NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Hospital Readmissions Among Nonvalvular Atrial Fibrillation Patients Treated with Oral Anticoagulants in the U.S.
Protocol number	B0661122
Protocol version identifier	1
Date of last version of protocol	July 12, 2018
EU Post Authorisation Study (PASS) Register Number	
Medicinal Product	Apixaban
Research question and objectives	Primary research question: What is the frequency of readmission for major bleeding (MB) within 1 month after an index hospitalization for nonvalvular atrial fibrillation (NVAF) patients treated with apixaban, dabigatran, rivaroxaban, or warfarin? Primary objective: • To evaluate and compare 1-month MB-related readmission rates of hospitalized NVAF patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban Secondary objectives: ○ To evaluate and compare 1-month all-cause readmission rates of hospitalized NVAF patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban ○ To determine average hospital length of stay (LOS) and costs associated with MB-related and all-cause readmissions occurring within 1 month of initial hospitalizations of hospitalized NVAF patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban Exploratory objectives:

	• To describe 1-month stroke-related readmission rates of hospitalized NVAF patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban • To describe average hospital LOS and costs associated with stroke-related readmissions occurring within 1 month of initial hospitalizations of hospitalized NVAF of patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban • To describe readmission rates, hospital LOS and costs associated with all-cause, MB-related and stroke-related readmissions occurring within 3 months of initial hospitalizations of hospitalized NVAF of patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AF	Atrial Fibrillation
AFL	Atrial Flutter
CCI	Charlson Comorbidity Index
$CHADS_2$	Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke
$CHADS_2$-VASc	Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category
DOAC	Direct-acting Oral Anticoagulant
HAS-BLED	Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratios, Elderly, Drugs/Alcohol
HIPAA	Health Insurance Portability and Accountability Act
ICD-9 CM	International Classification of Diseases, 9th Revision
ICD-10 CM	International Classification of Diseases, 10th Revision
MB	Major Bleeding
NVAF	Nonvalvular Atrial Fibrillation
OAC	Oral Anticoagulant
PSM	Propensity Score Matching

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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3. ABSTRACT

Title: Hospital Readmissions Among Nonvalvular Atrial Fibrillation Patients Treated with Oral Anticoagulants in the U.S.

Version: 1
Date of Protocol: March 26, 2018
Author: Jay Lin, PhD, MBA, Novosys Health; Christine L. Baker, JD, MPH, Pfizer

Rationale and background: Hospital readmission rates are a critical concern in the U.S. and in October of 2012 the Hospital Readmissions Reduction Program was implemented by the Centers for Medicare and Medicaid Services (CMS) to reduce the frequency of readmission among Medicare patients. It has therefore become increasingly important to examine hospital readmission rates and the factors associated with readmission. Although, readmission rates of NVAF patients have been studied to some extent in regard to all-cause readmissions, little information exists in the published literature on bleeding-related readmissions. We previously conducted an early evaluation that investigated rates of all-cause and bleeding-related readmissions among NVAF patients treated with dabigatran, rivaroxaban, and apixaban (January 1, 2012 through March 31, 2014). This current analysis will be a follow-up of our earlier assessment and will include in addition to NVAF patients treated with DOACs,patients treated with warfarin. Patients hospitalized for NVAF and treated with OACs will be identified from January 1, 2013 through June 30, 2017.

Research question: What is the frequency of readmission for major bleeding (MB) within 1 month after an index hospitalization for nonvalvular atrial fibrillation (NVAF) for patients treated with apixaban, dabigatran, rivaroxaban, or warfarin?

Note: we anticipate that the sample size of patients treated with edoxaban is low and thus do not include edoxaban in this study evaluation. This is consistent with previous alliance NVAF studies.

Objectives:

Primary objective:
- To evaluate and compare 1-month MB-related readmission rates of hospitalized NVAF patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban

Secondary objectives:
- To evaluate and compare 1-month all-cause readmission rates of hospitalized NVAF patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban
- To determine average hospital length of stay (LOS) and costs associated with MB-related and all-cause readmissions occurring within 1 month of initial hospitalizations of hospitalized NVAF patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban

Exploratory objectives:

- To describe 1-month stroke-related readmission rates of hospitalized NVAF patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban
- To describe average hospital LOS and costs associated with stroke-related readmissions occurring within 1 month of initial hospitalizations of hospitalized NVAF of patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban
- To describe readmission rates, hospital LOS and costs associated with all-cause, MB-related and stroke-related readmissions occurring within 3 months of initial hospitalizations of hospitalized NVAF of patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban

Study design: The study will be a retrospective cohort analysis using the Premier Hospital database. The overall study period will be from January 1, 2012 through September 30, 2017, to allow for a 1-month follow-up period for observation of readmissions.

