NON-INTERVENTIONAL (NI) STUDY REPORT

Study Information

Title	Real World Evaluation of Venous Thromboembolism (VTE): Analysis of Electronic Health Record Data
Protocol number	B0661086
Version identifier of the final study report	1.0
Date of last version of the final study report	05 May 2017
EU Post Authorisation Study (PAS) register number	EUPAS15478
Active substance	Oral anticoagulants (OACs)
Medicinal product	Eliquis (apixaban)
Marketing Authorisation Holder (MAH)	Bristol-Myers Squibb Company
Joint PASS	No
Research question and objectives	A retrospective study using electronic health record (EHR) data to assess anticoagulant treatment patterns, patient characteristics, and follow-up VTE recurrence & bleeding rate among newly treated patients with VTE
Country (-ies) of study	USA

Author	

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

1. ABSTRACT (STAND-ALONE DOCUMENT)

Not applicable

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
BHE	Boston Health Economics, Inc.
BMI	Body mass index
CPT	Current procedural terminology
DVT	Deep vein thrombosis
CCU	Critical care unit
EHR	Electronic health record
FDA	Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICU	Intensive care unit
IDN	Integrated delivery network
IHD	Instant Health Data
INR	International normalized ratio
IVCF	Inferior vena cava filter
LMWH	Low-molecular-weight heparin
NDC	National Drug Code

NOAC	Novel oral anticoagulant
OAC	Oral anticoagulant
PAC	Parenteral anticoagulant
PE	Pulmonary embolism
SNF	Skilled nursing facility
TTR	Time in therapeutic range
UFH	Unfractionated heparin
US	United States
VKA	Vitamin K antagonist therapies
VTE	Venous thromboembolism

3. INVESTIGATORS

Lead Country Investigator(s) of the Protocol

Not applicable

4. OTHER RESPONSIBLE PARTIES

Not applicable

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Task 1. Project Start-Up and Project Management	09 May 2016	09 May 2016	
Task 2. Prepare Study Protocol	12 July 2016	31 August 2016	Date protocol was completed
Task 3. Prepare Statistical Analysis Plan	3 weeks from protocol approval	14 September	First delivered date
Task 4. Submit Data Request and Load Data	1 week for submitting data request; 1-2 weeks for loading study data following receipt of study data	14 July 2016	
Task 5. Perform Preliminary Data Analyses and Prepare Preliminary Study Tables	Preliminary tables will be available 3 weeks following data loading in Task 4	04 October 2016	Date of first round prelim results provided
Task 6. Perform Final Data Analyses and Prepare Final Study Tables	Final tables will be available 2 weeks following receipt of all comments on prelim tables in Task 5	11 November 2016	
Task 7. Prepare Study Summary Report	3-4 weeks following client approval of final analyses in Task 6	23 December 2016	

6. RATIONALE AND BACKGROUND

Venous thromboembolism (VTE), which includes both deep vein thrombosis (DVT) and pulmonary embolism (PE), and refers to all thrombosis occurring in the veins (i.e., blood clots). DVT most commonly occurs in the deep veins of the leg, although it can also occur in veins of the upper extremities, the pelvis, abdomen, and cerebral venous sinuses.[1] PE is the most deadly form of VTE, including either the formation of a thrombosis in blood vessels or the embolization of thrombi from other areas of the body into pulmonary circulation.[1] It is estimated that the annual incidence of VTE is approximately 1-2 persons per 1,000 with the risk increasing significantly with age, presence of cancer, or prior VTE events.[2] Other risk factors include hospitalization, trauma, chemotherapy, central venous catheter use, prior superficial vein thrombosis, neurologic disease with paralysis, and liver disease.[3] VTE is associated with significant patient burden in terms of mortality and direct medical costs, as well as risk for developing post-thrombotic syndrome or chronic thromboembolic pulmonary hypertension.[4, 5]

Anticoagulation treatment for acute VTE typically begins with the administration of parenteral anticoagulant therapy ([PAC] e.g., low-molecular-weight heparin [LMWH], low-dose unfractionated heparin [UFH]) due to their fast-acting nature, followed by warfarin or other vitamin K antagonist therapies (VKAs). Patients then typically undergo a bridging process, where LMWH/UFH and VKA therapies are taken concurrently for a period of several days until a stable therapeutic international normalized ratio (INR) is achieved. Although warfarin significantly reduces the risk of VTE recurrence, warfarin also increases the baseline risk of bleeding compared to non-anticoagulated patients.[6-8] As a result, patients require close monitoring with INR blood tests and careful adjustment of dosages based on INR readings.[6-8]

While the American College of Chest Physicians and other professional associations periodically publish and revise specific treatment guidelines for VTE,[9] past research has shown poor compliance with their recommendations.[10-13] For example, a meta-analysis reported poor anticoagulation control with warfarin among VTE patients, where the quality of anticoagulation was defined by time spent in target INR range.[14] Time spent within therapeutic INR range is an important indicator of warfarin management quality because VTE patients outside the recommended range are at an increased risk for recurrent VTE or bleeding. One study reported increased rates of recurrent VTE and major bleeding when patients with time in therapeutic range (TTR) <45% were compared with those having TTR >65%.[15]

The FDA has approved several novel oral anticoagulants (NOACs), including apixaban (Eliquis®), dabigatran etexilate mesylate (Pradaxa®), edoxaban (Savaysa®), and rivaroxaban (Xarelto®). One recently published indirect treatment comparison study based on phase III clinical trial data reported that among the four available NOACs, apixaban resulted in less bleeding than the other NOACs for the treatment of acute VTE.[16] Other prior studies show that dabigatran, rivaroxaban, and apixaban are comparable both in efficacy and safety profiles to warfarin or other vitamin K antagonists in treatment of VTE.[17-20] The

NOACs have the added benefit of not requiring the routine coagulation monitoring needed for warfarin.

With the introduction of NOACs into the market for treatment of VTE, it is important to understand treatment patterns, patient characteristics, and clinical outcomes among VTE patients treated with OAC in the US integrated healthcare delivery networks.
This non-interventional study was designated as a Post-Authorisation Safety Study (PASS) and was conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

Using de-identified EHR data from a large, nationwide database of integrated delivery networks, the objectives of this project were to:

1. Assess demographic and clinical characteristics among VTE patients newly anticoagulated by anticoagulation type and setting of care
2. Assess anticoagulant treatment patterns among VTE patients newly anticoagulated by setting of care and identify predictors of selected NOAC use.
3. Evaluate characteristics of the initial inpatient admission for those hospitalized with VTE
4. Evaluate the rate of VTE recurrence and bleeding events during the follow-up period among VTE patients newly anticoagulated, by anticoagulation type and setting of care
5. Determine the feasibility of assessing quality of warfarin management among VTE patients newly anticoagulated. The average number of INR tests in the follow-up period was assessed to examine the availability of data methods

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	10/01/16	Substantial	Patient Selection		Ensure that all the time before index therapy were captured in the baseline period
2	11/22/16	Substantial	Patient selection		Previous major bleeding code list was deemed to be too broad
3	11/22/16	Substantial	Patient selection		Ensure serious VTE recurrences are included

9. RESEARCH METHODS

The final study protocol, statistical analysis plan, and list of codes used are included in Appendix 1, Appendix 2, and Appendix 4, respectively.

9.1. Study design

This retrospective cohort study involved analysis of the Optum Humedica EHR database using data from August 31, 2012 to March 31, 2016 for a study population of adult (≥18 years of age) VTE patients newly treated with an OAC. Since the various NOACs were approved at different dates (i.e., November 2012 for rivaroxaban; April 2014 for dabigatran; August 2014 for apixaban), the index VTE encounter (i.e. first VTE encounter) was identified starting on September 1, 2014 to allow for the time period when all NOACs were available. Edoxaban was not included in this study due to insufficient data stemming from its approval date of January 2015.

