estimate adjusted visits such as physician office visits, emergency room visits or other HCRU.

Milestones

Protocol and table shells: 12 August 2022
Start of data analysis: 15 August 2022

Final results: 21 October 2022
Final study reports and presentation: 18 November 2022

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
None				

6. MILESTONES

Milestone	Planned date
Protocol approval	12 August 2022 (estimated)
Start of analysis	15 August 2022 (estimated)
Analysis completion	21 October 2022 (estimated)
Final study report	18 November 2022 (estimated)

7. RATIONALE AND BACKGROUND

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in patients with cancer. The risk of developing VTE in these patients is four to seven times higher compared to patients without cancer, with a reported incidence of up to 15% per year.[1,2] Several cancer-associated risk factors for VTE have been identified, including patient-, treatment-, and tumor-related factors. Currently, patients with cancer often undergo imaging for tumor staging and evaluation of treatment response, which further increases the underlying possibility of VTE detection.[3] When VTE is diagnosed, anticoagulant therapy is indicated in most cases. 2021 American Society of Hematology (ASH) guidelines recommend direct-acting oral anticoagulants (OAC) or low molecular weight heparin (LMWH) in ambulatory patients with cancer at high risk for VTE or for initial treatment of VTE.[4] However, the management of VTE remains challenging in this patient population. The risk of recurrent VTE, despite anticoagulant therapy, and bleeding complications is higher among patients with cancer compared to those without cancer.[5] Recurrent VTE among patients with cancer is associated with significant healthcare resource use and, notably, hospitalizations.[6]

Apixaban, an oral factor Xa inhibitor has been previously shown to be efficacious in treating cancer-associated VTE without increased risk of major bleeding.[7] A study Cohen A. et al.[8] compared LMWH to apixaban for the treatment of VTE associated with cancer, however this study primarily focused on the effectiveness and safety profile of these treatments. Another study by Hlavaceck et al.[9] compared healthcare costs of major bleeding and CRNM bleeding but this study was conducted only among VTE patients. Apixaban has been demonstrated to decrease the risk of recurrent VTE and major bleeding in cancer patients with VTE, however, there is a lack of evidence comparing the direct medical cost of using LMWH with direct-acting OAC's among such patients. Therefore, this study will evaluate the costs and healthcare resource utilization (HCRU) associated with treating VTE cancer patients with apixaban compared to LMWH.

8. RESEARCH QUESTION AND OBJECTIVES

The purpose of this study is to evaluate the costs and HCRU associated with treating VTE cancer patients with apixaban compared to LMWH (dalteparin, enoxaparin, or tinzaparin).

The objectives of the study are as follows:

Primary objectives:

- To compare all-cause healthcare costs among VTE patients with cancer treated with apixaban vs LMWH
- To compare costs associated with recurrent VTE, major bleeding, and clinically relevant non-major (CRNM) bleeding among VTE patients with cancer treated with apixaban vs LMWH

Secondary objectives:

- To compare all-cause HCRU among VTE patients with cancer treated with apixaban vs LMWH
- To compare HCRU associated with recurrent VTE, major bleeding, and CRNM bleeding among VTE patients with cancer treated with apixaban vs LMWH

