NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Clinical and Economic Outcomes and Treatment Patterns for Non-Valvular Atrial Fibrillation Patients Who Newly Initiated Oral Anticoagulants in the US Medicare Population
Protocol number	B0661107
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Medicinal Product	Apixaban
Research question and objectives	Objectives: 1. Compare the risk of stroke/SE and major bleeding among patients who initiated oral anticoagulants (OACs; warfarin, apixaban, rivaroxaban, dabigatran, or edoxaban). 2. Compare all-cause and stroke/SE- and major-bleeding-related health care costs among patients who initiated OACs 3. Compare treatment patterns (discontinuation, switch, and dosage) among different treatment cohorts 4. Determine the prevalence of NVAF patients and the proportion of treated and untreated patients

	5. (Exploratory) Evaluate the risk of major adverse cardiac events (MACE) among NVAF patients who initiated oral anticoagulants
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TABLE OF CONTENTS

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACS	Acute Coronary Syndrome
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 and Medicaid Service
CPI	Consumer Price Index
DME	Durable Medical Equipment
ER	Emergency Room
FFS	Fee-for-service
HAS-BLED	Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding

Abbreviation	Definition
	History or Predisposition, Labile International Normalized Ratios, Elderly, Drugs/Alcohol
HCPCS	Healthcare Common Procedure Coding System
HHA	Home Health Agency
HIPAA	Health Insurance Portability and Accountability Act
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
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

1. RESPONSIBLE PARTIES

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2. ABSTRACT

Title: Clinical and Economic Outcomes and Treatment Patterns for Non-Valvular Atrial Fibrillation Patients who initiated Oral Anticoagulants in the US Medicare Population

Version: 1.0

Date of Protocol: September 8, 2017

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 and have been shown in clinical trials to be at least non-inferior to warfarin with respect to stroke and SE prevention and major bleeding risk. AF prevalence increases with age; it is estimated that >80% of US adults with AF are aged ≥65 years and approximately 37% are aged ≥80 years. However, insufficient evidence exists for elderly NVAF patients regarding the adoption of DOACs in a real-world clinical setting, whether the risks of stroke/SE and major bleeding are consistent with the controlled trials on which their approval was based, and how the use of DOACs has affected health spending for patients and insurers. The burden of NVAF is expected to double in the near future, with significant increases in hospitalization and health care costs. Understanding the treatment patterns as well as clinical and economic outcomes of NVAF treatments is critical to develop effective strategies to reduce the overall disease burden.

Objectives:

1. Compare the risk of stroke/SE and major bleeding among NVAF patients who initiated oral anticoagulants (OACs) (warfarin, apixaban, rivaroxaban, dabigatran, or edoxaban)
2. Compare all-cause and stroke/SE- and major-bleeding-related health care costs among NVAF patients who newly initiated OACs
3. Compare treatment patterns (discontinuation, switch, and dose) among NVAF patients who newly initiated OACs

4. Determine the prevalence of NVAF patients and the proportion of treated and untreated patients
5. (Exploratory) Evaluate the risk of major adverse cardiac events (MACE) among NVAF patients who initiated oral anticoagulants

Study Design: The study will be a longitudinal retrospective cohort analysis using the US Center of Medicare and Medicaid Services (CMS) "fee-for-service" (FFS) data from 01JAN2012-31DEC2015 (or most recent data available). The study will allow a 12-month baseline period prior to an identification period (01JAN2013-31DEC2015). This database only includes elderly patients with FFS Medicare; therefore, patients on managed-care plans are not included. Patients will be selected from the Medicare database according to the inclusion and exclusion criteria listed below.

Population: NVAF patients prescribed an OAC between 01JAN2013-31DEC2015 (or most recent data available) with continuous health plan enrollment during their baseline period will be included in the study. The first DOAC pharmacy claim date during the identification period will be designated as the index date. The first warfarin prescription date will be designated as the index date for patients without any DOAC claim. For the annual prevalence calculation, NVAF patients aged ≥65 years with continuous enrollment during each year from 2012 to 2015 will be included as the numerator. The Medicare population aged ≥65 years with continuous enrollment during each year from 2012 to 2015 will be included as the denominator.

