NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Study Information

Title	Predictors of Treatment and the Comparative Clinical and Economic Outcomes Among Non-Valvular Atrial Fibrillation Patients Treated Versus Untreated with Oral Anticoagulant Therapy
Protocol number	B0661142
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Medicinal product	Apixaban
Research question and objectives	**Primary Objective:** 1. Estimate patients ever-treated and never-treated with oral anticoagulants (OACs) and the predictors of OAC treatment among elderly Medicare non-valvular atrial fibrillation (NVAF) population. **Secondary Objectives:** 1. Analyze high-risk patient subgroups, such as CHA_2DS_2-VASc score and age subgroups, for the primary objectives. 2. Compare the risk of major bleeding (MB) and MB-related costs among elderly patients

	treated versus untreated with OACs in the Medicare NVAF population. 3. Compare the risk of stroke/systemic embolism (SE) and stroke/SE-related costs among elderly patients treated versus untreated with OACs in the Medicare NVAF population. 4. Compare the risk of death among elderly patients treated versus untreated with OACs in the Medicare NVAF population 5. Compare the all-cause health care costs among elderly patients treated versus untreated with OACs in the Medicare NVAF population.
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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

Annex 1. List of stand-alone documents

1. ABSTRACT (STAND-ALONE DOCUMENT)

Title: Predictors of Treatment and the Comparative Clinical and Economic Outcomes Among Non-Valvular Atrial Fibrillation (NVAF) Patients Treated Versus Untreated with Oral Anticoagulation Therapy

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

Objectives:

Primary

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

Secondary

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

Study Design: The study was a longitudinal retrospective cohort analysis using the US Centers for Medicare & Medicaid Services (CMS) Medicare dataset from 01JAN2012-31DEC2017. The study designated a 12-month baseline period prior to the identification

period (01JAN2013-31DEC2017). This database included patients enrolled in fee-for-service (FFS) Medicare; those enrolled in managed-care plans were excluded. Further, patient eligibility was based on selection from the database according to the following inclusion and exclusion criteria (Section 2).

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

For the primary and secondary objectives, the ever-treated with OAC population cohort included newly diagnosed NVAF patients who ever initiated OAC treatment (apixaban, dabigatran, edoxaban, rivaroxaban, and warfarin) during the identification period identified from 01JAN2013-31DEC2017. The never-treated with OAC population cohort included newly diagnosed NVAF patients without any OAC claim from 01JAN2013-31DEC2017.

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

For the primary objective and high-risk subgroup analyses, patients were excluded based on the following criteria: an AF diagnosis any time prior to the first AF diagnosis; medical claims indicating a diagnosis or procedure for mitral valvular heart disease or heart valve replacement/transplant; or use of OACs during the baseline period. For the secondary objective assessing effectiveness, safety, and cost outcomes, patients were further excluded if they had any of the following: venous thromboembolism; transient AF during the baseline period; pregnancy during the study period; hip/knee replacement surgery within 6 weeks pre-index date; or follow-up period = 0 day. In addition, among patients ever treated with an OAC, those with >1 OAC prescription claim at the index date were excluded as well.

Variables: Baseline demographic and clinical characteristics included age, gender, race, geographic region, Medicaid dual eligibility, Part-D low income subsidy, Charlson comorbidity index (CCI), and congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke ($CHADS_2$) score, and congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age 65-74 years, sex category (CHA_2DS_2-VASc) score, and hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratios, elderly, drugs/alcohol (HAS-BLED) scores, prior bleeding/stroke events, CHF, diabetes, hypertension, chronic obstructive

pulmonary disease, renal disease, myocardial infarction, dyspepsia or stomach discomfort, peripheral arterial disease, transient ischemic attack, coronary artery disease, history of falls, medication use, and index dose of DOAC. Baseline all-cause health care costs and utilization were included.

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

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

Data Sources: 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.

Data Analysis: Means, medians, and standard deviations was provided for continuous variables. Numbers and percentages were provided for dichotomous and polychotomous variables. Bivariate comparisons of baseline characteristics and outcomes measures were provided. Appropriate tests (eg, t-test, chi-square test) were used, based on the distribution of the measure. Logistic regression models were used to examine the predictors of OAC treatment. For the secondary objectives assessing effectiveness, safety, and costs, the cumulative incidence rate for clinical outcomes (stroke/SE, MB, and death) were calculated. Inverse probability weighting (IPW) was used to balance treatment cohorts. Cox regressions with time-varying treatment status and marginal structural models (MSMs) was used to compare the treatment effects, all-cause and stroke/SE and MB-related health care costs. Data analysis was executed using statistical software, statistical analysis system (SAS) version 9.4.

Results:

Primary Objective: A total of 1,204,507 patients met the selection criteria and were eligible for inclusion. There were 586,896 patients in the ever-treated cohort and 617,611 patients in the never-treated cohort. Patients aged 75 to 84 years, compared with those aged 65-74 years, males compared with females, patients with ischemic stroke, SE, obesity, and hypertension compared to their counterparts without these conditions had higher odds of being ever-treated, compared with the never-treated cohort patients.

Secondary Objective: A total of 1,421,187 patients were deemed eligible for inclusion. There were 583,350 patients in the ever-treated cohort and 837,837 patients in the never-treated cohort. OAC treated patients had a lower risk of stroke/SE (hazard ratio [HR]: 0.70; 95%

confidence interval [CI]: 0.68-0.72) and death (HR: 0.56; 95% CI: 0.55-0.56) compared with OAC untreated patients. OAC treated patients had a higher risk of MB (HR: 1.57; 95% CI: 1.54-1.59) compared with OAC untreated patients.

Conclusions:

Using the Medicare database, we found that the odds of treatment was higher among patients with ischemic stroke, SE, obesity, and hypertension. OAC treated patients were at a lower risk of stroke/SE or death and a higher risk of MB compared with OAC untreated patients.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AF	Atrial Fibrillation
NVAF	Non-valvular Atrial Fibrillation
CAD	Coronary Artery Disease
CCI	Charlson Comorbidity Index
CHF	Congestive Heart Failure
PAD	Peripheral Arterial Disease
MI	Myocardial Infarction
$CHADS_2$	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
CPT	Current Procedural Terminology
DOAC	Direct Oral Anticoagulant
FFS	Fee-For-Service
RWD	Real World Data

Abbreviation	Definition
HAS-BLED	Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratios, Elderly, Drugs/Alcohol
HCPCS	Health care Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
ICD-9/10-CM	International Classification of Diseases – Clinical Modification, 9th/10th Revision
INR	International Normalized Ratio
MB	Major Bleeding
NDC	National Drug Code
OAC	Oral Anticoagulants
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism
SAS	Statistical Analysis System
CMS	Centers for Medicaid and Medicare Services
PDE	Medicare Part D Drug Events
DRG	Disease Related Group
HHA	Home Health Agency

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
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4. OTHER RESPONSIBLE PARTIES

Not Applicable

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Draft Protocol	October 2018	October 2018	
Descriptive Results	August 2019	August 2020	Request new data
Multivariate Results	November 2020	November 2020	
Final report of study results	January 2020	May 2021	

6. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) is characterized by chaotic and irregular electrical activity in the heart's upper chambers and is the most common heart dysrhythmia diagnosed in the United States.[7] AF has become more prevalent in an aging US population, and this trend is expected to increase exponentially in the coming decades.[8] AF causes a significant financial burden, costing the US health care system approximately $26 billion dollars annually. Hospitalizations account for most of these costs (52%).[9]

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

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

AF is often left untreated after diagnosis. Using registry data of cardiology practices in the United States, it was reported that only 55.1% of patients deemed eligible for warfarin were treated with this agent, and among whom, 35% were not treated with any antithrombotic or antiplatelet.[20] Another US study on patients of outpatient physician practices reported that 23% of NVAF patients did not receive any form of thromboprophylaxis.[21] Moreover, although OACs are recommended for patients with AF and high cardio-embolic risk (according to CHA_2DS_2-VASc [Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category] scores), <50% of patients aged 80-89 years are treated with OAC.[22] This may be due to short life-expectancy, fear of bleeding, geriatric syndromes, poor general health, and the overall perception that the harm outweighs the benefits.[22] Yet untreated patients had a lower survival rate and higher association with ischemic stroke events compared to OAC treated patients.[23]

This study estimates prevalence of newly diagnosed but untreated NVAF patients, adds real-world evidence for the predictors of treatment among newly diagnosed NVAF patients. In addition, it evaluates the risk of major bleeding (MB), stroke/SE, and death as well as health care costs by comparing OAC treatment versus no OAC treatment.

7. RESEARCH QUESTION AND OBJECTIVES

Primary Objective

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

Secondary Objectives

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

8. AMENDMENTS AND UPDATES

None.

Table 1. Amendments to the Protocol

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

9. RESEARCH METHODS

9.1. Study design

The study was a longitudinal retrospective cohort analysis using the US fee-for-service (FFS) Medicare database. This database contained data from inpatient departments, outpatient departments, carrier claims, reported drug events, and beneficiaries' enrollment data. The following were determined and compared between treatment status (treated with apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin and untreated with OAC): outcomes including MB, stroke/SE, and death; and health care costs. The overall study period was from 01JAN2012-31DEC2017. The study designated a 12-month baseline period prior to an identification period (01JAN2013-31DEC2017). The date of first AF diagnosis during the study period was assigned as the index date.

Figure 1. Study Design Figure for the Primary Objective (for illustration purposes, may not be proportionate)

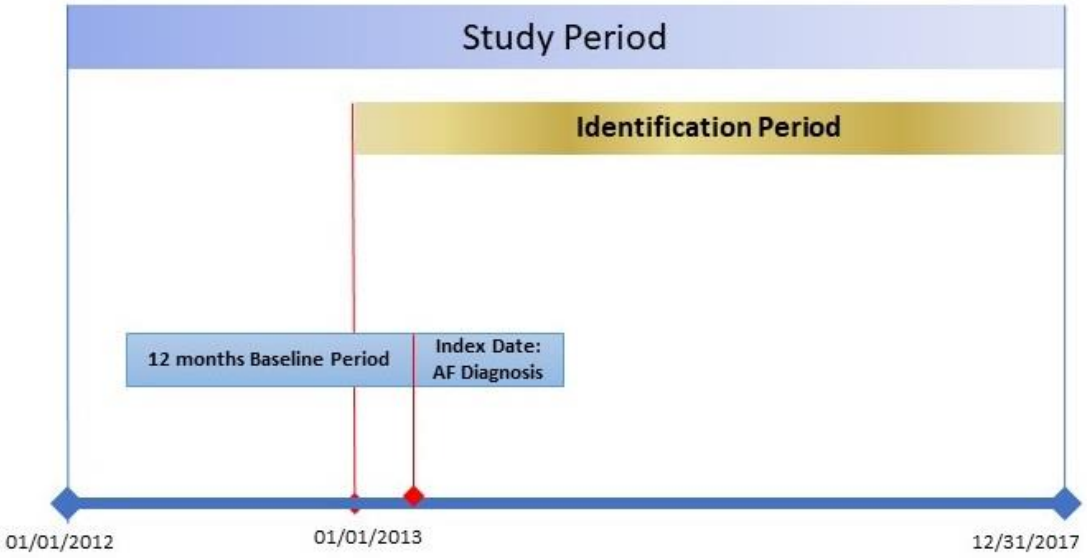


Figure 2. Study Periods for Untreated Patients in Secondary Clinical and Healthcare Cost Objectives (for illustration purposes only, may not be proportional)

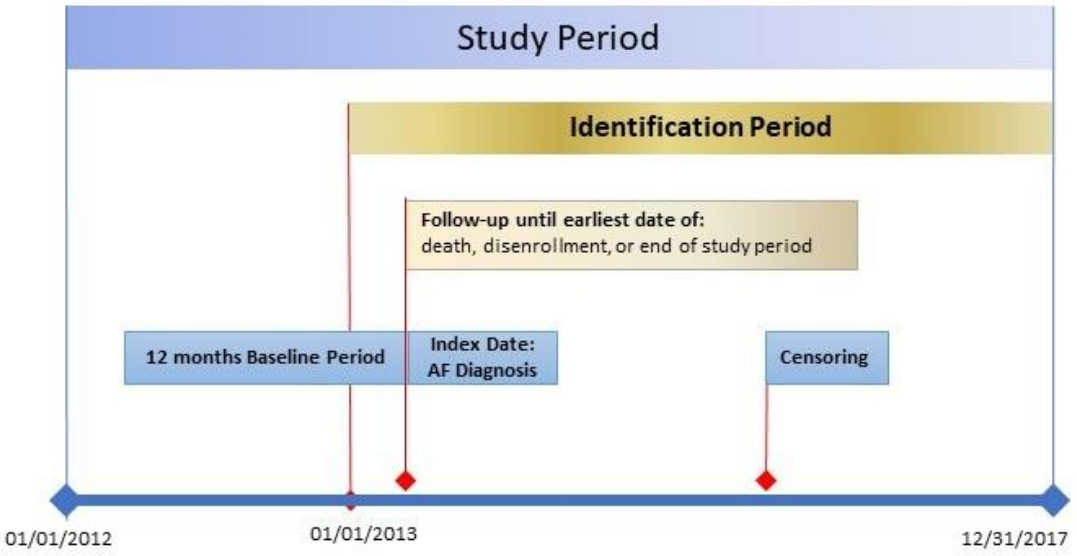
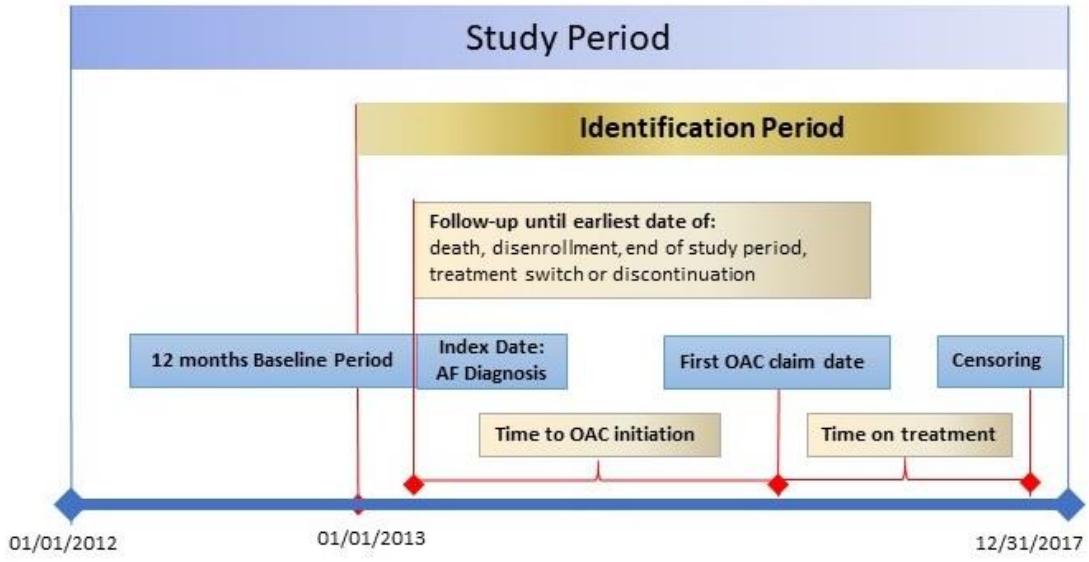


Figure 3 Study Periods for Treated Patients in Secondary Clinical and Healthcare Cost Objectives (for illustration purposes only, may not be proportional)



9.2. Setting

Ever treated with OAC and never treated with OAC patients were selected from 01JAN2013-31DEC2017. To ensure access to the patients' complete medical history, they were required to have continuous health plan enrollment for the 12 months before the first AF diagnosis date/index date (baseline period). Patient data was assessed from the index date until the earliest of death, health plan disenrollment, treatment switch (treated patients), discontinuation (treated patients), or 31DEC2017 (end of study).

9.3. Subjects

9.3.1. Inclusion Criteria

1) Patients had ≥1 inpatient claim or ≥2 outpatient claims (at least 7 days gap between the two outpatient claims) for AF (international classification of diseases, ninth revision, clinical modification [ICD-9-CM] code 427.31; ICD-10-CM: I480-I482, I4891) during 01JAN2013-31DEC2017. The first AF diagnosis claim dates during the identification period were designated as the index date[24];

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

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

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

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

9.3.2. Exclusion Criteria

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

Additional Exclusion Criteria (for secondary objectives):

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

9.3.3. Study Cohorts

Patients eligible according to the above criteria were assigned to the following cohorts for both the primary and secondary objective samples:

1) Ever-Treated Cohort: NVAF Patients had ≥1 pharmacy claim for apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin from 01JAN2013-31DEC2017 on or after the first AF diagnosis

   a. **Apixaban cohort:** Patients who initiated with apixaban on or after index date
   b. **Dabigatran cohort**: Patients who initiated with dabigatran on or after index date

c. **Edoxaban cohort:** Patients who initiated with edoxaban on or after index date. Given the small sample size, edoxaban patients were not included in the secondary clinical and healthcare utilization and costs analyses.

d. **Rivaroxaban cohort:** Patients who initiated with rivaroxaban on or after index date

e. **Warfarin cohort:** Patients who initiated with warfarin on or after index date

2) Never-Treated Cohort: NVAF patients with no pharmacy claim for an OAC from 01JAN2013-31DEC2017

9.4. Variables

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

Baseline Variables

Variable[a]	Role	Operational definition
Age	Baseline characteristic and potential predictor	Age was defined as of the index date, retained in the dataset as continuous, and divided by the following age groups: 65-74, 75-84, and ≥85 years.
Sex	Baseline characteristic and potential predictor	A flag was created for female beneficiaries on the index date and reported as a percentage.
Race/ethnicity	Baseline characteristic and potential predictor	A flag was created for White, Black, Hispanic, and other races/ethnicities on the index date.
US geographic region	Baseline characteristic and potential predictor	The US was divided into 5 regions: Northeast, South, Midwest, West, and Other. Geographic region was captured from enrollment data.
Index year	Baseline characteristic and potential predictor	A flag was created for patients with index date in the year of 2013-2017.
Medicaid dual eligibility	Baseline characteristic and potential predictor	A flag was created for patients with Medicaid dual eligibility.
Part-D low income subsidy	Baseline characteristic and potential predictor	A flag was created for patients with a Part-D low income subsidy.

Variable[a]	Role	Operational definition
Baseline Deyo-Charlson comorbidity index (CCI) score	Baseline characteristic and potential predictor	The Deyo-CCI score was created during the baseline.
Baseline Congestive heart failure, Hypertension, Age ≥ 75 years, Diabetes mellitus, Stroke ($CHADS_2$) score	Baseline characteristic and potential predictor	The $CHADS_2$ score was used to analyze the effect of stroke risk stratification on OAC use. The maximum score is 6. $CHADS_2$ scores: 2-3, 4-5, and ≥6.
Baseline CHA_2DS_2-VASc score	Baseline characteristic and potential predictor	The $CHADS_2VASc$ score was used as indicated above. The maximum score is 9. $CHADS_2$-VASc scores: 2-3, 4-5, and ≥6.
Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratios, Elderly, Drugs/Alcohol (HAS-BLED) score	Baseline characteristic and potential predictor	The HAS-BLED score was used to estimate the risk of MB. As the INR value was not available in the databases, a modified HAS-BLED score was calculated with a range of 0 to 8.
Baseline prior bleed	Baseline characteristic and potential predictor	A flag was created for patients with a bleeding-related claim during the baseline period.
Baseline prior stroke/SE	Baseline characteristic and potential predictor	A flag was created for patients with a stroke/SE claim during the baseline period.
Obesity	Baseline characteristic and potential predictor	A flag was created for patients with obesity claims during the baseline.
Congestive heart failure (CHF)	Baseline characteristic and potential predictor	A flag was created for patients with claims for CHF during the baseline period.
Diabetes	Baseline characteristic and potential predictor	A flag was created for patients with claims for diabetes in the baseline period.
Hypertension	Baseline characteristic	A flag was created for patients with claims for hypertension in the baseline period.