9. RESEARCH METHODS

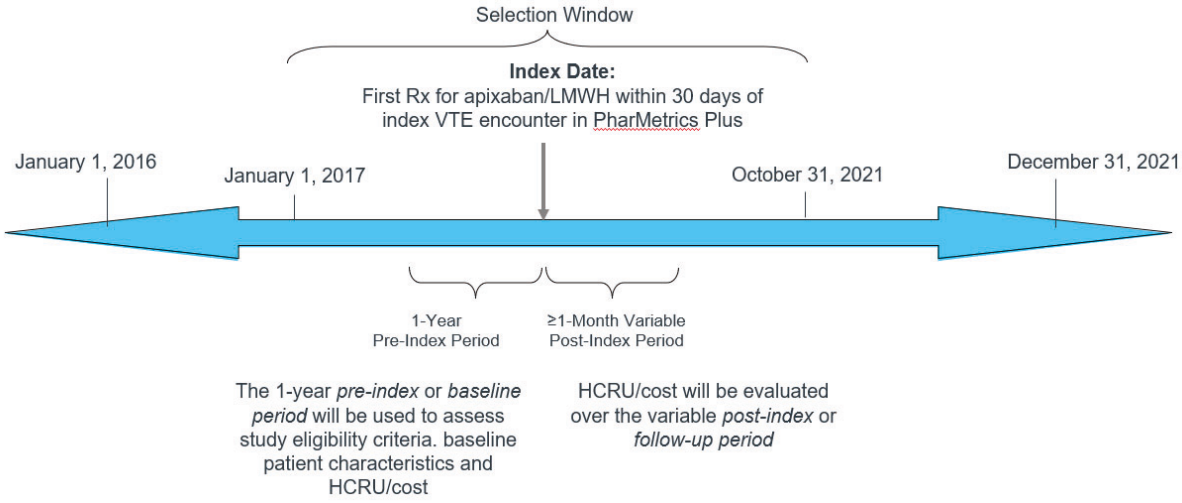
A retrospective database analysis will be conducted among newly diagnosed VTE patients with active cancer who received apixaban or a LMWH on or within 30 days following the VTE diagnosis. IQVIA's PharMetrics® Plus will be used for this analysis. See Annex 2.

9.1. Study period and study design

The analysis will be conducted using data from 01 January 2016 through 31 December 2021 or the latest available data at the time of extraction (i.e., the *study period*). Patients will be identified during a *selection window* of 01 January 2017 to 31 October 2021. The date of the first apixaban or LMWH prescription on or within the 30 days following a VTE diagnosis will be termed as the index date. Patients will be required to have continuous enrollment with medical and pharmacy benefits for 12-months prior to the index date to assess study eligibility criteria and to measure baseline characteristics *(the baseline or pre-index period)*. Patients will also be required to have continuous enrollment with medical and pharmacy benefits for at least one month (30 days) starting on and following the index date (the follow-up or post-index period) and will be followed through the earliest of the following: health plan disenrollment, index therapy discontinuation, switch to another anticoagulant (includes switch to the other study medication or unfractionated heparin, fondaparinux, warfarin, rivaroxaban, dabigatran, or edoxaban), or end of study period (31 December 2021).

Note: Patients in the LMWH cohort will NOT be considered to have discontinued or switched if they change to an LMWH other than the index LMWH (dalteparin, enoxaparin, or tinzaparin).

Figure 1. Study Period



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 ≥1 diagnosis code for VTE (inpatient [primary or secondary discharge diagnosis] or any position on an outpatient non-ancillary medical claim) between January 1, 2017 and October 31, 2021 (selection window).
    - Note: Qualifying outpatient encounters followed by qualifying inpatient encounters within 7 days will be considered an inpatient VTE event, unless LMWH or apixaban was initiated between encounters, in which case it will be classified as an outpatient VTE event
    - First date of claim with a VTE diagnosis code will be termed the 'index VTE encounter'
2. Evidence of having active cancer, defined as ≥2 medical claims with a cancer diagnosis (excluding nonmelanoma skin cancer) on different days during the 6 months before or within 30-days after the index VTE event