Variables: Clinical outcomes including time to stroke/SE and major bleeding; medical costs per patient per month (PPPM) related to stroke/SE and major bleeding during hospitalization and follow-up period; and all-cause health care costs and utilization will be determined and compared between NVAF patients prescribed apixaban, dabigatran, rivaroxaban, or warfarin. Baseline demographic and clinical characteristics will include age, gender, geographic region, Charlson comorbidity index (CCI), $CHADS_2$, CHA_2DS_2-VASc, HAS-BLED scores, prior bleed/stroke events, congestive heart failure (CHF), diabetes, hypertension, renal disease, myocardial infarction (MI), dyspepsia or stomach discomfort, peripheral arterial disease (PAD), transient ischemic attack, coronary artery disease (CAD), and medication use. Baseline health care costs and utilizations will include all-cause

health care costs and utilization. Anticoagulant treatment patterns will include treatment discontinuation rate, time to discontinuation, treatment switching, and change of dose.

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.

Study Size: All eligible patients available for analysis will be included. Using the ARISTOTLE stroke rates of 1.27% and 1.60% per year for apixaban and warfarin users, respectively, a survival analysis of stroke would need 25,621 patients per group. Using the ARISTOTLE major bleeding rate of 2.13% per year in the apixaban group and 3.09% per year in the warfarin group, a survival analysis of major bleeding would need 6,394 patients per group. The sample size calculation used the assumptions of an alpha of 0.05, power of 80%, an accrual period (ie, the period when patients are identified [01JAN2013-30SEP2015]) of 2.75 years, and a follow-up loss of 55% for the warfarin cohort and 40% for the apixaban cohort. This calculation assumes a uniform accrual and loss to follow-up during the identification period. To compute adjusted proportional hazard ratio (HR) in the propensity score matching (PSM) analysis, we will need robust variance estimation to be used; thus, the sample size presented here may be overestimated. Nevertheless, uncertainty around estimating sample size requirement for a real-world data (RWD) study based on randomized controlled trial (RCT) data should be considered. Apixaban and warfarin will also be compared to the other OACs. However, there are no direct clinical trial comparisons between the DOACs.

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. The cumulative incidence rate for clinical outcomes (stroke/SE and major bleeding) will be calculated. PSM will be used to balance the cohort characteristics. Cox regression and generalized linear models will be used when comparing the cohorts. Generalized linear models (GLMs) and 2-part models with bootstrapping will be used to evaluate all-cause as well as

stroke/SE- and major-bleeding-related health care costs. Data analysis will be executed using statistical software SAS version 9.3.

3. AMENDMENTS AND UPDATES

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

4. MILESTONES

5. RATIONALE AND BACKGROUND

AF is a medical condition characterized by chaotic and irregular electrical activity in the heart's upper chamber and is the most common heart dysrhythmia diagnosed in the United States.[1] AF prevalence has increased with an increasingly aging population in the United States and is expected to continue this trend substantially in the coming decades.[2]

AF carries a significant financial burden, costing the US health care system approximately $26 billion dollars annually. While hospitalizations account for most of these costs (52%), AF treatment costs cannot be ignored (23%).[3]

Vitamin K antagonists, such as warfarin, have been the treatment of choice for anticoagulation. International Normalized Ratio (INR) is a test used to monitor the thinness and thickness of the blood. To maximize benefits and minimize complications such as bleeding, warfarin therapy should be monitored and adjusted within a narrow therapeutic index of INR results.[4,5] The pharmacokinetic profile of warfarin is complex due to several drug-drug and drug-food interaction complications. It is difficult to achieve long-term stability among warfarin patients due to fluctuating INR values, which may be caused by diet, seasonal variation, alcohol consumption, etc.[3] The need for regular monitoring, risk of hemorrhage, and poor control of INR levels may lead to medication non-adherence.[6, 7]

However, due to its limited therapeutic index and possible drug and food interactions, only ~50% of AF patients in the United States receive warfarin therapy as recommended.[8] Over the last several years, DOACs, including dabigatran, apixaban, rivaroxaban, and edoxaban were approved in the Unites States for stroke prevention among NVAF patients. Clinical trials demonstrated that DOACs have similar-to-superior reduction in stroke and bleeding risks compared to warfarin.[9,10,11,12]

This study will add "real-world" evidence for the comparative risks of stroke/SE, major bleeding, related health care costs, and treatment patterns among elderly NVAF patients who initiated OACs.

6. Research Question and Objectives

The primary objectives of the study are:

1. Compare the risk of stroke/SE and major bleeding between NVAF patients who initiated OACs (warfarin, apixaban, rivaroxaban, dabigatran, or edoxaban).