Variable[a]	Role	Operational definition
	and potential predictor	
Chronic Obstructive Pulmonary Disease (COPD)	Baseline characteristic and potential confounder	A flag was created for patients with COPD claims during the baseline
Renal disease	Baseline characteristic and potential predictor	A flag was created for patients with claims for renal disease in the baseline period.
Myocardial infarction (MI)	Baseline characteristic and potential predictor	A flag was created for patients with claims for MI in the baseline period.
Dyspepsia or stomach discomfort	Baseline characteristic and potential predictor	A flag was created for patients with claims for dyspepsia or stomach discomfort in the baseline period.
Peripheral arterial disease (PAD)	Baseline characteristic and potential predictor	A flag was created for patients with claims for PAD in the baseline period.
Transient ischemic attack	Baseline characteristic and potential predictor	A flag was created for patients with claims for transient ischemic attack in the baseline period.
Coronary artery disease (CAD)	Baseline characteristic and potential predictor	A flag was created for patients with claims for CAD in the baseline period.
History of falls	Baseline characteristic and potential predictor	A flag was created for patients with claims for fall(s) in the baseline period.
Baseline medication use	Baseline characteristic and potential predictor	Individual flags were created for patients with prescription claims for angiotensin converting enzyme inhibitors, amiodarone, angiotensin receptor blockers, beta blockers, H2-receptor antagonists, proton pump inhibitors, anti-platelets, statins, nonsteroidal anti-inflammatory drugs (NSAIDs), inhibitors of warfarin, inducers of warfarin, dronedarone, digoxin, calcium channel

Variable[a]	Role	Operational definition
		blockers, renin angiotensin system antagonists, glucocorticoids, diuretics, metformin, sulfonylureas, thiazolidinedione, insulin, other diabetes drugs, antiulcer agents, and antidepressant.
Index dose of direct oral anticoagulant (DOAC)	Baseline characteristic	The index dose of the DOAC was evaluated and categorized as standard (5mg apixaban, 150mg dabigatran, 60mg edoxaban, and 20mg rivaroxaban,) or low dose (2.5mg apixaban, 75mg dabigatran, 30mg edoxaban, and 10 or 15mg rivaroxaban)
Baseline all-cause health care costs	Baseline characteristic	All-cause health care costs in the baseline period were computed for inpatient, office, outpatient hospital, ER, pharmacy, DME, SNF, HHA, and hospice costs. Costs were adjusted to 2017 US dollars using the medical care component of the CPI. Total medical and total health care costs were calculated.
Baseline all-cause health care utilization	Baseline characteristic	All-cause health care utilization in the baseline period were 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 were used.

Clinical and Treatment Pattern Outcome Variables

Variable	Role	Operational Definition
Stroke/SE	Outcome	Stroke/SE was identified using hospital claims with a stroke/SE diagnosis code as the first listed ICD-9-CM or ICD-10-CM code. Stroke/SE was classified into 3 categories: ischemic stroke, hemorrhage stroke, and SE. Time to stroke/SE was defined as the number of days from index date to the occurrence of the first stroke/SE requiring hospitalization.
MB	Outcome	MB was identified using hospital claims with a bleeding diagnosis code as the first listed ICD-9-CM or ICD-10-CM diagnosis or procedure code.[27] Time to MB was defined as the number of days from index date to the occurrence of the first MB event requiring hospitalization. MB was further stratified by gastrointestinal and intracranial hemorrhages and other MB.

Variable	Role	Operational Definition
Death	Outcome	Death information from the database was used. Time to death was defined as the number of days from index date to death.
Discontinuation (Treated Patients)	Outcome	Treated patients was considered to have discontinued if there was no additional refill for the index anticoagulant after 30 days of the previous prescription's run-out date.[28] The discontinuation date was defined as the run-out date plus 30 days.
Time to discontinuation (Treated Patients)	Outcome	Time to discontinuation was defined as the number of days from the OAC prescription index date to the discontinuation date.
Switch among anticoagulants (Treated Patients)	Outcome	A switch among anticoagulants was defined as a prescription filled for non-index anticoagulants within 30 days before or after the run-out date.[28] Time to switch was defined as the number of days from the OAC prescription index date to the first prescription date of the switch.
Time-to-switch (Treated Patients)	Outcome	Time to switch was defined as the number of days from the OAC prescription index date to the switch date.

Health Care Resource Utilization and Cost Outcome Variables

Variable	Role	Operational Definition
Follow-up stroke/SE-related hospitalization costs	Outcome	Stroke/SE-related hospitalization costs included the first stroke/SE hospitalization costs. Costs were adjusted as indicated above.
Follow-up MB-related hospitalization costs	Outcome	Follow-up MB-related hospitalization costs included the first MB hospitalization costs. Costs were adjusted as indicated above.
Follow-up all-cause health care costs	Outcome	All-cause health care costs in the follow-up period were computed for inpatient, office, ER, total outpatient (office, ER, and other outpatient), pharmacy, and other (DME, SNF, HHA, and hospice) costs. Costs were also be adjusted to 2017 US dollars using the medical care component of the CPI. Total medical (inpatient, outpatient, and other) and total health care (medical and pharmacy) costs were calculated PPPM.

9.5. Data sources and measurement

Medicare Inpatient Data

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

Medicare Outpatient Data

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

Medicare Carrier File

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

Medicare PDE Data

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

Skilled Nursing Facility

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

Home Health Agency (HHA)

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

Hospice

The Hospice file contains final action claims submitted by hospice providers. Once a beneficiary elects a hospice, all hospice-related claims are included in this file regardless of whether the beneficiary is in a Medicare FFS or Medicare managed-care plan. This file also includes level of hospice care received (eg, routine home care, inpatient respite care), terminal diagnosis (ICD-9-CM and ICD-10-CM diagnoses), dates of service, reimbursement amounts, hospice provider number, and beneficiary demographic information.

Durable Medical Equipment

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

Medicare Denominator File

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

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

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

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

9.6. Bias

For the primary objective, covariates were adjusted in the logistic regression model to assess for factors that could potentially influence treatment choice.

In order to balance possible confounding factors between the treatment cohorts, IPTW procedure was used when assessing clinical outcomes and a similar procedure was used for the economic outcomes. Details of these procedures are provided in Section 9.9.

9.7. Study Size

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

Using the AVERROES stroke/SE rates of 1.6% and 3.7% per year for apixaban and aspirin users, respectively, a Cox proportional hazards analysis of stroke/SE would need 225 patients per group with 10% loss of follow up (Table 2).

Table 2. Power Calculation (Stroke/SE)

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

Using the AVERROES MB rates of 1.4% per year in the apixaban group and 1.2% per year in the aspirin group, a Cox proportional hazards analysis of MB would need 11,837 patients per group (Table 3).

Table 3. Power Calculation (MB)

	MB (from AVERROES)	Follow-up Time (Maximum)	Loss of Follow up	Accrual Time	Total Estimated Sample Size (1:1 in each group)
Apixaban	1.4%	4 years	53.7% (Amin et al[Error! Bookmark not defined.])	4 years	
Untreated	1.2%		10%		23674
			15%		27498
			20%		31870
			25%		36848
			30%		42494

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

Stroke/SE and MB rates have been shown to be higher using real world data (RWD) compared to randomized controlled trial (RCT) data, so the sample size estimated to achieve 80% power may be overestimated.

9.8. Data transformation

Not applicable.

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

9.9. Statistical methods

9.9.1. Main summary measures

When performing descriptive analysis of continuous data, means, medians, and standard deviations were provided for continuous variables. When performing descriptive analysis of categorical data, numbers and percentages were provided for dichotomous and polychotomous variables. Bivariate comparisons of baseline characteristics and outcomes measures were provided. Appropriate tests (eg, t-test, chi-square test) were used based on the distributions of the measures. The cumulative incidence rate for clinical outcomes (MB, stroke/SE, and death) 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

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

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

Stepwise model selection was used to identify risk factors with a cutoff of 0.10. The covariate lists were finalized based on clinical rationale and model fitting.

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

Inverse Probability Weighting (IPW; Secondary Clinical Objectives)

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

The propensity score was defined as the probability of a patient receiving OAC treatment or being censored conditional on time-independent baseline covariates (age, gender, race, and clinical characteristics). The list of variables included in the logistic model was based on clinical rationale. The propensity score acts as a balancing score among the cohorts.

After calculating the propensity score, the distribution of the propensity scores were reviewed.

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

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

The distribution of the stabilized weight was reviewed and the stabilized weights were applied to the sample. After the weights were applied, the balance of the time-dependent and time-independent covariates was assessed.

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

For continuous variables, the balance of the distribution was also assessed. The high-order movements and interactions between variables should be similar between cohorts. The standardized difference was used to compare the mean of the square of continuous variables.

Graphical comparisons of the distribution of continuous variables were completed. Side-by-side boxplots and empirical cumulative distribution functions were used to compare the distribution of continuous covariates in the unweighted and weighted samples. Since the graphical approach can be subjective, a numerical method for comparing the distribution of continuous baseline covariates was completed. Kolmogorov-Smirnov test allows a comparison of the distribution of a continuous variable between two independent groups.[33, 34, 35, 36]

Time-Varying Cox Regression Models (Secondary Clinical Objectives)

Time-varying cox regression models were used to compare the time to stroke/SE, MB, and death between: 1) treated vs untreated; 2) each OAC vs untreated after inverse probability treatment weighting. Treatment was used as a time varying covariate, in order to account for the untreated period of an ever-treated patient. CHA_2DS_2-VASc and HAS-BLED scores were also included as time-dependent variables in the models. Weights generated using IPW were incorporated.

Marginal Structural Models (MSMs; Secondary Cost Objective)

A weighted generalized estimating equation (GEE) models was applied for the multivariate analysis of health care costs among: 1) treated vs untreated; 2) each OAC vs untreated. For cost outcomes, gamma distribution and a log link was used. IPW weights were incorporated to adjust for baseline covariates and any time dependent confounders. Time-dependent confounders were not included in the repeated measures model – as their effects have been incorporated into the weights.[32] Treatment was included as a time-dependent variable, and time-invariant covariates were included based on results of IPW and clinical rationale.

All data analysis was executed using the statistical software statistical analysis system (SAS) version 9.4.

9.9.3. Missing values

Missing data, if any, were not imputed.

9.9.4. Sensitivity analyses

Additional subgroup and sensitivity analyses were conducted, including:

- high-risk CHA_2DS_2-VASc score subgroups, specifically, 2-3, 4-5, and ≥6 (primary objective): assess whether the predictors of treatment were impacted by baseline CHA_2DS_2-VASc score.

- high-risk age subgroups, specifically, 65-74, 75-79, and ≥80 years (primary objective): assess whether the predictors of treatment were impacted by age.

- censor patients at 1 year (secondary clinical objectives): assess whether the differential follow-up time in each cohort affected the clinical outcomes.

- adjusting for the competing risks of death (secondary clinical objectives): assess whether death is a competing risk in the clinical outcome analyses.

- falsification outcomes, including chronic obstructive pulmonary disease, pneumonia, and urinary tract infection were assessed to examine the presence of residual confounding.

9.9.5. Amendments to the statistical analysis plan

None

9.10. Quality control

Standard STATinMED quality control procedures were used.

9.11. Protection of human subjects

Subject information and consent

Not Applicable

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

IRB/IEC review was 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; it followed generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology, Good Epidemiological Practice guidelines issued by the International Epidemiological Association, Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research, International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences, European Medicines Agency, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, the Guide on Methodological Standards in Pharmacoepidemiology, and the FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, or equivalents.

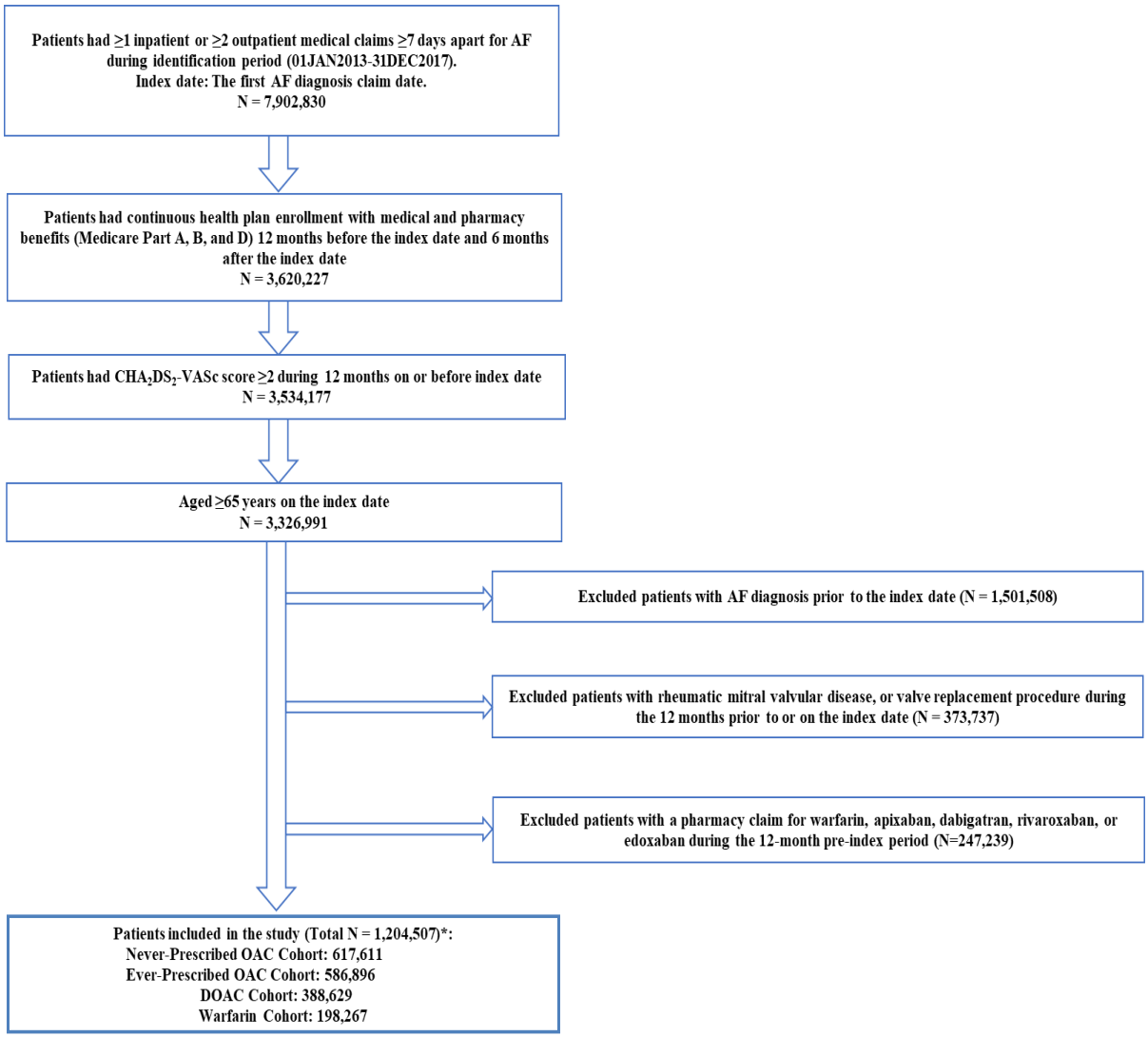
10. RESULTS

10.1. Participants

Primary Objective:

After applying all the selection criteria, a total of 1,204,507 patients were selected. Among the total patients, 586,896 patients (48.7%) were in the ever-prescribed cohort, while 617,611 (51.3%) patients were in the never-prescribed cohort. Of the 586,896 patients in the ever-prescribed cohort, there were 388,629 DOAC (203,204 apixaban, 28,421 dabigatran, 156,183 rivaroxaban, and 821 edoxaban), and 198,267 warfarin patients (Figure 4).

Figure 4. Patient Selection Flowchart

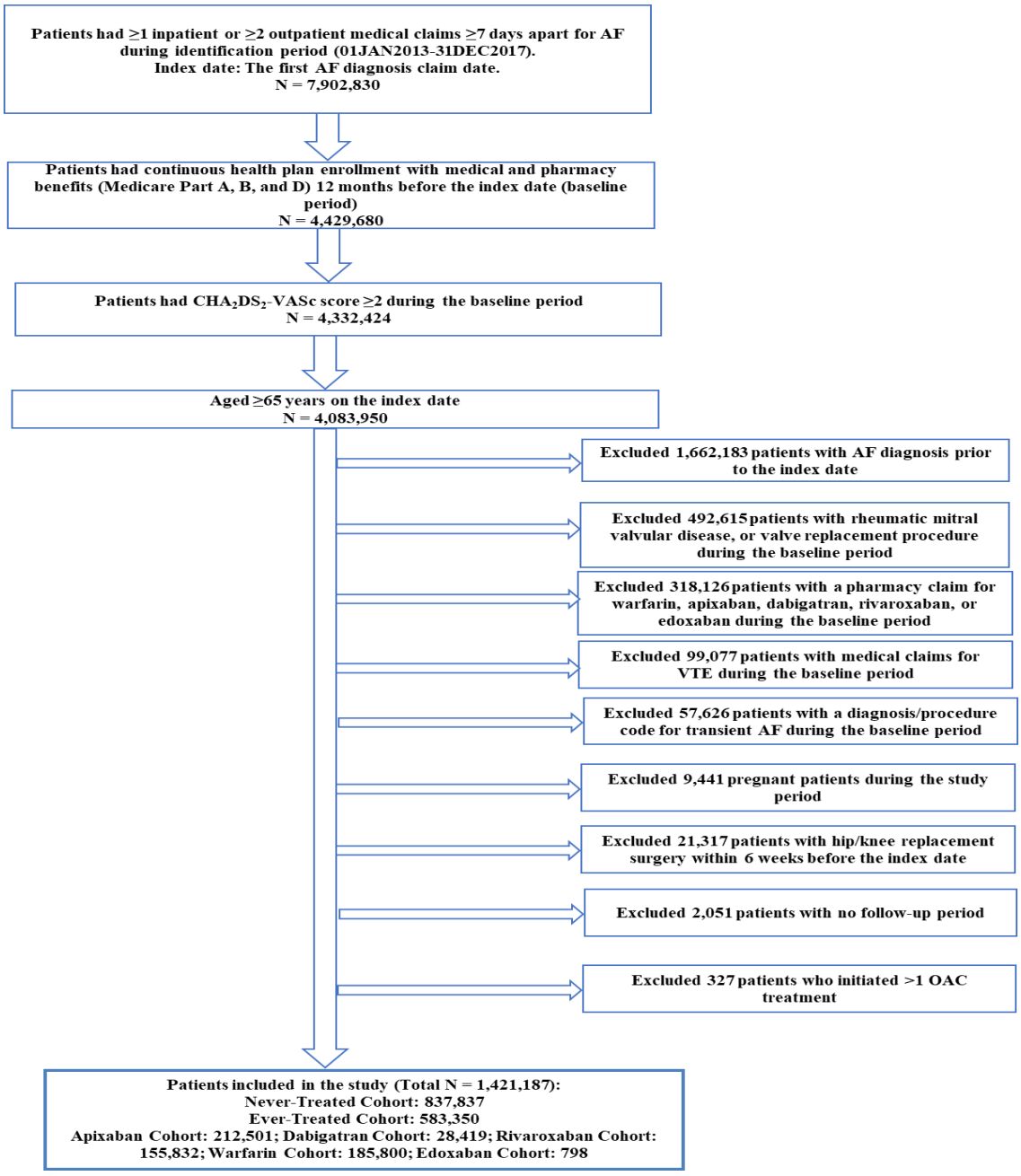


AF: Atrial Fibrillation; DOAC: Direct Oral Anticoagulants; ICD-9/10-CM: International Classification of Diseases 9th/10th Revision Clinical Modification

Secondary Objective:

After applying all selection criteria, there were 1,421,187 patients in the final sample. Of these, 837,837 patients (59.0%) were assigned to the never-treated cohort and 583,350 patients (41.0%) were assigned to the ever-treated cohort. Of the 583,350 ever-treated patients, there were 212,501 (36.4%) apixaban, 28,419 (4.9%) dabigatran, 155,832 (26.7%) rivaroxaban, and 185,800 (31.9%) warfarin treated patients (Figure 5).

