NON-INTERVENTIONAL STUDY PROTOCOL

Study Information

Title	Predictors of Treatment and the Comparative Clinical and Economic Outcomes among Non-Valvular Atrial Fibrillation Patients Treated versus Untreated with Oral Anticoagulant Therapy
Protocol number	B0661142
Protocol version identifier	1.0
Date of last version of protocol	13 June 2019
EU Post Authorization Study (PAS) Register Number	
Medicinal Product	Apixaban
Research question and objectives	**Primary Objective:** 1. Estimate patients ever-treated and never-treated with oral anticoagulants (OACs) and the predictors of OAC treatment among elderly Medicare non-valvular atrial fibrillation (NVAF) population. **Secondary Objectives:** 1. Analyze high-risk patient subgroups, such as CHA_2DS_2-VASc score and age subgroups, for the primary objectives. 2. Compare the risk of major bleeding and major bleeding-related costs among elderly patients treated versus untreated with OACs in the Medicare NVAF population. 3. Compare the risk of stroke/systemic embolism (SE) and stroke/SE-related costs among elderly patients

Do not distribute for purposes outside of specific activities related to development of FDAMAs114 compliant pieces. Content within this protocol is subject to change based on communication planning and input by external review committees.

	treated versus untreated with OACs in the Medicare NVAF population. 4. Compare the risk of death among elderly patients treated versus untreated with OACs in the Medicare NVAF population 5. Compare the all-cause health care costs among elderly patients treated versus untreated with OACs in the Medicare NVAF population.
Author	Allison Keshishian, MPH Phone: 734-222-5426 Email: akeshishian@statinmed.com Patrick Hlavacek, MPH, Director, HEOR Email: Patrick.Hlavacek@pfizer.com

Contents

Do not distribute for purposes outside of specific activities related to development of FDAMAs114 compliant pieces. Content within this protocol is subject to change based on communication planning and input by external review committees.

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AF	Atrial Fibrillation
CAD	Coronary Artery Disease
CCI	Charlson Comorbidity Index
$CHADS_2$	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category
CHF	Congestive Heart Failure
CI	Confidence Interval
CMS	Centers for Medicare & Medicaid Service
CPI	Consumer Price Index
DME	Durable Medical Equipment
DOACs	Direct Oral Anticoagulants
ER	Emergency Room
FFS	Fee-For-Service
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratios, Elderly, Drugs/alcohol

Abbreviation	Definition
HCPCS	Healthcare Common Procedure Coding System
HHA	Home Health Agency
HIPAA	Health Insurance Portability and Accountability Act
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IPTW	Inverse Probability Treatment Weighting
MACE	Major Adverse Cardiac Events
NI	Non-Interventional
NVAF	Non-Valvular Atrial Fibrillation
OAC	Oral Anticoagulants
PAD	Peripheral Arterial Disease
PPPM	Per Person Per Month
RCT	Randomized Controlled Trial
SE	Systemic Embolism
SNF	Skilled Nursing Facility

2. RESPONSIBLE PARTIES

Principal Investigators of the Protocol

Name, Degree(s)	Title	Affiliation	Address
Allison Keshishian, MPH	Sr. Project Manager	STATinMED Research	211 N. 4th Ave Ann Arbor, MI 48104
Qisu (Sue) Zhang, MPH	Sr. Statistical Analyst	STATinMED Research	
Lin Xie, MS, MA	Vice President, HEOR	STATinMED Research	
Daniel Wiederkehr, MPH	Sr. Director, HEOR	Pfizer	235 E 42nd St New York, New York 10017

3. ABSTRACT

Title: Predictors of Treatment and the Comparative Clinical and Economic Outcomes among Non-Valvular Atrial Fibrillation Patients Treated versus Untreated with Oral Anticoagulation Therapy

Version: 1.0

Date of Protocol: May 31, 2019

Rationale and Background: Non-valvular atrial fibrillation (NVAF) patients have a substantial risk of ischemic stroke and systemic embolism (SE). Several direct oral anticoagulants (DOACs) have been approved in recent years; clinical trials have shown them to be similar to or better than warfarin regarding the risks of stroke/SE and major bleeding.[1,2,3,4,5] Oral anticoagulant (OAC) prescription may be underutilized in AF patients at risk for stroke, and there are few data regarding OAC untreated NVAF patients in a real-world clinical setting.[6] There is no recent evidence on untreated NVAF patients in a real-world clinical setting. In addition, the modifiable and unmodifiable factors associated with non-treatment are currently unknown. The burden of NVAF is expected to increase significantly over time, particularly hospitalization and health care costs. To develop effective strategies for reducing the overall disease burden, it is critical to understand the factors related to non-treatment in NVAF patients and the associated clinical and economic outcomes.

Objectives:

Primary

1. Estimate patients ever-treated and never-treated with OACs and the predictors of OAC treatment among elderly Medicare NVAF patients.

Secondary

1. Analyze high-risk patient subgroups (eg, CHA_2DS_2-VASc and age) for the primary objectives.
2. Compare the risk of major bleeding and major bleeding-related costs among elderly patients treated versus untreated with OACs in the Medicare NVAF population.
3. Compare the risk of stroke/SE and stroke/SE-related costs among elderly patients treated versus untreated with OACs in the Medicare NVAF population.

4. Compare the risk of death among elderly patients treated versus untreated with OACs in the Medicare NVAF population.

5. Compare the all-cause health care costs among elderly patients treated versus untreated with OACs in the Medicare NVAF population.

Study Design: The study will be a longitudinal retrospective cohort analysis using the US Centers for Medicare & Medicaid Services (CMS) Medicare dataset from 01JAN2012-31DEC2016. The study will designate a 12-month baseline period prior to the identification period (01JAN2013-31DEC2016). This database only includes patients enrolled in fee-for-service (FFS) Medicare; those enrolled in managed-care plans will be excluded. Further, patient eligibility will be based on selection from the database according to the following inclusion and exclusion criteria (sections 2).

Population: Elderly patients (aged ≥65 years) will be required to have ≥1 inpatient or ≥ 2 outpatient medical claims (the 2 outpatient claims are ≥7 days apart) for AF during the identification period for the primary and secondary objectives. For the primary objective, two mutually-exclusive NVAF patient cohorts will be created: ever-treated with OAC and never-treated with OAC. For the secondary objective assessing clinical and healthcare utilization and costs, treatment status will be a time-varying covariate and ever-treated patients will contribute time-not-on-treatment to untreated effect.

For the primary and secondary objectives, the ever-treated with OAC population cohort will include newly diagnosed NVAF patients who ever initiated oral anticoagulant (OAC) treatment (apixaban, dabigatran, edoxaban, rivaroxaban, and warfarin) during the study period identified from 01JAN2013-31DEC2016. The never-treated with OAC population cohort will include newly diagnosed NVAF patients without any OAC claim from 01JAN2013-31DEC2016.