VTE patients treated with oral anticoagulation were identified and assigned to two mutually exclusive cohorts – the inpatient cohort and the outpatient cohort - based on the setting of initial care.

The main study measures included: (1) baseline demographic and clinical characteristics; (2) anticoagulant treatment patterns; (3) characteristics of the initial inpatient admission (for inpatient cohort); (4) the rate of follow-up VTE recurrence and bleeding events; and (5) number of INR tests and results among warfarin users.

Index VTE encounter:

- Inpatient cohort: the index VTE encounter for the inpatient cohort was defined as the first observed hospitalization with a principal diagnosis of VTE.
- Outpatient cohort: the index VTE encounter for the outpatient cohort was defined as the first observed VTE diagnosis in an outpatient setting.

Index date:

- Inpatient cohort: discharge date of index VTE encounter hospitalization
- Outpatient cohort: the date of the first OAC received within a 2-day period following the outpatient index VTE encounter

Index therapy: OAC therapy assigned on the index date

Baseline period: 12 months prior to the beginning of the index therapy date

Follow-up period: From the day after the index date until the earliest of the last encounter, OAC switch, death, or the end of the 6-month period post-index therapy.

Figures 1 and 2 provide a sample schematic for identifying patients for the inpatient and outpatient cohorts and their follow-up period.

Figure 1. Sample Analytical Timeline – Inpatient Cohort

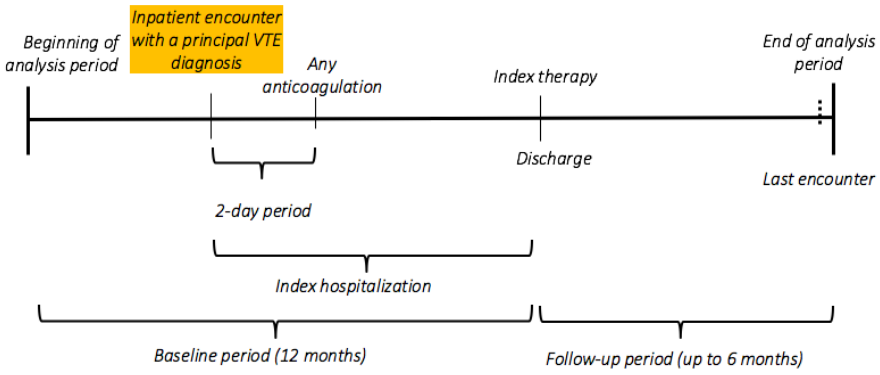
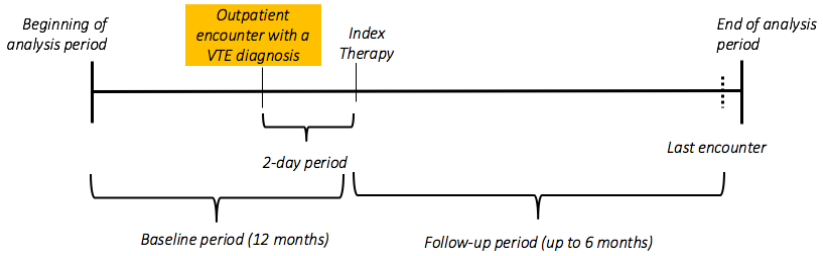


Figure 2. Sample Analytic Timeline – Outpatient Cohort



9.2. Setting

This retrospective study used the Optum Humedica EHR database, which is reflective of the US population according to comparative distributions of age, sex, and geographic region. Section 9.5 below contains further details regarding the data elements available in the Optum Humedica database. The study population consisted of adults with VTE newly treated with an oral anticoagulant and who had at least one medical encounter in the 12 months prior to the baseline period. Further information on patient selection and the follow-up period are included in section 9.3.

9.3. Subjects

The study population consisted of VTE patients naïve to anticoagulation treatment during the 12-month baseline period. The inclusion and exclusion criteria are detailed below.

Inclusion Criteria:

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

1. ≥ 1 VTE event on or after September 1, 2014, as defined below:

   a. An inpatient encounter with a principal VTE diagnosis and evidence of OAC/PAC within two days after inpatient admission
   b. An outpatient encounter with a VTE diagnosis at any position and evidence of an OAC (index therapy) within two days after VTE diagnosis.
2. Evidence of an OAC prescribed or administered on the discharge date (index therapy) for patients in the inpatient cohort. All patients in the outpatient cohort meeting criteria in Step 1b were included.
3. ≥ 1 medical encounter in the 12 months preceding the baseline period and ≥ 1 one medical encounter following the index date to proxy continuous enrollment
4. Age ≥18 years on index-date

Exclusion Criteria:
Patients meeting any of the following criteria were <u>not</u> included in the study (see Appendix 4 for relevant codes):

1. Evidence of ≥ 2 OAC medications on the index date
2. Evidence of atrial fibrillation/flutter, or chemotherapy/radiation therapy for malignancy (other than non-melanoma skin cancer) during the baseline period
3. Evidence of malignancy (other than non-melanoma skin cancer) during the 30-day period preceding index encounter
4. Evidence of OAC/PAC use during the 12 months preceding the index VTE encounter date

   Exception:
   - Patients with a "medically-ill" (see Appendix 4) principal diagnosis at an inpatient setting; and receiving OAC/PAC during the same hospitalization; and with hospital stay equal to or longer than 3 days
   - Patients receiving knee/hip replacement surgery (see Appendix 4); and receiving OAC/PAC during the same hospitalization
4. Evidence of inferior vena cava filter (IVCF) during the study period
5. Evidence of pregnancy during the study period

9.4. Variables

Baseline demographic and clinical characteristics were evaluated during the 12-month baseline period. All outcomes were evaluated during the variable follow-up period. The outcomes of interest included VTE recurrence, major bleeding, and any bleeding events. All relevant codes are listed in Appendix 4.

VTE recurrence was defined as:

- ≥1 inpatient encounter with a VTE principal diagnosis during the follow-up period

Major bleeding event was defined as an acute care inpatient admission during the follow-up period with:

- A principal diagnosis code for:
  - Gastrointestinal (GI) bleeding
  - Intracranial (ICH) bleeding
  - Other selected types/sites of bleeding (as defined in below)

  OR
  - A procedure code for the treatment of bleeding (as defined below)

Any bleeding event during the follow-up period was defined as:

- An acute-care inpatient admission with a principal or secondary diagnosis code for GI bleeding, ICH bleeding, or other selected types/sites of bleeding;
- An acute-care inpatient admission with a procedure code for the treatment of bleeding; or
- An ambulatory-care encounter with a diagnosis code for GI bleeding, ICH bleeding, or other selected types/sites of bleeding.