    OR

    ≥1 medical claim for a cancer diagnosis AND ≥1 claim for cancer treatment (eg: chemotherapy, radiation, immunotherapy, hormone therapy or cancer related surgery using national drug codes (NDC), international classification of diseases, tenth revision, clinical modification [ICD-10-CM] procedure codes or healthcare common procedure coding system [HCPCS] codes) during 6 months before or within 30 days after the index VTE encounter
3. ≥1 claim of apixaban or LMWH (dalteparin orenoxaparin) on or within 30 days following the index VTE encounter.
    a. The date of the first apixaban or LMWH prescription fill will be designated as the index date
4. ≥12 months of continuous enrollment prior to the index date (pre-index)
5. ≥1 months of continuous enrollment including and following the index date (post-index)
    a. Note: Each patient will have a variable follow-up period with a minimum of 1-month follow-up. Patients will be followed from the day after the index date through the earliest of the following: health plan disenrollment, index therapy discontinuation, switch to another anticoagulant, or study end (December 31, 2021).
    b. Discontinuation will be defined as occurrence of a ≥30 day gap from the run-out of days' supply of the index LMWH or apixaban prescription. The date of the discontinuation will be defined as the last day of the days' supply of the last filled prescription.
    c. Switching will be defined as a prescription for an anticoagulant other than the index apixaban/LMWH prescription (unfractionated heparin, fondaparinux, other OAC, or LMWH for patients indexed on apixaban; unfractionated

heparin, fondaparinux, or OAC (including apixaban) for patients indexed on LMWH) within 30 days following discontinuation of the index medication.

Note: Patients indexed on LMWH cohort will NOT be considered to have discontinued or switched if they change to an LMWH other than the index LMWH (dalteparin, enoxaparin, or tinzaparin)

6. ≥18 years of age at index

9.1.2. Exclusion criteria

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

1. ≥1 claim with a ICD-10 diagnosis code of atrial fibrillation/flutter during the 12-month pre-index
2. ≥1 claim with a ICD-10 procedure code of mechanical heart valve during the 12-month pre-index
3. ≥1 claim with a ICD-10 diagnosis code of VTE diagnosis during the 12-month prior to index VTE encounter
4. ≥1 prescription claim of OAC or parenteral anticoagulant (PAC) (unless prophylactic) before the index VTE encounter
    a. 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 an hospitalization associated with 'medically ill' (primary discharge diagnosis; codes provided separately) AND with a ≥3-day length of stay of the hospitalization
5. ≥1 claim with a ICD-10 procedure code or Common Procedural Terminology (CPT) code of inferior vena cava filter during the study period
6. ≥1 claim with a ICD-10 diagnosis code of antiphospholipid syndrome (APS) during the study period
7. ≥1 claim with a ICD-10 diagnosis code or procedure code (ICD-10 or HCPCS codes) of pregnancy during the study period
8. ≥1 prescription claim of an anticoagulant other than index apixaban or LMWH treatment between the index VTE encounter and index date. Other anticoagulants include heparin, fodaparinux, warfarin, dabigatran, rivaroxaban, and edoxaban
9. Data quality issues (with Medicare Cost coverage or State Children's Health Insurance Program (SCHIP), invalid year of birth or health plan enrollment dates) ('missing' will be reported for gender and region)

A preliminary attrition table will be provided to Pfizer/Bristol Myers Squibb (BMS) for review, at which time modifications to the inclusion and exclusion criteria may be implemented.

9.2. Cohorts

From the overall cohort of VTE patients with cancer, two cohorts of interest will be created based on the type of anticoagulation treatment received within 30 days following the index VTE encounter date.

- **Cohort #1** – Apixaban: Evidence of apixaban use (and no other anticoagulant [LMWH, other OAC, heparin or fodaparinux] between the index VTE encounter date and index date).
- **Cohort #2** – LMWH: Evidence of LMWH use (and no apixaban or other anticoagulant between the VTE index date and LMWH initiation date).

  LMWH should be used for at least 14 days to ensure that LMWH was not intended for short-term bridge therapy.

Analyses will be stratified by these two cohorts, as defined in section 8.3.1-8.3.3.

9.3. Variables

Unadjusted subject demographic and clinical characteristics and select HCRU and cost characteristics will be described for subjects in the apixaban and LMWH cohorts. Stabilized inverse probability of treatment weighting (IPTW) will be used to adjust for imbalances in measured confounders between the two therapy cohorts. Subject characteristics will then be reported for the therapy cohorts post-IPTW. Post-index economic outcomes of interest (i.e., HCRU and costs) will be evaluated following both IPTW and GLM adjustment.

