NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

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
Version identifier of the final study report	1.0
Date	04-August-2020
EU Post Authorization Study (PAS) register number	EUPAS25230
Active substance	Apixaban
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
Author	Allison Keshishian, MPH Phone: 734-222-5426 Email: akeshishian@statinmed.com Christine Baker, JD, MPH Director, HEOR Phone: 212-733-9545 Email:christine.l.baker@pfizer.com

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

Annex 1. List of stand-alone documents

Not applicable

Appendix 4. STATISTICAL ANALYSIS PLAN

Not applicable

Appendix 5. SAMPLE CASE REPORT FORM (CRF) / DATA COLLECTION TOOL (DCT))

Not applicable

Appendix 6. SAMPLE STANDARD SUBJECT INFORMATION SHEET AND INFORMED CONSENT DOCUMENT (ICD)

Not applicable

Appendix 7. LIST OF SUBJECT DATA LISTINGS

Not applicable

Appendix 7.8 Laboratory listings

Appendix 8. ADDITIONAL DOCUMENTS

Not applicable

1. ABSTRACT (STAND-ALONE DOCUMENT)

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

Date: 04-August-2020

Name and affiliation of the main author: Christine L. Baker, JD, MPH, Pfizer

Keywords: Apixaban, Dabigatran, Rivaroxaban, Warfarin, Non-valvular atrial fibrillation, · Medicare

Research question and objectives: 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.

The objectives of the study were:

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 was 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 allowed a 12-month baseline period prior to an identification period (01JAN2013-31DEC2015). This database only included elderly patients with FFS Medicare; therefore, patients on managed-care plans are not included. Patients were selected from the Medicare database according to the inclusion and exclusion criteria listed below.

Setting and subjects: NVAF patients prescribed an OAC between 01JAN2013-31DEC2015 (or most recent data available) with continuous health plan enrollment during their baseline period were included in the study. The first DOAC pharmacy claim date during the identification period was designated as the index date. The first warfarin prescription date was 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 were included as the numerator. The Medicare population aged ⩾65 years with continuous enrollment during each year from 2012 to 2015 was included as the denominator.

Data source: The study was 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.

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 were determined and compared between NVAF patients prescribed apixaban, dabigatran, rivaroxaban, or warfarin. Baseline demographic and clinical characteristics included age, gender, geographic region, Charlson comorbidity index (CCI), CHADS2, CHA2DS2-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 included all-cause health care costs and utilization. Anticoagulant treatment patterns included treatment discontinuation rate, time to discontinuation, treatment switching, and change of dose.

Results: 37,525 apixaban–warfarin, 18,131 dabigatran–warfarin, and 55,359 rivaroxaban–warfarin pairs were included. Compared to warfarin, apixaban (HR: 0.69; 95% CI 0.59–0.81) and rivaroxaban (HR: 0.82; 95% CI 0.73–0.91) had lower risk of stroke/SE, and dabigatran (HR: 0.88; 95% CI 0.72–1.07) had similar risk of stroke/SE. Apixaban (MB: HR: 0.61; 95% CI 0.57–0.67; net clinical outcome (NCO):HR: 0.64; 95% CI 0.60–0.69) and dabigatran (MB: HR: 0.79; 95% CI 0.71–0.89; NCO: HR: 0.84; 95% CI 0.76–0.93) had lower risk of

MB and NCO, and rivaroxaban had higher risk of MB (HR: 1.08; 95% CI 1.02–1.14) and similar risk of NCO (HR: 1.04; 95% CI 0.99–1.09). Compared to warfarin, apixaban had a lower risk for stroke/SE, MB, and NCO; dabigatran had a lower risk of MB and NCO; and rivaroxaban had a lower risk of stroke/SE but higher risk of MB. All DOACs had lower risk of major adverse cardiac events compared to warfarin.