Table 2. Major Bleeding and Any Bleeding Codes

Not provided in this report

A complete list of measures included in the analysis is provided below:

Table 3. Variables

Variable	Role	Operational definition
Treatment cohort	Exposure	Patients were placed into one of two cohorts (i.e., inpatient or outpatient) based on the setting of care for the index VTE event
Index therapy	Exposure	Patients were classified by the oral anticoagulant received
Baseline	Time period	12 month time period prior to index therapy (excludes index date)
Index date	Time Period	Date of the index therapy (1-day).
Age	Baseline characteristic	Continuous variable, age (in years) as of the index date
Age Group	Baseline characteristic	Categorical variable with possible values- 44 and below, 45-54, 55-64, 65-74, and 75 and above
Sex	Baseline characteristic	Dichotomous variable where sex = 1 if female and 0 if male
Geographic region	Baseline characteristic	Categorical variable with possible values - Northeast, Midwest, South, West, and Other/Unknown (based on US census classification) on index date
Health plan type	Baseline characteristic	Categorical variable with possible values – Commercial, Medicare, Medicaid, Other, Uninsured, and Unknown on index date
Qualifying diagnosis	Baseline characteristic	Categorical variable with possible values – DVT, PE, and PE with DVT
Weight	Baseline characteristic	Continuous variable, weight (kg) on or before the index date. If multiple readings were available, the reading closest to the index date was used.

Body Mass Index (BMI)	Baseline characteristic	Continuous variable, body mass index on or before the index date. If multiple readings were present, the most recent measure was used.
Creatinine clearance	Baseline characteristic	Continuous variable, creatinine clearance on or before the index date. If multiple readings were present, the most recent measure was used.
Charlson comorbidity index score	Baseline characteristic	Charlson comorbidity score was calculated based on applying the scoring system to the presence of select comorbidities during baseline.
Prescriber type	Baseline characteristic	Categorical variable containing the specialty of the physician who prescribed the index therapy
Concomitant medications	Baseline characteristic	Presence of concomitant medications (i.e. angiotensin converting enzyme inhibitor, amiodarone, angiotensin receptor blocker, beta blockers, H2-receptor antagonist, proton pump inhibitor, statins, anti-platelets) during baseline period
Presence of Charlson comorbidities	Baseline characteristic	Presence of comorbid conditions was based on ≥1 encounter with the relevant diagnoses during the baseline period. Variables were dichotomous where 1 indicates presence of the comorbid condition.
Chronic Kidney Disease (CKD)	Baseline characteristic	Presence of CKD, including any stage and individual stages I-IV, based on ≥1 encounter with the relevant diagnoses during the baseline period. Variables were dichotomous where 1 indicates presence of the comorbid condition
Ischemic heart disease	Baseline characteristic	Presence of ischemic heart disease based on ≥1 encounter with the relevant diagnoses during the baseline period. Variables were dichotomous where 1 indicates presence of comorbid condition.
Stroke or transient ischemic attack (TIA)	Baseline characteristic	Presence of stroke or transient ischemic attack based on ≥1 encounter with the relevant diagnoses during the baseline period. Variables were dichotomous where 1 indicates presence of comorbid condition.
Chronic Obstructive Pulmonary Disease (COPD)	Baseline characteristic	Presence of COPD based on ≥1 encounter with the relevant diagnoses during the baseline period. Variables were dichotomous where 1 indicates presence of comorbid condition.
Thrombocytopenia	Baseline characteristic	Presence of thrombocytopenia based on ≥1 encounter with the relevant diagnoses during the baseline period. Variables were dichotomous where 1 indicates presence of comorbid condition.
Anemia	Baseline characteristic	Presence of anemia based on ≥1 encounter with the relevant diagnoses during the baseline period. Variables were dichotomous where 1 indicates presence of comorbid condition.
Dyspepsia	Baseline characteristic	Presence of dyspepsia based on ≥1 encounter with the relevant diagnoses during the baseline period. Variables were dichotomous where 1 indicates presence of comorbid condition.
Hypertension	Baseline characteristic	Presence of hypertension based on ≥1 encounter with the relevant diagnoses during the baseline period. Variables were dichotomous where 1 indicates presence of comorbid condition.
Inflammatory bowel disease	Baseline characteristic	Presence of inflammatory bowel disease based on ≥1 encounter with the relevant diagnoses during the baseline period. Variables were dichotomous where 1 indicates presence of comorbid condition.
Falls	Baseline characteristic	Presence of falling based on ≥1 encounter with the relevant diagnoses during the baseline period. Variables were dichotomous where 1 indicates presence of comorbid condition.
Hormone therapy	Baseline characteristic	Presence of hormone therapy based on ≥1 encounter with the relevant therapy during the 3-month preceding index encounter. Variables were dichotomous where 1 indicates presence of comorbid condition.

Fracture/trauma involving the lower extremities	Baseline characteristic	Presence of fracture/trauma involving lower extremities based on ≥1 encounter with the relevant diagnoses during the 3-month preceding index encounter. Variables were dichotomous where 1 indicates presence of comorbid condition.
Pelvic or orthopedic surgery	Baseline Characteristic	Presence of selected surgeries involving lower extremities based on ≥1 encounter with the relevant diagnoses during the 3-month preceding index encounter. Variables were dichotomous where 1 indicates presence of comorbid condition.
Known thrombophilia/ Antiphospholipid antibody syndrome	Baseline characteristic	Dichotomous variable that equals 1 if there was ≥1 encounter with thrombophilia or antiphospholipid antibody syndrome during the baseline period.
Bleeding event in baseline	Baseline characteristic	Dichotomous variable that equals 1 if there was ≥1 encounter with bleeding during the baseline period. Reported by encounter service location (inpatient, ER, or outpatient).
Provoked VTE	Baseline characteristic	Provoked VTE was defined as events that were preceded during the 3-month pre-index encounter period by hormone therapy, fracture/trauma involving lower extremities, pelvic/orthopedic surgery, or hospitalization for any reason; unprovoked VTE was defined as all events not classified as provoked.
Initial anticoagulant treatment	Baseline characteristic	Categorical variable containing anticoagulant treatment received as the first treatment during the index hospitalization
In-hospital treatment strategy	Baseline characteristic	Categorical variable containing anticoagulant treatment received during the index hospitalization
Use of ICU/CCU during index hospitalizations	Baseline characteristic	Dichotomous variable that equals 1 if ICU/CCU was utilized
Length of stay for index hospitalizations	Baseline characteristic	Length of stay expressed in days including discharge date
Discharge destination	Baseline characteristic	Categorical variable containing discharge disposition for the index hospitalization
End of follow-up	Potential confounder	Date variable that reflects the earliest of the following scenarios – last encounter, OAC switch, death or 6-month period
Follow-up duration	Potential confounder	Duration of follow-up period expressed in days including end date.
VTE recurrence	Outcome	Dichotomous variable that equals 1 if there was ≥1 inpatient encounter with a VTE principal diagnosis after index inpatient VTE event discharge date or more than 2 days after the index outpatient VTE event.
VTE recurrence setting	Outcome	Dichotomous variable Inpatient as possible value.
Time to VTE recurrence in months	Outcome	Time from index therapy date to VTE recurrence in months
Length of stay due to VTE recurrence	Outcome	Hospital length of stay during the VTE recurrence encounter for those admitted to inpatient setting
ICU/CCU use during VTE recurrence hospitalization	Outcome	Dichotomous variable with 1 indicating patient use of ICU/CCU during VTE recurrence hospitalization
Discharge disposition for VTE recurrence hospitalization	Outcome	Categorical variable containing discharge disposition (e.g. home, transferred to hospital, skilled nursing facility, death, etc) for the VTE recurrence hospitalization