Population: Adult patients (age ≥18 years) hospitalized for NVAF, based on a primary or secondary discharge diagnosis code indicating NVAF, will be identified from the Premier Hospital database between January 1, 2013 and June 30, 2017. Patients who received apixaban, dabigatran, rivaroxaban, or warfarin during any time of the hospitalization (from admission to discharge) will be identified and grouped into study cohorts based on the oral anticoagulant (OAC) initiated. The first of such NVAF hospitalizations will be defined as the index hospitalization. Patients with more than one type of OAC drug usage during the index hospitalizations will be excluded so that patients can be exclusively assigned into each of the OAC patient cohorts.

Variables: Demographic, patient clinical characteristics, hospital characteristics, and key anticoagulant treatment-related information will be measured during the index hospitalization of NVAF patients. Other clinical characteristics (e.g. prior bleeding) of NVAF patients will be measured during a 12-month baseline period. The proportions of patients treated with apixaban, dabigatran, rivaroxaban, and warfarin that have MB-related, all-cause, and stroke-related readmissions that occur within 1 month of discharge of their initial hospitalization for NVAF will be evaluated. Hospital LOS and associated costs of MB-related and all-cause readmissions will be determined and compared between the other OAC cohorts and the apixaban cohort. Hospital cost data from the Premier database will reflect the hospital perspective (cost occurred to hospitals). Hospital LOS and associated costs of stroke-related readmissions will be evaluated by descriptive statistics as an exploratory analysis. Readmission rates, hospital LOS and costs associated with all-cause, MB-related and stroke-related readmissions occurring within 3 months of initial hospitalizations of hospitalized NVAF of patients will be evaluated by descriptive statistics as an exploratory analysis.

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

Study size: The preliminary data evaluation of the Premier database indicated that there are at least 30,000 patients for each of OAC cohort during the study period described for this study. With a two-sided test, an alpha-level of 0.05, and a 1:1 ratio of the comparison cohorts, and the assumed one-month MB-related readmission rate of 1.4%, and the assumed MB-related readmission rate difference of 0.5% between cohorts treated with other OACs vs. apixaban, we have estimated the following power calculation.

Power Calculation		
Nominal Power	**Actual Power**	**N Total-One Arm**
0.7	0.7	11,226
0.75	0.75	12,622
0.8	0.8	14,274
0.85	0.85	16,328
0.9	0.9	19,108
0.95	0.95	23,630

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

Data analysis: Means ± standard deviations, and medians will be provided for continuous variables. Numbers and percentages will be provided for dichotomous and polychotomous variables. Bivariate comparisons of baseline patient and hospital characteristics and readmission measurements will be provided, with appropriate tests (e.g., ANOVA test, chi-square test) used based on the distribution of the measure. A propensity score matching (PSM) 1:1 technique will be used to control for confounders when comparing each of the OAC cohorts vs. the apixaban cohort. A logistic regression analysis will be carried out on the matched patient cohorts to further evaluate the potential impact of treatment with the different OACs vs. treatment with apixaban on 1-month MB-related and all-cause readmissions. Only the index drug will be the covariate, since other patient characteristics are expected to be similar already after the PSM. Since the patient sample size attribution in the PSM process is not known, if the population sizes are not sufficient after the PSM attrition, a multivariable logistic regression analysis will be carried out to assess the potential impact of treatment with the different OACs compared to treatment with apixaban on 1-month MB-related and all-cause readmissions, separately. The independent covariates in the regression analyses will include key patient demographics and hospital characteristics. The final list of such covariates will be determined with inputs from the Pfizer team. Additionally, we will carry out a two-part model analysis and a generalized linear model with log transformation and gamma distribution to examine the impact of treatment with the 3 different OACs vs. apixaban on MB-related and all-cause hospital readmission costs. Measurements related to exploratory objectives will be analyzed using descriptive statistics. All data analysis will be executed using statistical software SAS version 9.4.