2. Compare all-cause and stroke/SE- and major-bleeding-related health care costs among NVAF patients who initiated OACs.

3. Compare treatment patterns (discontinuation, switch, and dose) among the cohorts.

4. Determine the prevalence of NVAF patients and the proportion of treated and untreated patients.

5. Exploratory: Evaluate the risk of major adverse cardiac events (MACE) among NVAF patients who initiated oral anticoagulants

7. Research Methods

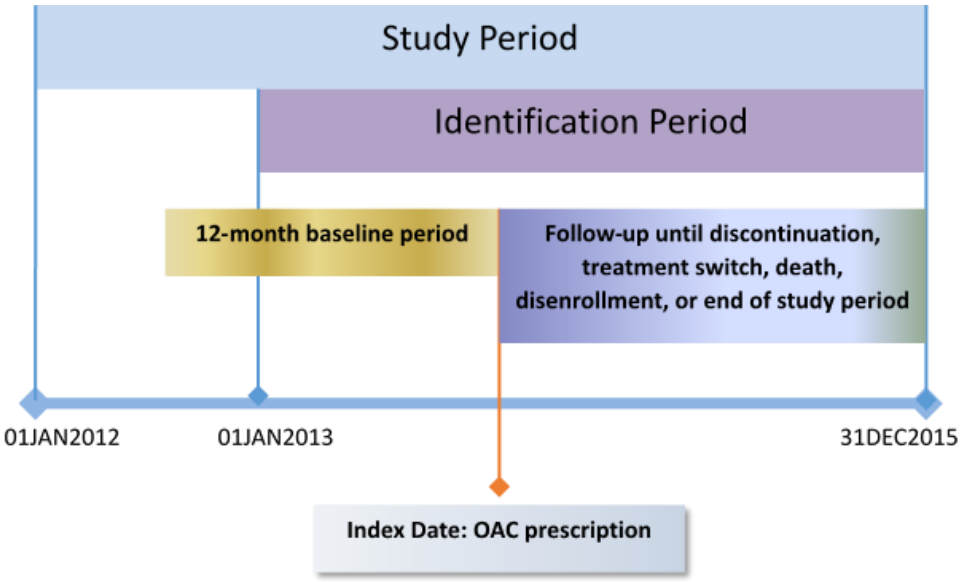
7.1. Study Design

The study will be a longitudinal retrospective cohort analysis using the US FFS Medicare database. It contains data from inpatient departments, outpatient departments, carrier claims, reported drug events, and beneficiaries' enrollment data. Demographic and clinical characteristics; anticoagulant treatment patterns; clinical outcomes including major bleeding, stroke/SE, and MACE; and health care costs and resource utilization will be determined and compared between NVAF patients prescribed warfarin, apixaban, dabigatran, rivaroxaban, or edoxaban. NVAF prevalence and the proportion of treated and untreated NVAF patients will also be examined. The overall study period will be from 01JAN2012-31DEC2015 (or most recent data available). The study will allow a 12-month baseline period prior to an index identification period (01JAN2013-31DEC2015). The first DOAC pharmacy claim date during the identification period will be designated as the index date. The

first warfarin prescription date will be designated as the index date for patients without any DOAC claim.

The annual prevalence of diagnosed NVAF will also be studied from 2012 to 2015 (or most recent data available). The percentages of treated and untreated NVAF patients will be calculated.

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



7.2. Setting

There will be two study populations. For the primary analysis, elderly patients prescribed OAC(s) will be enrolled from 01JAN2013-31DEC2015 (or most recent data available). Patient data will be assessed from the day after the index date until the earliest of the following dates: treatment discontinuation, switch from the index treatment, death, health plan disenrollment date, or 31DEC2015 (or most recent data available), whichever occurred earliest. Patients will be required to have an AF diagnosis before or on the index date as well as continuous health plan enrollment for 12 months prior to and including the index date (baseline period) to ensure that

the patients' complete medical history is available. To assess NVAF prevalence and proportion of treated and untreated patients, elderly NVAF patients will be selected from the Medicare Database between 01JAN2013 and 31DEC2015 (or most recent data available).

7.2.1. Inclusion Criteria

Primary Analysis:

Patients will be included in the study if they:

1) had ≥1 pharmacy claim for apixaban, rivaroxaban, dabigatran, edoxaban, or warfarin during the identification period (01JAN2013-31DEC2015 or most recent data available)—the first DOAC pharmacy claim date during the identification period will be designated as the index date. The first warfarin prescription date will be designated as the index date for patients without any DOAC claim;

2) were aged ≥65 years on the index date;

3) had continuous health plan enrollment with medical and pharmacy benefits (Medicare Part A, B, and D) for ≥12 months prior to and on the index date (baseline period); and

4) had ≥1 medical claim for AF (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 427.31; ICD-10-CM: I480-I482, I4891) at any time before or on index date.