9.3.1. Baseline Measures

Baseline demographic/clinical characteristics will be descriptively reported for the Apixaban and LMWH cohorts, both pre- and post-IPTW. Demographic characteristics will be measured as of the patient's index date while clinical characteristics will be measured over the 1-year pre-index baseline period.

Demographic Characteristics

- Age (mean, standard deviation [SD], median, interquartile range [IQR])
- Age group (18-24, 25-34, 35-44, 45-54, 55-64, 65-74, ≥75 years; n, %)
- Gender (male, female, unknown/missing; n, %)
- Geographic region (Northeast, Midwest, South, West, unknown/missing; n, %)
- Payer type (commercial, Medicaid, Medicare Risk, self-insured, other/unknown; n, %)
- Health plan type (consumer directed health care, health maintenance organization [HMO], indemnity, point-of-service [POS], preferred provider organization [PPO], other/unknown; n, %)

- Index date year (2017, 2018, 2019, 2020, 2021; n, %)
- Follow up duration in months (mean, SD, median, IQR)
    - Patients censored due to switching (n, %)
    - Patients censored due to discontinuation (n, %)

Clinical Characteristics

- Prescriber physician specialty (associated with the visit on or closest to the index date, as available) (n, %)
    - Primary care physician (PCP - general practice/family practice/internal medicine)
    - Cardiologist
    - Oncologist
    - Others
    - Unknown/missing
- Index VTE event setting (n, %)
    - Inpatient
        - Total inpatient cost of index VTE hospitalization (mean, SD, median)
        - Length of stay (LOS) of index hospitalization (mean, SD, median)
    - Outpatient
    - Note: Qualifying outpatient encounters followed by qualifying inpatient encounters within 7 days will be considered an inpatient VTE event, unless LMWH or apixaban was initiated between encounters, in which case it will be classified as an outpatient VTE event
- Index VTE type (n, %)
    - DVT
    - PE
    - DVT and PE
- Charlson Comorbidity Index (CCI, Dartmouth-Manitoba adaptation excluding cancer; continuous and categorical [0-1, 2, 3, 4+]) (n, %)
- NCI comorbidity index (continuous and categorical [0-1, 2, 3, 4+] (n, %))
- Comorbidities of interest (ICD-10 diagnosis codes; n, %)
    - Acquired immune deficiency syndrome (AIDS)
    - Alcohol/drug abuse

  - Anemia
  - Central Venous Catheter
  - Cerebrovascular disease
  - Coronary heart disease/ischemic heart disease
  - Congestive heart failure
  - Chronic obstructive pulmonary disease (COPD)
  - COVID-19
  - Dementia/Alzheimer's disease
  - Dyspepsia or stomach discomfort
  - Diabetes Mellitis
  - 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
- Baseline bleeds (ICD-10 diagnosis or procedure codes, CPT codes, HCPCS codes) (n, %)
  - Gastrointestinal
  - Intracranial

- Others
- History of falls (ICD-10 diagnosis codes) (n, %)
- Fracture/trauma involving lower extremities (ICD-10 diagnosis codes) (n, %)
- Orthopedic/pelvic surgeries (n, %)
- Time (in days) from index VTE encounter date to index date (mean, SD, median, IQR)
- Medications of interest (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
- Cancer-related variables (measured 6 months prior to the index VTE encounter date until 30 days after the index VTE encounter date)
  - Cancer site (n, %)
    - Bladder
    - Blood (leukemia, lymphoma, multiple myeloma)
    - Brain
    - Breast
    - Gastrointestinal (GI)
      - Upper GI
      - Lower GI
    - Gynecologic
    - Lung
    - Prostate
    - Testicular

- Cancer type (n, %)
  - Hematologic cancers
    - Leukemia
    - Lymphoma
    - Multiple myeloma
  - Non-hematologic cancers
- Cancer related treatments (n, %)
  - Chemotherapy
  - Hormone therapy
  - Immunotherapy
  - Radiation
  - Cancer related surgery
- Modified VTE Khorana Risk Scale[10] (n, %)
  - Very high risk (brain, stomach, and pancreas)
  - High risk (lung, lymphoma, gynecologic, bladder, testicular and renal cell carcinoma)
  - Other cancers