Figure 5. Selection Criteria for the Secondary Objective



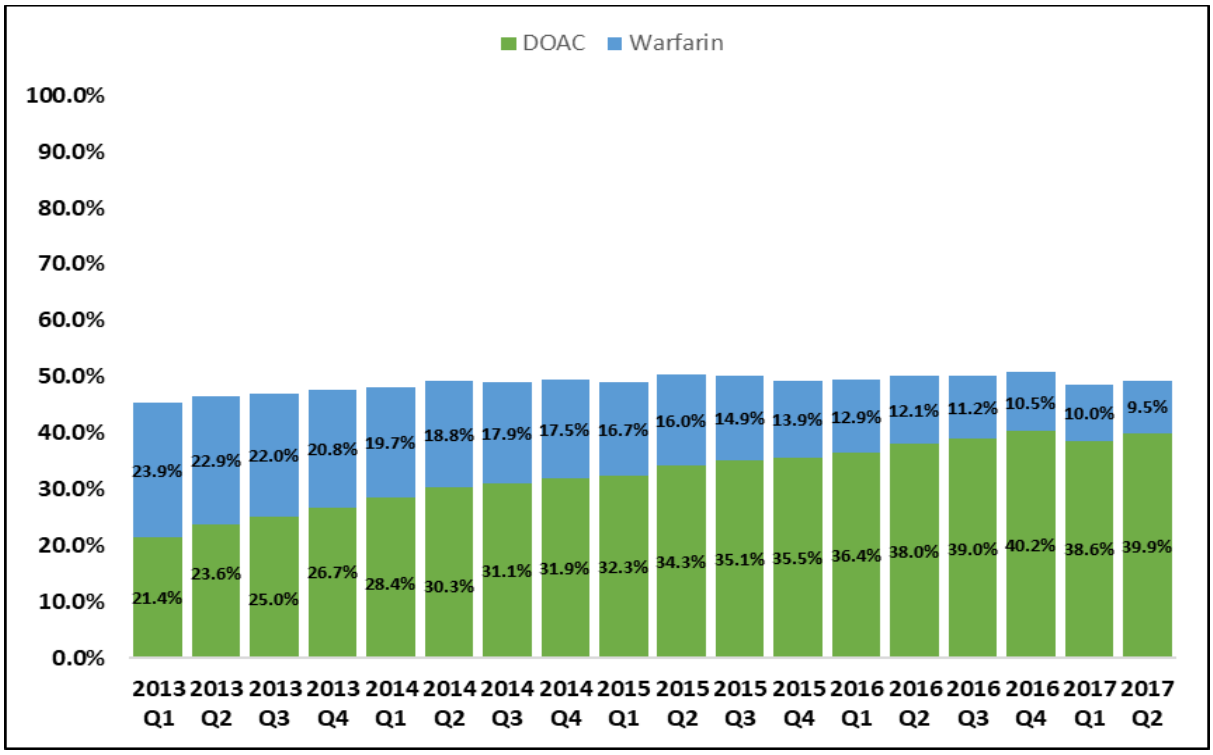
AF: Atrial Fibrillation; OAC: Oral Anticoagulants; VTE: Venous Thromboembolism

10.2. Descriptive data

Primary Objective:

The proportion of patients prescribed a DOAC increased from 21.4% in Q1 of 2013 to 39.9% in Q2 of 2017. The proportion of patients prescribed warfarin decreased from 23.9% in Q1 of 2013 to 9.5% in Q2 of 2017 (Figure 6).

Figure 6 Warfarin and DOAC Treated Patients Over Time



Q1: First Quarter; Q2: Second Quarter; Q3: Third Quarter; Q4: Fourth Quarter

Ever-prescribed patients were younger than never-prescribed patients (77.9 vs 80.4 years, p<0.001). Both DOAC (77.8 vs 80.4 years, p<0.001) and warfarin (78.2 vs 80.4 years, p<0.001) cohorts were younger than never-prescribed patients (Table 4).

The proportion of males was higher in the ever-prescribed (44.8% vs 41.8%), DOAC (44.9% vs 41.8%), and warfarin cohorts (44.7% vs 41.8%), compared with the never-treated cohort. The proportion of whites were higher in the ever-prescribed (89.7% vs 86.3%), DOAC (90.2% vs 86.3%), and warfarin (88.7% vs 86.3%) cohorts, compared with the never-prescribed cohort. CHA_2DS_2-VASc score was lower in the ever-prescribed (4.53 vs 4.76), DOAC (4.43 vs 4.76), and warfarin (4.71 vs 4.76) cohorts compared with the never-prescribed cohort. HAS-BLED score was lower in the ever-prescribed (3.26 vs 3.46), DOAC (3.20 vs 3.46), and warfarin (3.37 vs 3.46) cohorts compared with the never-prescribed cohort (Table 4).

Secondary Objective:

The proportion of males in the ever-treated cohort was higher compared with the never-treated cohort (45.6% vs 42.6%). Ever-treated cohort had a higher proportion of whites compared with the never-treated cohort (90.0% vs 86.4%). The average CHA_2DS_2-VASc score was lower in the ever-treated cohort, compared with the never-treated cohort (4.49 vs 4.84). The average HAS-BLED score was lower in the ever-treated cohort compared with the never-treated cohort (3.22 vs 3.53).

Obesity was higher among the ever-treated cohort patients compared with the never-treated cohort (21.2% vs 15.3%). CHF (26.5% vs 34.7%), chronic obstructive pulmonary disease (23.4% vs 31.3%), renal disease (23.7% vs 33.6%), and CAD (41.8% vs 48.0%) were less common in the ever-treated cohort compared with the never-treated cohort (Table 5).

10.3. Outcome data

Primary Objective:

Ever-Prescribed vs Never-Prescribed

Outcome data is presented in Table 6. Never-treated patients were followed for an average of 828 days and treated patients were followed for an average of 915 days.

The multivariable logistic regression model to assess predictors of OAC prescription found several characteristics which were significant predictors. Age ≥85 years (odds ratio [OR]: 0.55, 95% confidence interval [CI]: 0.55-0.56), female sex (OR 0.96, 95% CI 0.95-0.96), Black race (OR 0.78, 95% CI 0.77-0.79) and key comorbidities such as CAD (OR 0.89, 95% CI 0.88-0.90), diabetes (OR 0.92, 95% CI 0.91-0.93), renal disease (OR 0.86, 95% CI 0.86-0.87), history of falls (OR 0.72, 95% CI 0.71-0.73), GI bleeding (OR 0.43, 95% CI 0.41-0.44), and intracranial bleeding (OR 0.29, 95% CI 0.28-0.31) predicted underutilization of OAC therapy. Ischemic stroke (OR 1.94, 95% CI 1.89-1.98), SE (OR: 4.70, 95% CI 4.13-5.35), obesity (OR 1.38, 95% CI 1.36-1.39), CHF (OR 1.08, 95% CI 1.07-1.09) and hypertension (OR 1.10, 95% CI 1.09-1.11) were associated with higher odds of OAC prescription.(Figure 7)

The results for the warfarin vs never-prescribed and DOACs vs never-prescribed comparisons were generally consistent with the main analysis. (Figure 8 and 9)

DOACs vs Warfarin

Among AF patients ever-prescribed an OAC, additional multivariable logistic models identified several significant predictors of DOAC versus warfarin prescription. Characteristics that predicted lower odds of DOAC versus warfarin prescription included: age ≥85 (OR 0.92, 95% CI 0.91-0.94), Black race (OR: 0.78, 95% CI 0.76-0.80), ischemic stroke (OR 0.77, 95% CI 0.75-0.80), GI bleeding (OR 0.73, 95% CI 0.68-0.77), intracranial bleeding (OR 0.72, 95% CI 0.65-0.80), residence in the Midwest region (OR 0.75, CI 0.74-0.76), and inpatient visits (OR 0.82, CI 0.80-0.83). Transient ischemic attack (OR 1.22, 95%

CI 1.20-1.25), obesity (OR 1.07, 95% CI 1.05-1.08), and hypertension (OR 1.05, 95 CI 1.03-1.07) predicted higher odds of DOAC versus warfarin prescription. (Figure 10)

Secondary Objective:

Weighted descriptive results are presented in Tables 7 and 8.

The risk of stroke/SE was lower among the OAC treated (HR 0.70; CI- 0.68-0.72) and individual drug cohorts (apixaban: HR: 0.66; 95% CI 0.63-0.70; dabigatran: HR- 0.86; 95% CI: 0.74-1.00; rivaroxaban: HR 0.84; 95% CI 0.79-0.89; warfarin: HR 0.95; 95% CI: 0.91-0.99) compared with the untreated cohort. (Figure 11) Similar trends were observed for ischemic stroke.

OAC treated patients were at a higher risk of having a major bleed (HR: 1.57; 95% CI: 1.54-1.59) during their OAC-treated period compared with the non-OAC treated duration of patients. Consistent trends were observed across all individual OACs (apixaban HR: 1.13; 95% CI: 1.10-1.17; dabigatran HR: 1.45; 95% CI: 1.32-1.59; rivaroxaban HR: 1.84; 95% CI: 1.79-1.90; warfarin HR: 1.69; 95% CI: 1.65-1.73). Generally consistent trends were observed for GI bleeding and intracranial hemorrhage; however, there was no significant difference for intracranial hemorrhage between apixaban and dabigatran patients versus those who were untreated. (Figure 12) Patients with OAC treatment were associated with a lower risk of death compared to those who were untreated.

Economic Outcomes:

OAC treated patients had significantly lower all-cause total health care costs PPPM compared to OAC untreated patients ($4,381 vs $7,172; p<0.0001). This trend was apparent for all individual OACs (apixaban: $4,110 vs $6,719; dabigatran: $3,919 vs $6,710; rivaroxaban: $4,111 vs $6,728; warfarin: $4,608 vs $7,127; all p<0.001). While inpatient and other costs were significantly lower for OAC treated patients versus untreated patients, pharmacy costs were significantly higher for the OAC treated patients compared to the untreated patients.

Stroke/SE-related hospitalization costs PPPM were significantly lower for all OAC treated patients ($31 vs $41, <0.0001) and those treated with apixaban ($21 vs $43; p<0.0001), dabigatran ($30 vs $45; p<0.0001), and rivaroxaban ($27 vs $43, p<0.0001). MB-related hospitalization costs PPPM were significantly higher in the overall OAC treated cohort ($80 vs $60) and for those treated with rivaroxaban ($81 vs $66, p<0.0001) and warfarin ($104 vs $67, p<0.0001); however, the costs were significantly lower for those treated with apixaban ($53 vs $65; p<0.0001; Table 9).

10.4. Main results

Primary Objective:

Predictors of underutilization of OACs were age ≥85 years, female gender, black race, and key comorbidities such as CAD, diabetes, renal disease, history of falls, GI bleeding, and intracranial bleeding.

Secondary Objective:

The risk of stroke/SE and death was lower among AF patients being treated with OACs compared with those who are not treated with OACs. The risk of MB was higher among AF patients being treated with OACs compared with those who are not treated.

10.5. Other analyses

For the primary analysis, the sensitivity analyses examining subgroups of CHA_2DS_2-VASc and age showed consistent results with the main analysis. Results are available in the appendix results file.

For the secondary objectives, three sensitivity analyses were conducted. The first one was with death as a competing risk and the second was patients censored at one year of follow-up. Results showed consistent trends. In addition, falsification outcomes including, urinary tract infection, pneumonia, and chronic obstructive pulmonary disease (COPD) were examined. Falsification analysis for urinary tract infection was statistically significant for the comparisons examined using the cox regression models, which implies residual confounding. (Figures 13-15).

10.6. Adverse events / adverse reactions

Not applicable as this is a retrospective study using an insurance claims database where adverse event information is not readily available.

11. DISCUSSION

11.1. Key results

Primary Objective:

Over the study period, the proportion of patients prescribed warfarin reduced from 23.9% to 9.5% and DOAC prescription increased from 21.4% to 39.9%, becoming the most commonly prescribed OAC. Specific patient characteristics such as advanced age, female gender, black race, and presence of key comorbidities predicted underutilization of OAC therapy. Most of these variables also predicted lower DOAC prescription among eligible AF patients. There was an increase in OAC prescription with advancing age and history of ischemic stroke.

Secondary Objective:

The OAC treated cohort patients during their treated period had a lower risk of stroke/SE and death compared with the untreated period of all patients. The OAC treated cohort patients during their treated period had a higher risk of MB compared with the untreated period of all

patients. The results were consistent with the main analysis when patients were censored at one year and when death was used as a competing risk.

The risk of GI bleeding and intracranial hemorrhage were higher during the treated period of OAC treated cohort patients compared with the untreated period of all patients. The risk of ischemic stroke among the treated cohort patients during their treated period was lower compared with the untreated duration of all patients.

Several falsification analyses were performed using chronic obstructive pulmonary disease, pneumonia, and urinary tract infection as falsification outcomes. The results were statistically significant when urinary tract infection was used as a falsification outcome indicating a possibility of the presence of residual confounding.

11.2. Limitations

The study is limited by the nature of claims data, which may be constrained by issues such as over-the-counter use of aspirin, incorrect coding, claims without actual medicinal treatment, and other incomplete claims information. Moreover, although patients will be matched on baseline demographic and clinical characteristics, given the nature of retrospective observational studies, residual confounders may still exist, especially between the ever treated versus never treated NVAF patients. As a result, only associations between variables can be studied, without assessment of causal relationships. In addition, given the differences between the ever treated and never treated populations and the results from the primary objective for the predictors of treatment, the comparative analyses for stroke/SE, MB, and health care costs in the secondary objectives may not be feasible. Comorbidities at baseline (eg, presence of renal impairment) will be determined only by the presence of ICD-9-CM and ICD-10-CM diagnosis codes in the baseline period, not based on actual lab values or clinical assessment. Finally, warfarin treatment is continuously dose-adjusted so there is no low or high-dose strategy that can be defined.

11.3. Interpretation

One of the most devastating complication of AF is ischemic stroke and AF related strokes tend to have worse mortality and morbidity when compared to strokes unrelated to AF.[37, 38] Before the introduction of DOACs, warfarin was the standard anticoagulant used to reduce stroke risk in eligible AF patients. Warfarin is characterized by unpredictable pharmacokinetics, extensive food and drug interactions, and frequent need for laboratory monitoring.[39, 40] Several earlier studies have shown underutilization of OAC therapy in eligible AF patients for stroke risk reduction. Most of these studies were done in the era when warfarin was still the standard of care for stroke prevention in AF patients and such underutilization could be related to unfavorable warfarin profile. In a systematic review conducted by Ogilvie at al. on AF patients with a prior history of stroke, the utilization of OAC (warfarin) therapy was only 60%.[41] Similarly, in a study of about 9706 worldwide patients with AF, Suarez et al. showed a warfarin utilization rate of 39.5%.[42] They also showed that only 28% of patients above 75 years were prescribed warfarin treatment.

Additionally, a study of AF and CHF patients from the American Heart Association's Get With the Guidelines Heart Failure program, Piccini et al. showed median prevalence of 64.9% for warfarin treatment (interquartile range 55.5-73.4) among eligible patients.[43] In a more contemporary analysis of AF patients insured by private companies, Al-Khatib et al. demonstrated that nearly one third of such patients were not treated with an OAC.[44] Their study period encompassed the time frame in which DOACs were assimilated in clinical practice. Our more contemporary study of nearly 1.2 million elderly AF patients showed a gradual trend towards increase in DOAC prescription (which has become the more commonly prescribed OAC) but overall prevalence of OAC prescription continued to be below guideline-based recommendation in this at-risk of stroke patient population (CHA_2DS_2-VASc score ≥2).

Due to the low prevalence of OAC prescription in eligible AF patients, it is imperative to assess specific patient characteristics that are associated with OAC underutilization. In our study, advanced age ≥85 years (OR 0.55, 95% CI 0.55-0.56), female gender (OR 0.96, 95% CI 0.95-0.96), Black race (OR 0.78, 95% CI 0.77-0.79) and key comorbidities such as CAD (OR 0.89, 95% CI 0.88-0.90), diabetes (OR 0.92, 95% CI 0.91-0.93), renal disease (OR 0.86, 95% CI 0.86-0.87), history of falls (OR 0.72, 95% CI 0.71-0.73), GI bleeding (OR 0.43, 95% CI 0.41-0.44), and intracranial bleeding (OR 0.29, 95% CI 0.28-0.31) predicted underutilization of OAC therapy. In a study of about 674,841 AF patients who met criteria for anti-coagulation from the National Cardiovascular Data Registry (NCDR) Pinnacle registry, Lubitz et al. also demonstrated that female gender and renal disease predicted under prescription of OAC therapy.[45] In another study from the NCDR Pinnacle registry, Thompson et al. showed that OACs were underutilized in women as compared to men (56.7% vs. 61.3%, $p < 0.001$).[46] This lower utilization in women persisted at all levels of CHA_2DS_2-VASc score. The etiology behind this low utilization of OAC therapy in women is unclear but could be related to both patient and provider preference. Women are more likely to refuse OAC due to bleeding concerns and lack of logistic support required for frequent laboratory monitoring, especially if they are prescribed warfarin.[47] Indeed, our study has shown increased odds of DOAC prescription in women compared to men (OR 1.02, 95% CI 1.01-1.03) perhaps due to the aforementioned reason. There may be a bias on the part of providers in applying relevant guidelines to the female population that have also contributed to low OAC prescription prevalence.[48, 49] Similarly, the low prevalence of OAC prescription in patients with renal disease could be related to perceived risk of bleeding in such patients. In our study, patients with renal disease also have lower odds of DOAC prescription when compared to warfarin (OR 0.78, 95% CI 0.77-0.79). In a recent meta-analysis of 34,000 AF patients with mild to moderate chronic kidney disease, Ha et al. demonstrated no increased risk of bleeding with DOAC utilization (relative risk [RR] for MB: 0.80, 95% CI 0.61-1.04; RR for ICH 0.49, 95% CI 0.30-0.80) indicating that DOACs can be safely utilized in such patients.[50] Our study also showed that Black race was associated with lower utilization of OAC and DOAC prescription therapy. In a study conducted by Essien et al. with more than 12,000 AF patients, Black patients were less likely than White patients to receive DOAC therapy even after controlling for various clinical and socioeconomic factors (adjusted OR 0.63, 95% CI 0.49-0.83).[51] Improved access to health care should therefore increase the OAC

utilization in these patients. Our study also showed lower odds of OAC prescription in patients with CAD. This low prevalence can be attributed to increased bleeding risk in such patients as they are often concomitantly prescribed anti-platelet therapy, although recent studies have shown reduction in bleeding risk in these patients when dual therapy (DOAC with either aspirin or a P2Y12 inhibitor) was utilized instead of triple therapy.[52]

Our age interaction analysis showed increased odds of OAC prescription in AF patients with history of ischemic stroke with advancing age. Similarly, we also demonstrated increased odds of DOAC prescription in AF patients with prior history of ischemic stroke as they aged. In a study of approximately 9,000 patients, van Walraven et al. showed an increased risk of ischemic stroke with patients age (adjusted hazard ratio per decade of age increase 1.45, 95% CI 1.26-1.66).[53] They also demonstrated that as these patients get older, the absolute benefit of OAC in reducing the incidence of ischemic stroke increases. These results, along with our study findings, provide further evidence that advanced age should not be the only contraindication in prescribing an OAC for stroke risk mitigation; practice patterns appear to follow these important findings.

Secondary Objective:

Using the US Medicare database data, this study observed that among AF patients the risk of stroke/SE and death were lower among OAC-treated patients during their treated period compared with the untreated duration of all patients. The risk of MB, including its components, gastrointestinal and intracranial hemorrhage were higher among OAC treated patients compared with the untreated duration of all patients. Health care costs were higher among the treated cohort patients during their treated period compared with the untreated duration of all patients.

A prior study with Medicare data observed that the risk of MB was similar between apixaban and untreated patients, while other OACs, dabigatran, rivaroxaban, and warfarin had higher risk.[54] A study comparing warfarin patients with untreated controls reported lower rate of stroke among warfarin treated patients.[55] In general, consistent trends were observed in the current study. Health care costs were not previously compared between untreated patients and those treated with OACs.

11.4. Generalizability

The study was conducted with Medicare database data which includes people aged 65 or older, younger people with disabilities, and those with end-stage renal disease. Hence, the results may not be generalizable to the entire population of United States.

12. OTHER INFORMATION

Not applicable

13. CONCLUSIONS

This contemporary real-world study of elderly AF patients with a CHA_2DS_2-VASc ≥ 2 found that OAC utilization is still low among elderly US patients. Several key predictors of OAC underutilization were identified, including age ≥85 years; female gender; Black race; and key comorbidities such as CAD, diabetes, renal disease, history of falls, and GI and intracranial bleeding. Furthermore, age ≥85 years, Black race, ischemic stroke, and GI and intracranial bleeding predicted lower use of DOAC therapy compared to warfarin.