Discussion: Using Medicare FFS data from 2012 to 2015, this study showed that compared to warfarin among elderly patients with NVAF, apixaban was associated with significant lower risks of stroke/SE, MB, NCO, and MACE. Dabigatran was associated with significantly lower risks of MB, NCO, and MACE as well as a numerically lower risk of stroke/SE. Rivaroxaban was associated with lower risks of stroke/SE and MACE, but higher MB and numerically higher NCO risks compared to warfarin. In summary, in the elderly Medicare population with NVAF, compared to warfarin, the DOACs were associated with a lower to similar risk of stroke/SE and MACE, but with varying comparative risks for MB and NCO.

Marketing Authorization Holder(s): Bristol Myers-Squibb

Names of principal investigators:

Alpesh Amin[1], Allison Keshishian[2], Oluwaseyi Dina[3], Amol Dhamane[4], Anagha Nadkarni[4], Eric Carda[3], Cristina Russ[3], Lisa Rosenblatt[4], Jack Mardekian[3], Huseyin Yuce[5], Christine L. Baker[3]

Affiliations:
[1] Department of Medicine, University of California, 101 The City Drive South, Building 26, Room 1000, ZC-4076H, Orange, CA 92868, USA
[2] STATinMED, Ann Arbor, MI, USA
[3] Pfizer Inc., New York, NY, USA
[4] Bristol-Myers Squibb Company, Lawrenceville, NJ, USA
[5] New York City College of Technology, City University of New York, New York, NY, USA

2. 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 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

Abbreviation	Definition
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

3. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site are listed in Appendix 3.1.

Principal Investigator(s) 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
Lin Xie, MS, MA	Sr. Director, HEOR	STATinMED Research	
Christine L Baker	Sr. Director, HEOR	Pfizer	235 E 42nd St New York, New York 10017

Lead Country Investigator(s) of the Protocol

Not applicable

4. OTHER RESPONSIBLE PARTIES

Not applicable

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	01 NOV 2017	01 NOV 2017	
End of data collection	06 FEB 2020	06 FEB 2020	
Registration in the EU PAS register	10 AUG 2018	10 AUG 2018	
Final report of study results		31 AUG 2020	

6. 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.[i] 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.[ii]

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%).[iii]

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.[iv,v] 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.[iii] The need for regular monitoring, risk of hemorrhage, and poor control of INR levels may lead to medication non-adherence.[vi, vii]

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.[viii] 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.[ix,x,xi,xii]

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.