Milestones:

Milestone	Planned date
Draft study protocol	April 6, 2018
Final study protocol	
Registration in the EU PAS register	
Start of data analysis	
End of data analysis	
Final study report	

4. AMENDMENTS AND UPDATES

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

5. MILESTONES

Milestone	Planned date
Draft study protocol	April 6, 2018
Final study protocol	
Registration in the EU PAS register	
Start of data analysis	
End of data analysis	
Final study report	

6. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) is a cardiac rhythm disorder that is predominately nonvalvular (NVAF). It becomes increasingly more prevalent as people age and is associated with up to a 5-fold higher stroke risk in the U.S.[1,2] Taking into consideration the growing elderly population in the U.S., the number of persons with NVAF is estimated to double or possibly triple by 2050.[1,2] Consequently, the economic burden of NVAF, largely related to hospitalizations, is also predicted to increase from an estimated $13.9 billion annually in 2010 to nearly $30 billion annually by 2050.[3]

Patients with NVAF have been reported to have high rates of hospital readmission.[4,5] A retrospective database analysis of 8,035 AF and AF flutter (AFL) patients between 2007 and 2008 reported that 38% of AF/AFL patients were readmitted to the hospital for all causes within 12 months after discharge, with the highest proportion occuring within the first 1 month after discharge.[4] This study also found that readmissions for AF and AFL had longer hospital stays and were more costly than the initial hospitalizations.[4] A second study of 6,439 NVAF patients reported an all-cause 1-month readmission rate of 18% and that predictors of readmission included longer initial hospital length of stay, higher Charlson Comorbidity Index score, and hospital admission via the emergency room.[5]

Hospital readmission rates are a critical concern in the U.S. and in October of 2012 the Hospital Readmissions Reduction Program was implemented by the Centers for Medicare and Medicaid Services (CMS) to reduce the frequency of readmission among Medicare patients.[6] This program involves assigning financial penalties to hospitals with readmission rates considered excessive.[6] In 2013, CMS reported that two-thirds of hospitals in the U.S. received penalties totaling ~$280 million and these penalties are expected to increase in the upcoming years.[6] It has therefore become increasingly important to examine hospital readmission rates and the factors associated with readmission. Although, readmission rates of NVAF patients have been studied to some extent in regard to all cause readmissions (most

recent patient data from 2007 to 2008), little information exists in the published literature on bleeding-related readmissions. In the real-world setting bleeding is a significant burden healthwise and economic wise and represents a critical target for improving the quality of care of NVAF patients. In clinical trials NVAF patients treated with the different DOACs differed in bleeding rates and the DOACs with lower bleeding risk have potentially a greater likelihood of improving the anticoagulation management of NVAF patients in the real-world setting where bleeding rates are higher than observed in the clinical trial setting.[7-10] We previously conducted an early evaluation that investigated rates of all-cause and bleeding-related hospital readmissions among NVAF patients treated with dabigatran, rivaroxaban, and apixaban (January 1, 2012 through March 31, 2014).[11] In this early analysis of 74,730 patients identified from the Premier Hospital database, after controlling for differences in patient characteristics, compared with patients who received apixaban during their index hospitalizations, the odds of bleeding-related hospital readmissions were significantly greater by 1.4-fold ($p<0.01$) for patients who received rivaroxaban and 1.2-fold ($p=0.16$) numerically trending greater for patients who received dabigatran. This current analysis will be a follow-up of our earlier assessment and will include patients treated with warfarin in addition to NVAF patients treated with DOACs. Recent real-world evidence has suggested that unmeasured or unmeasurable secular trends in prescribing patterns may contribute to differential outcomes observed with DOACs.[12,13] For this study, patients hospitalized for NVAF and treated with OACs will be identified from January 1, 2013 through June 30, 2017, a time period in which dabigatran, rivaroxaban, and apixaban were all available, and 1- and 3-month readmission outcomes will be evaluated.

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

7. RESEARCH QUESTION AND OBJECTIVES

The study will address the following primary research question: What is the frequency of readmission for major bleeding (MB) within 1 month after an index hospitalization for NVAF patients treated with apixaban, dabigatran, rivaroxaban, or warfarin?

- The primary objective of the study is to evaluate and compare 1-month MB-related readmission rates of hospitalized NVAF patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban.
- The secondary objectives are:
    - To evaluate and compare 1-month all-cause readmission rates of hospitalized NVAF patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban
    - To determine average hospital length of stay (LOS) and costs associated with MB-related and all-cause readmissions occurring within 1 month of initial hospitalizations of hospitalized NVAF patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban

Exploratory objectives:

- To describe 1-month stroke-related readmission rates of hospitalized NVAF patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban
- To describe average hospital LOS and costs associated with stroke-related readmissions occurring within 1 month of initial hospitalizations of hospitalized NVAF of patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban
- To describe readmission rates, hospital LOS and costs associated with all-cause, MB-related and stroke-related readmissions occurring within 3 months of initial hospitalizations of hospitalized NVAF of patients treated with dabigatran, rivaroxaban, or warfarin vs. apixaban