For the primary and secondary objectives, the first AF diagnosis date during the identification period will be used as the index date for both ever-treated and never-treated cohorts. Across both ever-treated and never-treated cohorts, all patients will be required to have a CHA_2DS_2-VASc≥2 and 12-months of continuous health plan enrollment, with medical and pharmacy benefits before the index date (baseline period). For the primary objective and high-risk subgroup analyses, patients will also be required to have 6-month continuous health plan enrollment, with medical and pharmacy benefits after the index date.

For the primary objective and high-risk subgroup analyses, the following patients will be excluded: an AF diagnosis any time prior to the first AF diagnosis; medical claims indicating a diagnosis or procedure for mitral valvular heart disease or heart valve replacement/transplant;

or use of OACs during the baseline period. For the secondary objective assessing effectiveness, safety, and cost outcomes, patients will be further excluded if they had any of the following: venous thromboembolism; transient AF during the baseline period; pregnancy during the study period; hip/knee replacement surgery within 6 weeks pre-index date; or follow-up period = 0 day. In addition, among patients ever treated with an OAC, those with >1 OAC prescription claim at the index date will be excluded as well.

Variables: Baseline demographic and clinical characteristics will include age, gender, race, geographic region, Medicaid dual eligibility, Part-D low income subsidy, Charlson comorbidity index (CCI), $CHADS_2$, CHA_2DS_2-VASc, HAS-BLED scores, prior bleeding/stroke events, congestive heart failure, diabetes, hypertension, chronic obstructive pulmonary disease, renal disease, myocardial infarction, dyspepsia or stomach discomfort, peripheral arterial disease, transient ischemic attack, coronary artery disease, history of falls, medication use, and index dose of DOAC. Baseline all-cause health care costs and utilization will be included.

For the primary objective and high-risk subgroup analyses, the following cohorts will be compared: a) ever-treated with OAC vs. never-treated with OAC; b) initiated with DOAC vs. never-treated with OAC cohorts; c) initiated with warfarin vs. never-treated with OAC; and d) initiated with DOACs vs. never-treated with OAC.

For the secondary objectives assessing effectiveness, safety, and costs outcomes, the following outcomes will be compared between cohort pairs (treated vs untreated, apixaban vs untreated, dabigatran vs untreated, rivaroxaban vs untreated, and warfarin vs untreated): time to stroke/SE, major bleeding, and death; medical costs related to stroke/SE and major bleeding; and all-cause health care costs and utilization.

Data Sources: The study will be conducted using Medicare Inpatient Data, Medicare Outpatient Data, the Medicare Carrier File, Medicare Part D Drug Events (PDE) Data, the Skilled Nursing Facility (SNF) File, the Home Health Agency (HHA) File, the Hospice File, the Durable Medical Equipment (DME) File, and the Medicare Denominator File.

Data Analysis: Means, medians, and standard deviations will be provided for continuous variables. Numbers and percentages will be provided for dichotomous and polychotomous variables. Bivariate comparisons of baseline characteristics and outcomes measures will be provided. Appropriate tests (eg, t-test, chi-square test) will be used, based on the distribution of the measure. Logistic regression models will be used to examine the predictors of treatment. For the secondary objectives assessing effectiveness, safety, and costs, the cumulative incidence rate for clinical outcomes (stroke/SE, major bleeding, and death) will be calculated. Inverse probability weighting (IPW) will be used to balance treatment cohorts. Cox regressions

with time-varying treatment status and marginal structural models (MSMs) will be used to compare the treatment effects, all-cause and stroke/SE and major bleeding-related health care costs. Data analysis will be executed using statistical software SAS version 9.4.

4. AMENDMENTS AND UPDATES

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

5. MILESTONES

Milestone	Planned date
Draft Protocol	10/4/2018
Descriptive Analysis	7/1/2019
Multivariate Analysis	10/1/2019
Final Report	1/20/2020

6. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) is characterized by chaotic and irregular electrical activity in the heart's upper chambers and is the most common heart dysrhythmia diagnosed in the United States.[7] AF has become more prevalent in an aging US population, and this trend is expected to increase exponentially in the coming decades.[8]

AF causes a significant financial burden, costing the US health care system approximately $26 billion dollars annually. Hospitalizations account for most of these costs (52%).[9]

Vitamin K antagonists, such as warfarin, have been the treatment of choice for anticoagulation.[10] To maximize benefits and minimize complications such as bleeding, warfarin therapy must be monitored and adjusted within a narrow therapeutic index of INR results.[11,12] Moreover, the pharmacokinetic profile of warfarin is complex due to several drug-drug and drug-food interaction complications. It is also difficult to achieve long-term stability among warfarin patients due to fluctuating INR values, which may be caused by diet, seasonal variation, alcohol consumption, or other factors.[3] The need for regular monitoring, risk of hemorrhage, and poor control of INR levels may lead to medication therapy non-adherence.[13,14]

In fact, due to its limited therapeutic index and possible drug and food interactions, physicians only prescribe warfarin to about 50% of patients for whom it is recommended.[15] Over the last several years direct oral anti-coagulants (DOACs), including apixaban, dabigatran, edoxaban, and rivaroxaban were approved in the US for stroke prevention among NVAF patients. Clinical trials have demonstrated that DOACs reduce the risk of stroke as much or more than warfarin.[16,17,18,19]

AF is often left untreated after diagnosis. Using registry data of cardiology practices in the United States, it was reported that only 55.1% of patients deemed eligible for warfarin were treated with this agent, and among whom, 35% were not treated with any antithrombotic or antiplatelet.[20] Another US study on patients of outpatient physician practices reported that 23% of NVAF patients did not receive any form of thromboprophylaxis.[21] Moreover, although OACs are recommended for patients with AF and high cardio-embolic risk (according to CHA_2DS_2-VASc scores), <50% of patients aged 80-89 years are treated with OAC.[22] This may be due to short life-expectancy, fear of bleeding, geriatric syndromes, poor general health, and the overall perception that the harm outweighs the benefits.[22] Yet untreated patients had a lower survival rate and higher association with ischemic stroke events compared to OAC treated patients.[23]

This study will estimate prevalence of newly diagnosed but untreated NVAF patients, add real-world evidence for the predictors of treatment among newly diagnosed NVAF patients. In addition, it will evaluate the risks of major bleeding, stroke/SE, and death by comparing OAC treatment versus no OAC treatment. The comparative health care costs and utilization will also be evaluated.

7. Research Question and Objectives

Primary Objective

1. Estimate patients ever-treated and never-treated with OACs and the predictors of OAC treatment among elderly Medicare NVAF patients. The following comparative cohorts will be included:
    - ❖ Ever-treated versus never-treated with OACs
    - ❖ Treated with DOACs versus never-treated with OACs
    - ❖ Treated with warfarin versus never-treated with OACs
    - ❖ Treated with DOACs versus treated with warfarin

Secondary Objectives

1. Analyze high-risk patient subgroups, including CHA_2DS_2-VASc score and age subgroups, for the primary objective. The same comparative cohorts as the primary objective will be included. The following subgroups will be examined:
    - ❖ CHA_2DS_2-VASc score subgroups: 2-3, 4-5, and ≥6
    - ❖ Age subgroups: 65-74, 75-79, and ≥80 years
2. Compare the risk of major bleeding and major bleeding-related costs among elderly patients treated versus untreated with OACs in the Medicare NVAF population. The following comparative cohorts will be included:
    - ❖ Treated versus untreated with OACs
    - ❖ Apixaban versus untreated with OACs
    - ❖ Dabigatran versus untreated with OACs
    - ❖ Rivaroxaban versus untreated with OACs
    - ❖ Warfarin versus untreated with OACs
3. Compare the risk of stroke/SE and stroke/SE-related costs among elderly patients treated versus untreated with OACs in the Medicare NVAF population. The same

comparative cohorts as secondary objective 2 will be included.