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

7. 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

8. AMENDMENTS AND UPDATES

N/A

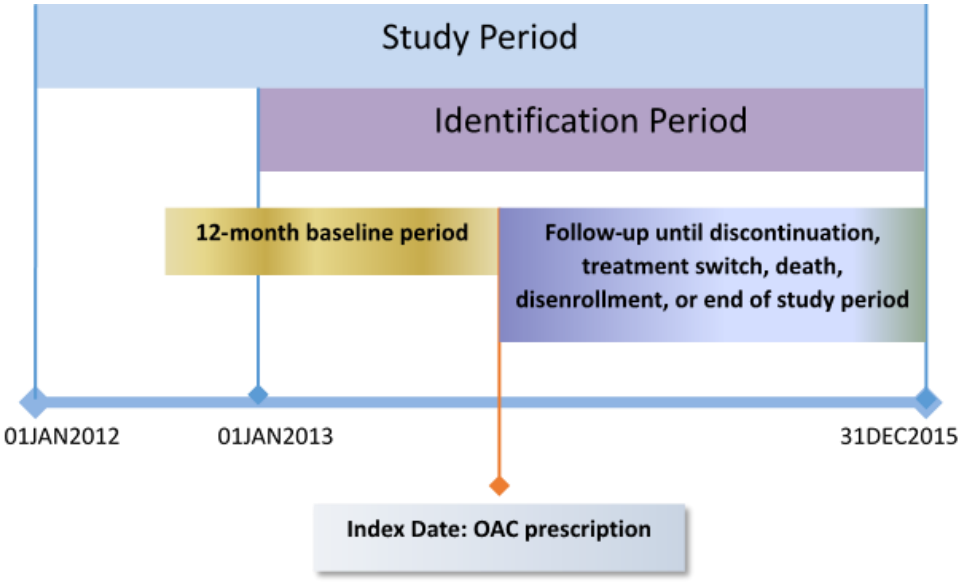
9. RESEARCH METHODS

9.1. Study design

The study was a longitudinal retrospective cohort analysis using the US FFS Medicare database. It contained 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 were determined and compared between NVAF patients prescribed warfarin, apixaban, dabigatran, rivaroxaban, or edoxaban. NVAF prevalence and the proportion of treated and untreated NVAF patients were examined. The overall study period was from 01JAN2012-31DEC2015 (or most recent data available). The study allowed a 12-month baseline period prior to an index identification period (01JAN2013-31DEC2015). The first DOAC pharmacy claim date during the identification period was designated as the index date. The first warfarin prescription date was designated as the index date for patients without any DOAC claim.

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

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



9.2. Setting

There were two study populations. For the primary analysis, elderly patients prescribed OAC(s) were enrolled from 01JAN2013-31DEC2015. Patient data were 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 were 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 were selected from the Medicare Database between 01JAN2013 and 31DEC2015 (or most recent data available).

9.3. Subjects

9.3.1. Inclusion criteria

Primary Analysis:

Patients were 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 have met 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)[xiii];

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

3) continuous health insurance enrollment through the study year

Patients must have met 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).

9.3.2. Exclusion criteria

Primary Analysis:

Patients with any of the following criteria were not 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 were 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.

Primary Analysis:

After applying the inclusion and exclusion criteria, eligible patients were 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 were 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

9.4. Variables

All data were extracted from the Medicare Database described in Section 8.4. Baseline variables were 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 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 $CHADS_2VASc$ score will be used to analyze the effect of stroke risk stratification on OAC use. The

Variable[a]	Role	Operational definition
		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 potential confounder	A flag will be created for patients with claims for hypertension in the 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.

Variable[a]	Role	Operational definition
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 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

Variable	Role	Operational Definition
		day after the 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
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.[xiv] 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.[xiv] 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.
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.

Variable	Role	Operational Definition
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
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)

Variable	Role	Operational definition
		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.

9.5. Data sources and measurement

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.

9.6. Bias

Propensity Score Matching

The PSM technique was used to control for confounders when comparing the cohorts.[11] Each subject in the reference cohort (apixaban and warfarin cohorts) was matched to a subject in the comparator cohort (e.g. rivaroxaban, dabigatran) with the closest propensity score. The analysis was 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).

9.7. Study Size

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.

9.8. Data transformation

This study used data in the Medicare Database. The Medicare database was de-identified and HIPAA compliant.

9.9. Statistical methods

9.9.1. Main summary measures

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

9.9.2. Main statistical methods

Propensity Score Matching

One-to-one propensity score matching (PSM) was conducted between DOACs and warfarin (apixaban versus warfarin, dabigatran versus warfarin, and rivaroxaban versus warfarin) to control for potential confounders such as baseline demographics and clinical characteristics. Using established methodology, propensity scores were generated by logistic regression. Age, sex, US geographic region, Charlson comorbidity index (CCI), CHA2DS2-VASc, and HAS-BLED scores, prior bleeding and stroke, comorbidities, baseline co-medications, and baseline inpatient visits were included in the models as covariates. The nearest neighbor without replacement method and a caliper of 0.01 were implemented in the PSM [18]. After PSM, the balance of covariates was checked based on standardized differences, with a threshold of 10%. For post-PSM cohorts, the incidence of primary and secondary outcomes was calculated as the number of events per 100 person-years.

Cox Proportional Hazard Model

Cox proportional hazards models with robust sandwich estimates were used to evaluate the hazard ratios (HRs) of stroke/SE, MB, NCO, and MACE in each matched cohort. After ensuring all the matched baseline covariates were balanced post-PSM, OAC treatment was included in the Cox models as the only independent variable.

Generalized Linear Model and 2-Part Model

GLM were 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 were 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 was 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 was 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 was 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 was considered to be <0.05.