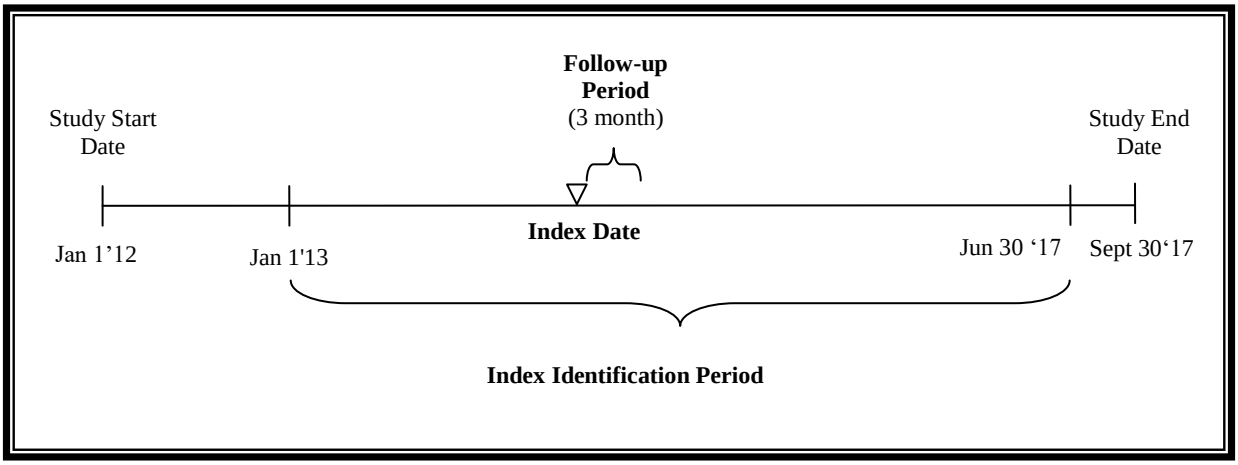
8. RESEARCH METHODS

8.1. Study design

The study will be a retrospective cohort analysis using the Premier Hospital database. The overall study period will be from January 1, 2012 through September 30, 2017, to allow for a 1 month follow up period for observation of readmissions and a 1-year baseline observation period. Adult patients (age ≥18 years) hospitalized for NVAF, based on a primary or secondary discharge diagnosis code indicating NVAF, will be identified from the Premier Hospital database between January 1, 2013 and June 30, 2017. Patients who received apixaban, dabigatran, rivaroxaban, or warfarin during any time of the hospitalization (from admission to discharge) will be identified and grouped into study cohorts based on the OAC initiated. The first of such NVAF hospitalizations will be defined as the index hospitalization. Patients with more than one type of OAC drug usage during the index hospitalizations will be excluded so that patients can be exclusively assigned into each OAC patient cohorts. Demographic, patient clinical characteristics, hospital characteristics, and key anticoagulant treatment-related information will be measured during the index hospitalization of NVAF patients. Other clinical characteristics (e.g. prior bleeding) of NVAF patients will be measured during a 12-month baseline period. The proportions of patients treated with apixaban, dabigatran, rivaroxaban, and warfarin that have MB-related, all-cause, and stroke-related readmissions that occur within 1 month of discharge of their initial hospitalization for NVAF will be evaluated. Hospital LOS and associated costs of MB-related, all-cause, and stroke-related readmissions will be determined and compared between the other OAC cohorts and the apixaban cohort.

Note: We anticipate that the sample size of patients treated with edoxaban is low and thus we have not included patients treated with edoxaban in this study evaluation. This is consistent with previous alliance NVAF studies.

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



8.2. Setting

Adult patients (age ≥18 years) hospitalized for NVAF, based on a primary or secondary discharge diagnosis code indicating NVAF, will be identified from the Premier Hospital database between January 1, 2013 and June 30, 2017. Patients who received apixaban, dabigatran, rivaroxaban, or warfarin during any time of the hospitalization (from admission to discharge) will be identified and grouped into study cohorts based on the OAC initiated. The first of such NVAF hospitalizations will be defined as the index hospitalization, with the corresponding hospital discharge date as the index date.