Baseline HCRU and costs

- Patients with a pre-index hospitalization (n, %)
- Patients with a pre-index emergency room (ER) visit (n, %)
- Patients with a pre-index outpatient physician office visit (n, %)
  - Number of pre-index outpatient physician office visits (mean, SD, median, IQR)
- Total all-cause healthcare costs (mean, SD median, IQR)
  - Inpatient
  - Outpatient medical
  - ER
  - Pharmacy

9.3.2. All-cause HCRU and Costs Over the Post-Index Period (Post-IPTW)

All-cause HCRU and costs will be reported for the Apixaban and LMWH cohorts over the variable post-index period (minimum 1 month enrollment), post-IPTW. Costs will be reported

as per patient per month (PPPM). Over the post-index period, a 30 day period will be used (to represent a month) to 'standardize' the period of time for which costs and HCRU will be reported. For each patient, costs will be divided by the variable post-index period in total-person days and then multiplied by 30 to calculate PPPM costs. For example, if a patient has total costs of $10,000 with 60 days of follow-up, the PPPM will be calculated as ($10,000/60) * 30 = $5,000.

HCRU will be expressed as both the proportion of patients with such utilization (e.g., the percentage of patients with at least one pharmacy claim, the percentage of patients with at least one physician office visits, etc.) as well as per-patient mean, SD, median and IQR number of visits/services. Costs will be expressed as per-patient mean, SD, median and IQR. Utilization and costs will be calculated on a per patient basis, averaged across the cohort. The denominator will include all patients in the cohort. Costs will be converted to 2021 US dollars (USD) using the medical component of the Consumer Price Index.

HCRU and costs will be reported for mutually exclusive categories: outpatient pharmacy, inpatient hospitalizations, and outpatient care. Outpatient care will comprise the following categories: ER visits, outpatient physician office visits, outpatient surgical visits, laboratory and pathology, radiology and all other services.

All-cause HCRU and costs will be reported for each of the following services:

- Pharmacy
    - Patients with ≥1 prescription fill (n, %)
    - Number of prescription fills per patient (mean, SD, median, IQR)
    - Total pharmacy cost per patient (mean, SD, median, IQR)
- Outpatient Services
    - Total outpatient medical care cost per patient (mean, SD, median, IQR)
    - Physician office visits
        - Patients with ≥1 physician office visit (n, %)
        - Number of physician office visits per patient (mean, SD, median, IQR)
        - Total physician office cost per patient (mean, SD, median, IQR)
    - ER only visits (ER visit without admission to hospital)
        - Patients with ≥1 ER visit (n, %)
        - Number of ER visits per patient (mean, SD, median, IQR)
        - Total ER cost per patient (mean, SD, median, IQR)
    - Laboratory/pathology tests
        - Patients with ≥1 laboratory test (n, %)
        - Number of laboratory tests per patient (mean, SD, median, IQR)

        - Total laboratory cost per patient (mean, SD, median, IQR)
    - Radiology
        - Patients with ≥1 outpatient radiology exam (n, %)
        - Number of outpatient radiology exams per patient (mean, SD, median, IQR)
        - Total radiology cost per patient (mean, SD, median, IQR)
    - Surgical services
        - Patients with ≥1 outpatient surgical visit (n, %)
        - Number of outpatient surgical visits per patient (mean, SD, median, IQR)
        - Total outpatient surgical visit cost per patient (mean, SD, median, IQR)
    - Ancillary/other services
        - Patients with ≥1 outpatient ancillary/other service (n, %)
        - Number of outpatient ancillary/other services per patient (mean, SD, median, IQR)
        - Total outpatient ancillary/other cost per patient (mean, SD, median, IQR)
            - Total HCPCS drug cost per patient (mean, SD, median, IQR)
- Inpatient hospitalizations
    - Patients with ≥1 hospitalization (n, %)
        - Average length of stay per patient for all hospitalizations (mean,
        - SD, median, IQR)
        - Number of hospitalizations per patient (mean, SD, median, IQR)
        - Total hospitalization days per patient (mean, SD, median, IQR)
        - Top 10 primary discharge diagnosis associated with the first hospitalization, overall (ICD 10-CM 3-digit level; n, %)
        - Total inpatient cost per patient (mean, SD, median, IQR)
    - Number of hospitalizations per patient (mean, SD, median, IQR)
    - Total inpatient cost per patient (mean, SD, median, IQR)
- Total all-cause cost per patient (total pharmacy + total outpatient + total inpatient; mean, SD, median, IQR)