4. Compare the risk of death among elderly patients treated versus untreated with OACs in the Medicare NVAF population. The same comparative cohorts as secondary objective 2 will be included.

5. Compare the all-cause health care costs among elderly patients treated versus untreated with OACs in the Medicare NVAF population. The same comparative cohorts as secondary objective 2 will be included.

8. Research Methods

8.1. Study Design

The study will be a longitudinal retrospective cohort analysis using the US fee-for-service (FFS) Medicare database. This database contains data from inpatient departments, outpatient departments, carrier claims, reported drug events, and beneficiaries' enrollment data. The following will be determined and compared between treatment status (treated with apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin and untreated with OAC): outcomes including major bleeding, stroke/SE, and death; and health care costs and resource utilization. The overall study period will be from 01JAN2012-31DEC2016. The study will designate a 12-month baseline period prior to an index identification period (01JAN2013-31DEC2016). The date of first AF diagnosis during the study period will be assigned as the index date.

Figure 1. Study Periods for Primary and High-Risk Subgroup Objectives
(for illustration purposes only, may not be proportional)

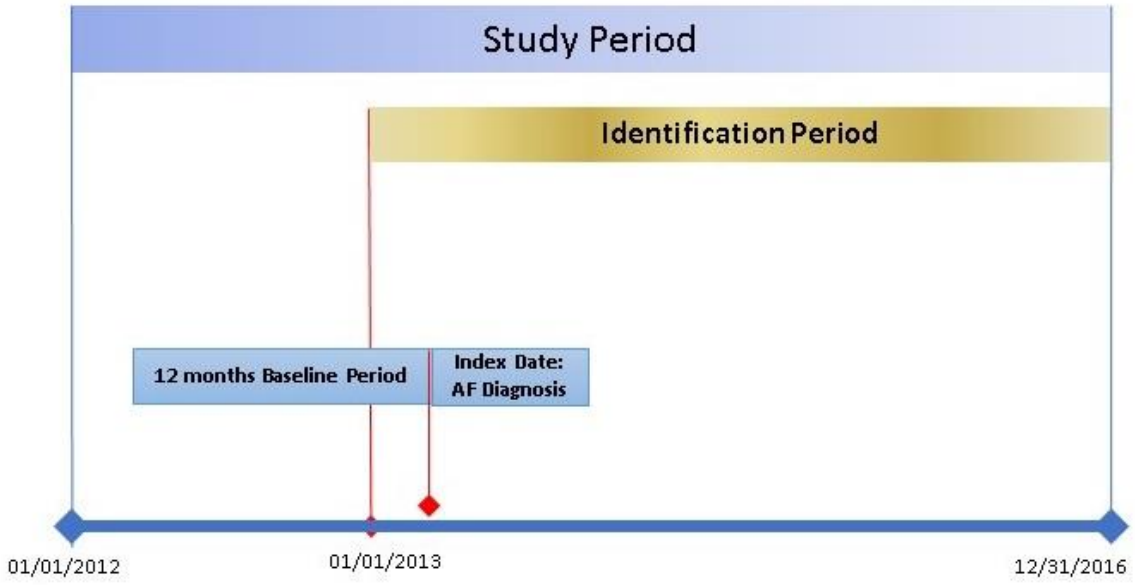


Figure 2. Study Periods for Untreated Patients in Secondary Clinical and Healthcare Cost Objectives (for illustration purposes only, may not be proportional)

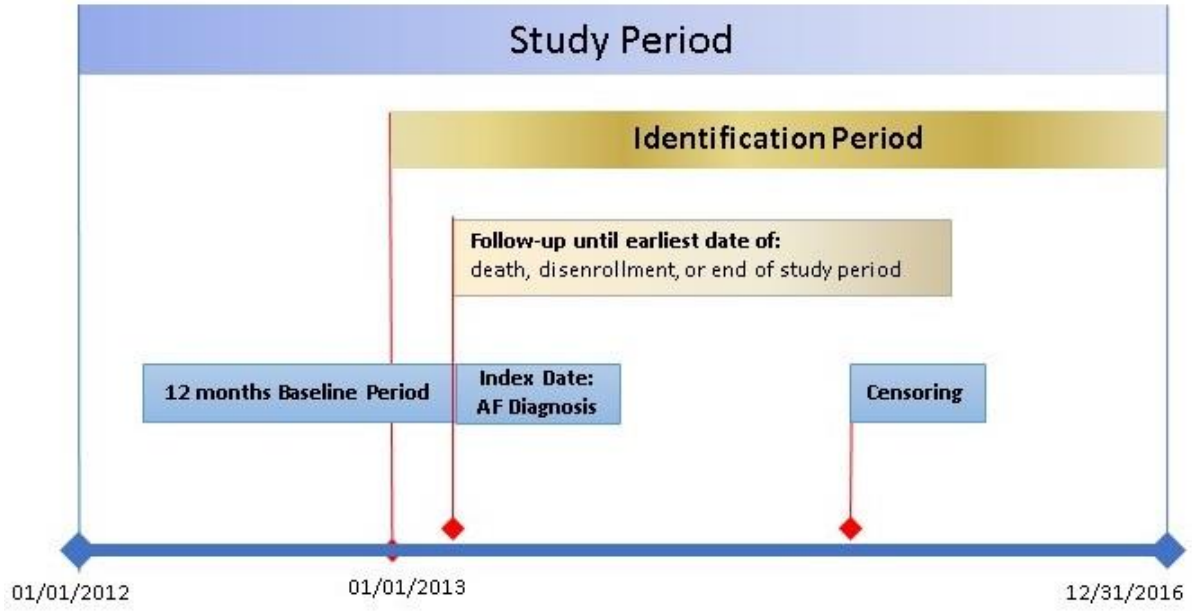
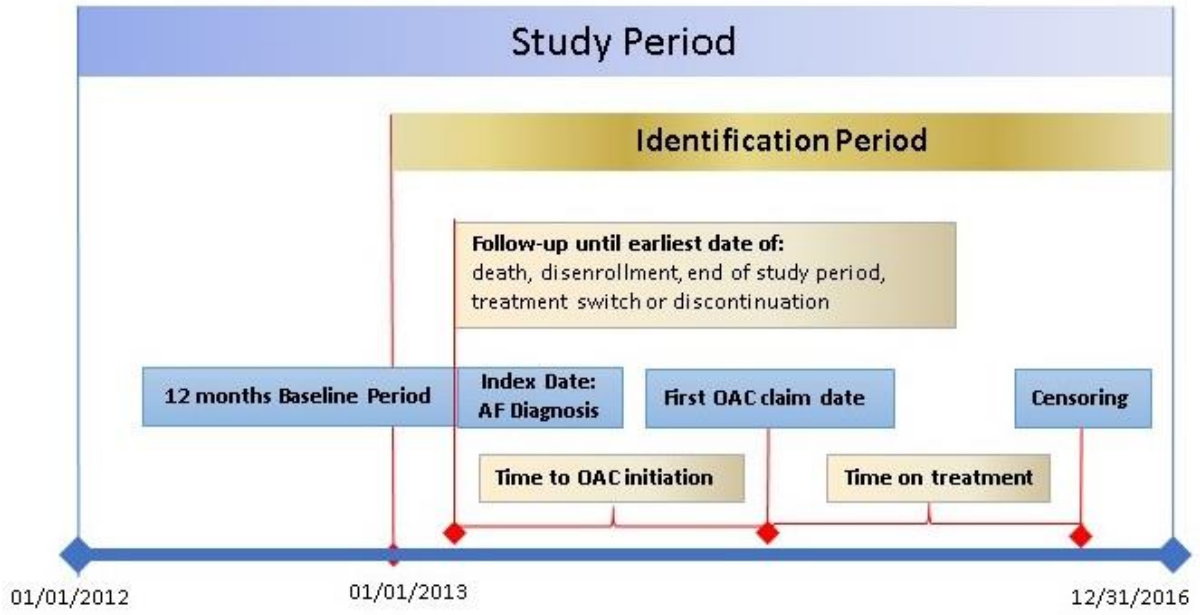