Major bleeding event in follow-up	Outcome	Dichotomous variable that equals 1 if there was ≥1 encounter with major bleeding during the follow-up period. Major bleeding was defined as an acute care inpatient admission with a principal diagnosis code for gastrointestinal (GI) bleeding, intracranial (ICH) bleeding or other selected types/sites of bleeding, or a procedure code for the treatment of bleeding.
Time to Major bleeding in months	Outcome	Time from index therapy date to Major bleeding in months, applicable only to patients where Major bleeding event in follow-up equals 1
Length of stay due to Major Bleeding recurrence	Outcome	Hospital length of stay during the Major Bleeding recurrence encounter for those admitted to inpatient setting
ICU/CCU use during Major Bleeding recurrence hospitalization	Outcome	Dichotomous variable with 1 indicating patient use of ICU/CCU during Major Bleeding recurrence hospitalization
Discharge disposition for Major Bleeding recurrence hospitalization	Outcome	Categorical variable containing discharge disposition for the Major Bleeding recurrence hospitalization
Any bleeding event in follow-up	Outcome	Dichotomous variable that equals 1 if there was ≥1 encounter with any bleeding during the follow-up period. See Appendix 4 for list of ICD-9-CM codes. Any bleeding event was defined as an acute-care inpatient admission with a diagnosis code for GI bleeding, ICH bleeding, or other selected types/sites of bleeding; an acute-care inpatient admission with a procedure code for the treatment of bleeding; or an ambulatory-care encounter with a diagnosis code for GI bleeding, ICH bleeding, or other selected types/sites of bleeding.
Any bleeding recurrence setting	Outcome	Categorical variable with Inpatient as possible value.
Time to Any bleeding in months	Outcome	Time from index therapy date to any bleeding in months, applicable only to patients where Any bleeding event in follow-up equals 1
Length of stay due to Any Bleeding recurrence	Outcome	Hospital length of stay during the any Bleeding recurrence encounter for those admitted to inpatient setting
ICU/CCU use during Any Bleeding recurrence hospitalization	Outcome	Dichotomous variable with 1 indicating patient use of ICU/CCU during Any Bleeding recurrence hospitalization
Discharge disposition for Any Bleeding recurrence hospitalization	Outcome	Categorical variable containing discharge disposition for the any Bleeding recurrence hospitalization
Number of INR tests during follow-up	Outcome	Average number of INR tests per patient in the follow-up period
Average INR value	Outcome	Average INR value per patient in the follow-up period
Distribution of INR test results	Outcome	Categorical variable with possible values - <2, 2-3, >3.

9.5. Data sources and measurement

The data source for this study was the Humedica EHR database, which is updated nightly, containing data on over 30 million individuals across 38 states.[21] Humedica integrates claims, prescription and practice management data and partners directly with the nation's leading medical groups, integrated delivery networks (IDNs), and hospital chains to directly obtain data from their EHR and various IT systems in real time. Humedica then normalizes, validates, and aggregates these data to generate a complete and longitudinal view of patient care. Information in addition to standard diagnosis and procedure details includes observational outcomes (e.g., BMI, smoking), use of over the counter drugs, laboratory results, prescriptions written, medication administered (in-hospital only), and other details of a patient's office or emergency room visit and/or hospital stay, as well as discharge location. Linked inpatient and outpatient records are available for about 40% of patients in the Humedica database.[22] Dates of the data window are August 31, 2012 through March 31, 2016.

Specific data fields in the Humedica data that are relevant to this study include:

- Demographic & Clinical Characteristics:
  - Age, sex, race, geographic region, complete history of comorbid diagnoses in all settings
- Encounters:
  - ICD-9, ICD-10 diagnosis codes
  - Procedure codes (CPT-4, HCPCS, ICD-9 and ICD-10 procedure)
  - Physician specialty (self-reported)
  - Visit type (e.g., inpatient, office or clinic, emergency, home health, not recorded)
  - Arrival, admit, and discharge dates, or date of service for outpatient visits
  - Facility (Private, non-private)
  - Teaching facility (Y/N)
- Prescription information:
  - Drug name and NDC for prescriptions written for all prescriptions captured in EHR system
  - Date & time administered (inpatient only)
- Discharge status:
  - Home, skilled nursing facility, rehabilitation center, death

9.6. Bias

Please refer to discussion section.

9.7. Study Size

Please refer to discussion section.

9.8. Data transformation

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), are documented in the Statistical Analysis Plan (SAP), which is dated, filed and maintained by the sponsor (Appendix 2).

9.9. Statistical methods

Statistical methods are further discussed in the Statistical Analysis Plan in Appendix 2.

9.9.1. Main summary measures

- See Section 9.9.2. below

9.9.2. Main statistical methods

Descriptive analysis

Descriptive summary statistics for all baseline and outcome were reported for each cohort (inpatient, outpatient) and by index therapy. All descriptive analyses included mean, median, standard deviation, minimum, maximum, and interquartile ranges (IQR) for continuous measures and proportions for binary and categorical measures.

The rate for clinical outcomes (VTE recurrence and major/any bleeding events) was calculated. The rate was calculated as the number of patients who experience one or more event divided by the observed time at risk at the time of initial event and was reported per 100-person months. Due to the small number of apixaban and dabigatran patients, all NOACs were combined into one group when assessing the rate of clinical outcomes.

Key measures were compared among patients treated with warfarin and NOACs. For categorical variables, chi-square/Fisher's exact test were used, and for continuous variables, one-way ANOVA test was used to test for differences among patients treated with warfarin and NOACs.

Regression analysis

Logistic regression models were used to evaluate: (1) predictors of use of each NOAC therapy compared to warfarin, and (2) predictors of use of each other NOAC therapy compared to apixaban. The intent was to separately model each NOAC, however, due to the limited numbers of patients receiving dabigatran as the index pharmacotherapy (<1% of both the inpatient and outpatient cohort), analyses were limited to comparisons of rivaroxaban and apixaban to warfarin, and a comparison of rivaroxaban to apixaban.

Covariates included demographics, comorbidities, pharmacotherapy, and other clinical characteristics from the 12-month baseline period. Inpatient and outpatient cohorts were evaluated separately.

Only 'saturated" models are presented, as no model reduction to remove non-statistically-significant covariates was conducted. Results of regression analysis are presented as adjusted odds ratios, 95% confidence intervals, and p-values.

9.9.3. Missing values

None

9.9.4. Sensitivity analyses

None

9.9.5. Amendments to the statistical analysis plan

None. See Appendix 2 for the statistical analysis plan.

9.10. Quality control

This study was scientifically rigorous and of high quality. Senior Advisors and Medical Directors were heavily involved in the design of this study. The study design utilizes current and rigorous analytical methods that are well accepted in the research field. Accuracy was ensured by designing an internal analytic work plan which provided a means for project documentation as well as a programming guideline for analysts/programmers. It included database descriptions, and variable definitions and creation instructions, as well as details on all assumptions and decision rules used in the programing. The project team (i.e., leader, manager, and analysts) reviewed and signed off on the plan before any programming was started. The lead programmer on the team reviewed all of his programming code. For quality assurance purposes, a second, independent programmer not assigned to the project reviewed all project code and intermediate output and signed off on all programming code.

9.11. Protection of human subjects

Subject information and consent

Not applicable

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

IRB/IEC was not required for this study

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices.

10. RESULTS

Full results tables for all analyses are present in Appendix 3

10.1. Participants

Study attrition and the final patient sample size information is presented in Appendix 3, Tables 1 and 2, respectively.

- Inpatient Cohort:

  After applying all inclusion/exclusion criteria, a total of 4,599 patients were identified for the inpatient cohort. Among them, 373 (8.1%) were prescribed apixaban on discharge, 32 (0.7%) dabigatran, 1,367 (29.7%) rivaroxaban, and 2,827 (61.5%) warfarin. Due to the small number, results on dabigatran patients need to be interpreted with caution.