8.2.1. Inclusion criteria

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

- Have a hospital discharge ICD-9-CM code of 427.31 or 427.32 (and corresponding ICD-10 codes) indicating a primary or secondary diagnosis of AF identified from the Premier Hospital database between January 1, 2013 and September 30, 2017.
- Received any of the OACs, apixaban, dabigatran, rivaroxaban, or warfarin during any time of the hospitalization from admission to discharge
- Have an age ≥18 years as of the initial hospitalization with an AF diagnosis

Note: All the medical codings, e.g. ICD-9, ICD-10, CPT/HCPCS codes used in the patient selection criteria are consistent with the Eliquis Harmonized Retrospective Study Protocol.

8.2.2. Exclusion criteria

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

- Had medical claims indicating one of the following conditions or procedures during the index hospitalizations or within 12 months prior to the index date:
    1. Rheumatic mitral valvular heart disease or mitral valve stenosis:

- ICD-9 diagnosis codes 394.0, 394.1, 394.2, 394.9, 396.0, 396.1, 396.8, 396.9, 424.0
- ICD-10 diagnosis codes I05.x, I08.0, I08.8, I08.9, and I34.x

2. Heart valve replacement/transplant:
   - ICD-9 diagnosis codes V422 and V433
   - ICD-10 diagnosis codes Z95.2, Z95.3, Z95.4
   - ICD-9 procedure codes 35.05-35.09, 35.20-35.28, and 35.97
   - ICD-10 procedure codes 02RFx-02RJ0KZ, 02RJ4x, 02UG3JZ, and X2RFx
3. Dialysis, kidney transplant, or end-stage chronic kidney disease:
   - ICD-9 diagnosis codes 585.6, 996.73, V45.1x, and V56.x
   - ICD-10 diagnosis codes N18.6, T82.8x8A, Z49.x, Z91.15, Z99.2
   - ICD-9 procedure codes 55.6x.
   - ICD-10 procedure codes 0TS00ZZ, 0TS10ZZ, and 0TYx.
   - Current Procedural Terminology (CPT) codes 90935, 90937, 90945, 90947, 90967 00868, 50300, 50320, 50323, 50325, 50327, 50328, 50329, 50340, 50360, 50365, and 50380
4. Venous thromboembolism (VTE):
   - Deep vein thrombosis (DVT):
     - ICD-9 diagnosis codes 451-453, 671.3, 671.4, and 671.9
     - ICD-10 diagnosis codes I80.00-I82.91, O22.3x, O22.9x, O87.1, and O87.9
   - Pulmonary embolism (PE):
     - ICD-9 diagnosis codes 415.1, 673.2, and 673.8
     - ICD-10 diagnosis codes I26.x, O88.2x, O88.8x, T80.0XXA, T81.718A, T81.72XA, T82.817A, and T82.818A
5. Reversible AF:
   - Pericarditis:
     - ICD-9 diagnosis codes 006.8, 017.9, 036.41, 074.21, 093.81, 098.83, 115.93, 390, 391, 392.0, 393, 411.0, 420.90, 420.91, 420.99, 423.0, 423.1, 423.2, 423.8, and 423.9
     - ICD-10 diagnosis codes A06.3, A06.8x, A17.83, A17.9, A18.82, A18.84, A18.89, A39.53, A52.06, A54.83, B33.23, B39.9, I00-I02.0, I09.2, I24.1, I30.x, I31.0, I31.1, I31.2, I31.3, I31.8, I31.9, I32
   - Hyperthyroidism or thyrotoxicity:
     - ICD-9 diagnosis codes 242.0, 242.1, 242.2, 242.3, 242.4, 242.8, and 242.9
     - ICD-10 diagnosis codes E05.x

    - Acute myocardial infarction:
        - ICD-9 diagnosis codes 410.x
        - ICD-10 diagnosis codes I21.01-I21.4, and I22.x
    - Acute myocarditis:
        - ICD-9 diagnosis codes 422.x
        - ICD-10 diagnosis codes A18.84, I40.x, and I41