NVAF Prevalence Analysis:

Patients must meet all the following inclusion criteria to be eligible for inclusion in the numerator of the prevalence calculation:

1) ≥1 inpatient claim or ≥2 outpatient claims for AF (ICD-9-CM: 427.31; ICD-10-CM: I480-I482, I4891) during the study year (2012-2015 or most recent data available)[13];

2) aged ≥65 years in the study year; and

3) continuous health insurance enrollment through the study year

Patients must meet all the following inclusion criteria to be eligible for inclusion in the denominator of the prevalence calculation:

1) aged ≥65 years in the study year; and

2) continuous health insurance enrollment through the study year

NVAF prevalence will be examined for each year from 2012 to 2015 (or most recent data available).

7.2.2. Exclusion Criteria

Primary Analysis:

Patients with any of the following criteria will not be included in the study:

1) medical claims indicating a diagnosis of rheumatic mitral valvular heart disease or valve replacement procedure (Appendix) during the 12 months prior to or on the index date;

2) medical claims indicating a diagnosis code for venous thromboembolism (VTE) (Appendix) during the 12 months prior to or on the index date;

3) medical claims indicating a diagnosis or procedure code of transient AF or cardiac surgery (Appendix) during the 12 months prior to or on the index date;

4) medical claims indicating pregnancy during the study period (Appendix);

5) medical claims indicating hip/knee replacement surgery within 6 weeks prior to the index date;

6) pharmacy claim for warfarin, apixaban, dabigatran, rivaroxaban, or edoxaban during the baseline period; or

7) >1 OAC prescription claim on the index date.

NVAF Prevalence Analysis:

Patients with any of the following criteria will not be included in the numerator of the prevalence calculation:

1) medical claims indicating a diagnosis of rheumatic mitral valvular heart disease or valve replacement procedure (Appendix) during the 12 months prior to or on the index date; or

2) medical claims indicating a diagnosis or procedure code of transient AF or cardiac surgery (Appendix) during the 12 months prior to or on the index date.

7.2.3. Cohorts

Primary Analysis:

After applying the inclusion and exclusion criteria, eligible patients will be assigned to the following cohorts based on the newly initiated OAC:

1) **Apixaban Cohort:** NVAF patients who initiated apixaban on the index date

2) **Dabigatran Cohort:** NVAF patients who initiated dabigatran on the index date

3) **Rivaroxaban Cohort:** NVAF patients who initiated rivaroxaban on the index date

4) **Edoxaban Cohort:** NVAF patients who initiated edoxaban on the index date

5) **Warfarin Cohort:** NVAF patients without any DOAC claim; the first warfarin prescription date will be designated as the index date.

NVAF Prevalence Analysis:

The proportion of patients treated with OAC(s) and those not prescribed any OAC among diagnosed NVAF patients will be calculated:

1) **Treated Cohort:** NVAF patients with ≥1 pharmacy claim for warfarin, apixaban, dabigatran, rivaroxaban, or edoxaban during each study year from 2012 to 2015 or most recent data available

2) **Untreated Cohort:** NVAF patients without any pharmacy claim for warfarin, apixaban, dabigatran, rivaroxaban, or edoxaban during each study year from 2012 to 2015 or most recent data available

7.3. Variables

All data will be extracted from the Medicare Database described in Section 8.4. Baseline variables will be measured for the 12 months prior to and including the index date.

Table 1. Baseline Variables

Variable[a]	Role	Operational definition
Age	Baseline characteristic and potential confounder	Age will be defined as of the index date and retained in the dataset as continuous as well as by the following age groups: 65-74, 75-79, and ≥80 years.
Gender	Baseline characteristic and potential confounder	A flag will be created for female beneficiaries and reported as a percentage.
Race	Baseline characteristic and potential confounder	A flag will be created for White, Black, Hispanic, and other races.
US Geographic Region	Baseline characteristic and potential confounder	The United States will be divided into 5 regions: Northeast, South, North Central, West, and Other. Geographic region will be captured