Figure 3. Study Periods for Treated Patients in Secondary Clinical and Healthcare Cost Objectives (for illustration purposes only, may not be proportional)

Do not distribute for purposes outside of specific activities related to development of FDAMAs114 compliant pieces. Content within this protocol is subject to change based on communication planning and input by external review committees.



8.2. Setting

Ever treated with OAC and never treated with OAC patients will be selected from 01JAN2013-31DEC2016. To ensure access to the patients' complete medical history, they will be required to have continuous health plan enrollment for the 12 months before the first AF diagnosis date/index date (baseline period). Patient data will be assessed from index date until the earliest of death, health plan disenrollment, treatment switch (treated patients), discontinuation (treated patients), or 31DEC2016 (end of study).

8.2.1. Primary Objective and High-Risk Subgroup Analyses

8.2.1.1. Inclusion Criteria

1) Patients had ≥1 inpatient claim or ≥2 outpatient claims (at least 7 days gap between the two outpatient claims) for AF (ICD-9-CM code 427.31; ICD-10-CM: I480-I482, I4891) during 01JAN2013-31DEC2016. The first AF diagnosis claim dates during the identification period will be designated as the index date[24];

   Note: Revised from ≥1 AF diagnoses based on literature review and clinical rationale to consolidate the diagnosis of AF.[25]

2) Patients had 12-month continuous health plan enrollment with medical and pharmacy benefits (Medicare Part A, B, and D) before the index date and 6-month continuous health

plan enrollment with medical and pharmacy benefits (Medicare parts A, B, and D) after the index date;

Note: Revised from no requirement for continuous health plan enrollment post-index date to generate comparable cohorts.[26]

3) Patients had CHA_2DS_2-VASc score ≥2 during 12 months on or before the index date;
4) Aged ≥65 years on the index date.

8.2.1.2. Exclusion Criteria

1) Exclude patients with AF diagnosis prior to the index date;
2) Exclude patients with medical claims indicating diagnosis of mitral valvular heart disease or valve replacement procedure (see Appendix) during the 12 months prior to or on the index date;
3) Exclude patients who had a pharmacy claim for apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin during the 12 months pre-index period.

8.2.2. Secondary Objectives

8.2.2.2. Additional Exclusion Criteria

1) Exclude patients with medical claims indicating a diagnosis code for venous thromboembolism (VTE; see Appendix) during the 12 months prior to or on the index date;
2) Exclude patients with medical claims indicating a diagnosis or procedure code of transient AF (see Appendix) during the 12 months prior to or on the index date;
3) Exclude patients with medical claims indicating pregnancy (see Appendix) during the study period;
4) Exclude patients with medical claims indicating hip/knee replacement surgery within 6 weeks prior to the index date;
5) Exclude patients with 0 days of follow-up;
6) Exclude patients who initiated more than one OAC treatment on the index date.

8.2.3. Cohorts

Patients eligible according to the above criteria will be assigned to the following cohorts:

1) **Ever-Treated Cohort:** NVAF Patients had ≥1 pharmacy claim for apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin from 01JAN2013-31DEC2016 on or after the first AF diagnosis
   a. **Apixaban cohort:** Patients who initiated with apixaban on or after index date
   b. **Dabigatran cohort**: Patients who initiated with dabigatran on or after index date
   c. **Edoxaban cohort:** Patients who initiated with edoxaban on or after index date. Given the small sample size, edoxaban patients will not be included in the secondary clinical and healthcare utilization and costs analyses.
   d. **Rivaroxaban cohort:** Patients who initiated with rivaroxaban on or after index date
   e. **Warfarin cohort:** Patients who initiated with warfarin on or after index date
2) **Never-Treated Cohort:** NVAF patients with no pharmacy claim for an OAC from 01JAN2013-31DEC2016

8.3. Variables

All data will be extracted from the Medicare Database (Section 8.4). Baseline variables will be measured for the prior 12 months through the index date (exclusive of the index date). All relevant ICD-9-CM, ICD-10-CM, and CPT codes are available in the Appendix.

Table 1. Baseline Variables

Variable[a]	Role	Operational definition
Age	Baseline characteristic and potential predictor	Age will be defined as of the index date, retained in the dataset as continuous, and divided by the following age groups: 65-74, 75-84, and ≥85 years.
Sex	Baseline characteristic and potential predictor	A flag will be created for female beneficiaries on the index date and reported as a percentage.
Race/ethnicity	Baseline characteristic and potential predictor	A flag will be created for White, Black, Hispanic, and other races/ethnicities on the index date.
US geographic region	Baseline characteristic and potential predictor	The US will be divided into 5 regions: Northeast, South, North Central, West, and Other. Geographic region will be captured from enrollment data.