- Had medical claims indicating a hip or knee replacement surgery during the index hospitalizations or within a 6-week period prior to the index date
    1. ICD-9 diagnosis codes V43.64 and V43.65
    2. ICD-10 diagnosis codes Z96.64x and Z96.65x
    3. ICD-9 procedure codes 81.40, 81.51, 81.52, 81.53, 81.54, and 81.55
    4. ICD-10 procedure codes 0SQ9x, 0SQBx, 0SR9019-0SR904Z, 0SR907Z, 0SR90Jz, 0SR90KZ, 0SRAx, 0SRB019-0SRB04Z, 0SRB07Z, 0SRB0Jx, 0SRB0KZ, 0SRC07Z, 0SRC0Jx, 0SRC0KZ, 0SRC0Lx, 0SRD07Z, 0SRD0Jx, 0SRD0KZ, 0SRD0Lx, 0SREx, 0SRRx-0SRWx, 0SW90JZ, 0SW93JZ, 0SW94JZ, 0SWA0JZ, 0SWA3JZ, 0SWA4JZ, 0SWB0JZ, 0SWB3JZ, 0SWB4JZ, 0SWC0JC, 0SWC0JZ, 0SWC3JC, 0SWC3JZ, 0SWC4JC, 0SWC4JZ, 0SWD0JC, 0SWD0JZ, 0SWD3JC, 0SWD3JZ, 0SWD4JC, 0SWD4JZ, 0SWE0JZ, 0SWE3JZ, 0SWE4JZ, 0SWR0JZ, 0SWR3JZ, 0SWR4JZ, 0SWS0JZ, 0SWS3JZ, 0SWS4JZ, 0SWT0JZ, 0SWT3JZ, 0SWT4JZ, 0SWU0JZ, 0SWU3JZ, 0SWU4JZ, 0SWV0JZ, 0SWV3JZ, 0SWV4JZ, 0SWW0JZ, 0SWW3JZ, and 0SWW4JZ.
- Had medical claims indicating pregnancy at any time during the study period
    1. ICD-9 diagnosis codes 630-679, V22, V23, V24, V27, V28, V61.6, V61.7, 792.3, and 796.5
    2. ICD-10 diagnosis codes A34, O00.00-O9A.53, Z33.1-Z37.9, Z39.x, and Z64.0
    3. ICD-9 procedure codes 72-75.9
    4. ICD-10 procedure codes 0DQPx-0DQQ8ZZ, 0DQRx, 0JCBx, 0Q82x, 0Q83x, 0TQBx, 0TQDx, 0U7C7ZZ, 0UCG0ZZ, 0UCG3ZZ, 0UCG4ZZ, 0UCM0ZZ, 0UJD7ZZ, 0UQ9x, 0UQCx, 0UQGx, 0UQMx, 0US90ZZ, 0US94ZZ, 0US9XZZ, 0W3Rx, 0W8NXZZ, 0WQNXZZ, 109x, 10A00ZZ, 10A03ZZ, 10A04ZZ, 10A07Z6, 10A07ZX, 10A07ZZ, 10A08ZZ, 10D0x, 10D1xZZ, 10Ex-10S0x, 10T20ZZ-10T24ZZ, 10Yx, 2Y44X5Z, 3027x, 3E030VJ, 3E033VJ, 3E040VJ, 3E043VJ, 3E050VJ, 3E053VJ, 3E060VJ, 3E063VJ, 3E0DXGC, 3E0E305-3E0E3TZ, 3E0E705, 3E0E729-3E0E7TZ, 3E0E805, 3E0E829-3E0E8TZ, 3E0P7GC, 4A0Hx, 4A0Jx, 4A1Hx, and 4A1Jx
- Received edoxaban during the index hospitalization or within 12 months prior to the index date
- Received multiple types of OACs during the index hospitalization

- Patients who died during the index hospitalizations

All the ICD-10 codes corresponding to the ICD-9 codes listed above will also be used to identify the conditions and procedures in the inclusion and exclusion criteria.

These inclusion and exclusion criteria are aligned with the Eliquis Harmonized Retrospective Study Protocol and are consistent with other previous apixaban retrospective database studies of patients with NVAF.

8.2.3. Cohorts

After applying the inclusion and exclusion criteria, eligible patients will be assigned to the following cohorts based on the OAC treatment received during index hospitalizations.

1. **Apixaban Cohort:** NVAF patients who initiated apixaban during hospitalization
2. **Dabigatran Cohort:** NVAF patients who initiated dabigatran during hospitalization
3. **Rivaroxaban Cohort:** NVAF patients who initiated rivaroxaban during hospitalization
4. **Warfarin Cohort:** NVAF patients who initiated warfarin during hospitalization

8.3. Variables

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

Table 1. Demographic Variables, Patient Clinical Characteristic Variables, and Hospital Characteristic Variables

Variable	Role	Operational definition
Age	Patient characteristic and potential confounder	Age will be defined as of the index date and used to assign patients to age groups: 18-34, 35-44, 45-54, 55-64, 65-74 and >75 years, evaluated on the index date.
Gender	Patient characteristic and potential confounder	Distribution of female and male patients and reported as count and percentage, evaluated on the index date.
Race	Patient characteristic and potential confounder	Patients with White, Black, and other/unknown race and reported as count and percentages, evaluated on the index date.
Payer Type	Patient characteristic and potential confounder	Patients with Medicare, Medicaid, commercial, and other/unknown insurance coverage and reported as counts and percentages, evaluated on the index date.
Index Hospitalization Deyo-Charlson Comorbidity Index	Patient characteristic and potential confounder	The Deyo-Charlson Comorbidity Index will be calculated for the index hospitalization .