Variable[a]	Role	Operational definition
		from enrollment data.
Medicaid Dual Eligibility	Baseline characteristic and potential confounder	A flag will be created for patients with Medicaid dual eligibility.
Part-D Low Income Subsidy	Baseline characteristic and potential confounder	A flag will be created for patients with Part-D low income subsidy.
Baseline Deyo-Charlson Comorbidity Index Score	Baseline characteristic and potential confounder	The Deyo-Charlson Comorbidity Index will be created during the baseline.
Baseline $CHADS_2$ Score	Baseline characteristic and potential confounder	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: 0, 1, 2, ≥3
Baseline CHA_2DS_2-VASc Score	Baseline Characteristics and Potential Confounders	The $CHADS_2$VASc score will be used to analyze the effect of stroke risk stratification on OAC use. The maximum score is 9. $CHADS_2$-VASc scores: 0, 1, 2, ≥3
HAS-BLED Score	Baseline characteristic and potential confounder	HAS-BLED score will be used to estimate the risk of major bleeding for patients.
Baseline Prior Bleed	Baseline characteristic and potential confounder	A flag will be created for patients with a bleeding-related claim during the baseline period.
Baseline Prior Stroke/SE	Baseline characteristic and potential confounder	A flag will be created for patients with a stroke/SE claim during the baseline period.
Congestive Heart Failure	Baseline characteristic and potential confounder	A flag will be created for patients with claims for congestive heart failure in the baseline period.
Diabetes	Baseline characteristic and potential confounder	A flag will be created for patients with claims for diabetes in the baseline period.
Hypertension	Baseline characteristic and	A flag will be created for patients with claims for hypertension in the

Variable[a]	Role	Operational definition
	potential confounder	baseline period.
Renal Disease	Baseline characteristic and potential confounder	A flag will be created for patients with claims for renal disease in the baseline period.
Myocardial Infarction	Baseline characteristic and potential confounder	A flag will be created for patients with claims for myocardial infarction in the baseline period.
Dyspepsia or Stomach Discomfort	Baseline characteristic and potential confounder	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 confounder	A flag will be created for patients with claims for peripheral arterial disease in the baseline period.
Transient Ischemic Attack	Baseline characteristic and potential confounder	A flag will be created for patients with claims for transient ischemic attack in the baseline period.
Coronary Artery Disease	Baseline characteristic and potential confounder	A flag will be created for patients with claims for coronary artery disease in the baseline period.
Baseline Medication Use	Baseline characteristic and potential confounder	Individual flags will be created for patients with prescription claims for angiotensin converting enzyme inhibitor, amiodarone, angiotensin receptor blocker, beta blockers, H2-receptor antagonist, proton pump inhibitors, anti-platelets, and statins.
Index Dose of DOAC	Baseline characteristic	The index dose of the DOAC will be evaluated and will be categorized as standard (20 mg rivaroxaban, 5 mg apixaban, 150 mg dabigatran, and 60 mg edoxaban) and low dose (10 or 15 mg rivaroxaban, 2.5 mg apixaban, 75 mg dabigatran, and 30

Variable[a]	Role	Operational definition
		mg edoxaban)
Baseline All-cause Health Care Costs	Baseline characteristic and potential confounder	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 2015 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 and potential confounder	All-cause health care utilizations 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 diagnosis 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 the day after the 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. Time to major bleeding will be defined as the number of days from the day after the index date to the occurrence of the first major bleeding event requiring hospitalization.

Variable	Role	Operational Definition
		Major bleeding may be further stratified by gastrointestinal and intracranial hemorrhages and other major bleeding
Discontinuation	Outcome	Patients will be considered discontinued if there was no additional refill for the index anticoagulant after 30 days of the run-out date of the previous prescription.[14] The run-out date will be defined as the previous prescription date plus days' supply of that prescription. Sensitivity: For objective 3, patients will be considered discontinued if there was no additional refill for the index anticoagulant after 30 days of the run-out date of the previous prescription. If the gap between 2 consecutive prescriptions or from the last prescription to end of study is longer than 30 days, patients will be considered discontinued if they did not have INR measurements at least every 42 days.
Time to discontinuation	Outcome	Time to discontinuation will be defined as the number of days from the date of index OAC prescription to the date of discontinuation.
Switch among Anticoagulants	Outcome	A switch among anticoagulants will be defined as a prescription filled for non-index anticoagulants within ±30 days after the date of discontinuation.[14] Time to switch will be defined as the number of days from the date of index OAC prescription to the first prescription date of the switch to non-index anticoagulants.
Time-to-Switch	Outcome	Time to switch will be defined as the number of days from the date of index OAC prescription to the date of switch.
Dose Change	Outcome	The number and percentage of patients with a dose change in the follow-up period will be calculated. The number of patients who switched from standard to low dose and low to standard dose will be calculated. The mean time to dose change will be evaluated.

