NON-INTERVENTIONAL (NI) STUDY REPORT

Study Information

Title	Effectiveness and Safety of Oral Anticoagulants in Older Adults with Non-valvular Atrial Fibrillation and Concomitant Coronary Artery Disease or Peripheral Artery Disease: Insights from Medicare
EU Post Authorisation Study (PAS) register number	EUPAS18970
Pfizer protocol number	B0661101
Date of last version of the final study report	N/A
Medicinal product	Apixaban
Research question and objectives	Aim 1: To compare the rate of a composite of myocardial infarction, stroke, and all-cause death and the rate of all-cause death among patients initiating OACs (warfarin, apixaban, rivaroxaban and dabigatran) Aim 2: To compare the rate of a composite of myocardial infarction, ischemic stroke, acute limb ischemia and all-cause death and the rate of a composite of myocardial infarction, ischemic stroke and all-cause death among patients initiating OACs Aim 3: To compare the rate of major bleeding, among patients initiating OACs Aim 4: To compare the rate of stroke and stroke/SE among patients initiating different OACs Aim 5: To compare health care resource

	utilization and costs among patients initiating OACs Aim 6: To compare the baseline demographic and clinical characteristics among patients initiating OACs
Author	Allison Keshishian, MPH Phone: 248-752-3448 Email: akeshishian@statinmed.com Xuemei Luo, PhD Phone : 860-441-6309 Email : xuemei.luo@pfizer.com

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES AND FIGURES

List of Tables

List of Figures

Appendix

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AF	Atrial Fibrillation
NVAF	Non-valvular Atrial Fibrillation
CAD	Coronary Artery Disease
CCI	Charlson Comorbidity Index
PAD	Peripheral Arterial Disease
MI	Myocardial Infarction
HF	Heart Failure
ACS	Acute Coronary Syndrome
ALI	Acute Limb Ischemia
$CHADS_2$	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
DVT	Deep Vein Thrombosis
FFS	Fee-For-Service
RWD	Real World Data
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

Abbreviation	Definition
HIPAA	Health Insurance Portability and Accountability Act
ICD-9 CM	International Classification of Diseases – Clinical Modification, 9th Revision
PSM	Propensity Score Matching
SAP	Statistical Analysis Plan
MB	Major Bleeding
NDC	National Drug Code
NOAC	Novel Oral Anticoagulant
OAC	Oral Anticoagulants
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism
CABG	Coronary Bypass Surgery
PCI	Percutaneous Coronary Intervention
SAS	Statistical Analysis System
CMS	Center for Medicaid and Medicare Services
PDE	Medicare Part D Drug Events
DRG	Disease Related Group
HHA	Home Health Agency
GHP	Group Health Plan
EDB	Enrollment Database
SE	Systemic Embolism
ACM	All-cause mortality
MACE	Composite of stroke/SE, MI and all-cause death

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Allison Keshishian, MPH	Sr. Project Manager	STATinMED Research
Lin Xie, MS, MA	Sr. Director, HEOR	STATinMED Research
Xuemei Luo, PhD	Sr. Director, HEOR	Pfizer Inc
Manuela Di Fusco	Sr. Manager, HEOR	Pfizer Inc

4. OTHER RESPONSIBLE PARTIES

Not Applicable.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection			
End of data collection			
Registration in the EU PAS register	N/A		
Study progress report I (Protocol)	May 2017	May 2017	
Descriptive Results	Oct 2017	Nov-Dec 2017	
Multivariate Results			
Final report of study results	Feb 2018	March 2018	

6. RATIONALE AND BACKGROUND

Atrial fibrillation (AF), the most common cardiac dysrhythmia in the United States, is predicted to increase in prevalence from 5.2 million in 2010 to 12.1 million cases in 2030.[1,2] AF increases the risk of stroke by five-fold and is associated with 15-20% of all strokes,[3,4] ultimately leading to high-risk functional or neurological deficits and higher mortality rate.[5,6] Prior studies have shown that the prevalence of coronary artery disease (CAD) among AF-diagnosed patients ranges from 18-45%.[7,8,9,10,11] CAD patients are at high risk for myocardial infarction (MI) and cardiovascular-related death.[12,13,14] Additionally, the prevalence of peripheral artery disease (PAD) among AF-diagnosed patients was found to be in the range of 4-17%.[15,16] PAD has been found to be an independent risk factor for AF and increases the risk of stroke and MI.[17] AF management has been proven to be complicated by the presence of concomitant CAD and PAD. Concomitant AF with CAD has been strongly associated with all-cause mortality, coronary death, and major coronary events.[18] Therefore, owing to the considerable clinical burden, CAD and/or PAD co-diagnosed with AF are of significant concern in clinical practice.