Variable	Role	Operational definition
Baseline $CHADS_2$	Patient characteristic and potential confounder	The $CHADS_2$ score evaluated from the available records of the index hospitalization and baseline period will be used to estimate stroke risk. The maximum score is 6. $CHADS_2$ scores: 0, 1,2, ≥3
Baseline $CHADS_2$-VASc Score	Patient characteristic and potential confounder	The $CHADS_2$VASc score evaluated from the available records of the index hospitalization and baseline period will be used to estimate stroke risk. The maximum score is 9. $CHADS_2$-VASc scores: 0, 1,2, ≥3
Baseline HAS-BLED Score	Patient characteristic and potential confounder	HAS-BLED score evaluated from the available records of the index hospitalization and baseline period will be used to estimate the risk of MB for patients.
Baseline Prior Bleed	Patient characteristic and potential confounder	Patients with a bleeding diagnosis on hospital records during the baseline period and reported as count and percentage. Bleeding diagnosis will have a breakdown of any, gastrointestinal, and intracranial.
Index Stroke/Transient Ischemic Attack (TIA)	Patient characteristic and potential confounder	Patients with a stroke/TIA diagnosis on hospital records during their index hospitalization and reported as count and percentage.
Baseline Prior Stroke/TIA	Patient characteristic and potential confounder	Patients with a stroke/TIA diagnosis on hospital records during the baseline period and reported as count and percentage.
Index Hospitalization Congestive Heart Failure	Patient characteristic and potential confounder	Patients with a diagnosis on hospital records for congestive heart failure in the index hospitalization and reported as count and percentage.
Index Hospitalization Diabetes	Patient characteristic and potential confounder	Patients with a diagnosis on hospital records for diabetes in the index hospitalization and reported as count and percentage.
Index Hospitalization Hypertension	Patient characteristic and potential confounder	Patients with a diagnosis on hospital records for hypertension in the index hospitalization and reported as count and percentage.
Index Hospitalization Peripheral Vascular Disease	Patient characteristic and potential confounder	Patients with a diagnosis on hospital records for peripheral vascular disease in the index hospitalization and reported as count and percentage.

Variable	Role	Operational definition
Index Hospitalization Pulmonary Disease	Patient characteristic and potential confounder	Patients with a diagnosis on hospital records for pulmonary disease in the index hospitalization and reported as count and percentage.
Index Hospitalization DOAC Dose Strength	Patient characteristic and potential confounder	Patients with apixaban, dabigatran, and rivaroxaban dose strengths of high, low, and unknown during the index hospitalization and reported as count and percentage.
Other Anticoagulants During Index Hospitalization	Patient characteristic and potential confounder	Patients who receive enoxaparin, dalteparin, tinzaparin heparin, and fondaparinux during the index hospitalization and reported as count and percentage.
Index Hospital Geographic Region	Patient characteristic and potential confounder	East North Central, East South Central, Middle Atlantic, Mountain, New England, Pacific, South Atlantic, West North Central, West South Central. Reported as count and percentage
Index Hospital Urban/Rural Status	Patient characteristic and potential confounder	Rural, urban- reported as count and percentage
Index Hospital Teaching Status	Patient characteristic and potential confounder	Yes/No- reported as count and percentage
Index Hospital Bed Size	Patient characteristic and potential confounder	0-99, 100-199, 200-200, 300-399, 400-499, ≥500- reported as count and percentage