Variable[a]	Role	Operational definition
Index year	Baseline characteristic and potential predictor	A flag will be created for patients with index date in the year of 2013-2016.
Medicaid dual eligibility	Baseline characteristic and potential predictor	A flag will be created for patients with Medicaid dual eligibility.
Part-D low income subsidy	Baseline characteristic and potential predictor	A flag will be created for patients with a Part-D low income subsidy.
Baseline Deyo-Charlson comorbidity index score	Baseline characteristic and potential predictor	The Deyo-Charlson comorbidity index score will be created during the baseline.
Baseline $CHADS_2$ score	Baseline characteristic and potential predictor	The $CHADS_2$ score will be used to analyze the effect of stroke risk stratification on OAC use. The maximum score is 6. $CHADS_2$ scores: 2-3, 4-5, and ≥6.
Baseline CHA_2DS_2-VASc score	Baseline characteristic and potential predictor	The $CHADS_2VASc$ score will also be used as indicated above. The maximum score is 9. $CHADS_2$-VASc scores: 2-3, 4-5, and ≥6.
HAS-BLED score	Baseline characteristic and potential predictor	The HAS-BLED score will be used to estimate the risk of major bleeding. As the INR value is not available in the databases, a modified HAS-BLED score was calculated with a range of 0 to 8.
Baseline prior bleed	Baseline characteristic and potential predictor	A flag will be created for patients with a bleeding-related claim during the baseline period.
Baseline prior stroke/SE	Baseline characteristic and potential predictor	A flag will be created for patients with a stroke/SE claim during the baseline period.
Obesity	Baseline characteristic and potential predictor	A flag will be created for patients with obesity claims during the baseline.

Do not distribute for purposes outside of specific activities related to development of FDAMAs114 compliant pieces. Content within this protocol is subject to change based on communication planning and input by external review committees.

Variable[a]	Role	Operational definition
Congestive heart failure	Baseline characteristic and potential predictor	A flag will be created for patients with claims for congestive heart failure during the baseline period.
Diabetes	Baseline characteristic and potential predictor	A flag will be created for patients with claims for diabetes in the baseline period.
Hypertension	Baseline characteristic and potential predictor	A flag will be created for patients with claims for hypertension in the baseline period.
Chronic Obstructive Pulmonary Disease (COPD)	Baseline characteristic and potential confounder	A flag will be created for patients with COPD claims during the baseline
Renal disease	Baseline characteristic and potential predictor	A flag will be created for patients with claims for renal disease in the baseline period.
Myocardial infarction	Baseline characteristic and potential predictor	A flag will be created for patients with claims for myocardial infarction in the baseline period.
Dyspepsia or stomach discomfort	Baseline characteristic and potential predictor	A flag will be created for patients with claims for dyspepsia or stomach discomfort in the baseline period.
Peripheral arterial disease	Baseline characteristic and potential predictor	A flag will be created for patients with claims for peripheral arterial disease in the baseline period.
Transient ischemic attack	Baseline characteristic and potential predictor	A flag will be created for patients with claims for transient ischemic attack in the baseline period.
Coronary artery disease	Baseline characteristic	A flag will be created for patients with claims for coronary artery disease in the baseline period.

Do not distribute for purposes outside of specific activities related to development of FDAMAs114 compliant pieces. Content within this protocol is subject to change based on communication planning and input by external review committees.

Variable[a]	Role	Operational definition
	and potential predictor	
History of falls	Baseline characteristic and potential predictor	A flag will be created for patients with claims for fall(s) in the baseline period.
Baseline medication use	Baseline characteristic and potential predictor	Individual flags will be created for patients with prescription claims for angiotensin converting enzyme inhibitors, amiodarone, angiotensin receptor blockers, beta blockers, H2-receptor antagonists, proton pump inhibitors, anti-platelets, statins, nonsteroidal anti-inflammatory drugs (NSAIDs), inhibitors of warfarin, inducers of warfarin, dronedarone, digoxin, calcium channel blockers, renin angiotensin system antagonists, glucocorticoids, diuretics, metformin, sulfonylureas, thiazolidinedione, insulin, other diabetes drugs, antiulcer agents, and antidepressant.
Index dose of NOAC	Baseline characteristic	The index dose of the NOAC will be evaluated and categorized as standard (5mg apixaban, 150mg dabigatran, 60mg edoxaban, and 20mg rivaroxaban,) or low dose (2.5mg apixaban, 75mg dabigatran, 30mg edoxaban, and 10 or 15mg rivaroxaban,)
Baseline all-cause health care costs	Baseline characteristic	All-cause health care costs in the baseline period will be computed for inpatient, office, outpatient hospital, ER, pharmacy, DME, SNF, HHA, and hospice costs. Costs will be adjusted to 2016 US dollars using the medical care component of the CPI. Total medical and total health care costs will be calculated.
Baseline all-cause health care utilization	Baseline characteristic	All-cause health care utilization in the baseline period will be computed for inpatient admissions, office visits, outpatient hospital visits, ER visits, pharmacy use, DME, SNF, HHA, and hospice use.

[a] Unless specified, all primary and secondary diagnosis codes will be used.

Table 2. Clinical and Treatment Pattern Outcome Variables

Variable	Role	Operational Definition
Stroke/SE	Outcome	Stroke/SE will be identified using hospital claims with a stroke/SE diagnosis code as the first listed ICD-9-CM or ICD-10-CM code. Stroke/SE will be classified into 3 categories: ischemic stroke, hemorrhage stroke, and SE. Time to stroke/SE will be defined as the number of days from index date to the occurrence of the first stroke/SE requiring hospitalization.
Major bleeding	Outcome	Major bleeding will be identified using hospital claims with a bleeding diagnosis code as the first listed ICD-9-CM or ICD-10-CM diagnosis or procedure code.[27] Time to major bleeding will be defined as the number of days from index date to the occurrence of the first major bleeding event requiring hospitalization. Major bleeding may be further stratified by gastrointestinal and intracranial hemorrhages and other major bleeding.
Death	Outcome	Death information from the database will be used. Time to death will be defined as the number of days from index date to death.
Discontinuation (Treated Patients)	Outcome	Treated patients will be considered to have discontinued if there was no additional refill for the index anticoagulant after 30 days of the previous prescription's run-out date.[28] The discontinuation date will be defined as the run-out date plus 30 days.
Time to discontinuation (Treated Patients)	Outcome	Time to discontinuation will be defined as the number of days from the OAC prescription index date to the discontinuation date.
Switch among anticoagulants (Treated Patients)	Outcome	A switch among anticoagulants will be defined as a prescription filled for non-index anticoagulants within 30 days before or after the run-out date.[28] Time to switch will be defined as the number of days from the OAC prescription index date to the first prescription date of the switch.
Time-to-switch (Treated Patients)	Outcome	Time to switch will be defined as the number of days from the OAC prescription index date to the switch date.

Table 3. Health Care Resource Utilization and Cost Outcome Variables

Variable	Role	Operational Definition
Follow-up stroke/SE-related hospitalization costs	Outcome	Follow-up stroke/SE-related medical costs will include the first stroke/SE hospitalization costs. Costs will be adjusted as indicated above.
Follow-up major bleeding-related hospitalization costs	Outcome	Follow-up major bleeding-related medical costs will include the first major bleeding hospitalization costs. Costs will be adjusted as indicated above.
Follow-up all-cause health care costs	Outcome	All-cause health care costs in the follow-up period will be computed for inpatient, office, ER, total outpatient (office, ER, and other outpatient), pharmacy, and other (DME, SNF, HHA, and hospice) costs. Costs will also be adjusted to 2016 US dollars using the medical care component of the CPI. Total medical (inpatient, outpatient, and other) and total health care (medical and pharmacy) costs will be calculated PPPM.