Given the high risk of clinical outcomes, vitamin K antagonists such as warfarin and direct oral anticoagulants (DOACs) dabigatran, rivaroxaban, apixaban, and edoxaban have been frequently prescribed for stroke/systemic embolism (SE) prevention among non-valvular AF patients. Clinical trials have shown that DOACs are at least as effective as warfarin in stroke/SE and major bleeding (MB) risk reduction.[19,20,21,22] These results are also supported by several recent real-world studies showing similar trends.[23,24,25,26,27,28,29,30,31,32,33] Given the increased risk of stroke associated with CAD/PAD, post-hoc analyses of trial data have been conducted to evaluate the efficacy and safety of rivaroxaban and apixaban in NVAF patients with concomitant CAD, PAD, and/or MI.[34,35,36,37] However, the current literature lacks comparative assessment of clinical outcomes such as stroke/SE, MI, MB, and death among NVAF patients with CAD/PAD who were managed with warfarin and DOACs in routine clinical practice. Therefore, we conducted a "real-world" observational study to compare the risk of stroke/SE, MB, and composite outcomes (stroke/MI/all-cause mortality [ACM] and stroke/MI/ACM/revascularization [RV]) among NVAF patients with CAD/PAD prescribed warfarin, apixaban, rivaroxaban, or dabigatran in a Medicare-enrolled population.

This was not a PASS study nor a commitment or requirement to any regulatory agency.

7. RESEARCH QUESTION AND OBJECTIVES

Aim 1: To compare the rate of a composite of MI, stroke, and all-cause death and the rate of all-cause death among patients initiating OACs (warfarin, apixaban, rivaroxaban and dabigatran)

Aim 2: To compare the rate of a composite of MI, ischemic stroke, acute limb ischemia and all-cause death and the rate of a composite of MI, ischemic stroke, and all-cause death among patients initiating OACs

Aim 3: To compare the rate of MB, among patients initiating OACs

Aim 4: To compare the rate of stroke and stroke/SE among patients initiating different OACs

Aim 5: To compare health care resource utilization and costs among patients initiating OACs

Aim 6: To compare the baseline demographic and clinical characteristics among patients initiating OACs

8. AMENDMENTS AND UPDATES

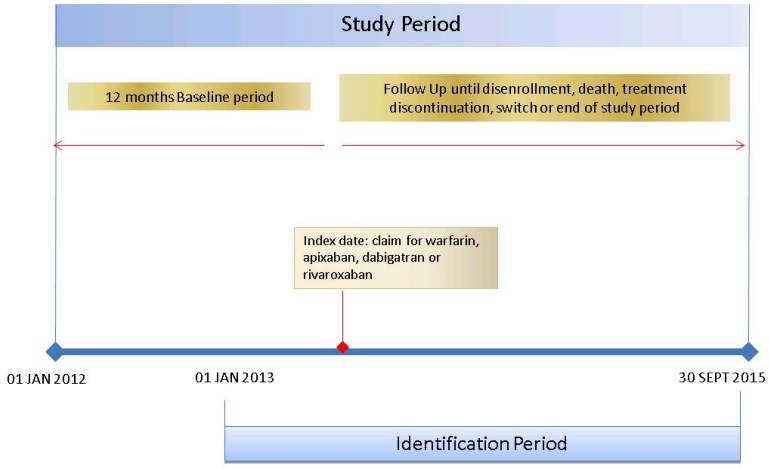
None.

9. RESEARCH METHODS

9.1. Study design & Setting

The study was a longitudinal retrospective cohort analysis using the 100% CMS Medicare fee-for-service (FFS) database. Demographics, clinical characteristics, clinical outcomes (including MB, stroke, SE, all-cause mortality, and composite endpoints (see Objectives), and economic outcomes were determined and compared among NVAF patients who were prescribed warfarin, apixaban, dabigatran, or rivaroxaban. The study period was from January 1, 2012 through September 30, 2015. The study allowed for a 12-month baseline period prior to the identification period (January 1, 2013 through September 30, 2015). For patients with a DOAC prescription, the earliest DOAC prescription (apixaban, dabigatran or rivaroxaban) date to occur during the identification period was defined as the index date. For patients who were prescribed only warfarin and had no DOAC claims, the first warfarin claim date during the identification period was defined as the index date.