Variable	Role	Operational Definition
Net Clinical Outcome	Outcome	The net clinical outcome will be defined as the first stroke/SE or major bleeding event requiring hospitalization in the follow-up period. The incidence rate of net clinical outcome will also be examined.
Net Clinical Outcome (Include Death)	Outcome	Net clinical outcome (include death) will be defined as the first stroke/SE, major bleeding, or death in the follow-up period. The incidence rate of the net clinical outcome will also be examined.
All-Cause Mortality	Outcome	Patients who died during the follow-up period will be labeled by binary indicators. The incidence rate of mortality will be calculated.
MACE	Exploratory Outcome	A composite outcome of stroke (hemorrhagic and ischemic stroke), MI, and all-cause death will be evaluated among NVAF patients. The frequency and time to the first occurrence of stroke, MI, or all-cause death will be calculated.

Table 3. Health Care Resource Utilization and Cost Outcome Variables

Variable	Role	Operational definition

Variable	Role	Operational definition
First Stroke/SE-related Direct Hospitalization Costs	Outcome	First stroke/SE-related direct hospitalization costs will be defined as hospitalization costs associated with the first stroke/SE event in the follow-up period. Costs will be adjusted to 2015 US dollars using the medical care component of the CPI. Costs will be calculated PPPM.
First Major Bleeding-related Direct Hospitalization Costs	Outcome	First major-bleeding-related direct hospitalization costs will be defined as hospitalization costs associated with the first major bleeding event in the follow-up period. Costs will be adjusted to 2015 US dollars using the medical care component of the CPI.
Follow-up Stroke/SE-related Medical Costs	Outcome	Follow-up stroke/SE-related medical costs will include the first stroke/SE hospitalization costs plus costs related to all stroke events (primary and secondary position) in the inpatient or outpatient setting after the first stroke. Costs will be adjusted to 2015 US dollars using the medical care component of the CPI.
Follow-up Major-Bleeding-related Medical Costs	Outcome	Follow-up major-bleeding-related medical costs will include the first major bleeding hospitalization costs plus costs related to all major bleeding events (primary and secondary position) in the inpatient or outpatient setting after the first major bleed. Costs will be adjusted to 2015 US dollars using the medical care component of the CPI.
Follow-up All-cause Health Care Utilization	Outcome	All-cause health care utilizations in the follow-up period will be computed for inpatient admissions, office visits, ER visits, outpatient (office, ER, and other outpatient) visits, pharmacy claims, and other services (DME, SNF, HHA, and hospice use). Resource use will be calculated PPPM.
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, outpatient (office, ER, and other outpatient), pharmacy, and other (DME, SNF, HHA, and hospice) costs. Costs will be adjusted to 2015 US dollars using the medical care component of the CPI. Total medical (inpatient and outpatient) and total health care (medical and pharmacy) costs will be calculated PPPM.

Table 4. NVAF Prevalence Analysis Variables

Variable	Role	Operational definition
NVAF Prevalence	Outcome	The numerator of the prevalence calculation will be the number of NVAF patients identified during each study year. The denominator of the calculation will be obtained from the 5% Medicare data. The sample size for the denominator will be calculated by multiplying the number of patients in the 5% Medicare data by 20 to get the estimated 100% Medicare sample. The prevalence of NVAF will be calculated each year from 2012 to 2015.
Proportion of Treated & Untreated patients	Outcome	The proportion of NVAF patients treated/untreated with OAC will be calculated each year from 2012 to 2015.

7.4. Data sources

Medicare Inpatient Data

The inpatient claim file contains final action claims data submitted by inpatient hospital providers for reimbursement of facility costs. Some information contained in this file 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. Each observation in this file is at the claim level.

Medicare Outpatient Data

The outpatient claim file contains final action claims data submitted by institutional outpatient providers. Examples of institutional outpatient providers include hospital outpatient departments, rural health clinics, renal dialysis facilities, outpatient rehabilitation facilities, comprehensive outpatient rehabilitation facilities, and community mental health centers. Some information contained in this file 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. Each observation in this file is 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 of the claims are from non-institutional providers, such as physicians, physician assistants, clinical social workers and nurse practitioners. Claims for other providers, such as free-standing facilities, are also found in the Carrier file. Examples include independent clinical laboratories, ambulance providers, and free-standing ambulatory surgical centers. This file 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. The PDE data are different from individual drug claim transactions: they 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 diagnosis and procedure codes, 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. This file includes number of visits, type of visit (skilled nursing care, home health aides, physical therapy, speech therapy, occupational therapy, and medical social services), diagnosis (ICD-9-CM diagnosis, ICD-10-CM diagnosis), 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 will be found in this file regardless of whether the beneficiary is in Medicare FFS or a Medicare managed-care plan. This file includes level of hospice care received (eg, routine home care, inpatient respite care), terminal diagnosis (ICD-9-CM diagnosis, ICD-10-CM diagnosis), 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 diagnosis, ICD-10-CM diagnosis), services provided (CMS HCPCS codes), dates of service, reimbursement amounts, DME provider numbers, and beneficiary demographic information.