9.3.3. Recurrent VTE, major bleeding, and CRNM bleeding related HCRU and costs in the post-index period

Recurrent VTE will be identified based on inpatient claims with VTE as the primary discharge diagnosis (ICD-10 diagnosis codes). If the admissions for recurrent VTE occur within 7 days of the index VTE event, irrespective of care setting, the events will not be considered as recurrent VTE events due to the proximity to the index VTE event and the index date.

Major bleeding will be defined by primary discharge diagnosis in the inpatient setting, including GI bleeding, intracranial hemorrhage (ICH), and other major bleeding.

CRNM bleeding will be defined as an inpatient encounter 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.**Error! Bookmark not defined.** **Error! Bookmark not defined.** 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.

For the two therapy cohorts, the following outcomes related to recurrent VTE, major bleeding and CRNM will be reported post-IPTW.

- Recurrent VTE across the cohort
    - Patients with ≥1 such event (n, %)
        - Number of hospitalizations for VTE events (denoted by inpatient hospitalizations that meet the definition above) (mean, median, SD, IQR)
        - Time (in days) from index date to first recurrent VTE event (mean, median, SD, IQR)
- Major bleeding across the cohort
    - Patients with ≥1 such event (n, %)
        - Number of hospitalizations for major bleeding events (denoted by inpatient hospitalizations that meet the definition above) (mean, median, SD, IQR)
        - Time (in days) from index date to first major bleeding event (mean, median, SD, IQR)
- CRNM bleeding across the cohort
    - Patients with ≥1 such event (n, %)

- Number of CRNM bleeding events (denoted by inpatient or outpatient events that meet the definition above) (mean, median, SD, IQR)
- Time (in days) from index date to first CRNM bleeding event (mean, median, SD, IQR)

The Cost, and HCRU, for each event will be defined as the cost associated with the hospitalization for the respective event (i.e., recurrent VTE, MB, or CRNM bleeding) as well as all subsequent event-related medical costs (pharmacy costs will not be included). These can be determined via an appropriate diagnosis code that relates to the event of interest. Major bleeding-related medical costs will be defined as costs associated with the first major bleeding hospitalization plus all subsequent bleeding costs occurring in the inpatient (primary or secondary diagnosis) or outpatient setting (any position). Recurrent VTE-related medical costs will be defined as the costs associated with the first recurrent VTE hospitalization plus all subsequent VTE costs in the inpatient (primary or secondary diagnosis) or outpatient (any position) setting. Similarly, CRNM bleeding-related medical costs will be defined as hospitalization costs or outpatient costs associated with the first CRNM bleeding as defined above and all the subsequent CRNM bleeding costs in the inpatient (primary or secondary diagnosis) or outpatient (any position) setting.

The outpatient services and inpatient hospitalization HCRU and cost variables presented in section 8.3.2 will also be reported for recurrent VTE-related, major bleeding-related and CRNM bleedingrelated utilization and costs.

9.4. Data sources

This study will utilize data from IQVIA's PharMetrics® Plus. IQVIA's collaboration with Health Intelligence Company, which operates as Blue Health Intelligence, allows IQVIA's bio-pharmaceutical clients sole access to one of the largest United States (US) health plan claims databases and adds IQVIA's market leading health plan claims database. The aggregated database comprises adjudicated claims for more than 190 million unique enrollees across the US. Enrollees with both medical and pharmacy coverage in 2020 represented 40 million lives. Data are available from 2010 onwards, with a typical 4- to 6-month lag due to claims adjudication.