This retrospective real-world study of elderly AF patients observed that the risk of stroke/SE and death were lower during the treated period of the OAC-treated patients. The risk of MB and its components, gastrointestinal and intracranial hemorrhage was higher during the treated period of the OAC-treated patients. Falsification analyses reveal presence of possible residual confounding. Health care costs were lower among treated patients compared with untreated patients. These findings may help physicians and payers in decision making.

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15. LIST OF SOURCE TABLES AND FIGURES

TABLES

Table 4. Baseline Descriptive Results for Never-Treated and Ever-treated Cohorts

	Overall Population		Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort				Ever-Treated with OAC Cohort							
									DOAC Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
Sample Size	1,204,507		617,611		586,896				388,629				198,267			
Age	79.17	8.11	80.35	8.66	77.93	7.29	<.0001	30.29	77.78	7.25	<.0001	32.19	78.22	7.36	<.0001	26.60
65-74 years	397,728	33.02%	184,992	29.95%	212,736	36.25%	<.0001	13.41	143,916	37.03%	<.0001	15.04	68,820	34.71%	<.0001	10.19
75-84 years	472,389	39.22%	219,470	35.54%	252,919	43.09%	<.0001	15.52	167,004	42.97%	<.0001	15.27	85,915	43.33%	<.0001	16.01
≥ 85 years	334,390	27.76%	213,149	34.51%	121,241	20.66%	<.0001	31.38	77,709	20.00%	<.0001	33.04	43,532	21.96%	<.0001	28.17
≥ 75 years	806,779	66.98%	432,619	70.05%	374,160	63.75%	<.0001	13.41	244,713	62.97%	<.0001	15.04	129,447	65.29%	<.0001	10.19
Sex																
Male	521,229	43.27%	258,047	41.78%	263,182	44.84%	<.0001	6.18	174,655	44.94%	<.0001	6.38	88,527	44.65%	<.0001	5.79
Female	683,278	56.73%	359,564	58.22%	323,714	55.16%	<.0001	6.18	213,974	55.06%	<.0001	6.38	109,740	55.35%	<.0001	5.79
Race																
White	1,059,077	87.93%	532,722	86.26%	526,355	89.68%	<.0001	10.56	350,403	90.16%	<.0001	12.14	175,952	88.74%	<.0001	7.53
Black	79,096	6.57%	47,273	7.65%	31,823	5.42%	<.0001	9.04	18,572	4.78%	<.0001	11.93	13,251	6.68%	<.0001	3.76
Other	66,334	5.51%	**37616**	6.09%	28,718	4.89%	<.0001	5.26	19,654	5.06%	<.0001	4.51	9,064	4.57%	<.0001	6.77
US Geographic Region																
Northeast	235,227	19.53%	117,899	19.09%	117,328	19.99%	<.0001	2.27	76,436	19.67%	<.0001	1.46	40,892	20.62%	<.0001	3.85
Midwest	305,208	25.34%	148,821	24.10%	156,387	26.65%	<.0001	5.86	91,920	23.65%	<.0001	1.04	64,467	32.52%	<.0001	18.77
South	455,974	37.86%	239,362	38.76%	216,612	36.91%	<.0001	3.81	157,130	40.43%	<.0001	3.43	59,482	30.00%	<.0001	18.51
West	205,974	17.10%	110,357	17.87%	95,617	16.29%	<.0001	4.19	62,579	16.10%	<.0001	4.70	33,038	16.66%	<.0001	3.19

	Overall Population		Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort				Ever-Treated with OAC Cohort							
									DOAC Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
Other	2,124	0.18%	1,172	0.19%	952	0.16%	0.0003	0.66	564	0.15%	<.0001	1.09	388	0.20%	0.5988	0.14
Medicaid Dual Eligibility	355,987	29.55%	213,457	34.56%	142,530	24.29%	<.0001	22.70	86,619	22.29%	<.0001	27.47	55,911	28.20%	<.0001	13.74
Part-D low income subsidy	388,515	32.26%	230,173	37.27%	158,342	26.98%	<.0001	22.17	96,778	24.90%	<.0001	26.96	61,564	31.05%	<.0001	13.14
Deyo-CCI Score	3.17	2.73	3.41	2.83	2.91	2.60	<.0001	18.41	2.76	2.53	<.0001	24.19	3.20	2.72	<.0001	7.53
$CHADS_2$ Score	2.71	1.34	2.77	1.36	2.64	1.32	<.0001	10.28	2.56	1.30	<.0001	15.90	2.78	1.34	0.0357	0.54
0-1	218,919	18.17%	104,712	16.95%	114,207	19.46%	<.0001	6.50	81,740	21.03%	<.0001	10.41	32,467	16.38%	<.0001	1.55
2-3	667,743	55.44%	339,494	54.97%	328,249	55.93%	<.0001	1.93	218,341	56.18%	<.0001	2.44	109,908	55.43%	0.0003	0.94
4-5	282,106	23.42%	152,194	24.64%	129,912	22.14%	<.0001	5.92	80,225	20.64%	<.0001	9.57	49,687	25.06%	0.0002	0.97
≥6	35,739	2.97%	21,211	3.43%	14,528	2.48%	<.0001	5.67	8,323	2.14%	<.0001	7.86	6,205	3.13%	<.0001	1.71
CHA_2DS_2-VASc Score	4.65	1.61	4.76	1.63	4.53	1.58	<.0001	14.82	4.43	1.57	<.0001	20.67	4.71	1.60	<.0001	3.53
1	0	0.00%	0	0.00%	0	0.00%	NA	0.00	0	0.00%	NA	0.00	0	0.00%	NA	0.00
2-3	309,106	25.66%	143,759	23.28%	165,347	28.17%	<.0001	11.22	117,395	30.21%	<.0001	15.71	47,952	24.19%	<.0001	2.14
4-5	549,830	45.65%	280,725	45.45%	269,105	45.85%	<.0001	0.80	177,882	45.77%	0.0018	0.64	91,223	46.01%	<.0001	1.12
≥6	345,571	28.69%	193,127	31.27%	152,444	25.97%	<.0001	11.74	93,352	24.02%	<.0001	16.26	59,092	29.80%	<.0001	3.18
HAS-BLED Score	3.36	1.24	3.46	1.27	3.26	1.21	<.0001	16.46	3.20	1.19	<.0001	21.27	3.37	1.24	<.0001	7.30
0-2 = low&moderate risk	323,939	26.89%	150,703	24.40%	173,236	29.52%	<.0001	11.55	119,908	30.85%	<.0001	14.47	53,328	26.90%	<.0001	5.72
3-4 = high risk	656,649	54.52%	336,331	54.46%	320,318	54.58%	0.1805	0.24	212,710	54.73%	0.0067	0.56	107,608	54.27%	0.1558	0.37
5 = high risk	223,919	18.59%	130,577	21.14%	93,342	15.90%	<.0001	13.51	56,011	14.41%	<.0001	17.67	37,331	18.83%	<.0001	5.79
Prior bleed	304,973	25.32%	179,020	28.99%	125,953	21.46%	<.0001	17.39	76,274	19.63%	<.0001	21.95	49,679	25.06%	<.0001	8.86

	Overall Population		Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort				Ever-Treated with OAC Cohort							
									DOAC Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
Prior MB (inpatient & primary)	38,381	3.19%	28,836	4.67%	9,545	1.63%	<.0001	17.49	5,093	1.31%	<.0001	19.82	4,452	2.25%	<.0001	13.29
Gastrointestinal bleeding	16,854	1.40%	12,640	2.05%	4,214	0.72%	<.0001	11.40	2,282	0.59%	<.0001	12.83	1,932	0.97%	<.0001	8.80
Intracranial bleeding	7,638	0.63%	6,108	0.99%	1,530	0.26%	<.0001	9.25	862	0.22%	<.0001	9.90	668	0.34%	<.0001	8.04
Other MB	16,789	1.39%	12,446	2.02%	4,343	0.74%	<.0001	10.96	2,226	0.57%	<.0001	12.79	2,117	1.07%	<.0001	7.70
Bleeding																
No bleeding	899,534	74.68%	438,591	71.01%	460,943	78.54%	<.0001	17.39	312,355	80.37%	<.0001	21.95	148,588	74.94%	<.0001	8.86
Intracranial bleeding	7,638	0.63%	6,108	0.99%	1,530	0.26%	<.0001	9.25	862	0.22%	<.0001	9.90	668	0.34%	<.0001	8.04
Gastrointestinal bleeding	16,783	1.39%	12,580	2.04%	4,203	0.72%	<.0001	11.35	2,275	0.59%	<.0001	12.79	1,928	0.97%	<.0001	8.75
Other bleeding	12,611	1.05%	9,179	1.49%	3,432	0.58%	<.0001	8.91	1,692	0.44%	<.0001	10.79	1,740	0.88%	<.0001	5.63
Non-MB	267,941	22.24%	151,153	24.47%	116,788	19.90%	<.0001	11.03	71,445	18.38%	<.0001	14.88	45,343	22.87%	<.0001	3.77
Prior stroke/SE	144,682	12.01%	77,823	12.60%	66,859	11.39%	<.0001	3.72	40,192	10.34%	<.0001	7.09	26,667	13.45%	<.0001	2.52
Prior stroke/SE (inpatient & primary)	40,005	3.32%	16,220	2.63%	23,785	4.05%	<.0001	7.95	13,704	3.53%	<.0001	5.21	10,081	5.08%	<.0001	12.79
Ischemic Stroke	35,744	2.97%	13,605	2.20%	22,139	3.77%	<.0001	9.23	12,992	3.34%	<.0001	6.95	9,147	4.61%	<.0001	13.32
Hemorrhagic Stroke	3,054	0.25%	2,398	0.39%	656	0.11%	<.0001	5.54	327	0.08%	<.0001	6.27	329	0.17%	<.0001	4.23
Systemic Embolism (SE)	1,362	0.11%	315	0.05%	1,047	0.18%	<.0001	3.76	404	0.10%	<.0001	1.90	643	0.32%	<.0001	6.32
Obesity	226,040	18.77%	99,037	16.04%	127,003	21.64%	<.0001	14.37	82,922	21.34%	<.0001	13.63	44,081	22.23%	<.0001	15.80

	Overall Population		Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort				Ever-Treated with OAC Cohort							
									DOAC Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
CHF	345,585	28.69%	189,105	30.62%	156,480	26.66%	<.0001	8.76	94,513	24.32%	<.0001	14.15	61,967	31.25%	<.0001	1.37
Diabetes	470,374	39.05%	244,240	39.55%	226,134	38.53%	<.0001	2.08	144,033	37.06%	<.0001	5.11	82,101	41.41%	<.0001	3.80
Hypertension	1,068,403	88.70%	544,917	88.23%	523,486	89.20%	<.0001	3.05	346,085	89.05%	<.0001	2.59	177,401	89.48%	<.0001	3.96
Chronic Obstructive Pulmonary Disease (COPD)	317,610	26.37%	178,607	28.92%	139,003	23.68%	<.0001	11.91	87,941	22.63%	<.0001	14.42	51,062	25.75%	<.0001	7.11
Renal disease	318,674	26.46%	179,699	29.10%	138,975	23.68%	<.0001	12.31	82,353	21.19%	<.0001	18.30	56,622	28.56%	<.0001	1.19
MI	176,312	14.64%	98,318	15.92%	77,994	13.29%	<.0001	7.45	46,696	12.02%	<.0001	11.28	31,298	15.79%	0.1577	0.36
Dyspepsia or stomach discomfort	278,574	23.13%	157,020	25.42%	121,554	20.71%	<.0001	11.20	78,200	20.12%	<.0001	12.67	43,354	21.87%	<.0001	8.38
Peripheral vascular disease	608,546	50.52%	333,554	54.01%	274,992	46.86%	<.0001	14.34	173,898	44.75%	<.0001	18.60	101,094	50.99%	<.0001	6.05
Transient ischemic attack	100,765	8.37%	53,598	8.68%	47,167	8.04%	<.0001	2.32	31,913	8.21%	<.0001	1.68	15,254	7.69%	<.0001	3.59
CAD	541,822	44.98%	294,580	47.70%	247,242	42.13%	<.0001	11.21	158,793	40.86%	<.0001	13.80	88,449	44.61%	<.0001	6.19
History of falls	117,690	9.77%	75,136	12.17%	42,554	7.25%	<.0001	16.66	26,673	6.86%	<.0001	18.14	15,881	8.01%	<.0001	13.83
Baseline medication usage																
ACE/ARB	671,852	55.78%	323,724	52.42%	348,128	59.32%	<.0001	13.93	232,399	59.80%	<.0001	14.92	115,729	58.37%	<.0001	12.00
Amiodarone	25,953	2.15%	16,909	2.74%	9,044	1.54%	<.0001	8.28	6,118	1.57%	<.0001	8.02	2,926	1.48%	<.0001	8.80
Beta blockers	552,976	45.91%	270,271	43.76%	282,705	48.17%	<.0001	8.86	186,247	47.92%	<.0001	8.36	96,458	48.65%	<.0001	9.82
H2-receptor antagonist	89,443	7.43%	51,268	8.30%	38,175	6.50%	<.0001	6.87	24,545	6.32%	<.0001	7.63	13,630	6.87%	<.0001	5.39

	Overall Population		Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort				Ever-Treated with OAC Cohort							
									DOAC Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
Proton pump inhibitor	378,930	31.46%	204,186	33.06%	174,744	29.77%	<.0001	7.08	115,268	29.66%	<.0001	7.33	59,476	30.00%	<.0001	6.60
Statins	644,129	53.48%	315,799	51.13%	328,330	55.94%	<.0001	9.66	218,810	56.30%	<.0001	10.38	109,520	55.24%	<.0001	8.24
Anti-platelets	187,140	15.54%	103,992	16.84%	83,148	14.17%	<.0001	7.38	54,377	13.99%	<.0001	7.89	28,771	14.51%	<.0001	6.40
NSAIDS	278,213	23.10%	136,148	22.04%	142,065	24.21%	<.0001	5.13	97,497	25.09%	<.0001	7.17	44,568	22.48%	<.0001	1.04
Inhibitors of warfarin	830,933	68.99%	426,809	69.11%	404,124	68.86%	0.0032	0.54	269,511	69.35%	0.0102	0.53	134,613	67.89%	<.0001	2.61
Inducers of warfarin	457,094	37.95%	237,889	38.52%	219,205	37.35%	<.0001	2.41	143,943	37.04%	<.0001	3.05	75,262	37.96%	<.0001	1.15
Dronedarone	3,195	0.27%	1,568	0.25%	1,627	0.28%	0.0128	0.45	1,301	0.33%	<.0001	1.49	326	0.16%	<.0001	1.96
Digoxin	46,273	3.84%	30,359	4.92%	15,914	2.71%	<.0001	11.53	10,141	2.61%	<.0001	12.14	5,773	2.91%	<.0001	10.35
Calcium Channel Blockers	437,203	36.30%	216,272	35.02%	220,931	37.64%	<.0001	5.46	145,487	37.44%	<.0001	5.03	75,444	38.05%	<.0001	6.30
Renin Angiotensin System Antagonists	552,378	45.86%	272,780	44.17%	279,598	47.64%	<.0001	6.97	183,739	47.28%	<.0001	6.25	95,859	48.35%	<.0001	8.39
Glucocorticoids	453,787	37.67%	232,035	37.57%	221,752	37.78%	0.0154	0.44	148,103	38.11%	<.0001	1.11	73,649	37.15%	0.0007	0.88
Diuretics	584,784	48.55%	289,157	46.82%	295,627	50.37%	<.0001	7.11	191,824	49.36%	<.0001	5.09	103,803	52.36%	<.0001	11.09
Metformin	234,487	19.47%	113,428	18.37%	121,059	20.63%	<.0001	5.71	78,501	20.20%	<.0001	4.65	42,558	21.46%	<.0001	7.77
Sulfonylureas	120,304	9.99%	59,933	9.70%	60,371	10.29%	<.0001	1.94	37,107	9.55%	0.0099	0.53	23,264	11.73%	<.0001	6.56
Thiazolidinedione	21,048	1.75%	10,019	1.62%	11,029	1.88%	<.0001	1.96	7,367	1.90%	<.0001	2.08	3,662	1.85%	<.0001	1.72
Insulin	116,798	9.70%	63,905	10.35%	52,893	9.01%	<.0001	4.52	31,126	8.01%	<.0001	8.10	21,767	10.98%	<.0001	2.05
Other Diabetes Drugs	64,643	5.37%	31,984	5.18%	32,659	5.56%	<.0001	1.71	22,551	5.80%	<.0001	2.74	10,108	5.10%	0.1586	0.36

	Overall Population		Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort				Ever-Treated with OAC Cohort							
									DOAC Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
Antiulcer Agents	322,744	26.79%	174,107	28.19%	148,637	25.33%	<.0001	6.47	97,028	24.97%	<.0001	7.30	51,609	26.03%	<.0001	4.86
Antidepressant	362,741	30.12%	211,061	34.17%	151,680	25.84%	<.0001	18.25	99,040	25.48%	<.0001	19.08	52,640	26.55%	<.0001	16.64
Baseline all-cause health care costs																
Inpatient Admission Costs	$1,014	$1,953	$1,182	$2,198	$838	$1,638	<.0001	17.74	$693	$1,370	<.0001	26.68	$1,122	$2,033	<.0001	2.83
Outpatient Costs (ER, Office, and other)	$605	$998	$637	$1,078	$571	$905	<.0001	6.69	$538	$829	<.0001	10.37	$636	$1,037	0.5021	0.17
ER Costs	$43	$73	$48	$80	$38	$65	<.0001	13.96	$36	$64	<.0001	16.04	$41	$67	<.0001	9.99
Office Visit Costs	$272	$548	$280	$594	$263	$495	<.0001	3.16	$265	$488	<.0001	2.86	$259	$508	<.0001	3.73
Prescription Costs	$315	$774	$334	$801	$296	$745	<.0001	4.90	$301	$771	<.0001	4.18	$286	$693	<.0001	6.39
DME Costs	$35	$201	$39	$221	$31	$178	<.0001	3.66	$29	$156	<.0001	5.33	$37	$215	0.0016	0.81
SNF Costs	$143	$645	$194	$749	$90	$509	<.0001	16.32	$68	$433	<.0001	20.64	$132	$630	<.0001	8.93
HHA Costs	$73	$246	$96	$283	$49	$197	<.0001	19.12	$45	$190	<.0001	20.76	$56	$210	<.0001	16.03
Hospice Costs	$23	$273	$40	$362	$4	$118	<.0001	13.34	$4	$106	<.0001	13.73	$6	$139	<.0001	12.59
Other Costs (DME, SNF, HHA, and Hospice)	$274	$818	$369	$952	$174	$631	<.0001	24.06	$146	$552	<.0001	28.66	$231	$760	<.0001	16.02
Total Medical Costs (Inpatient & Outpatient, including other costs)	$1,893	$2,697	$2,188	$3,015	$1,583	$2,274	<.0001	22.65	$1,376	$1,946	<.0001	31.98	$1,988	$2,765	<.0001	6.90