- Outpatient Cohort:

  Among outpatients with ≥ 1 VTE outpatient encounter and evidence of an OAC received within 2 days of diagnosis, 7,510 patients met eligibility criteria, of whom 632 (8.4%) were prescribed apixaban, 60 (0.8%) dabigatran, 3,092 (41.2%) rivaroxaban, and 3,726 (49.6%) warfarin. Due to the small sample size of dabigatran patients, results for those patients need to be interpreted with caution.

The final overall count of patients for each cohort (i.e. inpatient and outpatient), stratified by index pharmacotherapy, is presented in Appendix 3, Table 2.

10.2. Demographic and Clinical Characteristics

Demographic characteristics, clinical characteristics, and comorbidities are presented in Appendix 3, Tables 3, 4, and 5, respectively.

Baseline Demographics

- Inpatient Cohort:

  The mean age of the inpatient cohort was 60.5 years and about half of the inpatient cohort (55.6%) were female. Apixaban and warfarin patients had similar mean age (62 years), older than rivaroxaban patients (mean age: 56.4 year).

- Outpatient Cohort:

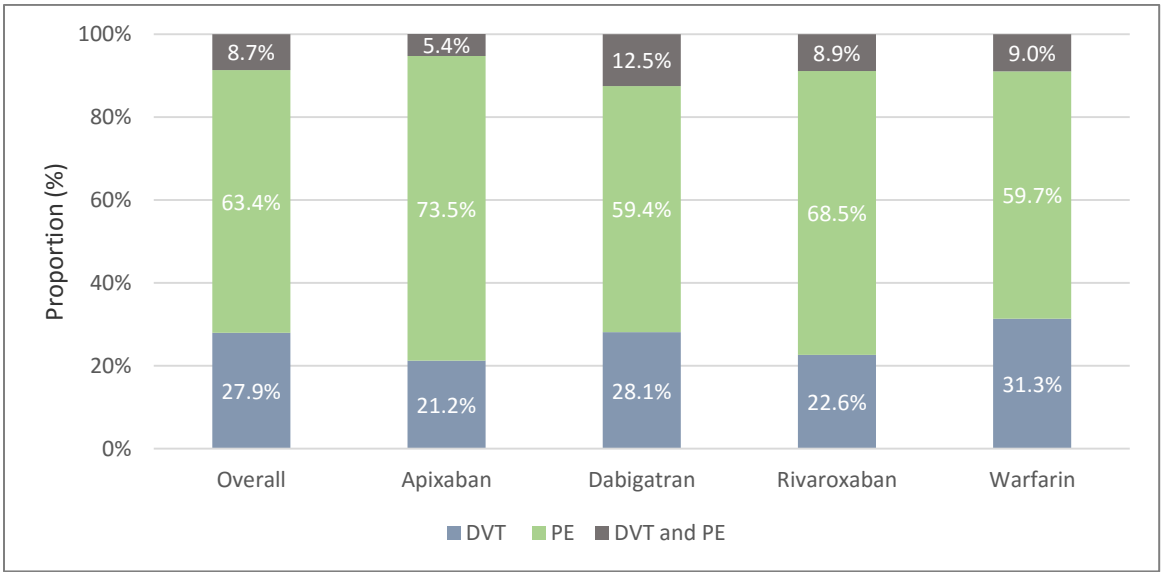
  The mean age of the outpatient cohort was 60 years and about half of the outpatient cohort were female (51.4%). Apixaban patients (62.3 years) had higher mean age than warfarin (60.7 years) and rivaroxaban patients (58.2 years).

Baseline Clinical Characteristics

- Inpatient cohort

Figure 3 depicts the classification of VTE encounters for the inpatient cohort. Initial VTE encounters were classified as DVT only, PE only, or DVT and PE. Significant differences were observed across groups for the proportion of patients experiencing DVT (p<0.0001). Similarly, the proportion of patients experiencing PE was significantly different across groups (p<0.0001). Of note, 73.5% of apixaban patients had a qualifying diagnosis of PE (the more serious form of VTE), compared with 59.4% of dabigatran patients, 68.5% of rivaroxaban patients, and 59.7% of warfarin patients (Appendix 3, Table 4).

Figure 3. Qualifying VTE Diagnoses – Inpatient Cohort



Similarly, apixaban patients in the inpatient group had a higher Charlson comorbidity score compared to rivaroxaban patients (p<0.0001). As measured at baseline, the Charlson comorbidity scores for the inpatient cohort were 1.46, 1.91, 1.00 and 1.53 for apixaban, dabigatran, rivaroxaban, and warfarin patients, respectively

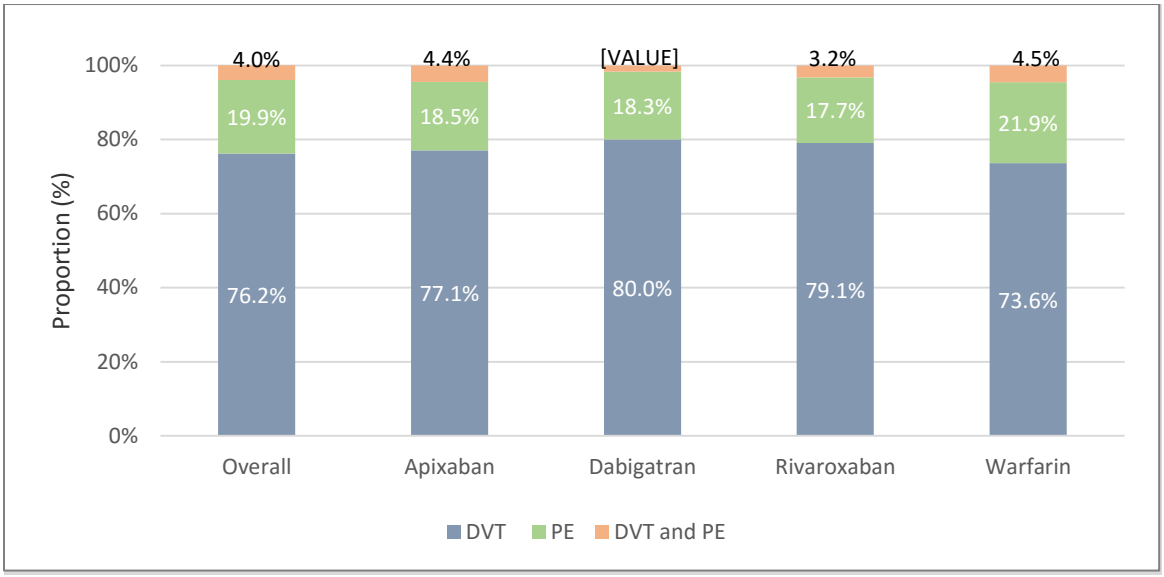
The most common comorbidities within the inpatient cohort included: hypertension (65.8%), chronic pulmonary disease (35.6%), anemia (27.9%), diabetes without complications (24.8%), and ischemic heart disease (22.0%).

- Outpatient cohort

Figure 4 depicts the classification of VTE encounters for the outpatient cohort. The majority of outpatient encounters were DVT related. Initial VTE encounters were classified as DVT only, PE only, or DVT and PE. Significant differences were observed across groups for the proportion of patients experiencing DVT (p<0.0001). Similarly, the proportion of patients experiencing PE was significantly different across groups (p<0.0002). Of note, 77.1% of apixaban patients had a qualifying diagnosis of

DVT only (the less serious form of VTE), compared with 80.0% of dabigatran patients, 79.1% of rivaroxaban patients, and 73.6% of warfarin patients (Appendix 3, Table 4).

Figure 4. Qualifying VTE Diagnoses – Outpatient Cohort



As measured at baseline, the Charlson comorbidity scores for the outpatient cohort were 0.87, 0.88, 0.67, and 0.89 for apixaban, dabigatran, rivaroxaban, and warfarin patients, respectively.