Medicare Denominator File

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

Some information contained in this file includes the beneficiary's unique identifiers, state and county codes, ZIP codes, dates of birth, dates of death, sex, race, 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 constructed on an annual basis. The file does not contain data for all beneficiaries ever entitled to Medicare: the file only contains data for beneficiaries entitled during the year of the data. These data are available annually in May of the current year 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.

7.5. Sample Size

Our goal is to provide the most updated picture; hence, all eligible patients available for analysis will be included. A power calculation was completed for survival analysis comparing the difference between stroke and major bleeding rates using an alpha of 0.05, power of 80%, an accrual period (identification period where patients are selected into the study) of 2 years, and a loss of follow-up of 55% for the warfarin cohort and 40% for the apixaban cohort. Using the ARISTOTLE stroke rates of 1.27% and 1.60% per year for apixaban and warfarin users, respectively, a survival analysis of stroke would need 25,621 patients per group. Using the ARISTOTLE major bleeding rate of 2.13% per year in the apixaban group and 3.09% per year in the warfarin group, a survival analysis of major bleeding would need 6,394 patients per group.

To compute adjusted proportional HR in the PSM analysis, we will need robust variance estimation to be used; thus, the sample size presented here may be overestimated. Nevertheless, uncertainty around estimating sample size requirement for a RWD study based on RCT data should be considered. Apixaban and warfarin will be compared to the other OACs. However, there are no direct clinical trial comparisons between the DOACs.

7.6. Data Management

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

7.7. Data Analysis

Means, medians, and standard deviations will be provided for continuous variables when performing descriptive analysis of continuous data. Numbers and percentages will be provided for dichotomous and polychotomous variables when performing descriptive analysis of categorical data. 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. The cumulative incidence rate for clinical outcomes (major bleeding event and stroke/SE) 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.

Propensity Score Matching

The PSM technique will be used to control for confounders when comparing the cohorts.[11] Each subject in the reference cohort (apixaban and warfarin cohorts) will be matched to a subject in the comparator cohort (e.g. rivaroxaban, dabigatran) with the closest propensity score. The analysis will be completed using warfarin or apixaban as the reference cohort. As in a true RCT, the “no treatment subject” (eg, a subject in the Warfarin Cohort) functions as the control group for the selected treatment subject. As in a true RCT, the “no treatment subject” (e.g., a subject in the Warfarin Cohort) functions as the control group for the selected treatment subject (e.g. apixaban, dabigatran, or rivaroxaban).

After PSM, no significant differences are expected among all pre-index measures between the patient cohorts, and the treatment effect that is calculated based on the matched population is considered to be the true effect. PSM with a different ratio (1:2 or 1:3) can also be considered if the matched sample size using a ratio of 1:1 is too small. Covariates to be included in the logistic regression model will include variables such as age, geographic region, CCI score, and comorbidities.

The distribution of baseline characteristics will be presented before and after the matching process. Further, balance of covariates between treatment groups will be determined using absolute standardized difference of the mean ≤0.10. The final list of covariates included in the PSM will be determined based on clinical rationale and the baseline descriptive tables after matching.

If significant differences in the patient characteristics remain, a multivariate regression technique may be conducted over the propensity score-adjusted data to

further adjust baseline differences. Further multivariate analysis will be decided upon review of the post-matching results.

Cox Proportional Hazard Model

Cox proportional hazard models will be fit to compare the time to stroke/SE, major bleeding, discontinuation, and switch between the apixaban, warfarin, rivaroxaban, dabigatran, and edoxaban cohorts. This model tests proportional hazards models on survival (or time-to-event) data via maximum likelihood, with exponential Weibull and Gompertz distributions to be considered.

The proportional hazards proportionality assumption will be evaluated by visually inspecting the Kaplan-Meier plot among the matched cohort and confirmed by testing the significance of interactions between treatment and the log of time as well as each time-dependent covariate and the log of time. If this assumption is violated, interaction term of time may be added based on final decision. PSM will be used if sample size allows.

Generalized Linear Model and 2-Part Model

GLM will be applied for the multivariable analysis of health care costs among the warfarin, apixaban, dabigatran, rivaroxaban, and edoxaban cohorts. For cost outcomes, gamma distribution and log link will likely be used.

Since a large proportion of 0s usually exists in health care cost variables (eg, major bleeding costs, inpatient or ER costs), 2-part models may also be implemented in which the first part is a logistic regression of any service use and the second part is a GLM regression of cost, conditional on baseline demographics and clinical characteristics. Bootstrapping with the 2-part model may be conducted to generate the 95% confidence interval (CI).