	Overall Population		Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort				Ever-Treated with OAC Cohort							
									DOAC Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
Total Costs	$2,208	$2,895	$2,522	$3,209	$1,879	$2,481	<.0001	22.41	$1,677	$2,179	<.0001	30.78	$2,274	$2,945	<.0001	8.04
Baseline all-cause health care utilizations																
Inpatient Admission Visit	650,224	53.98%	351,888	56.98%	298,336	50.83%	<.0001	12.35	184,585	47.50%	<.0001	19.06	113,751	57.37%	0.0019	0.80
Outpatient Visit (ER, Office, and other)	1,176,852	97.70%	598,928	96.97%	577,924	98.47%	<.0001	10.04	383,580	98.70%	<.0001	11.89	194,344	98.02%	<.0001	6.70
ER Visit	428,273	35.56%	234,104	37.90%	194,169	33.08%	<.0001	10.09	125,059	32.18%	<.0001	12.02	69,110	34.86%	<.0001	6.34
Office Visit	1,148,295	95.33%	584,056	94.57%	564,239	96.14%	<.0001	7.48	376,718	96.94%	<.0001	11.76	187,521	94.58%	0.8232	0.06
Pharmacy Claim	1,174,237	97.49%	600,119	97.17%	574,118	97.82%	<.0001	4.19	381,082	98.06%	<.0001	5.83	193,036	97.36%	<.0001	1.19
Durable Medical Equipment (DME)	449,800	37.34%	235,335	38.10%	214,465	36.54%	<.0001	3.23	137,259	35.32%	<.0001	5.78	77,206	38.94%	<.0001	1.72
Skilled Nursing Facility (SNF) Visit	98,864	8.21%	67,121	10.87%	31,743	5.41%	<.0001	20.07	16,751	4.31%	<.0001	24.95	14,992	7.56%	<.0001	11.45
HHA Visit	173,256	14.38%	112,342	18.19%	60,914	10.38%	<.0001	22.46	37,743	9.71%	<.0001	24.65	23,171	11.69%	<.0001	18.32
Hospice Visit	20,710	1.72%	18,921	3.06%	1,789	0.30%	<.0001	21.56	1,049	0.27%	<.0001	21.95	740	0.37%	<.0001	20.81
# of Inpatient Admission Visit (PPPM)	0.07	0.09	0.07	0.09	0.06	0.08	<.0001	18.74	0.05	0.07	<.0001	25.60	0.07	0.08	<.0001	6.18
# of Outpatient Visit (PPPM)	1.54	1.26	1.56	1.31	1.52	1.20	<.0001	2.92	1.51	1.17	<.0001	3.97	1.55	1.26	0.0003	0.92
# of ER Visit (PPPM)	0.05	0.11	0.06	0.11	0.04	0.10	<.0001	11.89	0.04	0.09	<.0001	14.00	0.05	0.10	<.0001	7.89
# of Office Visit (PPPM)	1.21	1.11	1.21	1.15	1.20	1.07	<.0001	1.42	1.21	1.06	0.8994	0.03	1.17	1.10	<.0001	4.09

	Overall Population		Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort				Ever-Treated with OAC Cohort							
									DOAC Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
# of Pharmacy Visit (PPPM)	2.22	1.70	2.38	1.85	2.05	1.52	<.0001	19.62	2.02	1.48	<.0001	21.70	2.11	1.59	<.0001	15.68
# of DME Visit (PPPM)	0.20	0.44	0.21	0.46	0.18	0.41	<.0001	6.49	0.17	0.39	<.0001	9.25	0.20	0.44	<.0001	1.36
# of SNF Visit (PPPM)	0.02	0.08	0.02	0.09	0.01	0.06	<.0001	17.20	0.01	0.05	<.0001	21.26	0.02	0.07	<.0001	10.12
# of HHA Visit (PPPM)	0.02	0.08	0.03	0.09	0.02	0.06	<.0001	19.73	0.02	0.06	<.0001	21.46	0.02	0.07	<.0001	16.45
# of Hospice Visit (PPPM)	0.01	0.06	0.01	0.08	0.00	0.03	<.0001	14.33	0.00	0.02	<.0001	14.73	0.00	0.03	<.0001	13.58

***Std Difference=100*|actual std diff|. Std Difference greater than 10 is considered significant.**

Table 5. Baseline Descriptive Results for Ever-Treated and Never-treated Cohorts (fixed cohorts)

	Overall Population		Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort				Ever-Treated with OAC Cohort															
									Apixaban Cohort				Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
Sample Size	1,421,187		837,837		583,350				212,501				28,419				155,832				185,800			
Age	79.93	8.40	81.26	8.83	78.00	7.33	<.0001	40.21	78.38	7.42	<.0001	35.33	77.01	7.01	<.0001	53.33	77.32	7.14	<.0001	49.13	78.29	7.38	<.0001	36.58
65-74 years	433,896	30.53%	224,043	26.74%	209,853	35.97%	<.0001	20.00	72,877	34.29%	<.0001	16.46	11,599	40.81%	<.0001	30.09	61,249	39.30%	<.0001	26.96	63,838	34.36%	<.0001	16.60
75-84 years	539,679	37.97%	289,061	34.50%	250,618	42.96%	<.0001	17.43	91,006	42.83%	<.0001	17.16	12,118	42.64%	<.0001	16.78	66,620	42.75%	<.0001	17.01	80,518	43.34%	<.0001	18.20
≥ 85 years	447,612	31.50%	324,733	38.76%	122,879	21.06%	<.0001	39.39	48,618	22.88%	<.0001	34.91	4,702	16.55%	<.0001	51.27	27,963	17.94%	<.0001	47.46	41,444	22.31%	<.0001	36.31
≥ 75 years	987,291	69.47%	613,794	73.26%	373,497	64.03%	<.0001	20.00	139,624	65.71%	<.0001	16.46	16,820	59.19%	<.0001	30.09	94,583	60.70%	<.0001	26.96	121,962	65.64%	<.0001	16.60
Sex																								
Male	622,667	43.81%	356,507	42.55%	266,160	45.63%	<.0001	6.20	94,276	44.36%	<.0001	3.66	13,628	47.95%	<.0001	10.87	72,969	46.83%	<.0001	8.61	84,914	45.70%	<.0001	6.35
Female	798,520	56.19%	481,330	57.45%	317,190	54.37%	<.0001	6.20	118,225	55.64%	<.0001	3.66	14,791	52.05%	<.0001	10.87	82,863	53.17%	<.0001	8.61	100,886	54.30%	<.0001	6.35
Race																								
White	1,249,395	87.91%	724,163	86.43%	525,232	90.04%	<.0001	11.21	192,479	90.58%	<.0001	13.02	25,610	90.12%	<.0001	11.47	140,571	90.21%	<.0001	11.77	165,874	89.28%	<.0001	8.71
Black	92,980	6.54%	63,381	7.56%	29,599	5.07%	<.0001	10.25	9,971	4.69%	<.0001	12.00	1,202	4.23%	<.0001	14.19	6,971	4.47%	<.0001	13.03	11,416	6.14%	<.0001	5.62
Others	78,812	5.55%	50,293	6.00%	28,519	4.89%	<.0001	4.91	10,051	4.73%	<.0001	5.65	1,607	5.65%	0.0150	1.49	8,290	5.32%	<.0001	2.96	8,510	4.58%	<.0001	6.36
US Geographic Region																								
Northeast	270,227	19.01%	155,348	18.54%	114,879	19.69%	<.0001	2.93	41,275	19.42%	<.0001	2.25	6,228	21.91%	<.0001	8.41	29,936	19.21%	<.0001	1.71	37,261	20.05%	<.0001	3.83
North Central	360,018	25.33%	203,343	24.27%	156,675	26.86%	<.0001	5.93	49,316	23.21%	<.0001	2.50	6,855	24.12%	0.5649	0.35	38,738	24.86%	<.0001	1.37	61,661	33.19%	<.0001	19.80
South	543,700	38.26%	327,897	39.14%	215,803	36.99%	<.0001	4.41	89,470	42.10%	<.0001	6.04	10,614	37.35%	<.0001	3.68	59,992	38.50%	<.0001	1.31	55,388	29.81%	<.0001	19.72
West	244,527	17.21%	149,537	17.85%	94,990	16.28%	<.0001	4.16	32,166	15.14%	<.0001	7.31	4,667	16.42%	<.0001	3.78	26,878	17.25%	<.0001	1.58	31,104	16.74%	<.0001	2.93
Other	2,715	0.19%	1,712	0.20%	1,003	0.17%	<.0001	0.75	274	0.13%	<.0001	1.85	55	0.19%	0.6914	0.24	288	0.18%	0.1144	0.44	386	0.21%	0.7684	0.08
Medicaid Dual Eligibility	425828	29.96%	289057	34.50%	136,771	23.45%	<.0001	24.55	44,331	20.86%	<.0001	30.84	6,487	22.83%	<.0001	26.03	35,300	22.65%	<.0001	26.45	50,488	27.17%	<.0001	15.92
Part-D low income subsidy	466460	32.82%	313691	37.44%	152,769	26.19%	<.0001	24.34	50,025	23.54%	<.0001	30.54	7,316	25.74%	<.0001	25.36	39,290	25.21%	<.0001	26.59	55,961	30.12%	<.0001	15.53
Deyo-CCI Score	3.44	2.92	3.81	3.06	2.90	2.60	<.0001	32.14	2.95	2.62	<.0001	30.49	2.51	2.41	<.0001	47.31	2.59	2.44	<.0001	44.28	3.17	2.71	<.0001	22.22

	Overall Population		Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort				Ever-Treated with OAC Cohort															
									Apixaban Cohort				Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
$CHADS_2$ Score	2.75	1.34	2.84	1.36	2.62	1.31	<.0001	16.70	2.61	1.30	<.0001	17.43	2.47	1.28	<.0001	27.62	2.48	1.29	<.0001	27.23	2.76	1.33	<.0001	5.63
0-1	245,544	17.28%	130,226	15.54%	115,318	19.77%	<.0001	11.10	41,701	19.62%	<.0001	10.74	6,588	23.18%	<.0001	19.42	35,888	23.03%	<.0001	19.06	30,963	16.66%	<.0001	3.05
2-3	788,576	55.49%	460,695	54.99%	327,881	56.21%	<.0001	2.46	120,397	56.66%	<.0001	3.37	15,964	56.17%	<.0001	2.39	87,701	56.28%	<.0001	2.60	103,383	55.64%	<.0001	1.32
4-5	341,740	24.05%	215,211	25.69%	126,529	21.69%	<.0001	9.41	45,691	21.50%	<.0001	9.87	5,354	18.84%	<.0001	16.51	29,386	18.86%	<.0001	16.47	45,933	24.72%	<.0001	2.22
≥6	45,327	3.19%	31,705	3.78%	13,622	2.34%	<.0001	8.42	4,712	2.22%	<.0001	9.19	513	1.81%	<.0001	12.03	2,857	1.83%	<.0001	11.83	5,521	2.97%	<.0001	4.50
CHA_2DS_2-VASc Score	4.70	1.61	4.84	1.63	4.49	1.57	<.0001	21.78	4.50	1.56	<.0001	21.45	4.28	1.54	<.0001	35.35	4.31	1.54	<.0001	33.38	4.67	1.59	<.0001	10.66
1	0	0.00%	0	0.00%	0	0.00%		0.00	0	0.00%		0.00	0	0.00%		0.00	0	0.00%		0.00	0	0.00%		0.00
2-3	350,214	24.64%	181,946	21.72%	168,268	28.85%	<.0001	16.46	60,558	28.50%	<.0001	15.69	9,612	33.82%	<.0001	27.28	51,577	33.10%	<.0001	25.73	46,286	24.91%	<.0001	7.56
4-5	647,898	45.59%	379,588	45.31%	268,310	45.99%	<.0001	1.38	98,476	46.34%	<.0001	2.08	12,853	45.23%	0.7927	0.16	70,849	45.46%	0.2461	0.32	85,765	46.16%	<.0001	1.71
≥6	423,075	29.77%	276,303	32.98%	146,772	25.16%	<.0001	17.28	53,467	25.16%	<.0001	17.28	5,954	20.95%	<.0001	27.35	33,406	21.44%	<.0001	26.15	53,749	28.93%	<.0001	8.77
HAS-BLED Score	3.40	1.25	3.53	1.28	3.22	1.20	<.0001	24.37	3.24	1.20	<.0001	22.85	3.07	1.15	<.0001	37.59	3.11	1.16	<.0001	34.12	3.32	1.24	<.0001	16.28
0-2 = low&moderate risk	368,873	25.96%	191,710	22.88%	177,163	30.37%	<.0001	17.00	62,903	29.60%	<.0001	15.32	9,848	34.65%	<.0001	26.23	51,836	33.26%	<.0001	23.26	52,318	28.16%	<.0001	12.13
3-4 = high risk	772,781	54.38%	454,681	54.27%	318,100	54.53%	0.0021	0.52	117,016	55.07%	<.0001	1.60	15,281	53.77%	0.0974	1.00	84,818	54.43%	0.2423	0.32	100,556	54.12%	0.2471	0.30
5 = high risk	279,533	19.67%	191,446	22.85%	88,087	15.10%	<.0001	19.86	32,582	15.33%	<.0001	19.22	3,290	11.58%	<.0001	30.20	19,178	12.31%	<.0001	27.97	32,926	17.72%	<.0001	12.78
Prior bleed	357,856	25.18%	245,017	29.24%	112,839	19.34%	<.0001	23.24	39,075	18.39%	<.0001	25.70	4,692	16.51%	<.0001	30.67	27,732	17.80%	<.0001	27.24	41,186	22.17%	<.0001	16.25
Prior stroke/SE	185,780	13.07%	120,090	14.33%	65,690	11.26%	<.0001	9.21	23,505	11.06%	<.0001	9.84	2,873	10.11%	<.0001	12.92	14,669	9.41%	<.0001	15.25	24,582	13.23%	<.0001	3.20
Obesity	252,381	17.76%	128,451	15.33%	123,930	21.24%	<.0001	15.34	45,396	21.36%	<.0001	15.63	5,669	19.95%	<.0001	12.13	32,811	21.06%	<.0001	14.88	39,860	21.45%	<.0001	15.85
CHF	445,491	31.35%	291,027	34.74%	154,464	26.48%	<.0001	17.99	54,618	25.70%	<.0001	19.77	6,280	22.10%	<.0001	28.30	35,505	22.78%	<.0001	26.64	57,878	31.15%	<.0001	7.63
Diabetes	550,718	38.75%	328,283	39.18%	222,435	38.13%	<.0001	2.16	78,659	37.02%	<.0001	4.46	10,582	37.24%	<.0001	4.01	56,578	36.31%	<.0001	5.93	76,293	41.06%	<.0001	3.84
Hypertension	1,256,258	88.39%	736,268	87.88%	519,990	89.14%	<.0001	3.96	190,266	89.54%	<.0001	5.24	25,148	88.49%	0.0018	1.90	138,033	88.58%	<.0001	2.17	165,838	89.26%	<.0001	4.33
Chronic Obstructive Pulmonary Disease (COPD)	398,872	28.07%	262,480	31.33%	136,392	23.38%	<.0001	17.90	48,170	22.67%	<.0001	19.60	6,110	21.50%	<.0001	22.43	34,705	22.27%	<.0001	20.56	47,240	25.43%	<.0001	13.12
Renal disease	419,294	29.50%	281,251	33.57%	138,043	23.66%	<.0001	22.05	52,093	24.51%	<.0001	20.05	4,778	16.81%	<.0001	39.34	28,186	18.09%	<.0001	35.94	52,806	28.42%	<.0001	11.15
MI	223,176	15.70%	146,257	17.46%	76,919	13.19%	<.0001	11.88	27,339	12.87%	<.0001	12.83	3,044	10.71%	<.0001	19.48	17,320	11.11%	<.0001	18.20	29,131	15.68%	<.0001	4.78

	Overall Population		Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort				Ever-Treated with OAC Cohort															
									Apixaban Cohort				Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
Dyspepsia or stomach discomfort	324,504	22.83%	209,740	25.03%	114,764	19.67%	<.0001	12.89	41,725	19.64%	<.0001	12.99	5,136	18.07%	<.0001	16.99	29,695	19.06%	<.0001	14.46	38,035	20.47%	<.0001	10.90
Peripheral vascular disease	713,772	50.22%	448,820	53.57%	264,952	45.42%	<.0001	16.35	93,264	43.89%	<.0001	19.46	12,043	42.38%	<.0001	22.54	66,836	42.89%	<.0001	21.49	92,431	49.75%	<.0001	7.65
Transient ischemic attack	127,893	9.00%	79,065	9.44%	48,828	8.37%	<.0001	3.75	20,368	9.58%	0.0373	0.50	2,148	7.56%	<.0001	6.74	11,440	7.34%	<.0001	7.56	14,825	7.98%	<.0001	5.17
CAD	645,478	45.42%	401,932	47.97%	243,546	41.75%	<.0001	12.54	88,970	41.87%	<.0001	12.30	10,957	38.56%	<.0001	19.09	60,924	39.10%	<.0001	17.98	82,351	44.32%	<.0001	7.33
History of falls	149,091	10.49%	108,717	12.98%	40,374	6.92%	<.0001	20.33	15,208	7.16%	<.0001	19.43	1,524	5.36%	<.0001	26.61	9,931	6.37%	<.0001	22.48	13,670	7.36%	<.0001	18.67
Baseline medication usage																								
ACE/ARB	775,574	54.57%	429,147	51.22%	346,427	59.39%	<.0001	16.48	127,245	59.88%	<.0001	17.49	17,307	60.90%	<.0001	19.59	92,582	59.41%	<.0001	16.53	108,817	58.57%	<.0001	14.80
Amiodarone	30,558	2.15%	21,687	2.59%	8,871	1.52%	<.0001	7.53	3,197	1.50%	<.0001	7.66	492	1.73%	<.0001	5.90	2,421	1.55%	<.0001	7.27	2,740	1.47%	<.0001	7.90
Beta blockers	644,137	45.32%	361,992	43.21%	282,145	48.37%	<.0001	10.37	102,525	48.25%	<.0001	10.13	13,855	48.75%	<.0001	11.15	74,083	47.54%	<.0001	8.72	91,279	49.13%	<.0001	11.90
H2-receptor antagonist	107,899	7.59%	70,433	8.41%	37,466	6.42%	<.0001	7.58	13,739	6.47%	<.0001	7.40	1,670	5.88%	<.0001	9.84	9,429	6.05%	<.0001	9.11	12,570	6.77%	<.0001	6.20
Proton pump inhibitor	442,283	31.12%	272,237	32.49%	170,046	29.15%	<.0001	7.24	62,631	29.47%	<.0001	6.53	7,890	27.76%	<.0001	10.32	44,708	28.69%	<.0001	8.26	54,557	29.36%	<.0001	6.77
Statins	736,810	51.84%	411,106	49.07%	325,704	55.83%	<.0001	13.58	119,937	56.44%	<.0001	14.81	15,898	55.94%	<.0001	13.80	86,405	55.45%	<.0001	12.80	102,987	55.43%	<.0001	12.76
Anti-platelets	219,293	15.43%	137,216	16.38%	82,077	14.07%	<.0001	6.43	30,696	14.45%	<.0001	5.35	3,730	13.13%	<.0001	9.18	20,479	13.14%	<.0001	9.13	27,065	14.57%	<.0001	5.01
NSAIDS	307,367	21.63%	170,408	20.34%	136,959	23.48%	<.0001	7.59	50,241	23.64%	<.0001	7.98	7,094	24.96%	<.0001	11.06	39,159	25.13%	<.0001	11.45	40,280	21.68%	<.0001	3.29
Inhibitors of warfarin	978,130	68.82%	576,801	68.84%	401,329	68.80%	0.5538	0.10	148,780	70.01%	<.0001	2.54	19,406	68.29%	0.0455	1.20	106,490	68.34%	<.0001	1.09	126,055	67.84%	<.0001	2.15
Inducers of warfarin	538,603	37.90%	323,384	38.60%	215,219	36.89%	<.0001	3.52	78,319	36.86%	<.0001	3.59	10,042	35.34%	<.0001	6.76	56,932	36.53%	<.0001	4.26	69,634	37.48%	<.0001	2.31
Dronedarone	3,413	0.24%	1,819	0.22%	1,594	0.27%	<.0001	1.14	649	0.31%	<.0001	1.73	104	0.37%	<.0001	2.76	529	0.34%	<.0001	2.32	306	0.16%	<.0001	1.20
Digoxin	54,571	3.84%	38,909	4.64%	15,662	2.68%	<.0001	10.44	4,917	2.31%	<.0001	12.74	858	3.02%	<.0001	8.47	4,255	2.73%	<.0001	10.17	5,604	3.02%	<.0001	8.49
Calcium Channel Blockers	513,136	36.11%	292,565	34.92%	220,571	37.81%	<.0001	6.01	80,975	38.11%	<.0001	6.62	10,807	38.03%	<.0001	6.46	57,278	36.76%	<.0001	3.83	71,181	38.31%	<.0001	7.04
Renin Angiotensin System Antagonists	643,385	45.27%	364,745	43.53%	278,640	47.77%	<.0001	8.50	101,588	47.81%	<.0001	8.58	13,647	48.02%	<.0001	9.01	72,758	46.69%	<.0001	6.35	90,269	48.58%	<.0001	10.14
Glucocorticoids	535,434	37.68%	316,886	37.82%	218,548	37.46%	<.0001	0.74	81,049	38.14%	0.0068	0.66	10,454	36.79%	0.0004	2.14	58,431	37.50%	0.0149	0.67	68,316	36.77%	<.0001	2.18
Diuretics	692,484	48.73%	399,626	47.70%	292,858	50.20%	<.0001	5.01	105,105	49.46%	<.0001	3.53	13,995	49.25%	<.0001	3.10	75,840	48.67%	<.0001	1.94	97,537	52.50%	<.0001	9.61