The most common comorbidities within the outpatient cohort included: hypertension (46.7%), chronic pulmonary disease (19.2%), diabetes without complications (17.2%), dyspepsia (14.4%), and anemia (13.2%).

Follow-up Duration

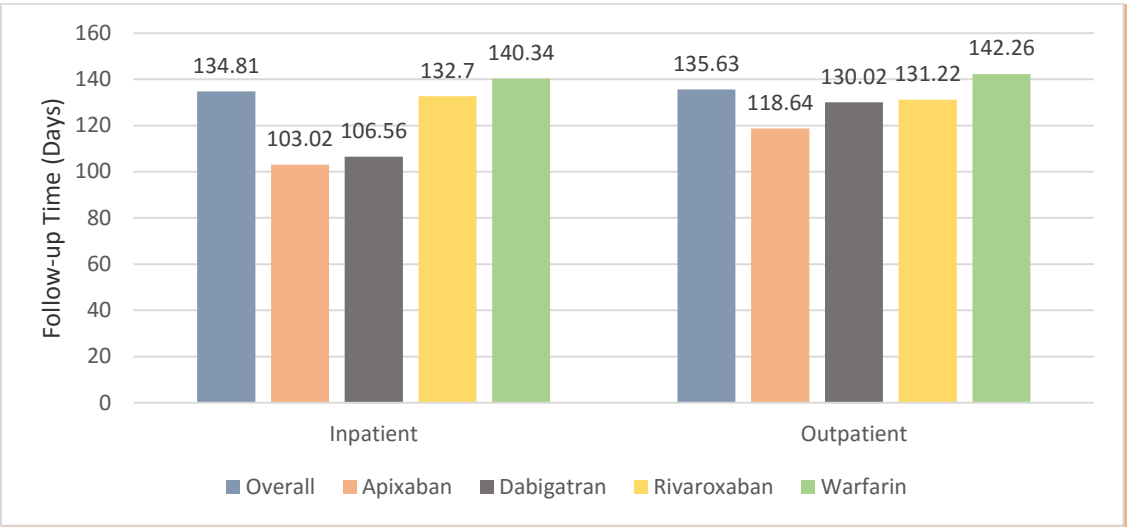
- Inpatient cohort

  The follow-up duration was shortest for those who received apixaban and longest for those receiving warfarin, 103.0 days on average vs 140.3 days, respectively. The left side of Figure 5, below, depicts follow-up time across all patients from the inpatient cohort.

- Outpatient cohort

  The follow-up duration was shortest for those who received apixaban and longest for those receiving warfarin, 118.6 days on average vs 142.3 days, respectively. The right side of Figure 5, below, depicts follow-up time across all patients from the outpatient cohort.

Figure 5. Follow-up Duration



10.3. Predictors of Selected NOAC Use

Logistic regression results for inpatient and outpatient cohorts are presented in Appendix 3, Tables 11 and 12, respectively.

- Inpatient cohort

  Table 11 shows three separate multivariate logistic regression analyses focused on identifying predictors of index therapy within the inpatient cohort. A limited number of factors were found to predict the use of apixaban vs. warfarin. Among the inpatient cohort, having a PE diagnosis was associated with a statistically significant ($p \leq 0.05$) higher likelihood of using apixaban vs. warfarin whereas receiving beta-blockers and having falls during baseline were associated with a lower chance of using apixaban vs. warfarin. Patients residing in the Northeast and the South were more likely to use apixaban vs. warfarin than those residing in Midwest.

  More factors were found to predict the use of rivaroxaban vs. warfarin among the inpatient cohort. Increased age, having thrombophilia, DVT diagnosis, anemia, congestive heart failure, myocardial infarction, using prompt pump inhibitors, and having falls at baseline were associated with a lower chance of using rivaroxaban vs. warfarin ($p \leq 0.05$). Patients residing in the Northeast and the South were more likely to use rivaroxaban vs. warfarin than those residing in Midwest.

  Several factors were found to predict the use of rivaroxaban vs. apixaban among the inpatient cohort. Increased age, having congestive heart failure, PE diagnosis, myocardial infarction and using H2 receptor antagonist were associated with a lower chance of using rivaroxaban vs. apixaban ($p \leq 0.05$). Use of beta blockers was associated with an increased chance of using rivaroxaban vs. apixaban.

- Outpatient cohort

  Table 12 shows multivariate logistic regression analysis to identify predictors of using apixaban or rivaroxaban for the outpatient cohort. A number of factors were found to predict the use of apixaban vs. warfarin. Among the outpatient cohort, thrombophilia, diabetes without complications, inflammatory bowel disease, stroke or TIA, were associated with a lower chance of using apixaban vs. warfarin ($p \leq 0.05$). Patients with renal disease, presence of a tumor, receipt of angiotensin receptor blockers and hypertension were more likely to use apixaban vs. warfarin. Patients residing in the Northeast, South and West were more likely to use apixaban vs. warfarin than those residing in Midwest.

  Several factors were also found to predict the use of rivaroxaban vs. warfarin among the outpatient cohort. Increased age, BMI, having thrombophilia, any primary malignancy, congestive heart failure, myocardial infarction, using beta blockers, and pelvic/orthopedic surgery were associated with a lower chance of using rivaroxaban vs. warfarin ($p \leq 0.05$). Patients exhibiting dyspepsia were associated with a higher chance of using using rivaroxaban vs warfarin. Patients residing in the Northeast and the South were also more likely to use rivaroxaban vs. warfarin than those residing in Midwest.

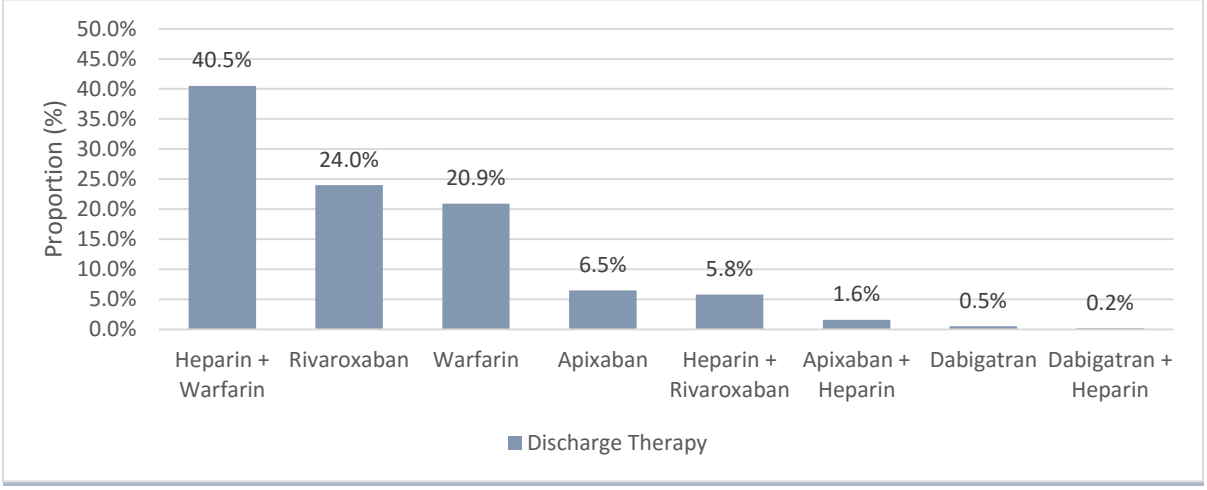
  Fewer factors were also found to predict the use of rivaroxaban vs. apixaban among the outpatient cohort. Increased age, having dementia, renal disease, and living in the Northeast (compared to the Midwest) were associated with a lower chance of using rivaroxaban vs. apixaban ($p \leq 0.05$). Any CKD, stroke or TIA, or living in the South (compared to Midwest) was associated with an increased chance of using rivaroxaban vs. apixaban.