8.4. Data Sources

Medicare Inpatient Data

The inpatient claim file contains final action claims data submitted by inpatient hospital providers for facility cost reimbursement. Information therein includes ICD-9-CM diagnosis and ICD-9 procedure codes, ICD-10-CM diagnosis and ICD-10 procedure codes, Diagnosis Related Groups, dates of service, reimbursement amounts, hospital providers, and beneficiary demographic information. All file observations are at the claim level.

Medicare Outpatient Data

The outpatient claim file contains final action claims data submitted by institutional outpatient providers. Examples of such providers include hospital outpatient departments, rural health clinics, renal dialysis facilities, outpatient rehabilitation facilities, comprehensive outpatient rehabilitation facilities, and community mental health centers. File information includes diagnosis and procedure codes (ICD-9-CM diagnosis and ICD-9 procedure codes, ICD-10-CM and ICD-10 procedure codes, CMS Healthcare Common Procedure Coding System [HCPCS] codes), dates of service, reimbursement amounts, outpatient provider numbers, revenue center codes, and beneficiary demographic information. All file observations are at the claim level.

Medicare Carrier File

The Carrier file (also known as the Physician/Supplier Part B claims file) contains final action FFS claims submitted on a CMS-1500 claim form. Most claims are from non-institutional providers such as physicians, physician assistants, clinical social workers, and nurse practitioners. The Carrier file also contains claims for other providers such as free-standing facilities. Examples include independent clinical laboratories, ambulance providers, and free-standing ambulatory surgical centers. This file also includes diagnosis and procedure codes, dates of service, reimbursement amounts, provider numbers, and patient demographic information.

Medicare PDE Data

The Medicare PDE data contains prescription drug costs and payment data that enable CMS to make payments to the plans and otherwise administer Part D benefits. When a beneficiary fills a prescription under Medicare Part D, a prescription drug plan sponsor must submit a summary record to CMS. Unlike individual drug claim transactions, the PDE data are summary extracts using CMS-defined standard fields.

Skilled Nursing Facility

The SNF file contains final action FFS claims data submitted by SNF providers. This file includes ICD-9-CM and ICD-10-CM diagnosis and procedure codes, dates of service, reimbursement amount, SNF provider number, and beneficiary demographic information.

Home Health Agency

The HHA file contains final action FFS claims submitted by HHA providers. It includes number of visits, type of visit (skilled nursing care, home health aides, physical therapy, speech therapy, occupational therapy, or medical social services), diagnosis (ICD-9-CM and ICD-10-CM diagnoses), date of visits, reimbursement amount, HHA provider number, and beneficiary demographic information.

Hospice

The Hospice file contains final action claims submitted by hospice providers. Once a beneficiary elects a hospice, all hospice-related claims are included in this file regardless of whether the beneficiary is in a Medicare FFS or Medicare managed-care plan. This file also includes level of hospice care received (eg, routine home care, inpatient respite care), terminal

diagnosis (ICD-9-CM and ICD-10-CM diagnoses), dates of service, reimbursement amounts, hospice provider number, and beneficiary demographic information.

Durable Medical Equipment

The DME file contains final action FFS claims submitted by DME suppliers. This file includes diagnosis (ICD-9-CM and ICD-10-CM diagnoses), services provided (CMS HCPCS codes), dates of service, reimbursement amounts, DME provider numbers, and beneficiary demographic information.

Medicare Denominator File

The denominator file contains yearly demographic and enrollment information for enrolled or entitled Medicare beneficiaries. The file combines information from administrative enrollment records regarding Medicare beneficiary entitlement status with third-party payer information and group health plan enrollment information. It is an abbreviated version of selected data elements of the enrollment database.

Some information therein includes the beneficiary's unique identifiers, state and county codes, ZIP codes, dates of birth, dates of death, sex, race/ethnicity, age, monthly entitlement indicators (A/B/Both), reasons for entitlement, state buy-in indicators, and monthly managed-care indicators (Yes/No).

Data are collected on an ongoing basis, with the files updated annually. The file does not contain data for all beneficiaries ever entitled to Medicare, only beneficiaries entitled during the year of the data. These data are available every May for the previous year.

All patient identifiers in the database have been fully encrypted, and the database is fully compliant with the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

8.5. Sample Size

Since the primary objectives are to evaluate the predictors of NVAF treatments, power calculation was conducted for the secondary objectives using the AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial.[29]

Using the AVERROES stroke/SE rates of 1.6% and 3.7% per year for apixaban and aspirin users, respectively, a Cox proportional hazards analysis of stroke/SE would need 225 patients per group with 10% loss of follow up (Table 4).

Table 4. Power Calculation (Stroke/SE)

	Stroke/SE (from AVERROES)	Follow-up Time (Maximum)	Loss of Follow up	Accrual Time	Total Estimated Sample Size (1:1 in each group)
Apixaban	3.7%	4 years	53.7% (Amin et al[30])	4 years	
Untreated	1.6%		10%		450
			15%		522
			20%		604
			25%		696
			30%		802

Using the AVERROES major bleeding rates of 1.4% per year in the apixaban group and 1.2% per year in the aspirin group, a Cox proportional hazards analysis of major bleeding would need 11,837 patients per group (Table 5).

Table 5. Power Calculation (Major Bleeding)

	Major Bleeding (from AVERROES)	Follow-up Time (Maximum)	Loss of Follow up	Accrual Time	Total Estimated Sample Size (1:1 in each group)
Apixaban	1.4%	4 years	53.7% (Amin et al[30])	4 years	
Untreated	1.2%		10%		23674
			15%		27498
			20%		31870
			25%		36848
			30%		42494

An alpha of 0.05, power of 80%, and accrual period of 4 years were used in the calculation.

Stroke/SE and major bleeding rates have been shown to be higher using real world data (RWD) compared to randomized controlled trial (RCT) data, so the sample size estimated to achieve 80% power may be overestimated. To compute adjusted proportional HR in the PSM analysis, a robust variance estimation will be required to be used and thus, the sample size presented here may be overestimated. This uncertainty around estimating sample size requirement for a RWD study based on RCT data should be taken into account.

8.6. Data Management

This study will use data in the Medicare Database. The Medicare database is de-identified and HIPAA compliant.

8.7. Data Analysis

When performing descriptive analysis of continuous data, means, medians, and standard deviations will be provided for continuous variables. When performing descriptive analysis of categorical data, numbers and percentages will be provided for dichotomous and polychotomous variables. Bivariate comparisons of baseline characteristics and outcomes measures will be provided. Appropriate tests (eg, t-test, chi-square test) will be used based on the distributions of the measures. The cumulative incidence rate for clinical outcomes (major bleeding, stroke/SE, and death) will be calculated. The incidence rate will be calculated as the number of patients who experience the event divided by the observed time at risk. An unadjusted Kaplan-Meier curve will be drawn to illustrate time-to-event. The sample size of each cohort will be evaluated before proceeding with multivariate analysis.