	Overall Population		Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort				Ever-Treated with OAC Cohort															
									Apixaban Cohort				Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
Metformin	272,284	19.16%	151,532	18.09%	120,752	20.70%	<.0001	6.61	42,810	20.15%	<.0001	5.24	6,000	21.11%	<.0001	7.63	31,494	20.21%	<.0001	5.40	40,264	21.67%	<.0001	8.99
Sulfonylureas	141,497	9.96%	81,683	9.75%	59,814	10.25%	<.0001	1.68	20,328	9.57%	0.0109	0.62	2,852	10.04%	0.1097	0.96	14,582	9.36%	<.0001	1.33	21,970	11.82%	<.0001	6.69
Thiazolidinedione	24,273	1.71%	13,332	1.59%	10,941	1.88%	<.0001	2.18	4,001	1.88%	<.0001	2.23	549	1.93%	<.0001	2.59	2,953	1.89%	<.0001	2.32	3,427	1.84%	<.0001	1.95
Insulin	141,440	9.95%	89,263	10.65%	52,177	8.94%	<.0001	5.75	17,819	8.39%	<.0001	7.74	2,216	7.80%	<.0001	9.88	11,599	7.44%	<.0001	11.21	20,495	11.03%	<.0001	1.21
Other Diabetes Drugs	74,583	5.25%	42,192	5.04%	32,391	5.55%	<.0001	2.31	12,766	6.01%	<.0001	4.26	1,591	5.60%	<.0001	2.51	8,585	5.51%	<.0001	2.12	9,384	5.05%	0.7923	0.07
Antiulcer Agents	377,351	26.55%	232,643	27.77%	144,708	24.81%	<.0001	6.73	52,301	24.61%	<.0001	7.18	6,766	23.81%	<.0001	9.06	38,033	24.41%	<.0001	7.66	47,423	25.52%	<.0001	5.08
Antidepressant	445,939	31.38%	296,983	35.45%	148,956	25.53%	<.0001	21.66	54,352	25.58%	<.0001	21.56	6,818	23.99%	<.0001	25.26	39,194	25.15%	<.0001	22.54	48,382	26.04%	<.0001	20.49
Baseline all-cause health care costs																								
Inpatient Admission Costs	$1,068	$1,952	$1,307	$2,232	$726	$1,391	<.0001	31.25	$661	$1,239	<.0001	35.80	$527	$1,085	<.0001	44.47	$596	$1,191	<.0001	39.73	$941	$1,694	<.0001	18.49
Outpatient Costs (ER, Office, and other)	$601	$1,051	$638	$1,151	$548	$886	<.0001	8.73	$537	$836	<.0001	9.99	$480	$743	<.0001	16.25	$501	$785	<.0001	13.83	$610	$1,028	<.0001	2.55
ER Costs	$44	$73	$50	$80	$36	$62	<.0001	18.60	$37	$63	<.0001	17.01	$30	$54	<.0001	28.32	$33	$60	<.0001	22.67	$38	$64	<.0001	15.64
Office Visit Costs	$266	$587	$276	$648	$251	$484	<.0001	4.39	$258	$475	<.0001	3.29	$245	$454	<.0001	5.63	$251	$487	<.0001	4.44	$245	$496	<.0001	5.43
Prescription Costs	$322	$815	$342	$857	$293	$750	<.0001	6.16	$309	$832	<.0001	3.90	$282	$693	<.0001	7.70	$286	$710	<.0001	7.13	$281	$691	<.0001	7.94
DME Costs	$36	$198	$40	$216	$30	$170	<.0001	4.90	$27	$145	<.0001	6.67	$28	$164	<.0001	6.14	$28	$137	<.0001	6.68	$36	$216	<.0001	1.80
SNF Costs	$147	$645	$202	$753	$67	$433	<.0001	22.04	$60	$397	<.0001	23.71	$44	$354	<.0001	26.82	$54	$387	<.0001	24.69	$89	$512	<.0001	17.55
HHA Costs	$75	$248	$96	$281	$44	$187	<.0001	21.86	$44	$183	<.0001	22.06	$35	$179	<.0001	25.84	$40	$180	<.0001	23.83	$49	$198	<.0001	19.44
Hospice Costs	$36	$327	$58	$412	$5	$123	<.0001	17.57	$4	$107	<.0001	17.98	$4	$108	<.0001	18.14	$4	$115	<.0001	17.89	$7	$146	<.0001	16.77
Other Costs (DME, SNF, HHA, and Hospice)	$294	$832	$397	$967	$146	$556	<.0001	31.79	$135	$515	<.0001	33.78	$111	$482	<.0001	37.35	$126	$499	<.0001	35.15	$180	$649	<.0001	26.25
Total Medical Costs (Inpatient & Outpatient, including other costs)	$1,963	$2,718	$2,341	$3,068	$1,420	$1,995	<.0001	35.61	$1,333	$1,815	<.0001	40.00	$1,118	$1,601	<.0001	49.97	$1,224	$1,722	<.0001	44.91	$1,731	$2,384	<.0001	22.21
Total Costs	$2,285	$2,933	$2,683	$3,282	$1,712	$2,221	<.0001	34.66	$1,642	$2,088	<.0001	37.86	$1,401	$1,820	<.0001	48.35	$1,510	$1,944	<.0001	43.51	$2,011	$2,583	<.0001	22.76

	Overall Population		Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort				Ever-Treated with OAC Cohort															
									Apixaban Cohort				Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
Baseline all-cause health care utilizations																								
Inpatient Admission Visit	805,544	56.68%	521,154	62.20%	284,390	48.75%	<.0001	27.32	102,238	48.11%	<.0001	28.62	11,862	41.74%	<.0001	41.84	69,303	44.47%	<.0001	36.11	100,711	54.20%	<.0001	16.27
Outpatient Visit (ER, Office, and other)	1,369,340	96.35%	795,933	95.00%	573,407	98.30%	<.0001	18.39	209,325	98.51%	<.0001	19.88	27,985	98.47%	<.0001	19.65	153,666	98.61%	<.0001	20.64	181,641	97.76%	<.0001	14.83
ER Visit	503,418	35.42%	314,474	37.53%	188,944	32.39%	<.0001	10.80	69,239	32.58%	<.0001	10.39	8,192	28.83%	<.0001	18.57	48,310	31.00%	<.0001	13.80	62,990	33.90%	<.0001	7.59
Office Visit	1,334,788	93.92%	775,743	92.59%	559,045	95.83%	<.0001	13.93	205,786	96.84%	<.0001	19.09	27,384	96.36%	<.0001	16.55	150,395	96.51%	<.0001	17.34	174,692	94.02%	<.0001	5.73
Pharmacy Claim	1,382,773	97.30%	812,091	96.93%	570,682	97.83%	<.0001	5.64	208,501	98.12%	<.0001	7.66	27,843	97.97%	<.0001	6.64	152,630	97.95%	<.0001	6.45	180,924	97.38%	<.0001	2.70
Durable Medical Equipment (DME)	522,701	36.78%	314,787	37.57%	207,914	35.64%	<.0001	4.01	74,323	34.98%	<.0001	5.40	9,557	33.63%	<.0001	8.24	53,413	34.28%	<.0001	6.87	70,362	37.87%	0.0163	0.62
Skilled Nursing Facility (SNF) Visit	121,058	8.52%	96,598	11.53%	24,460	4.19%	<.0001	27.52	8,194	3.86%	<.0001	29.10	841	2.96%	<.0001	33.52	5,327	3.42%	<.0001	31.22	10,078	5.42%	<.0001	22.05
HHA Visit	212,103	14.92%	156,985	18.74%	55,118	9.45%	<.0001	26.94	20,337	9.57%	<.0001	26.53	2,149	7.56%	<.0001	33.53	13,261	8.51%	<.0001	30.15	19,306	10.39%	<.0001	23.83
Hospice Visit	51,517	3.62%	49,308	5.89%	2,209	0.38%	<.0001	32.02	807	0.38%	<.0001	32.01	73	0.26%	<.0001	33.06	484	0.31%	<.0001	32.60	844	0.45%	<.0001	31.38
# of Inpatient Admission Visit (PPPM)	0.07	0.09	0.08	0.09	0.05	0.07	<.0001	32.62	0.05	0.07	<.0001	34.54	0.04	0.06	<.0001	45.54	0.05	0.07	<.0001	40.79	0.06	0.08	<.0001	22.18
# of Outpatient Visit (PPPM)	1.47	1.25	1.48	1.31	1.47	1.17	<.0001	0.67	1.49	1.15	0.0017	0.73	1.41	1.12	<.0001	5.54	1.44	1.12	<.0001	3.20	1.48	1.22	0.0614	0.47
# of ER Visit (PPPM)	0.05	0.10	0.06	0.11	0.04	0.09	<.0001	13.31	0.04	0.08	<.0001	14.13	0.04	0.08	<.0001	20.66	0.04	0.10	<.0001	15.37	0.05	0.10	<.0001	9.65
# of Office Visit (PPPM)	1.14	1.09	1.13	1.13	1.15	1.04	<.0001	1.72	1.19	1.03	<.0001	5.00	1.14	1.02	0.1744	0.78	1.15	1.01	<.0001	1.78	1.11	1.06	<.0001	2.01
# of Pharmacy Visit (PPPM)	2.26	1.76	2.42	1.90	2.03	1.51	<.0001	22.85	2.02	1.49	<.0001	23.20	1.95	1.46	<.0001	27.49	1.97	1.47	<.0001	26.50	2.09	1.58	<.0001	18.85
# of DME Visit (PPPM)	0.20	0.45	0.22	0.48	0.18	0.41	<.0001	8.81	0.17	0.39	<.0001	11.00	0.16	0.39	<.0001	12.59	0.17	0.39	<.0001	11.66	0.20	0.44	<.0001	3.58
# of SNF Visit (PPPM)	0.02	0.08	0.03	0.10	0.01	0.05	<.0001	22.91	0.01	0.05	<.0001	24.43	0.01	0.04	<.0001	27.61	0.01	0.05	<.0001	25.36	0.01	0.06	<.0001	18.67
# of HHA Visit (PPPM)	0.03	0.08	0.03	0.09	0.02	0.06	<.0001	23.09	0.02	0.06	<.0001	23.35	0.01	0.05	<.0001	28.56	0.01	0.06	<.0001	25.02	0.02	0.07	<.0001	20.43
# of Hospice Visit (PPPM)	0.01	0.07	0.01	0.09	0.00	0.03	<.0001	19.56	0.00	0.03	<.0001	19.90	0.00	0.03	<.0001	20.15	0.00	0.03	<.0001	19.98	0.00	0.03	<.0001	18.73

Std Difference=100|actual std diff|. Std Difference greater than 10 is considered significant.

Table 6. Descriptive Outcomes of Never-treated and Ever-treated Cohorts

	Never-Treated Cohort (Reference)		Ever-Treated Cohort		DOAC Cohort		Warfarin Cohort	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD
Sample Size	617,611		586,896		388,629		198,267	
Follow-up Time (in days)	827.59	464.00	915.07	467.36	874.55	457.17	994.49	476.82
minimum	182		182		182		182	
Q1	420		509		478		587	
median	740		872		814		989	
Q3	1,182		1,300		1,237		1,400	
maximum	1,826		1,826		1,826		1,826	
Death	197,395	31.96%	109,194	18.61%	57,206	14.72%	51,988	26.22%
Time to Death	634.81	368.16	730.92	394.29	716.55	389.74	746.73	398.66
Death Incidence Rate (per 100 person-years)	14.10		7.42		6.14		9.62	
Disenrollment	15,760	2.55%	8,972	1.53%	4,921	1.27%	4,051	2.04%
Part A & B only	539	0.09%	304	0.05%	171	0.04%	133	0.07%
Part D only	13,622	2.21%	7,844	1.34%	4,270	1.10%	3,574	1.80%
Part A & B & D	1,599	0.26%	824	0.14%	480	0.12%	344	0.17%
Time to Disenrollment	15.46	110.15	10.62	96.63	8.63	86.41	14.50	113.93
Study End	404,456	65.49%	468,730	79.87%	326,502	84.01%	142,228	71.74%
Time to Study End	609.24	586.97	768.46	572.25	760.44	538.61	784.18	632.73

Std Difference=100|actual std diff|. Std Difference greater than 10 is considered significant.

Table 7. Weighted Baseline Descriptive Results for Ever-Treated and Never-treated Cohorts (fixed cohorts) Note: time-varying analysis will be conducted in the models

	Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort			
	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*
Sample Size	837,837		583,350			
Age	80.08	8.64	79.51	7.84	0.0000	6.91
65-74 years	256,938	30.67%	178,719	30.64%	0.7018	0.07
75-84 years	316,980	37.83%	219,759	37.67%	0.0511	0.33
≥ 85 years	263,920	31.50%	184,872	31.69%	0.0158	0.41
≥ 75 years	580,899	69.33%	404,631	69.36%	0.7018	0.07
Sex						
Male	366,409	43.73%	254,508	43.63%	0.2192	0.21
Female	471,428	56.27%	328,842	56.37%	0.2192	0.21
Race/Ethnicity						
White	736,102	87.86%	511,937	87.76%	0.0750	0.30
Black	55,149	6.58%	38,976	6.68%	0.0194	0.40
Other	46,586	5.56%	32,437	5.56%	0.9956	0.00
US Geographic Region						
Northeast	159,571	19.05%	111,044	19.04%	0.8808	0.03
North Central	211,813	25.28%	147,285	25.25%	0.6578	0.08
South	320,517	38.26%	223,206	38.26%	0.9280	0.02
West	144,330	17.23%	100,692	17.26%	0.5925	0.09
Other	1,606	0.19%	1,123	0.19%	0.9047	0.02
Medicaid Dual Eligibility	251,079	29.97%	175,918	30.16%	0.0156	0.41
Part-D low income subsidy	276,528	33.00%	191,199	32.78%	0.0043	0.49
Deyo-CCI Score	3.44	2.92	3.46	2.93	0.0000	0.71
$CHADS_2$ Score	2.74	1.34	2.78	1.36	0.0000	3.03
0-1	146,991	17.54%	98,756	16.93%	0.0000	1.63
2-3	465,270	55.53%	318,917	54.67%	0.0000	1.73
4-5	198,804	23.73%	146,114	25.05%	0.0000	3.07
≥6	26,771	3.20%	19,563	3.35%	0.0000	0.89
CHA_2DS_2-VASc Score	4.69	1.61	4.73	1.63	0.0000	2.36
1	0	0%	0	0.00%		0.00
2-3	207,210	24.73%	141,501	24.26%	0.0000	1.10
4-5	382,302	45.63%	263,093	45.10%	0.0000	1.06
≥6	248,324	29.64%	178,756	30.64%	0.0000	2.19
HAS-BLED Score	3.43	1.26	3.39	1.25	0.0000	3.19
0-2 = low&moderate risk	211,938	25.30%	153,880	26.38%	0.0000	2.47

	Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort			
	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*
3-4 = high risk	456,495	54.48%	316,665	54.28%	0.0179	0.40
5 = high risk	169,403	20.22%	112,805	19.34%	0.0000	2.21
Prior bleed	211,138	25.20%	148,100	25.39%	0.0114	0.43
Prior stroke/SE	109,747	13.10%	76,883	13.18%	0.1608	0.24
Obesity	149,899	17.89%	104,695	17.95%	0.3913	0.15
CHF	262,468	31.33%	183,701	31.49%	0.0383	0.35
Diabetes	325,616	38.86%	228,403	39.15%	0.0005	0.59
Hypertension	740,784	88.42%	516,211	88.49%	0.1715	0.23
Chronic Obstructive Pulmonary Disease (COPD)	235,529	28.11%	165,465	28.36%	0.0010	0.56
Renal disease	247,160	29.50%	172,682	29.60%	0.1896	0.22
MI	132,004	15.76%	92,670	15.89%	0.0359	0.36
Dyspepsia or stomach discomfort	192,132	22.93%	135,174	23.17%	0.0008	0.57
Peripheral vascular disease	422,145	50.39%	295,263	50.62%	0.0070	0.46
Transient ischemic attack	75,764	9.04%	53,007	9.09%	0.3689	0.15
CAD	382,627	45.67%	268,321	46.00%	0.0001	0.66
History of falls	87,993	10.50%	62,388	10.69%	0.0002	0.63
Baseline medication usage						
ACE/ARB	457,762	54.64%	319,470	54.76%	0.1300	0.26
Amiodarone	18,066	2.16%	12,961	2.22%	0.0085	0.45
Beta blockers	379,541	45.30%	264,414	45.33%	0.7530	0.05
H2-receptor antagonist	63,766	7.61%	44,816	7.68%	0.1134	0.27
Proton pump inhibitor	261,654	31.23%	183,691	31.49%	0.0011	0.56
Statins	436,440	52.09%	305,690	52.40%	0.0003	0.62
Anti-platelets	130,233	15.54%	92,040	15.78%	0.0002	0.64
NSAIDS	182,446	21.78%	127,693	21.89%	0.1063	0.28
Baseline all-cause health care utilizations						
Inpatient Admission Visit	474,875	56.68%	331,389	56.81%	0.1260	0.26

Std Difference=100|actual std diff|. Std Difference greater than 10 is considered significant.

Table 8. Weighted Baseline Descriptive Results for Ever-Treated and Never-treated Cohorts (fixed cohorts) Note: time-varying analysis will be conducted in the models

	Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort															
			Apixaban Cohort				Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
Sample Size	837,837		212,501				28,419				155,832				185,800			
Age	80.08	8.64	79.59	7.88	0.0000	6.00	79.51	7.76	0.0000	6.92	79.52	7.80	0.0000	6.86	79.49	7.82	0.0000	7.16
65-74 years	257,070	30.68%	65,088	30.63%	0.6342	0.12	8,523	29.99%	0.0129	1.50	47,155	30.26%	0.0009	0.92	57,030	30.69%	0.9198	0.03
75-84 years	316,912	37.83%	80,093	37.69%	0.2530	0.28	10,693	37.62%	0.4935	0.41	58,582	37.59%	0.0828	0.48	70,239	37.80%	0.8642	0.04
≥ 85 years	263,855	31.49%	67,321	31.68%	0.0959	0.40	9,203	32.38%	0.0015	1.91	50,095	32.15%	0.0000	1.40	58,530	31.50%	0.9374	0.02
≥ 75 years	580,767	69.32%	147,413	69.37%	0.6342	0.12	19,896	70.01%	0.0129	1.50	108,677	69.74%	0.0009	0.92	128,770	69.31%	0.9198	0.03
Sex																		
Male	366,433	43.74%	92,348	43.46%	0.0210	0.56	12,289	43.24%	0.0984	1.00	67,450	43.28%	0.0010	0.91	81,461	43.84%	0.3961	0.22
Female	471,404	56.26%	120,153	56.54%	0.0210	0.56	16,130	56.76%	0.0984	1.00	88,382	56.72%	0.0010	0.91	104,339	56.16%	0.3961	0.22
Race/Ethnicity																		
White	736,111	87.86%	186,254	87.65%	0.0082	0.64	24,987	87.92%	0.7433	0.20	136,759	87.76%	0.2784	0.30	163,134	87.80%	0.4925	0.18
Black	55,105	6.58%	14,260	6.71%	0.0270	0.54	1,841	6.48%	0.5125	0.40	10,380	6.66%	0.2215	0.34	12,488	6.72%	0.0236	0.58
Other	46,620	5.56%	11,987	5.64%	0.1691	0.33	1,591	5.60%	0.8092	0.15	8,693	5.58%	0.8245	0.06	10,178	5.48%	0.1401	0.38
US Geographic Region																		
Northeast	159,552	19.04%	40,334	18.98%	0.5098	0.16	5,383	18.94%	0.6644	0.26	29,051	18.64%	0.0002	1.02	35,479	19.10%	0.6043	0.13
North Central	211,526	25.25%	53,773	25.30%	0.5824	0.13	7,132	25.10%	0.5691	0.34	39,151	25.12%	0.3043	0.28	46,991	25.29%	0.6903	0.10
South	320,850	38.30%	81,132	38.18%	0.3288	0.24	10,929	38.46%	0.5833	0.33	59,854	38.41%	0.3950	0.23	71,312	38.38%	0.4887	0.18
West	144,304	17.22%	36,824	17.33%	0.2503	0.28	4,921	17.31%	0.6883	0.24	27,461	17.62%	0.0001	1.05	31,671	17.05%	0.0666	0.47
Other	1,606	0.19%	438	0.21%	0.1719	0.33	54	0.19%	0.9923	0.01	315	0.20%	0.3787	0.24	346	0.19%	0.6276	0.12

	Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort															
			Apixaban Cohort				Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
Medicaid Dual Eligibility	251,035	29.96%	63,987	30.11%	0.1809	0.32	8,635	30.39%	0.1257	0.92	47,738	30.63%	0.0000	1.46	55,978	30.13%	0.1586	0.36
Part-D low income subsidy	276,477	33.00%	69,120	32.53%	0.0000	1.01	9,471	33.33%	0.2501	0.69	51,693	33.17%	0.1810	0.37	61,474	33.09%	0.4704	0.19
Deyo-CCI Score	3.44	2.92	3.47	2.88	0.0002	0.89	3.52	3.02	0.0000	2.64	3.48	2.94	0.0000	1.27	3.45	2.96	0.2698	0.28
$CHADS_2$ Score	2.74	1.34	2.76	1.35	0.0000	1.50	2.80	1.37	0.0000	4.39	2.79	1.37	0.0000	3.69	2.80	1.35	0.0000	4.60
0-1	147,326	17.58%	36,712	17.28%	0.0008	0.81	4,775	16.80%	0.0007	2.07	26,621	17.08%	0.0000	1.32	30,183	16.24%	0.0000	3.57
2-3	464,945	55.49%	116,870	55.00%	0.0000	1.00	15,460	54.40%	0.0003	2.19	84,536	54.25%	0.0000	2.50	101,718	54.75%	0.0000	1.50
4-5	198,715	23.72%	51,977	24.46%	0.0000	1.74	7,150	25.16%	0.0000	3.35	39,007	25.03%	0.0000	3.06	47,872	25.77%	0.0000	4.75
≥6	26,851	3.20%	6,943	3.27%	0.1454	0.35	1,034	3.64%	0.0000	2.38	5,669	3.64%	0.0000	2.38	6,028	3.24%	0.3839	0.22
CHA_2DS_2-VASc Score	4.69	1.61	4.72	1.62	0.0000	2.20	4.74	1.65	0.0000	3.23	4.74	1.65	0.0000	3.02	4.73	1.61	0.0000	2.73
1	0	0%	0	0.00%	NA	0.00	0	0.00%	NA	0.00	0	0.00%	NA	0.00	0	0.00%	NA	0.00
2-3	207,610	24.78%	51,681	24.32%	0.0000	1.07	6,844	24.08%	0.0075	1.62	37,892	24.32%	0.0001	1.08	44,316	23.85%	0.0000	2.16
4-5	381,902	45.58%	95,909	45.13%	0.0002	0.90	12,755	44.88%	0.0197	1.41	69,650	44.70%	0.0000	1.78	84,615	45.54%	0.7486	0.08
≥6	248,324	29.64%	64,910	30.55%	0.0000	1.98	8,820	31.04%	0.0000	3.04	48,291	30.99%	0.0000	2.94	56,869	30.61%	0.0000	2.11
HAS-BLED Score	3.43	1.26	3.38	1.24	0.0000	3.43	3.38	1.26	0.0000	3.38	3.38	1.25	0.0000	3.59	3.39	1.26	0.0000	2.41
0-2 = low&moderate risk	212,020	25.31%	55,748	26.23%	0.0000	2.12	7,531	26.50%	0.0000	2.72	41,075	26.36%	0.0000	2.41	49,058	26.40%	0.0000	2.51
3-4 = high risk	456,479	54.48%	116,306	54.73%	0.0396	0.50	15,320	53.91%	0.0555	1.15	84,888	54.47%	0.9479	0.02	99,919	53.78%	0.0000	1.42
5 = high risk	169,338	20.21%	40,447	19.03%	0.0000	2.97	5,568	19.59%	0.0107	1.55	29,869	19.17%	0.0000	2.63	36,823	19.82%	0.0001	0.98
Prior bleed	211,053	25.19%	53,481	25.17%	0.8277	0.05	7,205	25.35%	0.5361	0.37	39,511	25.35%	0.1698	0.38	47,448	25.54%	0.0019	0.80
Prior stroke/SE	109,672	13.09%	27,835	13.10%	0.9123	0.03	3,781	13.30%	0.2935	0.63	20,832	13.37%	0.0028	0.82	24,477	13.17%	0.3326	0.25

	Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort															
			Apixaban Cohort				Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
Obesity	149,901	17.89%	38,145	17.95%	0.5269	0.15	5,082	17.88%	0.9689	0.02	28,099	18.03%	0.1851	0.37	33,175	17.86%	0.7140	0.09
CHF	262,308	31.31%	67,116	31.58%	0.0143	0.59	9,004	31.68%	0.1801	0.81	49,178	31.56%	0.0503	0.54	58,072	31.26%	0.6591	0.11
Diabetes	325,489	38.85%	83,440	39.27%	0.0004	0.85	11,113	39.11%	0.3820	0.53	61,141	39.24%	0.0040	0.79	72,336	38.93%	0.5041	0.17
Hypertension	740,798	88.42%	188,035	88.49%	0.3761	0.22	25,161	88.54%	0.5357	0.37	137,916	88.50%	0.3347	0.27	164,419	88.49%	0.3642	0.23
Chronic Obstructive Pulmonary Disease (COPD)	235,473	28.10%	60,497	28.47%	0.0009	0.81	8,167	28.74%	0.0199	1.40	44,808	28.75%	0.0000	1.44	52,675	28.35%	0.0334	0.54
Renal disease	246,972	29.48%	63,196	29.74%	0.0181	0.57	8,514	29.96%	0.0805	1.05	45,993	29.51%	0.7666	0.08	54,727	29.45%	0.8464	0.05
MI	131,908	15.74%	33,816	15.91%	0.0554	0.46	4,598	16.18%	0.0481	1.19	24,761	15.89%	0.1479	0.40	29,335	15.79%	0.6325	0.12
Dyspepsia or stomach discomfort	192,097	22.93%	49,196	23.15%	0.0288	0.53	6,550	23.05%	0.6341	0.29	36,598	23.49%	0.0000	1.32	43,038	23.16%	0.0289	0.56
Peripheral vascular disease	421,994	50.37%	107,603	50.64%	0.0265	0.54	14,476	50.94%	0.0592	1.14	79,228	50.84%	0.0006	0.95	93,890	50.53%	0.1959	0.33
Transient ischemic attack	75,771	9.04%	19,579	9.21%	0.0149	0.59	2,644	9.30%	0.1327	0.90	14,273	9.16%	0.1452	0.40	16,770	9.03%	0.8069	0.06
CAD	382,521	45.66%	97,348	45.81%	0.2006	0.31	13,234	46.57%	0.0024	1.83	72,025	46.22%	0.0000	1.13	84,824	45.65%	0.9863	0.00
History of falls	87,986	10.50%	22,740	10.70%	0.0075	0.65	3,073	10.81%	0.0925	1.01	17,032	10.93%	0.0000	1.38	19,868	10.69%	0.0149	0.62
Baseline medication usage																		
ACE/ARB	457,809	54.64%	116,586	54.86%	0.0661	0.45	15,611	54.93%	0.3320	0.59	86,084	55.24%	0.0000	1.21	101,436	54.59%	0.7086	0.10
Amiodarone	18,061	2.16%	4,746	2.23%	0.0285	0.53	642	2.26%	0.2346	0.71	3,517	2.26%	0.0119	0.69	4,101	2.21%	0.1680	0.35
Beta blockers	379,470	45.29%	96,417	45.37%	0.5033	0.16	12,933	45.51%	0.4696	0.44	70,542	45.27%	0.8645	0.05	83,816	45.11%	0.1566	0.36

	Never-Treated with OAC Cohort (Reference)		Ever-Treated with OAC Cohort															
			Apixaban Cohort				Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*	N/Mean	%/SD	p-value	STD*
H2-receptor antagonist	63,749	7.61%	16,212	7.63%	0.7515	0.08	2,137	7.52%	0.5777	0.34	12,121	7.78%	0.0205	0.64	14,279	7.69%	0.2619	0.29
Proton pump inhibitor	261,630	31.23%	66,798	31.43%	0.0656	0.45	9,165	32.25%	0.0003	2.19	49,713	31.90%	0.0000	1.45	58,243	31.35%	0.3111	0.26
Statins	436,443	52.09%	111,396	52.42%	0.0065	0.66	15,007	52.81%	0.0175	1.43	81,932	52.58%	0.0004	0.97	96,773	52.08%	0.9565	0.01
Anti-platelets	130,213	15.54%	33,493	15.76%	0.0126	0.60	4,719	16.60%	0.0000	2.89	24,828	15.93%	0.0001	1.07	29,102	15.66%	0.1909	0.34
NSAIDS	182,584	21.79%	46,686	21.97%	0.0766	0.43	6,281	22.10%	0.2127	0.75	34,580	22.19%	0.0005	0.96	40,736	21.92%	0.2112	0.32
Baseline all-cause health care utilizations																		
Inpatient Admission Visit	474,732	56.66%	120,950	56.92%	0.0335	0.52	16,100	56.65%	0.9785	0.02	88,556	56.83%	0.2236	0.34	105,083	56.56%	0.4099	0.21

Std Difference=100|actual std diff|. Std Difference greater than 10 is considered significant.

Table 9. MSM Models Comparing the Untreated Cohort With the Treated and Individual Drug Cohorts

	OAC Treated vs Untreated		Apixaban vs Untreated		Dabigatran vs Untreated		Rivaroxaban vs Untreated		Warfarin vs Untreated	
Variable	**Marginal Effect**	**p-value**	**Marginal Effect**	**p-value**	**Marginal Effect**	**p-value**	**Marginal Effect**	**p-value**	**Marginal Effect**	**p-value**
Total healthcare costs	$4,381 vs $7,172	<.0001	$4,110 vs $6,719	<.0001	$3,919 vs $6,710	<.0001	$4,111 vs $6,728	<.0001	$4,608 vs $7,127	<.0001
Medical costs	$3,761 vs $6,881	<.0001	$3,367 vs $6,423	<.0001	$3,228 vs $6,411	<.0001	$3,418 vs $6,434	<.0001	$4,201 vs $6,834	<.0001
Inpatient	$1,919 vs $4,170	<.0001	$1,675 vs $3,743	<.0001	$1,617 vs $3,699	<.0001	$1,732 vs $3,751	<.0001	$2,153 vs $4,061	<.0001
Outpatient	$1,081 vs $935	<.0001	$984 vs $886	<.0001	$951 vs $856	<.0001	$980 vs $877	<.0001	$1,180 vs $877	<.0001
Other costs	$772 vs $1,764	<.0001	$675 vs $1,792	<.0001	$596 vs $1,855	<.0001	$674 vs $1,804	<.0001	$937 vs $1,883	<.0001
Pharmacy Costs	$664 vs $288	<.0001	$775 vs $295	<.0001	$749 vs $299	<.0001	$754 vs $293	<.0001	$469 vs $289	<.0001
MB hospitalization costs	$80 vs $60	<.0001	$53 vs $65	<.0001	$63 vs $70	0.1621	$81 vs $66	<.0001	$104 vs $67	<.0001
Stroke/SE hospitalization costs	$31 vs $41	<.0001	$21 vs $43	<.0001	$30 vs $45	0.0104	$27 vs $43	<.0001	$44 vs $45	0.7576