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

Detailed methodology for summary and statistical analyses of this study's data was documented in a Statistical Analysis Plan (SAP), which was dated, filed, and maintained by the sponsor.

9.9.3. Missing values

Not applicable

9.9.4. Sensitivity analyses

Sensitivity analysis was conducted wherein patients were censored at 6 months of follow-up, creating more balance between cohorts

9.9.5. Amendments to the statistical analysis plan

Not applicable

9.10. Quality control

Not applicable

9.11. Protection of human subjects

Subject information and consent

Not applicable

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

IRB/IEC review is not required.

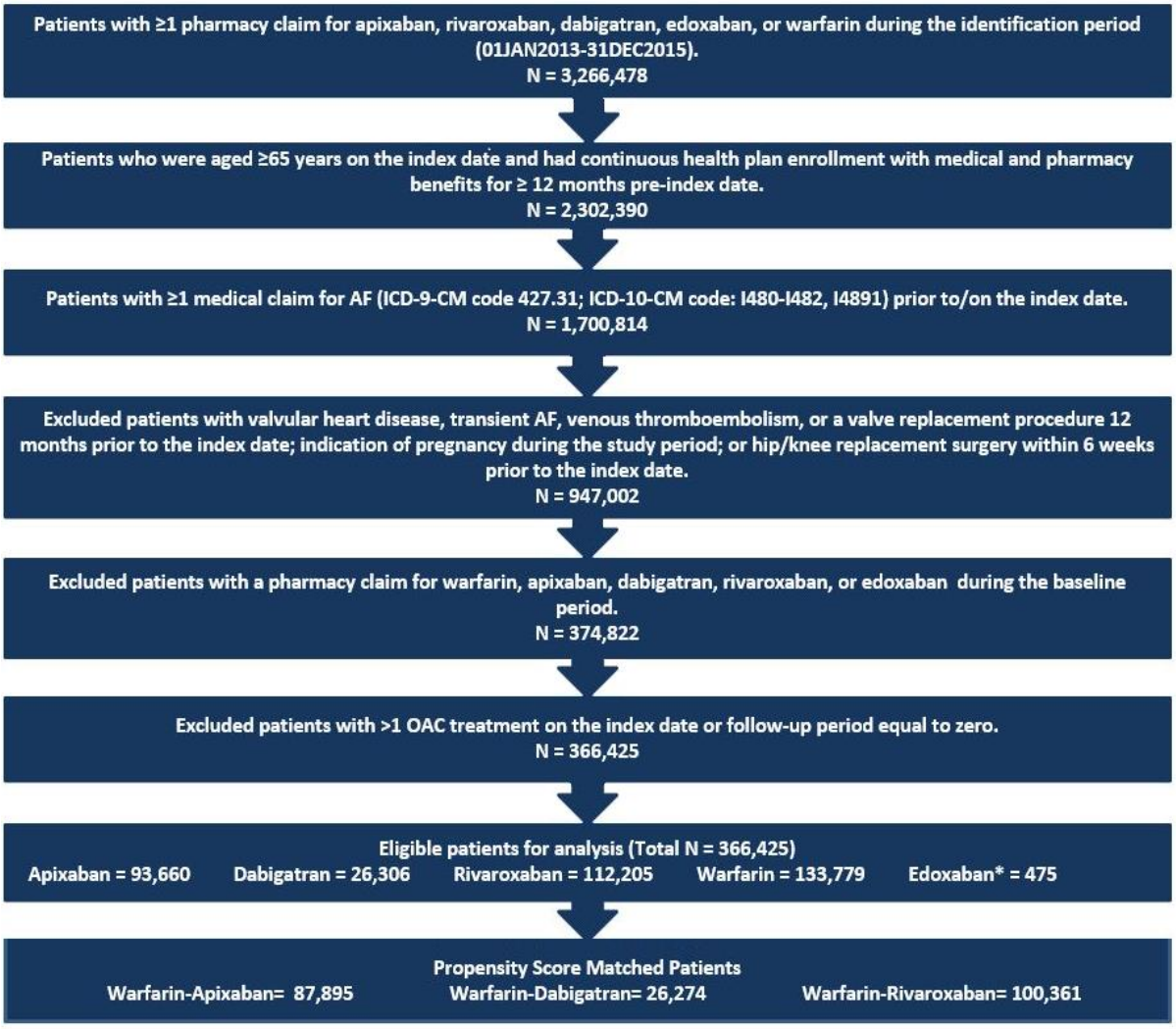