For the evaluation of stroke/SE- and major-bleeding-related costs, bootstrapping will be conducted by random sampling with replacement from an approximating distribution. A 1,000-bootstrap sample of the same size as the original data will be created, and the 2-part models will be performed on each sample. The percentile method will be used to compute the 95% CI (ie, the full distribution of all bootstrapped iterations, with the top and bottom 2.5% cut off to obtain the 95% CI).

Statistical significance at the alpha level of 0.05 will be evaluated by assessing if the 95% CI of the difference in adjusted costs between cohorts included 0. Accordingly, if the difference included 0, the P-value will be considered to be <0.05.

All data analysis will be executed using statistical software STATA and SAS version 9.3.

Detailed methodology for summary and statistical analyses of this study's data 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.

7.8. Subgroup and Sensitivity Analysis

Additional subgroup and sensitivity analyses may be considered, including, but not limited to:

- baseline risk of stroke (assessed by $CHAD_2DS_2$-VASc score);
- baseline risk of bleeding (assessed by HAS-BLED score);
- age;
- gender;
- renal disease;
- CAD;
- PAD;
- CHF;
- prior stroke/SE;
- prior major bleeding;
- malignancy; and
- dosage of DOAC.

The sample size will be reviewed for each subgroup before proceeding with multivariate analysis. Sensitivity analyses may include:

- Censoring patients after six months' post-index date,
- Evaluating patients with at least 30 of follow-up,
- Discontinuation including INR measurement (Objective 3): Patients will be considered discontinued if there was no additional refill for the index anticoagulant after 30 days of the run-out date of the previous prescription. If the gap between 2 consecutive prescriptions or from the last prescription to end of study is longer than 30 days, patients will be considered discontinued if they did not have INR measurements at least every 42 days.[15,16]

7.9. Quality Control

Not applicable.

7.10. 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 limitations of the study lie in the nature of claim data, including the coding issue, claim without actual intake of medicine, missing information, etc. The only association between variables will be studied without a causal relationship being assessed. Comorbidities at baseline (eg, presence of renal impairment) are determined 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. Furthermore, warfarin treatment is continuously dose-adjusted so there is no low- or high-dose strategy which can be defined.

Only the prevalence of diagnosed NVAF can be studied. However, it was reported that 10% to 27% of the patients with AF were undiagnosed, and the prevalence of undiagnosed AF is 1% to 2% in the US.[17] Thus, the prevalence in our study may also underestimate the real prevalence in the Medicare population.

7.11. Other Aspects

Not applicable.

8. Protection of Human Subjects

8.1. Patient Information and Consent

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

8.2. Patient Withdrawal

Not applicable.

8.3. Institutional Review Board/Independent Ethics Committee

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

8.4. 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).

9. Management and Reporting of Adverse Events/Adverse Reactions

This study does not meet the criteria for adverse event (AE) reporting. All AEs collected will be reported in aggregate in the final study report; no individual or expedited reporting is required.

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

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 that the investigator becomes aware of.

10. References

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

[2] 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.

[3] 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.

[4] 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.

[5] 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.

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

[7] 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.

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

[9] Lip GYH, Halperin JL, Petersen P, Rodgers GM, Pall D, Renfurm RW. 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.

[10] 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.

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

[12] Lanssen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomized double-blind trial. *Lancet.* 2010;375(9717):807-15.

[13] Lakshminarayan K, Solid CA, Collins AJ, Anderson DC, Herzog CA. Atrial fibrillation and stroke in the general medicare population: a 10-year perspective (1992 to 2002). *Stroke.* 2006;37(8):1969-74.

[14] 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.

[15] Go, A. S., Hylek, E. M., Chang, Y., Phillips, K. A., Henault, L. E., Capra, A. M., ... & Singer, D. E. (2003). Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice?.*Jama*, *290*(20), 2685-2692.

[16] Rosendaal, F. R., Cannegieter, S. C., Van der Meer, F. J., & Briet, E. (1993). A method to determine the optimal intensity of oral anticoagulant therapy.*Thrombosis and haemostasis*, *69*(3), 236-239.

[17] Turakhia MP, Shafrin J, Bognar K, et al. (2015). Economic burden of undiagnosed nonvalvular atrial fibrillation in the United States. The American journal of cardiology, 116(5), 733-739.

13. List of Tables

14. List of Figures

ANNEX 1. List of Standalone Documents

None

ANNEX 2. Additional Information

Not applicable.