The secondary objectives are optional, depending on the sample sizes and results from the primary objectives. For example, given the potential differences between ever-treated and never-treated with OAC patients, should the predictors/confounders from the primary objective be considered profound for the comparisons between the cohorts, objectives 2-5 will not be conducted.

Logistic Regression: Predictors for OAC Treatment/non-treatment (Primary Objectives)

A logistic regression will be used to examine risk factors associated with OAC treatment (OAC, DOAC, or warfarin)/non-treatment with OACs and DOAC treatment/warfarin treatment. Predictor data will be examined during the 12 months baseline period before the index date.

Stepwise model selection will be used to identify risk factors. The final covariate lists will be finalized based on clinical rationale and model fitting.

Odds ratios, p-values, and 95% confidence intervals (CIs) for all model covariates will be provided. Diagnostic tests will be performed for the multivariate models. Hosmer-Lemeshow tests will be performed and the area under the Receiver Operating Characteristic curve will be checked.

Inverse Probability Weighting (IPW; Secondary Objectives)

IPW uses propensity scores to obtain estimates of the average treatment and censoring effect.[31,32] Propensity scores will be calculated using repeated measures logistic models with: 1) ever-treated with OAC and never-treated with OAC cohorts; 2) each DOAC treated and never-treated with OAC cohorts included in the model, using never-treated patients as the reference (i.e. control cohort). Appropriate correlation structure will be chosen based on the data and clinical rationale.

The propensity score is defined as the probability of a patient receiving OAC/DOAC treatment or being censored conditional on both time-dependent covariates (e.g., comorbidities) and time-independent baseline covariates (age, gender, race, and baseline value for each of the time-dependent variables). The list of variables included in the logistic model will be based on clinical rationale. The propensity score acts as a balancing score among the cohorts.

After calculating the propensity score, the distribution of the propensity scores will be reviewed.

Each patient's weight is equal to the inverse of the probability of their treatment option and censoring (weight=1/propensity score). The numerator of the weight is the propensity score that a patient is on observed treatment/censored in a time period conditional on the baseline covariates. Denominator of the weight is the same propensity score conditional on time-dependent (factors such as CHA2DS2-VASc score, history of bleeding, etc.) and time-independent confounders. If an ever-treated patient has a very low propensity score, a very large weight can be created. Large weights can increase the variability of estimated treatment effect. In order to address this, the weights will be stabilized. Stabilized weights for treatment and censoring will be calculated for each time period of a patient. This reduces the variability of the weights.

$$SW = \prod_{k=0}^{t} \frac{f[A(k)|\bar{A}(k-1), V]}{f[A(k)|\bar{A}(k-1), \bar{L}(k)]}$$

The distribution of the stabilized weight will be reviewed. If no extreme outliers are observed, the stabilized weights will be applied to the sample. In cases of extreme outliers, the large weights could be set to a less extreme value (e.g. recoding all weights that are outside 5th and 95th percentile to the 5th and 95th value, respectively). If needed, truncation can be done after stabilizing the weights.

After the weights are applied, the balance of the time-dependent and time-independent covariates will be assessed.

First, the means and proportions of baseline variables will be compared. The standardized difference compares the difference in means in units of the standard deviation. If the standardized difference is less than 10%, the covariates will be considered balanced.

For continuous variables, the balance of the distribution will also be assessed. The high-order movements and interactions between variables should be similar between cohorts. The standardized difference will be used to compare the mean of the square of continuous variables. Graphical comparisons of the distribution of continuous variables will be completed. Side-by-side boxplots and empirical cumulative distribution functions will be used to the compare the distribution of continuous covariates in the unweighted and weighted samples. Since the graphical approach can be subjective, a numerical method for comparing the distribution of continuous baseline covariates will also be completed. Kolmogorov-Smirnov test allows a comparison of the distribution of a continuous variable between two independent groups.[33,34,35,36]

Time-Varying Cox Regression Models (Secondary Clinical Objectives)

Time-varying Cox models will be used to compare the time to stroke/SE, major bleeding, and death between: 1) treated vs untreated; 2) each OAC vs untreated after inverse probability treatment weighting. Treatment will be used as a time varying covariate, in order to account for the untreated period of an ever-treated patient. Weights generated using IPW will be incorporated.

Marginal Structural Models (MSMs; Secondary Cost Objective)

A weighted generalized estimating equation (GEE) models will be applied for the multivariate analysis of health care costs among: treated vs untreated; 2) each OAC vs untreated. For cost outcomes, gamma distribution and a log link will be used. IPW weights will be incorporated to adjust for baseline covariates and any time dependent confounders. Time-dependent confounders will not be included in the repeated measures model – as their effects have been incorporated into the weights.[32] Treatment will be included as a time-dependent variable, and time-invariant covariates may be included based on results of IPW and clinical rationale.

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

8.8. Subgroup and Sensitivity Analysis

Additional subgroup and sensitivity analyses will be conducted, including:

- high-risk CHA_2DS_2-VASc score subgroups, specifically, 2-3, 4-5, and ≥6 (primary objective): assess whether the predictors of treatment would be impacted by baseline CHA_2DS_2-VASc score.
- high-risk age subgroups, specifically, 65-74, 75-79, and ≥80 years (primary objective): assess whether the predictors of treatment would be impacted by age.
- censor patients at 6 months (secondary clinical objectives): assess whether the differential follow-up time in each cohort would affect the clinical outcomes.
- use a certain allowable gap for drug exposure, such as 14 days (secondary clinical objectives): assess whether the allowable gap in OAC days of supply for treated patients would have an impact on the clinical outcomes, since a shorter allowable gap will increase the likelihood of having the patients truly on treatment.
- multivariable Cox regression (secondary clinical objectives): assess whether statistical methods on the multivariable analysis would affect the clinical outcomes.
- adjusting for the competing risks of death (secondary clinical objectives): assess whether death is a competing risk in the clinical outcome analyses.

8.9. Quality Control

8.10. Standard STATinMED quality control procedures will be used. Research Methods Strengths and Limitations

This study will use the 100% Medicare Database, a large national database representative of the US population. The sample size will be large enough to analyze detailed demographic and clinical characteristics of patients, health outcomes, treatment patterns, and health care utilization and costs.

The study is limited by the nature of claims data, which may be constrained by issues such as over-the-counter use of aspirin, incorrect coding, claims without actual medicinal treatment, and other incomplete claims information. Moreover, although patients will be matched on baseline demographic and clinical characteristics, given the nature of retrospective observational studies, residual confounders may still exist, especially between the ever treated versus never treated NVAF patients. As a result, only associations between variables can be studied, without assessment of causal relationships. In addition, given the differences between the ever treated and never treated populations and the results from the primary objective for

the predictors of treatment, the comparative analyses for stroke/SE, major bleeding, and health care costs in the secondary objectives may not be feasible. Comorbidities at baseline (eg, presence of renal impairment) will be determined only by the presence of ICD-9-CM and ICD-10-CM diagnosis codes in the baseline period, not based on actual lab values or clinical assessment. Finally, warfarin treatment is continuously dose-adjusted so there is no low or high-dose strategy that can be defined.