Ethical conduct of the study

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

10. RESULTS

10.1. Participants

Patient Flow



10.2. Descriptive data

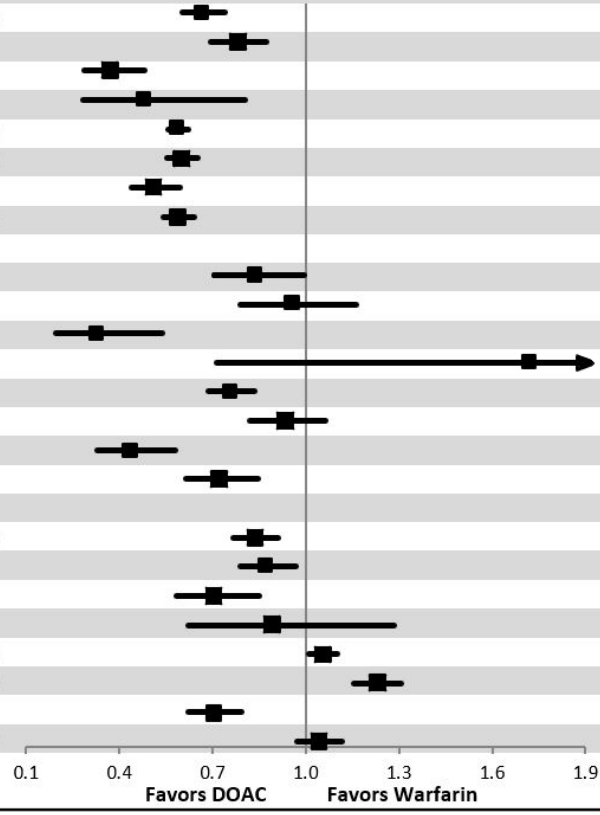
The study included eligible 198,171 patients; 81,410 (41.1%) was prescribed warfarin, 38,466 (19.4%) apixaban, 18,162 (9.2%) dabigatran, and 60,133 (30.3%) rivaroxaban. Edoxaban was excluded due to small sample size (N = 150). Before PSM, patients who initiated warfarin were older with a mean age of 79 years, followed by those who initiated apixaban (78 years), rivaroxaban (78 years), and dabigatran (77 years). In addition, warfarin patients also had higher CCI and CHA2DS2-VASc scores than DOAC patients (See Table 1 in publication).