10.4. Inpatient Treatment Patterns

Treatment patterns for the inpatient cohort corresponding to both index (discharge) therapy and in-hospital treatment strategy are presented in Appendix 3, Table 6.

As shown in the top portion of Table 6, as well as in Figure 6, the most common treatment strategy on discharge among the entire cohort was heparin plus warfarin (40.5%). This was followed by rivaroxaban (24.0%), warfarin (20.9%), apixaban (6.5%) and heparin plus rivaroxaban (5.8%).

Figure 6. Index (Discharge) Treatment Strategy



Among the top 20 most common treatment strategies in the hospital, which represented 77% (n=3,560) of all hospitalized patients, the majority of these patients started treatment with heparin (n=2,179, 61.2%) or heparin in combination with warfarin (n=1,127, 31.7%). A small percentage of patients started treatment with rivaroxaban only (n=117, 3.2%) or rivaroxaban in combination with heparin (n=137, 3.8%).

Among the 2,179 patients who started treatment with heparin only, various treatments after heparin initiation were received. Specifically, of the heparin only users, 28.1% (n=613) were later prescribed heparin in combination with warfarin, 14.8% (n=324) were later taken off heparin and received rivaroxaban only, and 11.1% (n=242) of patients received heparin in combination with rivaroxaban before terminating heparin and continuing with rivaroxaban only. Among patients who started with heparin and warfarin as a combination (n=1,127), the next treatments included warfarin only (n=255, 22.6%), warfarin only followed by warfarin and heparin in combination (n=182, 16.1%), while 51.5% (n=580) of heparin and warfarin combination patients remained on this treatment throughout the hospitalization period.

10.5. VTE Hospitalization Characteristics

VTE hospitalization characteristics for the inpatient cohort are presented in Appendix 3, Table 7.

Overall, warfarin patients exhibited the highest rate of ICU/CCU use (20.3%). The rates of ICU/CCU use for apixaban, dabigatran, and rivaroxaban were 13.9%, 12.9%, and 15.1%, respectively. Warfarin patients also had the longest length of stay with an average of 6.94 days per patient. The length of stay for apixaban, dabigatran, and rivaroxaban was 5.06, 5.41, and 4.41, respectively. The discharge disposition was also evaluated, however, the variable was poorly populated with only 2.2% of all patients exhibiting a discharge disposition.

10.6. Rate of VTE Recurrence and Bleeding

VTE Recurrence and Bleeding rates are presented in Appendix 3, Tables 8 and 9, respectively

VTE Recurrence

The rate of VTE recurrence per 100 person months was 0.97 for the overall inpatient cohort and 0.50 for the overall outpatient cohort. Among the inpatient cohort, the rates were 0.74 for patients treated with NOACs, and 1.11 for patients treated with warfarin. The corresponding rates for the outpatient cohort were 0.47 for NOAC and 0.53 for warfarin patients. The mean time to VTE recurrence for the inpatient cohort was about 29 days (SD: 32.1) among patients with NOACs and 49 days (SD: 48.7) among warfarin patients. For the outpatient cohort, the mean time to VTE recurrence was 32.7 (SD: 43.4) and 41.2 (SD: 47) days for the NOAC and warfarin patients respectively.

Bleeding

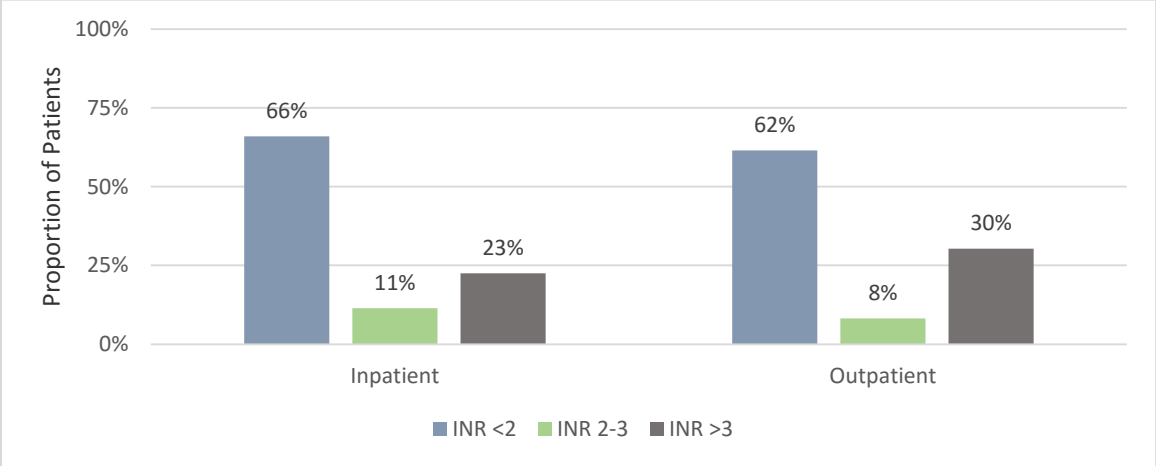
Major bleeding and any bleeding were assessed as safety outcomes. Among the inpatient cohort, the rate of major bleeding per 100 person months was 0.41 and 0.59 for the NOAC and warfarin patients, respectively. The rate of any bleeding per 100 person months was 3.4 and 3.2 for the NOAC and warfarin patients respectively. For the outpatient cohort, the rate of major bleeding per 100 person months was 0.23 for NOAC and 0.24 for warfarin patients. The rate of any bleeding was 2.4 and 2.3 for NOAC and warfarin patients respectively.

10.7. Warfarin Management

INR values and warfarin management are presented in Appendix 3, Table 10.

Warfarin management was assessed among patients. Overall, 82.9% of warfarin patients in the inpatient cohort and 85.3% of patients in the outpatient cohort had INR records present in the data. The average number of INR tests per patient was 13.8 for inpatients and 11.7 for outpatients. Figure 7 shows the distribution of INR test values. Among the inpatient cohort, 66% of patients had INR

Figure 7. Distribution of INR Test Results



10.8. Other analyses

None

10.9. Adverse events / adverse reactions

Not applicable

11. DISCUSSION

11.1. Key results

The recent approval of NOACs after decades of VKAs being the standard of VTE care necessitates study of the characteristics and treatment patterns among VTE patients who initiated NOAC or warfarin therapy.

Some differences in baseline characteristics, comorbidities, and pharmacotherapy were detected among VTE patients initiating NOAC or warfarin treatment from inpatient and outpatient settings. Patients treated with apixaban tended to have similar characteristics as those treated with warfarin. However, when compared to patients treated with rivaroxaban, both apixaban and warfarin patients were older and more likely to have a more severe comorbidity profile. Apixaban patients were also more likely to have a qualifying PE, the more severe type of VTE event, than warfarin or rivaroxaban patients.

Multivariate regression analysis further revealed that increased age and having some specific comorbidities were associated with a lower chance of using rivaroxaban vs. using warfarin or apixaban for both inpatient and outpatient cohorts. Regional differences in treatment patterns were also observed. Patients residing in the Northeast and the South were more likely to use apixaban or rivaroxaban vs. warfarin than those residing in the Midwest.