8.11. 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/Independent Ethics Committee

Institutional Review Board/Independent Ethics Committee review is not required.

9.4. Ethical Conduct of the Study

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

10. Management and Reporting of Adverse Events/Adverse Reactions

This study involves unstructured data that exist as structured data by the time of study start or a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, 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 of which the investigator becomes aware.

11. References

[1] Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet.* 2014;383:955-962.

[2] Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139-1151.

[3] Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365:883-891.

[4] Granger CB, Alexander JH, McMurray JJ, Renato DL, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981-992.

[5] Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22), 2093-2104.

[6] Hsu JC, Maddox TM, Kennedy KF, Katz DF, Marzec LN, Lubitz SA, Gehi AK, Turakhia MP, Marcus GM. JAMA Cardiol. 2016 Apr 1;1(1):55-62. doi: 10.1001/jamacardio. 2015.0374.

[7] Shea JB, Sears SF. Cardiology patient pages. A patient's guide to living with atrial fibrillation. *Circulation.* 2008;117(20):e340-3.

[8] Marinigh R, Lip GY, Fiotti N, Giansante C, Lane DA. Age as a risk factor for stroke in atrial fibrillation patients: implications for thromboprophylaxis. *J Am Coll Cardiol.* 2010;56(11):827-37.

[9] Limone BL, Baker WL, Kluger J, Coleman CI. Novel anticoagulants for stroke prevention in atrial fibrillation: a systematic review of cost-effectiveness models. *PLoS One.* 2013;8(4):e62183.

[10] Fihn SD. The Risk for and Severity of Bleeding Complications in Elderly Patients Treated with Warfarin. *Annals of Internal Medicine*. 1996;124(11):970. doi:10.7326/0003-4819-124-11-199606010-00004.

[11] Melamed OC, Horowitz G, Elhayany A, Vinker S. Quality of anticoagulation control among patients with atrial fibrillation. *Am J Manag Care.* 2011;17(3):232-7.

[12] Connolly SJ, Pogue J, Eikelboom J, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control

achieved by centers and countries as measured by time in therapeutic range. *Circulation.* 2008;118(20):2029-37.

[13] Helgason CM, Do MA, Nutescu E. Warfarin in patients with stroke and reasons for discontinuation. *J Stroke Cerebrovasc Dis*. 2004;13(2):70-3.

[14] Fang MC, Go AS, Chang Y, et al. Warfarin discontinuation after starting warfarin for atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2010;3(6):624-31.

[15] Harburger JM. Aronow WS. Newer anticoagulants for non-valvular atrial fibrillation. *Pharmaceuticals (Basel)*. 2012;5(5):469-80.

[16] Lip GYH, Halperin JL, Petersen P, et al. A Phase II, double-blind, randomized, parallel group, dose-finding study of the safety and tolerability of darexaban compared with warfarin in patients with non-valvular atrial fibrillation: the oral factor Xa inhibitor for prophylaxis of stroke in atrial fibrillation study 2 (OPAL-2). *J Thrombos Haemost.* 2015;13(8):1405-13.

[17] O'Donoghue ML, Ruff CT, Giugliano RP, et al. Edoxaban vs. warfarin in vitamin K antagonist experienced and naive patients with atrial fibrillation. *Eur Heart J.* 2015;36(23):1470-7.

[18] Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med.* 2013;368(8):699-708.

[19] Lanssen MR, Raskob GE, Gallus A, et al.. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomized double-blind trial. *Lancet.* 2010;375(9717):807-15.

[20] Chan PS, Maddox TM, Tang F, Spinler S, & Spertus JA. Practice-level variation in warfarin use among outpatients with atrial fibrillation (from the NCDR PINNACLE program). *Am J Cardiol*. 2011;108(8), 1136-1140.

[21] Boulanger L, Kim J, Friedman M, et al. Patterns of use of antithrombotic therapy and quality of anticoagulation among patients with non-valvular atrial fibrillation in clinical practice. *Int J Clin Pract*. 2006;60(3):258-64.

[22] Bo M, Grisoglio E, Brunetti E, et al. Oral anticoagulant therapy for older patients with atrial fibrillation: a review of current evidence. *Eur J of Intern Med*. 2017;41, 18-27.

[23] Currie CJ, Jones M, Goodfellow J, et al. Evaluation of survival and ischaemic and thromboembolic event rates in patients with non-valvar atrial fibrillation in the general population when treated and untreated with warfarin. *Heart*. 2006;92:196-200.

[24] Yu AY, Malo S, Svenson LW, Wilton SB, & Hill MD. Temporal trends in the use and comparative effectiveness of direct oral anticoagulant agents versus warfarin for nonvalvular atrial fibrillation: a Canadian population-based study. *J Am Heart Assoc*. 2017;6(11), e007129.

[25] Gray MP, Saba S, Zhang Y, Hernandez I. Outcomes of Patients With Atrial Fibrillation Newly Recommended for Oral Anticoagulation Under the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society Guideline. *J Am Heart Assoc*. 2018;7(1). doi:10.1161/JAHA.117.007881

[26] Willey V, Franchino-Elder J, Fu A-C, et al. Treatment and persistence with oral anticoagulants among newly diagnosed patients with non-valvular atrial fibrillation: a retrospective observational study in a US commercially insured and Medicare Advantage population. *BMJ Open*. 2018;8(6):e020676. doi:10.1136/BMJOPEN-2017-020676

[27] Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray W, et al. An automated database case definition for serious bleeding related to oral anticoagulant use. *Pharmacoepidemiol Drug Saf.* 2011;20:560-566.

[28] Teutsch C, Huisman MV, Lip GY, et al. Persistence with dabigatran therapy for stroke prevention in patients with non-valvular atrial fibrillation: the Gloria-AF Registry. *Blood.* 2016;128:2616.

[29] Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9), 806-817.

[30] Amin A, Keshishian A, Zhang Q, et al. P3844 Effectiveness, safety, and composite clinical outcomes of apixaban, dabigatran, rivaroxaban, relative to warfarin in non-valvular atrial fibrillation patients in the US Medicare population. *European Heart Journal*. 2018;39(suppl_1), ehy563-P3844.

[31] Hernán MA, Brumback BA, Robins JM. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. Stat Med. 2002;21(12):1689-1709. doi:10.1002/sim.1144

[32] Faries DE & Kadziola ZA. (2010). Analysis of longitudinal observational data using marginal structural models. Analysis of observational health care data using SAS, 211.

[33] Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Statist Med. 2015;34:3661-3679

[34] Thoemmes F, Ong AD. A primer on inverse probability of treatment weighting and marginal structural models. Curr Epidemiol Rep. 2017;4(1):40-59

[35] Leslie S, Thiebaud P. Using propensity scores to adjust for treatment selection bias. SAS Global Forum. 2007

[36] Xu S, Ross C, Raebel MA. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Health. 2010;13(2):273-277

12. List of Tables

13. List of Figures

ANNEX 1. List of Standalone Documents

Not applicable.

ANNEX 2. Additional Information