PharMetrics Plus has diverse representation of geography, employers, payers, providers and therapy areas. Patients in each zip code and every Metropolitan Statistical Area of the US are included, with coverage of data from 90% of US hospitals, 80% of all US doctors, and representation from 85% of the Fortune 100 companies. In addition to standard fields such as inpatient and outpatient diagnosis and procedures, retail and mail-order prescription records, PharMetrics Plus has detailed information on the pharmacy and medical benefit (copayment, deductible), the inpatient stay (admission type and source, discharge status) and provider details (specialty, provider identifier [ID]). All zip codes in the US are covered and reported allowing more granular patient segmentation and comparisons by geography. Payment amounts include the negotiated rate between the plan and providers (allowed) and the actual amount paid by health plans to the provider for all services rendered. Charge amount is also available for a subset of claims. Other data elements include dates of service, demographic

variables (age, gender, and geographic region), product type (e.g., HMO, PPO), payer type (e.g., commercial, self-insured), and start and stop dates of health-plan enrollment.

Due to the broad reach of the data, records in PharMetrics Plus are representative of the national, commercially insured population in terms of age and gender for individuals aged 65 and under. The data are also longitudinal, with more than 20 million patients who have both medical and pharmacy coverage with 3 or more years of continuous enrollment. Data contributions are subjected to a series of quality checks to ensure a standardized format and to minimize error rates. All data are Health Insurance Portability and Accountability Act (HIPAA)-compliant to protect patient privacy.

PharMetrics Plus will be largely commercially- or self-insured and may not be representative of un-insured or Medicare or Medicaid populations. Further research will be warranted to understand the costs of patient archetypes among these other populations, particularly those aged 65+ and covered by traditional fee-for-service Medicare. Additionally, there is a lack of visibility into HCRU or prescriptions obtained outside of the plan benefit.

9.5. Study size

An earlier feasibility study estimated that there were 4,972 VTE patients with cancer with evidence of apixaban in PharMetrics® Plus. 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.

Sample size calculation was conducted to identify minimum number of patients in each cohort required for the analysis using the recurrent VTE event rates from Cohen et al.**Error! Bookmark not defined.** and Agneli et al.**Error! Bookmark not defined.** to achieve a power of 80% at a 5% level of significance (two-sided). Using recurrent VTE rates 4.362% (148 recurrent VTE cases in 3,393 patients) in apixaban cohort and 6.483% (396 recurrent VTE cases in 6,108 patients) in LMWH cohort from Cohen et al., we require a minimum sample of 1,788 patients in each cohort to achieve 80% power. A minimum sample of 1,867 patients in each cohort is required to achieve 80% power at a 5% level of significane (two-sided) using recurrent VTE event rates from Agneli at al. of 5.6% in apixaban cohort and 7.9% in dalteparin cohort. Based on the sample size calculations, for the current study we need a minimum sample in the range of 1,788-1,867 patients in each cohort.

9.6. Data management

See sections 8.4 and 8.7.

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

Not applicable.

9.6.2. 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.

9.7. Data analysis

Descriptive statistics will be produced for all relevant study measures previously described, for the 2 therapy cohorts of interest. 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 and IQR. As relevant, continuous variables will also be categorized into intervals.