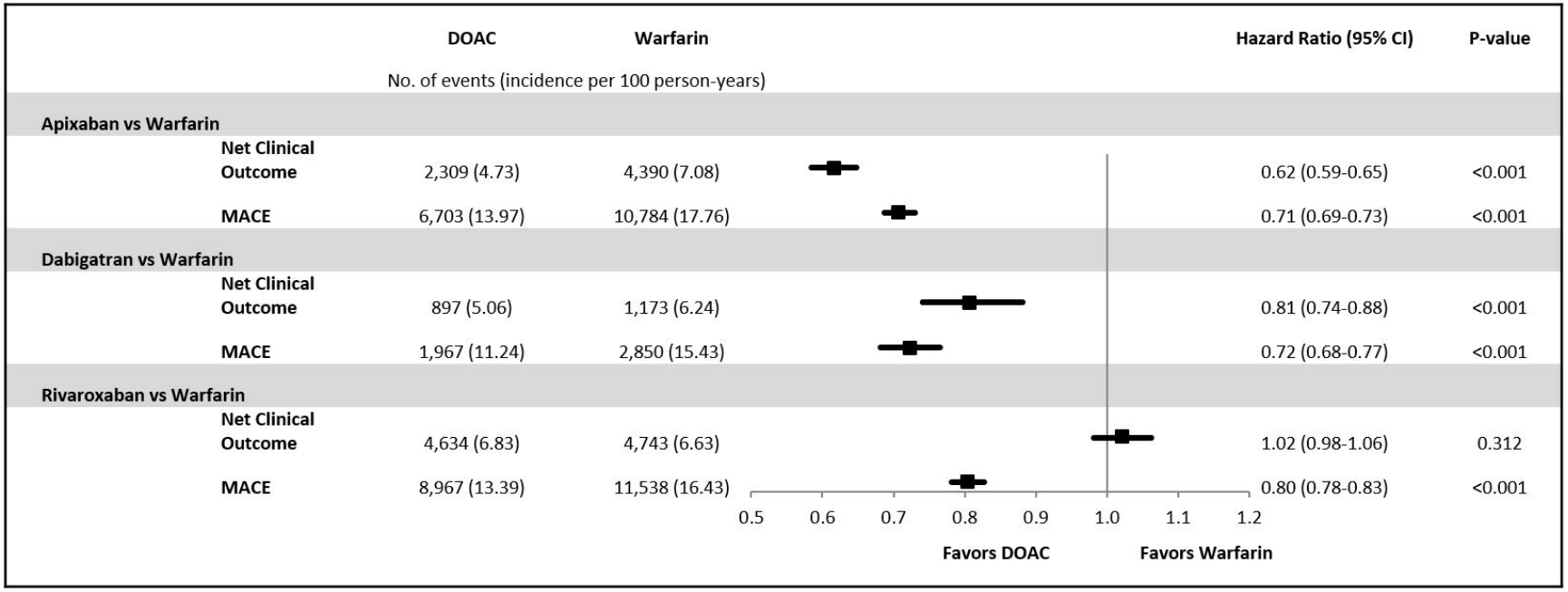
Through PSM, 37,525 apixaban, 18,131 dabigatran, and 55,359 rivaroxaban patients were separately matched to warfarin patients. Baseline characteristics were balanced after matching with mean standardized differences < 10%. For the matched cohorts, the means were: age: 77–78 years, CHA2DS2-VASc scores: 4.4–4.6, and HAS-BLED scores: 3.2–3.4 (Table 2 in publication). Patient data were assessed for a mean duration of 8–10 months. 71%, 80%, and 66% of patients were prescribed the standard dose of DOAC (apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg), respectively.