Table 2. Outcome Measurements: Readmissions and Associated LOS and Cost/Charges

Variable	Role	Operational definition
MB-related Readmission	Outcome	Defined as readmissions with a bleeding diagnosis at the first position of the hospital discharge diagnosis codes. Number and percentage of patients with MB-related readmissions within 1 or 3 months of initial NVAF hospitalization in study cohorts will be reported. Associated LOS and cost for MB-related readmissions will be determined. Likelihood of first MB-related readmission was assessed for each OAC cohort vs. the apixaban cohort. LOS and hospital cost per patient for cohorts will be estimated and compared by multivariable regression analysis. Measurements for 3-month readmissions will be evaluated using descriptive statistics as an exploratory analysis.
All-cause Readmission	Outcome	Number and percentage of patients with all-cause readmissions within 1 or 3 months of initial NVAF hospitalization in study cohorts will be reported. Associated LOS and cost for all-cause readmissions will be determined. Likelihood of first all-cause readmission was assessed for each OAC cohort vs. the apixaban cohort. LOS and hospital cost per patient for cohorts will be estimated and compared by multivariable regression analysis. Measurements for 3-month readmissions will be evaluated using descriptive statistics as an exploratory analysis.
Stroke-related Readmission	Outcome	Defined as readmissions with a stroke diagnosis at the first position of the hospital discharge diagnosis codes. Cases will be excluded if traumatic brain injury (ICD-9: 800-804, 850-854) was present during hospitalization. Number and percentage of patients with stroke-related readmissions within 1 or 3 months of initial NVAF hospitalization in study cohorts will be reported. Associated LOS and cost for stroke-related readmissions will be determined. Measurements for stroke-related readmissions will be evaluated using descriptive statistics as an exploratory analysis.

8.4. Data sources

The data source is the Premier Hospital database, which provides hospital billing information on a patient's hospital stay as well as information on ICD-9 and ICD-10 codes and current procedural terminology codes. Specifically, the database contains a date-stamped log of all billed items, including medications, laboratory, diagnostic, and therapeutic services, and primary and secondary diagnoses for each patient's hospitalization. Identifier-linked files provide demographic and payer information. Detailed service-level information for each

hospital day is recorded and this includes details on medication received. Billed items are standardized by the database vendor after the hospital both reviews and consents to the items.

8.5. Study size

The preliminary data evaluation of the Premier database indicated that there are at least 30,000 patients for each of OAC cohort during the study period described for this study. With a two-sided test, an alpha-level of 0.05, and a 1:1 ratio of the comparison cohorts, and the assumed one-month MB-related readmission rate of 1.4%, and the assumed MB-related readmission rate difference of 0.5% between cohorts treated with other OACs vs. apixaban, we have estimated the following power calculation.

Table 3. Power Calculation

Power Calculation		
Nominal Power	**Actual Power**	**N Total-One Arm**
0.7	0.7	11,226
0.75	0.75	12,622
0.8	0.8	14,274
0.85	0.85	16,328
0.9	0.9	19,108
0.95	0.95	23,630

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

8.6. Data management

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

8.7. Data analysis

Means ± standard deviations, and medians will be provided for continuous variables. Numbers and percentages will be provided for dichotomous and polychotomous variables. Bivariate comparisons of baseline patient and hospital characteristics and readmission measurements will be provided, with appropriate tests (e.g., ANOVA test, chi-square test) used based on the distribution of the measure. A propensity score matching (PSM) 1:1 technique will be used to control for confounders when comparing each of the OAC cohorts vs. the apixaban cohort. A logistic regression analysis will be carried out on the matched patient cohorts to further evaluate the potential impact of treatment with the different OACs vs. treatment with apixaban on 1-month MB-related and all-cause readmissions. Only the index drug will be the covariate, since other patient characteristics are expected to be similar already after the PSM. Since the patient sample size attribution in the PSM process is not known, if the population sizes are not sufficient after the PSM attrition, a multivariable logistic regression analysis will be carried out to assess the potential impact of treatment with the different OACs compared to treatment with apixaban on 1-month MB-related and all-

cause readmissions, separately. The independent covariates in the regression analyses will include key patient demographics and hospital characteristics. The final list of such covariates will be determined with inputs from the Pfizer team. Additionally, we will carry out a two-part model analysis and a generalized linear model with log transformation and gamma distribution to examine the impact of treatment with the 3 different OACs vs. apixaban on MB-related and all-cause hospital readmission costs. Measurements related to exploratory objectives will be analyzed using descriptive statistics. All data analysis will be executed using statistical software SAS version 9.4.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

8.8. Quality control

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

8.9. Strengths and limitations of the research methods

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

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

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

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

9.2. Patient withdrawal

Not applicable.

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

IRB/IEC review is not required.

9.4. Ethical Conduct of the Study

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

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study includes unstructured data (e.g., narrative fields in the database) that will be converted to structured (i.e., coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual AE reports.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

COMMUNICATION OF ISSUES

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

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

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13. LIST OF TABLES

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14. LIST OF FIGURES

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

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Table 1. ICD-9 and ICD-10 Codes for Clinical Conditions

Diagnosis Codes