Stabilized IPTW will be used to balance patient characteristics between apixaban and LMWH cohorts.[11,12] Weights will be constructed by estimating each subject's probability of receiving treatment based on covariates. For comparisons of baseline characteristics between the apixaban and LMWH cohorts, both pre- and post-IPTW, standardized mean difference (SMD) will be calculated to evaluate the difference in baseline covariates between cohorts. SMD is calculated as the difference in means or proportions of a variable divided by the pooled standard deviation. SMD of ≥0.10 between groups is considered meaningful.[13] For comparisons of events and HCRU/cost over the variable post-index period post-IPTW, comparisons will be conducted using weighted chi-square tests for categorical variables and weighted t-tests (mean) for continuous variables (note there is no corresponding weighted test for the median). Comparisons between independent samples (e.g., among patients with ≥1 hospitalization) and pre-IPTW samples will be conducted using the parametric t-test (mean) and non-parametric Wilcoxon rank-sum test (median) for continuous variables; data will be reported for the unweighted sample. A p-value <0.05 will be considered statistically significant. However, to account for multiple comparisons, a Bonferroni correction may be implemented such that the critical p-value (p<.05) may be divided by the number of comparisons (i.e., 3 comparisons, in order to yield a new critical p-value, .05/3 = 0.0167). Analyses will be conducted using SAS® (statistical analysis software) Release 9.4 (SAS Institute Inc., Cary, NC).

IQVIA will develop up to 4 multivariable analysis models, to be mutually agreed upon Pfizer/ BMS and IQVIA. For example these may include weighted generalized linear models (GLM) with log transformation and gamma distribution to estimate adjusted (all-cause) cost ratio

between the two cohorts. A negative binomial distribution may be developed to estimate adjusted visits such as physician office visits, emergency room visits or other HCRU.Two-part regression analyses will be used to evaluate the impact of the LMWH treatments relative to apixaban on recurrent VTE-related, major bleeding-related, CRNM-related medical HCRU or costs. The 2-part regression analyses[14] will be used to avoid the analytical issues associated with the large number of data with 0 values for HCRU andcosts for VTE-related, major bleeding-related, CRNM related HCRU and costs. In the two-part model, first the probability of observing a positive versus zero outcome will be determined using a binary choice model. In the second part of the model, conditional on a positive outcome, an appropriate regression model such as a GLM model for costs or a negative binomial model for HCRU will be fit for the positive outcome. Covariates to be considered for inclusion into the models will include demographic and clinical characteristics of interest guided by the univariate findings. These candidate variables will be considered and retained in the model if significant (SMD ≥0.10) using a stepwise approach. Collinearity among the variables of interest will be evaluated during model development.

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

9.8. Quality control

Not applicable.

9.9. Limitations of the research methods

While claims data are valuable for the efficient and effective examination of healthcare outcomes, treatment patterns, HCRU, and costs, all claims databases have certain inherent limitations affecting generalizability because the claims are collected for the purpose of payment within the commercially-insured population and not research. Results and conclusions are limited to the patient population, which consisted of patients enrolled in managed care plans, and may not be generalizable to other or non-commercially-insured populations in the US. These limitations do not significantly reduce the strength of this study and its results, but they must be considered during interpretation.

Presence of a diagnosis code on a medical encounter or outside claim may have not been conclusive of positive presence of disease, as the diagnosis code may have been incorrectly coded or included as rule-out criteria rather than actual disease. This risk may be minimal in this study. Presence of a claim for a dispensed medication does not indicate that the medication was consumed or that it was taken as prescribed. Medications provided as samples by the physician are not observable in the pharmacy data.

Only patients with a continuous eligibility were included, and thus patients who did not maintain membership for at least 13 months (i.e., 12 months prior to and 1-month following the index date) were not included in the sample.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves structured 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.

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 Pfizer is not required.

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

Not applicable.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Tables of study results will be shared with Pfizer throughout the analytic phase of the study. The draft and final study report will be provided to Pfizer 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 a Pfizer product, Pfizer should be informed immediately.

13. REFERENCES

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14. LIST OF TABLES

See table shells

15. LIST OF FIGURES

Figure 1. Study Period

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Table shells will be provided in a separate file.

Codes used in this study are provided in separate files. Categories include:

VTE and cancer diagnosis
Diagnosis codes of interest
Comorbidities of interest
Medications of interest
Procedures of interest
Major bleeding and CRNM bleeding diagnosis

Number	Document reference number	Date	Title
1		16 June 2022	IQVIA Pfizer Apixaban LMWH_Final Table Shells_20220616

2		16 June 2022	VTE Cancer study Codes

ANNEX 2. Additional Information

Not applicable