10.3. Outcomes

10.3.1. Stroke/SE and MB

	DOAC	Warfarin	Hazard Ratio (95% CI)	P-value
	No. of events (incidence per 100 person-years)			
Apixaban vs Warfarin				
Stroke/SE	586 (1.19)	1,036 (1.65)	0.67 (0.60-0.74)	<0.001
Ischemic	490 (1.00)	735 (1.17)	0.78 (0.70-0.88)	<0.001
Hemorrhagic	76 (0.15)	251 (0.40)	0.37 (0.29-0.48)	<0.001
SE	20 (0.04)	50 (0.08)	0.48 (0.28-0.80)	0.006
Major Bleeding	1,839 (3.75)	3,671 (5.90)	0.59 (0.56-0.62)	<0.001
GI Bleeding	886 (1.80)	1,718 (2.74)	0.60 (0.55-0.65)	<0.001
ICH	245 (0.50)	600 (0.95)	0.51 (0.44-0.59)	<0.001
Other Bleeding	808 (1.64)	1,595 (2.54)	0.59 (0.54-0.64)	<0.001
Dabigatran vs Warfarin				
Stroke/SE	231 (1.29)	292 (1.53)	0.84 (0.71-1.00)*	0.046
Ischemic	198 (1.11)	219 (1.15)	0.96 (0.79-1.16)	0.674
Hemorrhagic	20 (0.11)	65 (0.34)	0.33 (0.20-0.54)	<0.001
SE	13 (0.07)	<11 (0.04)	1.72 (0.72-4.16)	0.225
Major Bleeding	694 (3.90)	967 (5.12)	0.76 (0.69-0.84)	<0.001
GI Bleeding	434 (2.43)	493 (2.59)	0.93 (0.82-1.06)	0.298
ICH	68 (0.38)	164 (0.86)	0.44 (0.33-0.58)	<0.001
Other Bleeding	249 (1.39)	367 (1.93)	0.72 (0.61-0.85)	<0.001
Rivaroxaban vs Warfarin				
Stroke/SE	917 (1.34)	1,149 (1.58)	0.84 (0.77-0.91)	<0.001
Ischemic	681 (0.99)	814 (1.12)	0.88 (0.79-0.97)	0.010
Hemorrhagic	182 (0.26)	272 (0.37)	0.71 (0.58-0.85)	<0.001
SE	54 (0.08)	63 (0.09)	0.89 (0.62-1.29)	0.543
Major Bleeding	3,978 (5.85)	3,946 (5.49)	1.06 (1.01-1.10)	0.017
GI Bleeding	2,228 (3.26)	1,897 (2.62)	1.23 (1.16-1.31)	<0.001
ICH	429 (0.62)	644 (0.88)	0.70 (0.62-0.80)	<0.001
Other Bleeding	1,640 (2.39)	1,648 (2.28)	1.04 (0.97-1.12)	0.238





10.3.2. Cost data

	Warfarin Cohort			Apixaban Cohort			Difference between Marginal Effects	95% CI for Difference between Marginal Effects		P-Value
	Marginal Effect	95% Percentile CI for Marginal Effect		Marginal Effect	95% Percentile CI for Marginal Effect					
Sample Size										
Bootstrap Two-Part Model (1,000 Replications)										
Major Bleeding-related Medical Costs during follow-up (PPPM)	$468.88	$437.05	$504.77	$288.92	$261.71	$316.62	-$179.96	-$222.45	-$137.46	<.0001
Major Bleeding-related Hospitalization Costs (PPPM)	$118.13	$105.67	$132.31	$60.75	$53.70	$68.47	-$57.37	-$71.93	-$42.82	<.0001

Stroke/SE-related Medical Costs during follow-up (PPPM)	$111.06	$89.33	$133.07	$53.82	$43.33	$64.37	-$57.24	-$80.84	-$33.65	<.0001
Stroke/SE-related Hospitalization Costs (PPPM)	$50.47	$35.20	$68.21	$25.62	$19.43	$32.78	-$24.85	-$42.34	-$7.36	0.005

	Warfarin Cohort			**Dabigatran Cohort**			**Difference between Marginal Effects**	**95% CI for Difference between Marginal Effects**		**P-Value**
	Marginal Effect	**95% Percentile CI for Marginal Effect**		**Marginal Effect**	**95% Percentile CI for Marginal Effects**					
Bootstrap Two-Part Model (1,000 Replications)										
Major Bleeding-related Medical Costs during follow-up (PPPM)	$414.35	$372.37	$457.04	$326.37	$289.54	$367.39	-$87.98	-$145.41	-$30.56	0.0030
Major Bleeding-related Hospitalization Costs (PPPM)	$111.58	$94.79	$133.16	$76.27	$63.34	$90.47	-$35.32	-$59.16	-$11.47	0.0040
Stroke/SE-related Medical Costs during follow-up (PPPM)	$122.36	$88.81	$162.49	$73.37	$57.23	$90.21	-$48.99	-$88.37	-$9.62	0.0150
Stroke/SE-related Hospitalization Costs (PPPM)	$66.47	$39.88	$101.91	$41.44	$29.59	$54.13	-$25.03	-$57.83	$7.78	0.135

	Warfarin Cohort			**Rivaroxaban Cohort**			**Difference between Marginal Effects**	**95% CI for Difference between Marginal Effects**		**P-Value**
	Marginal Effect	**95% Percentile CI for Marginal Effect**		**Marginal Effect**	**95% Percentile CI for Marginal Effects**					
Sample Size										
Bootstrap Two-Part Model (1,000 Replications)										