The analysis of the 20 most common inpatient treatment patterns indicated that most of the VTE patients started the treatment with heparin, or heparin in combination with warfarin, during hospitalization. A small percentage of these evaluated patients started treatment with rivaroxaban only, or with rivaroxaban in combination with heparin. None of these evaluated

patients started the treatment with apixaban or dabigatran. Among patients who started the treatment with heparin, some of them used heparin plus warfarin bridging therapy whereas some others used warfarin only for the treatment after the initial therapy. Among patients who used rivaroxaban or apixaban as an initial treatment or the treatment after the initial anticoagulant therapy, some of them used NOACs in combination with heparin even though NOACs can be used independently.

For the inpatient cohort, the major bleeding rate and the rate of VTE recurrence were numerically lower for patients treated with NOACs compared with patients treated warfarin. For outpatient cohort, both major bleeding and VTE recurrence rates were similar between the two cohorts.

11.2. Limitations

This study is predominately descriptive in nature. Although multivariate methods were used to identify factors associated with index therapy, no statistical adjustment was conducted for any comparison of outcomes. The EHR data source did now allow for evaluation of the duration of OAC use. Bleeding outcomes may be underestimated due to medical visits not captured in the EHR data source. Generalizability of findings may be limited to the source data population.

11.3. Interpretation

This study demonstrates characteristic differences among patients treated with different OACs. Patients treated with apixaban or warfarin tended to be older and sicker compared to patients treated with rivaroxaban. Since differences in patient characteristics may impact outcomes such as recurrent VTE or bleeding and were not controlled for in this descriptive study, it is important to cautiously interpret the results on the rates of VTE recurrence or bleeding by NOACs vs. warfarin.

There are some additional considerations when interpreting the rates of VTE recurrence or bleeding. The timing of the index interval with respect to when the study NOACs became available may also impact these results. When a new drug enters the market, it is often initially prescribed selectively; referred to as preferential prescribing or patient channeling.[24-25] For example, patients with a history of not tolerating an established treatment, or who have a certain medical profile, may be preferentially prescribed a new treatment such as recently approved NOACs quickly after market availability. This may result in biased treatment group comparisons.[24,25]

11.4. Generalizability

Although the Humedica EHR database contains data on over 30 million individuals across 38 states[21], it may be inappropriate to consider the current study findings generalizable to the entire US population. Generalizability of the study findings may be limited to the source data population.

12. OTHER INFORMATION

Not Applicable

13. CONCLUSIONS

This study demonstrates characteristic differences among VTE patients treated with different OACs. VTE patients treated with apixaban or warfarin tended to be older and sicker compared to patients treated with rivaroxaban for both inpatient and outpatient cohorts. While some differences in the rate of recurrence VTE or bleeding were observed for the inpatient cohort, it is important to cautiously interpret these results due to the descriptive nature of this study and potential patient channeling bias. Future studies with larger sample are needed to compare the effectiveness and safety of various OACs among VTE patients.

13.1. REFERENCES

1. NCBI. Definition of Venous Thromboembolism. NCBI 2003;Available at: URL: http://www.ncbi.nlm.nih.gov/books/NBK36775/. Accessed Feb 24, 2016.
2. Galioto NJ, Danley DL, Van Maanen RJ. Recurrent venous thromboembolism. Am Fam Physician 2011;83(3):293-300.
3. Ruppert A, Lees M, Steinle T. Clinical burden of venous thromboembolism. Curr Med Res Opin 2010;26(10):2465-2473.
4. Ginsberg JS, Hirsh J, Julian J et al. Prevention and treatment of postphlebitic syndrome: results of a 3-part study. Arch Intern Med 2001;161(17):2105-2109.
5. Pengo V, Lensing AW, Prins MH et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 2004;350(22):2257-2264.
6. Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, Cushman M, Moll S, Kessler CM, Elliott CG, Paulson R, Wong T, Bauer KA, Schwartz BA, Miletich JP, Bounameaux H, Glynn RJ; PREVENT Investigators. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med. 2003 Apr 10;348(15):1425-34.
7. Schulman S, Granqvist S, Holmström M, Carlsson A, Lindmarker P, Nicol P, Eklund SG, Nordlander S, Lärfars G, Leijd B, Linder O, Loogna E. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group. N Engl J Med. 1997 Feb 6;336(6):393-8.
8. Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, Turpie AG, Green D, Ginsberg JS, Wells P, MacKinnon B, Julian JA. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med. 1999 Mar 25;340(12):901-7. Erratum in: N Engl J Med 1999 Jul 22;341(4):298.
9. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schu++nemann HJ. Executive Summary Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. CHEST Journal 2012;141(2_suppl):7S-47S.

10. Caprini JA, Tapson VF, Hyers TM et al. Treatment of venous thromboembolism: Adherence to guidelines and impact of physician knowledge, attitudes, and beliefs. Journal of Vascular Surgery 2005;42(4):726-733.
11. Ganz DA, Glynn RJ, Mogun H, Knight EL, Bohn RL, Avorn J. Adherence to guidelines for oral anticoagulation after venous thrombosis and pulmonary embolism. J Gen Intern Med 2000;15(11):776-781.
12. Tapson VF, Hyers TM, Waldo AL et al. Antithrombotic therapy practices in US hospitals in an era of practice guidelines. Arch Intern Med 2005;165(13):1458-1464.
13. Williams C, Koo J, Hass J. Evaluation of the Management of Acute Venous Thromboembolism and Its Outcomes: One Institution's Experience. P T 2008;33(2):107-117.
14. Erkens PM, ten Cate H, Büller HR, Prins MH. Benchmark for time in therapeutic range in venous thromboembolism: a systematic review and meta-analysis. PLoS One. 2012;7(9):e42269.
15. Veeger N, Piersma-Wichers M, Tijssen JG, Hillege HL, van der Meer J. Individual time within target range in patients treated with vitamin K antagonists: main determinant of quality of anticoagulation and predictor of clinical outcome: a retrospective study of 2300 consecutive patients with venous thromboembolism. Br J Haematol. 2005;128:513–519.
16. Mantha S, Ansell J. Indirect comparison of dabigatran, rivaroxaban, apixaban and edoxaban for the treatment of acute venous thromboembolism. J Thromb Thrombolysis. 2015 Feb;39(2):155-65.
17. Agnelli G, Buller HR, Cohen A et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369(9):799-808.
18. Bauersachs R, Berkowitz SD, Brenner B et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363(26):2499-2510.
19. Buller HR, Prins MH, Lensin AW et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366(14):1287-1297.
20. Schulman S, Kearon C, Kakkar AK et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 2009;361(24):2342-2352.
21. Humedica. Humedica Life Sciences: Detailed Clinical Data. Humedica 2013; Available at: URL: http://www.humedica.com/solutions/life-sciences/detailed-clinical-data/. Accessed June 21, 2016.
22. Humedica. Humedica. Humedica Life Sciences 2012; Available at: URL: http://www.humedica.com/solutions/lifesciences.html. Accessed June 21, 2016.
23. Yeh C, Gross P, Weitz J. Evolving use of new oral anticoagulants for treatment of venous thromboembolism. Blood 2015; 124(7): 1020-1028.
24. Schneeweiss S, Gagne JJ, Glynn RJ, et al. Assessing the comparative effectiveness of newly marketed medications: methodological challenges and implications for drug development. Clin Pharmacol Therapeut 2011; 90:777-90
25. Schoof N, Schnee J, Schneider G, Gawlik M, Zint K, Clemens A, Bartels DB. Characteristics of patients with non-valvular atrial fibrillation using dabigatran or warfarin in the US. Curr Med Res Opin. 2014 May;30(5):795-804.

14. LIST OF SOURCE TABLES AND FIGURES

Not applicable