FIGURES

Figure 7. Predictors of OAC Prescription

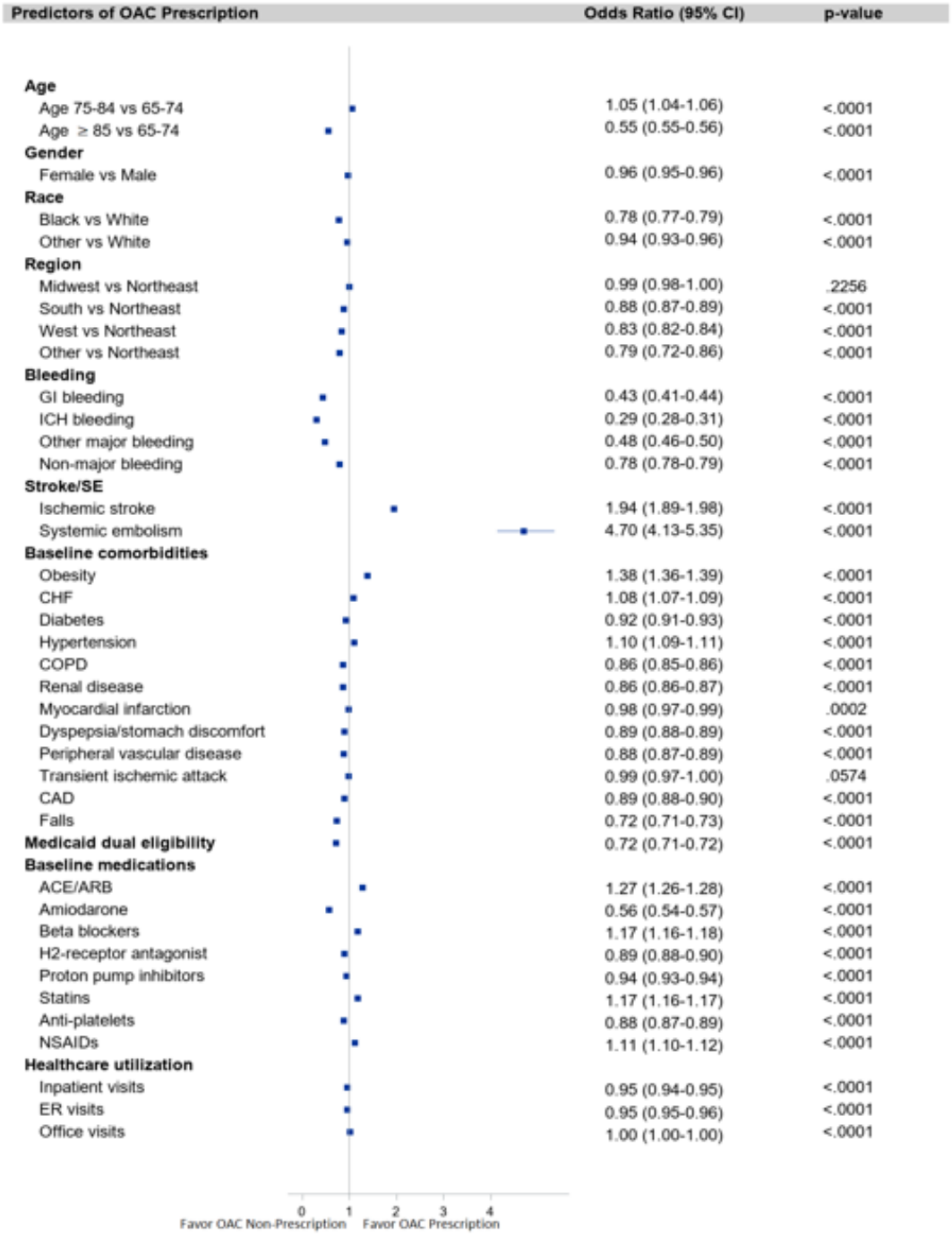


Figure 8. Predictors of Warfarin Prescription

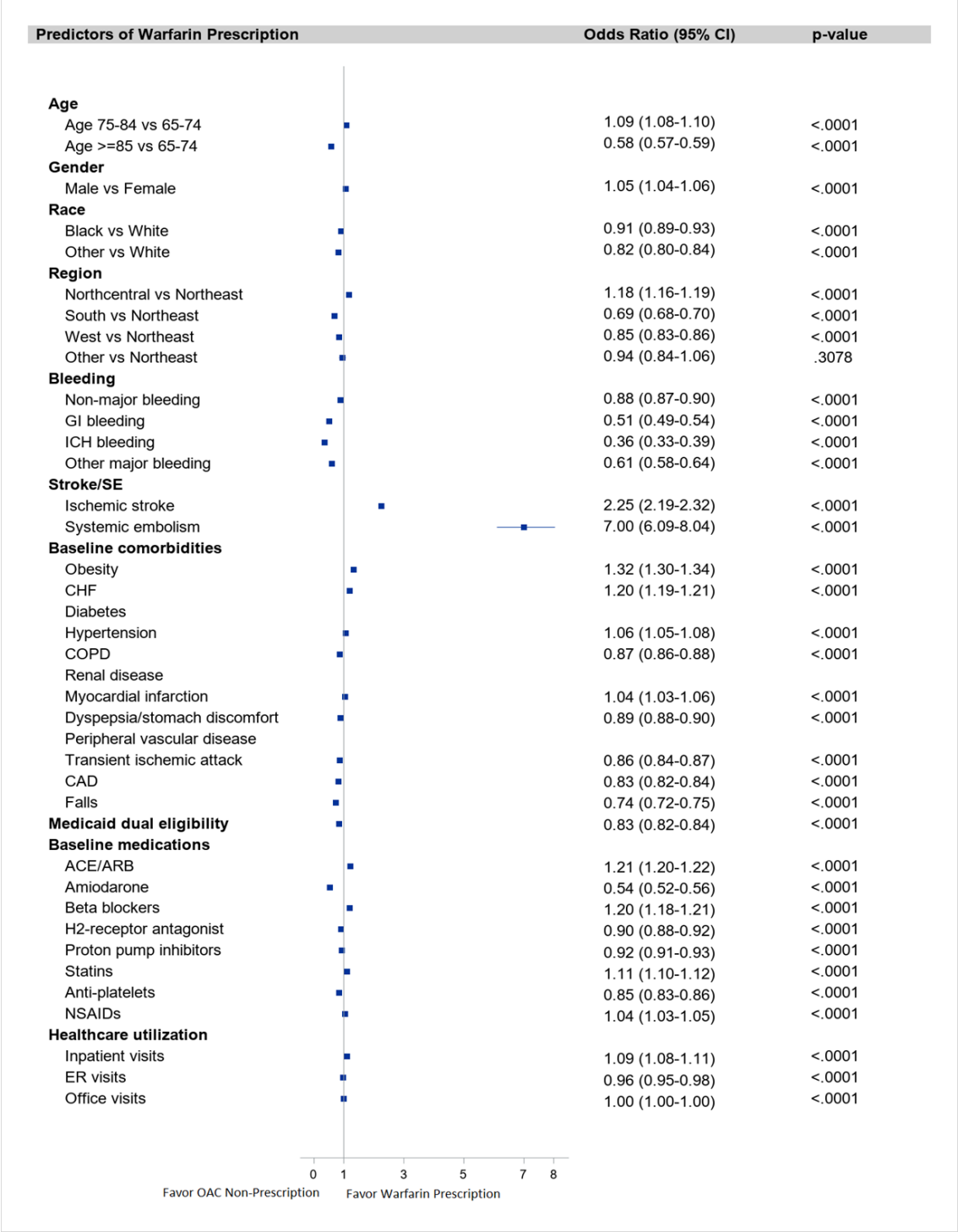


Figure 9. Predictors of DOAC Prescription

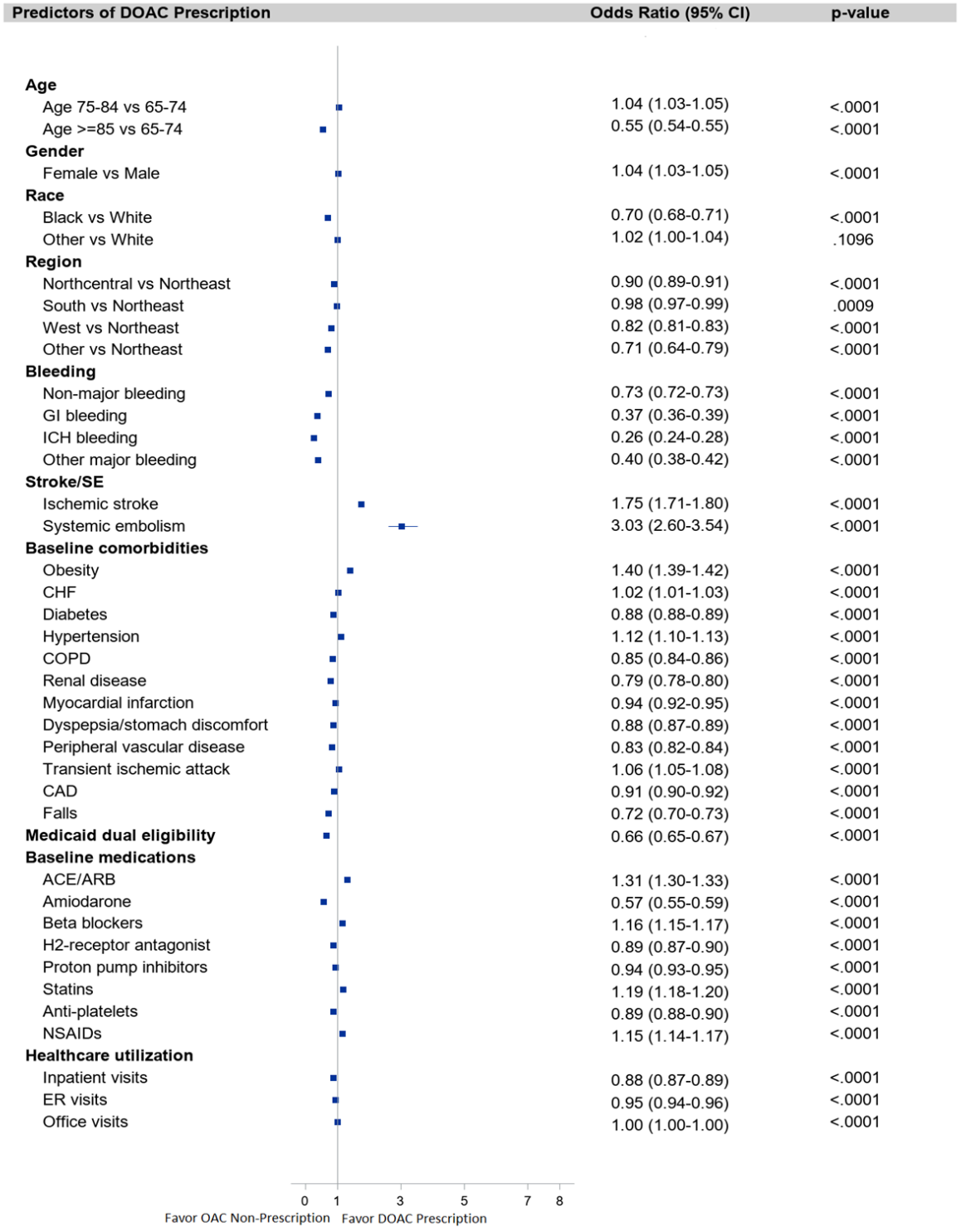


Figure 10. Predictors of DOAC Prescription

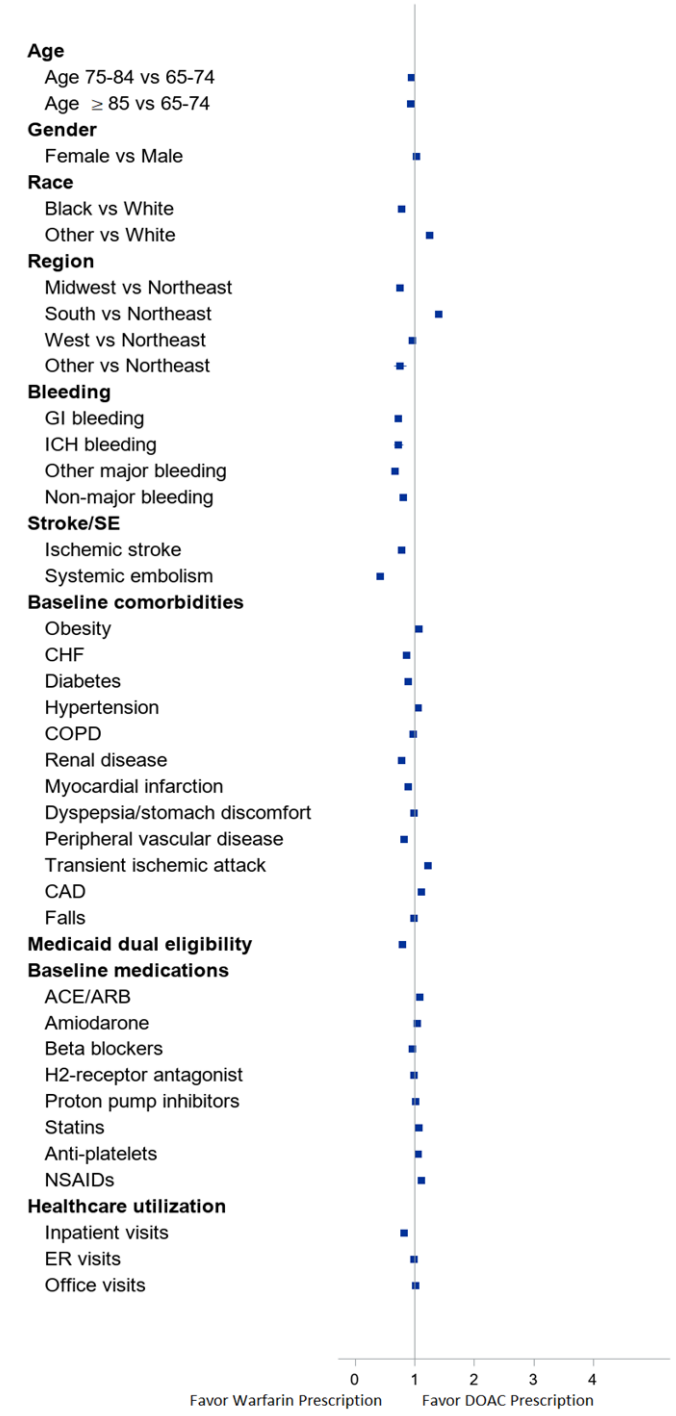
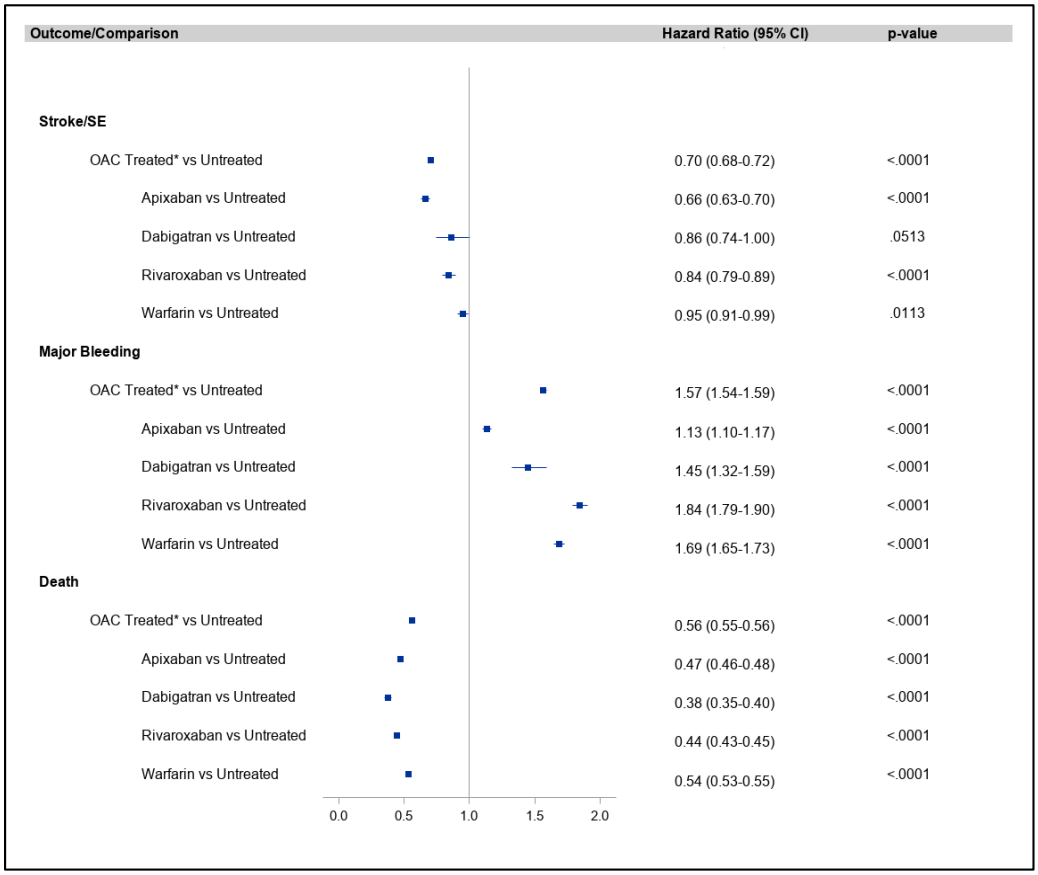
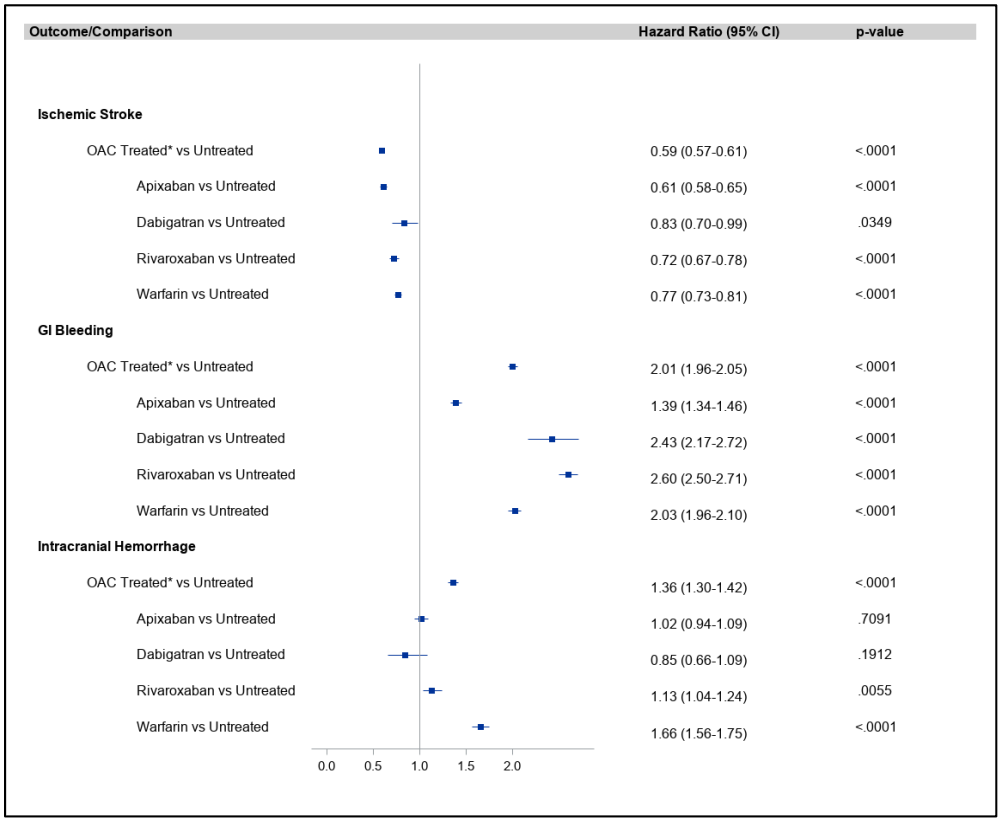


Figure 11. Adjusted risk of stroke/SE, MB, and death based on OAC treatment after first AF diagnosis



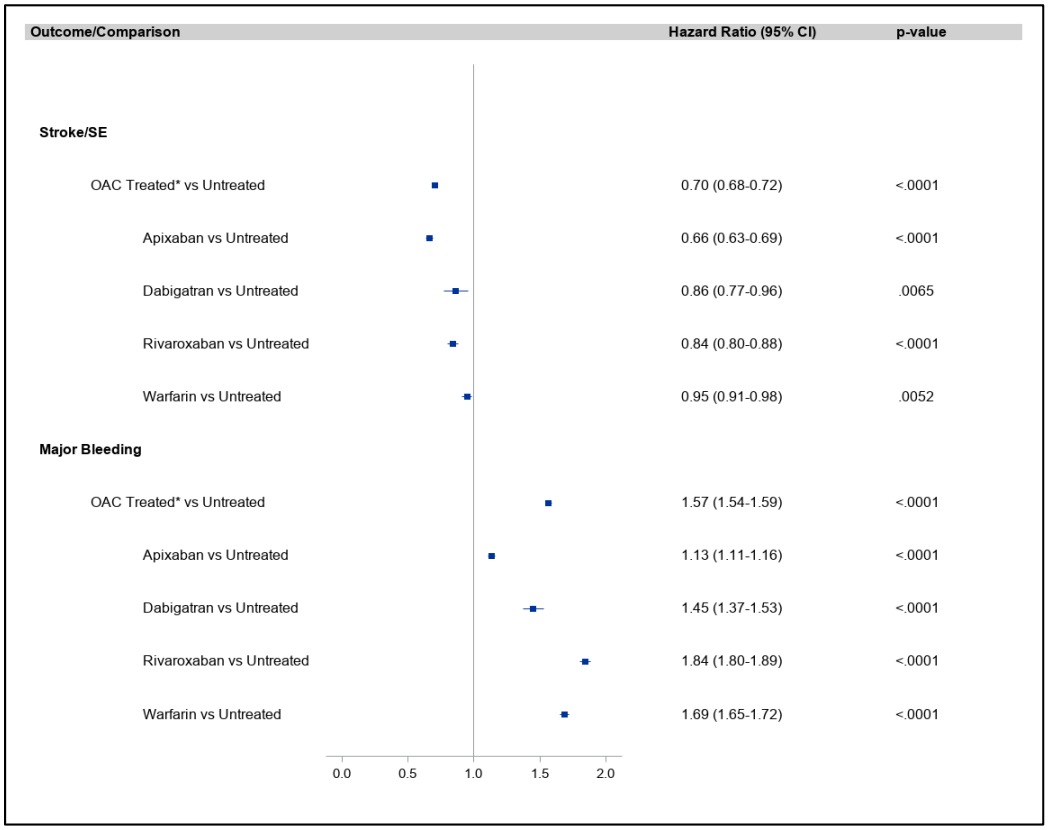
*OAC Treated cohort includes apixaban, dabigatran, edoxaban, rivaroxaban, and warfarin treated patients

Figure 12. Adjusted risk of ischemic stroke, gastrointestinal bleeding, and intracranial hemorrhage based on OAC treatment status after first AF diagnosis



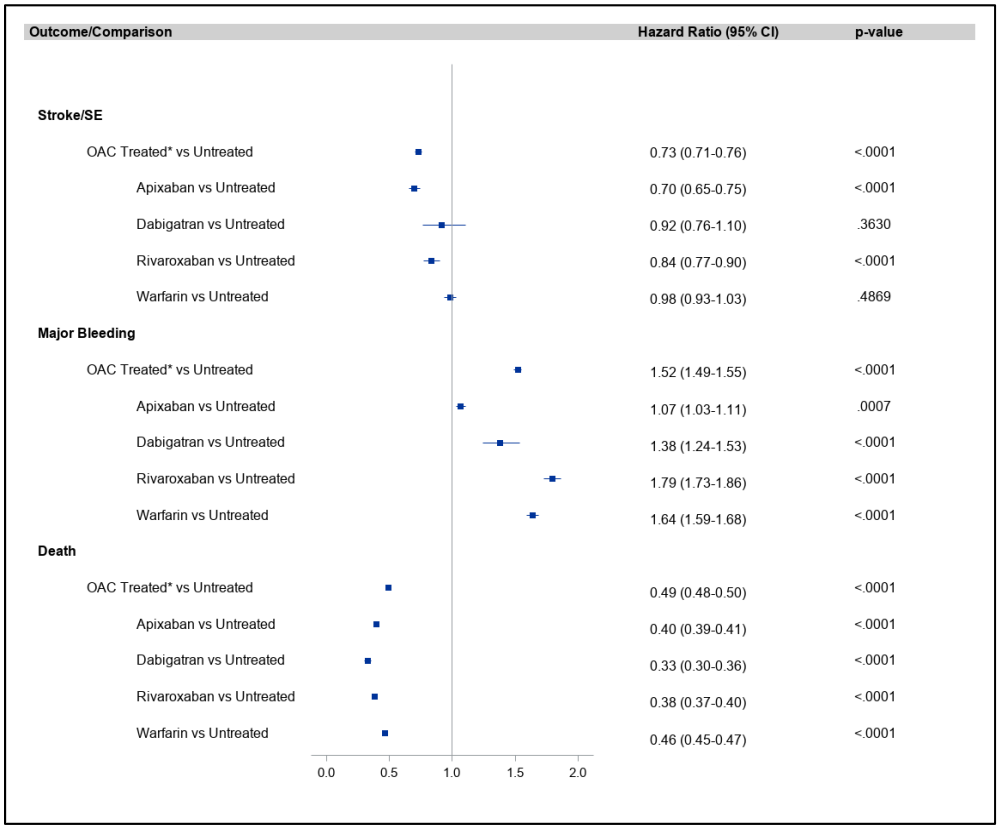
*OAC Treated cohort includes apixaban, dabigatran, edoxaban, rivaroxaban, and warfarin treated patients

Figure 13. Sensitivity analysis: Adjusted risk of stroke/SE, MB, and death based on OAC treatment status after first AF diagnosis with death as a competing risk



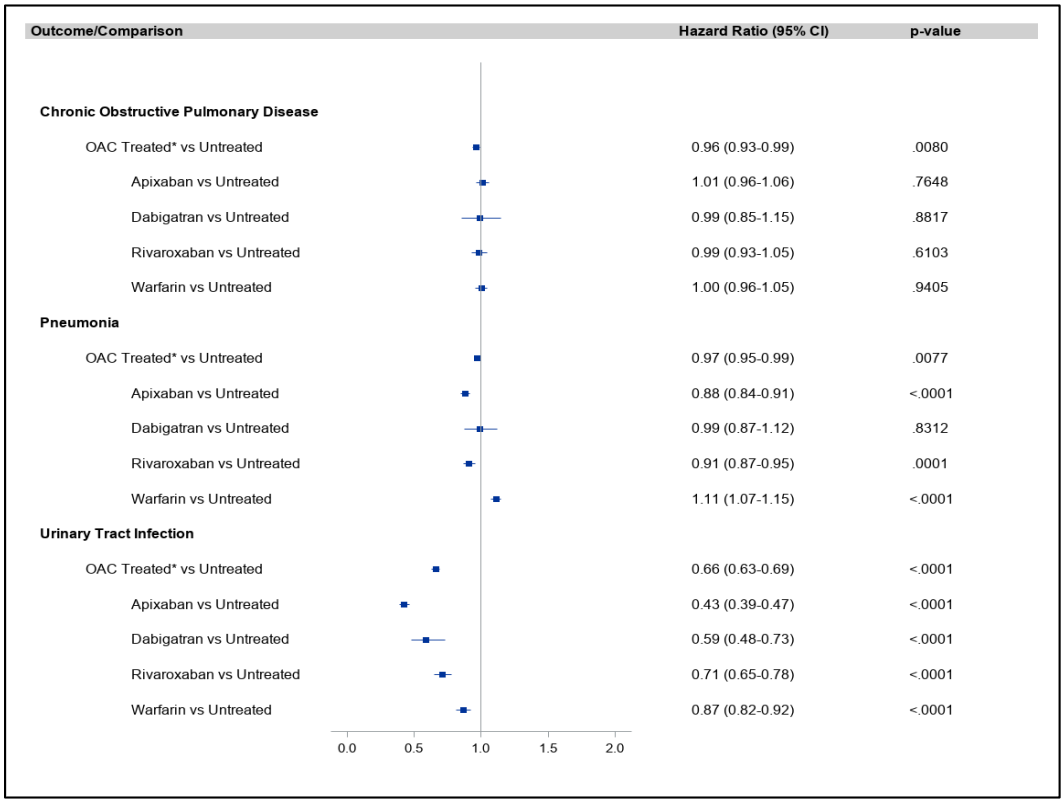
*OAC Treated cohort includes apixaban, dabigatran, edoxaban, rivaroxaban, and warfarin treated patients

Figure 14. Adjusted risk of stroke/SE, MB, and death based on OAC treatment after first AF diagnosis - censored at one year



*OAC Treated cohort includes apixaban, dabigatran, edoxaban, rivaroxaban, and warfarin treated patients

Figure 15. Adjusted risk of falsification outcomes based on OAC treatment status



Annex 1. List of stand-alone documents

Appendix 1. SIGNATURES

None

Appendix 8. ADDITIONAL DOCUMENTS

Not Applicable