Major Bleeding-related Medical Costs during follow-up (PPPM)	$468.73	$440.40	$498.68	$463.21	$436.41	$489.68	-$5.52	-$46.22	$35.19	0.791
Major Bleeding-related Hospitalization Costs (PPPM)	$125.91	$113.68	$141.29	$115.33	$105.33	$126.00	-$10.58	-$27.31	$6.15	0.215
Stroke/SE-related Medical Costs during follow-up (PPPM)	$121.80	$102.72	$142.82	$81.33	$69.04	$94.86	-$40.47	-$65.02	-$15.92	0.001
Stroke/SE-related Hospitalization Costs (PPPM)	$56.82	$42.45	$72.95	$33.20	$27.59	$40.38	-$23.62	-$39.45	-$7.80	0.003

10.4. Other analyses

Sensitivity analysis: In the sensitivity analysis wherein the follow-up period was censored at 6 months, the results were consistent with the main analysis.

10.5. Adverse events / adverse reactions

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

11. DISCUSSION

11.1. Key results

Using Medicare FFS data from 2012 to 2015, this study showed that compared to warfarin among elderly patients with NVAF, apixaban was associated with significant lower risks of stroke/SE, MB, NCO, and MACE. Dabigatran was associated with significantly lower risks of MB, NCO, and MACE as well as a numerically lower risk of stroke/SE. Rivaroxaban was associated with lower risks of stroke/SE and MACE, but higher MB and numerically higher NCO risks compared to warfarin.

The study results supplement RCT findings for apixaban, dabigatran, and rivaroxaban compared to warfarin and their corresponding age subgroup analyses [20–25]. In the RE-LY trial, patients (overall and $\geqslant$ 75 years) with 150 mg dabigatran had lower rates of stroke/SE and similar rates of MB compared to warfarin [20, 23]. In this real-world study among NVAF patients aged $\geqslant$ 65 years, 150 mg and 75 mg dabigatran showed numerically lower stroke/SE and significantly lower MB risks versus warfarin. Although NCO was not studied in the RE-LY trial's elderly group, overall dabigatran and warfarin patient analysis demonstrated that compared to warfarin, 150 mg twice-daily dabigatran was associated with a non-significantly lower risk of net clinical benefit (a composite of stroke/SE, pulmonary embolism, MI, death, and MB) [20]. In this study, elderly dabigatran patients were associated with significantly lower NCO and MACE risks than warfarin patients.

11.2. Limitations

This study has several limitations. Given its observational nature, confounding factors may have impacted the results. To control for potential confounders, a comprehensive list of baseline covariates was included in the PSM, including patient demographics and clinical characteristics. However, variables such as over-the-counter use of aspirin, serum creatinine/creatinine clearance, and laboratory test result values are not captured in the Medicare data. As claims data analysis, the study may also be subject to coding errors and inaccurate or incomplete clinical information. For example, treatments recorded based on

prescription claims include no evidence of drug adherence. Moreover, since international normalized ratio values were not obtained, the quality of warfarin treatment could not be evaluated and the calculation for HAS-BLED score was modified. Moreover, proper dosage for DOACs based on age, renal function, and weight could not be assessed.

11.3. Interpretation

See Key results (11.1) and Conclusions (13) sections.

11.4. Generalizability

12. OTHER INFORMATION

Not applicable

13. CONCLUSIONS

In summary, in the elderly Medicare population with NVAF, compared to warfarin, the DOACs were associated with a lower to similar risk of stroke/SE and MACE, but with varying comparative risks for MB and NCO.

14. REFERENCES

See below

15. LIST OF SOURCE TABLES AND FIGURES

Not applicable

---

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

[ii] 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.

[iii] 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.

[iv] 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.

[v] 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.

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

[vii] 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.

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

[ix] 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.

[x] 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.

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

[xii] 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.

[xiii] 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.

[xiv] 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.