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



9.2. Subjects

Inclusion Criteria

Patients were included in the study if they:

a) had ≥1 pharmacy claim for apixaban, dabigatran, rivaroxaban, or warfarin during the identification period (01JAN2013-30SEP2015). For patients with a DOAC prescription, the first DOAC (apixaban, dabigatran, or rivaroxaban) pharmacy claim date during the identification period was designated as the index date. The first warfarin prescription date was designated as the index date for patients who were prescribed only warfarin and without any DOAC claim;

b) were aged ≥ 65 years as of the index date;

c) had continuous medical and pharmacy health plan enrollment (Part A, B, and D) for at least 12 months prior to and on the index date;

d) had at least 1 diagnosis of AF (refer to ICD-9-CM codes in Appendix 3, Table 1) prior to or on the index date; and

e) had at least one diagnosis claim of CAD and/or PAD during the 12 months prior to or on the index date.

Exclusion Criteria

Patients were excluded from the study if they:

a) had medical claims indicating a diagnosis of valvular heart disease during the 12-months prior to or on the index date;

b) had medical claims indicating a diagnosis of venous thromboembolism (VTE) during the 12 months prior to or on the index date;

c) had medical claims indicating a diagnosis or procedure code of transient AF ([heart valve replacement/transplant, pericarditis, hyperthyroidism and thyrotoxicity]) during the 12 months prior to or on the index date;

d) had medical claims indicating pregnancy during the study period;

e) had a pharmacy claim for warfarin, apixaban, dabigatran, or rivaroxaban during the 12-months prior to the index date; or

f) had >1 OAC prescription claim on the index date.

All codes for the selection criteria are detailed in the Table 1, Appendix 3.

Follow-up Period

The follow-up period was defined as the time between the day after the index date and end of study period (30-September-2015). Patient data were assessed from the day after the index date to 30 days after the date of discontinuation, switch, death, end of study period, or end of continuous medical and pharmacy enrollment, whichever occurred earliest.

To assess first MB, stroke/SE, MI, acute limb ischemia, or death event, patients were censored at first occurrence of either event occurring anytime during the period while prescribed the drug or within 30 days from the last day of days' supply of treatment prescription, 30 days after date of discontinuation, switch, death, end of study or end of continuous medical and pharmacy enrollment, whichever was earlier.

Discontinuation was defined as no evidence of index OAC prescription for 30 days from the last day of days' supply of last filled prescription.[38] The discontinuation date was the last day of the days' supply of last filled prescription. The follow-up was censored at 30 days after the index drug discontinuation date.[39] Patients that received a prescription for an OAC (warfarin, apixaban, dabigatran or rivaroxaban) other than the index OAC drug prescription during the follow-up period were considered switchers if the OAC prescription was within ± 30 days of last days' supply. The follow-up was censored as of the index drug switch date.

Treatment/Cohort Labels:

After applying the inclusion and exclusion criteria, eligible patients were assigned to the following cohorts based on the newly initiated OAC.

- Apixaban Cohort: NVAF patients who initiated apixaban on the index date.

- Dabigatran Cohort: NVAF patients who initiated dabigatran on the index date.
- Rivaroxaban Cohort: NVAF patients who initiated rivaroxaban on the index date.
- Warfarin Cohort: NVAF patients who initiated warfarin on the index date, after all the DOACs are identified.

9.3. Variables

Table 1. Baseline Demographic and Clinical Characteristic Variables[a]

Variable	Role	Operational definition
Age	Baseline characteristic and potential confounder	Age was defined as of the index date and used to assign patients to the following age groups: 65-74, 75-79, and ≥80 years.
Sex	Baseline characteristic and potential confounder	A flag was created for female beneficiaries and reported as a percentage.
US Geographic Region	Baseline characteristic and potential confounder	The United States was divided into five regions: Northeast, South, North Central, West, and Other. Geographic region was captured from enrollment data.
Prior Stroke/SE	Baseline characteristic and potential confounder	A flag was created for patients who had a stroke/SE claim during the baseline period.
Ischemic Stroke	Baseline characteristics and potential confounder	A flag was created for patients who had an ischemic stroke (primary inpatient discharge codes) claim 1 month prior to index date during the baseline period.
Hemorrhagic stroke	Baseline characteristic and potential confounder	A flag was created for patients who had a hemorrhagic stroke (primary inpatient discharge codes) claim 1 month prior to index date during the baseline period
Lacunar stroke	Baseline characteristic and potential confounder	A flag was created for patients who had a lacunar stroke claim during the baseline period.
Congestive Heart Failure	Baseline characteristic and potential confounder	A flag was created for patients with claims for congestive heart failure in the baseline period.
Diabetes	Baseline characteristic and potential confounder	A flag was created for patients with claims for diabetes in the baseline period.
Hypertension	Baseline characteristic and potential confounder	A flag was created for patients with claims for hypertension in the baseline period.
Renal Disease	Baseline characteristic and potential confounder	A flag was created for patients with claims for renal disease in the baseline period. A flag for chronic kidney disease stage V, ESRD or dialysis was created in baseline period.
Liver Disease	Baseline characteristic and potential confounder	A flag was created for patients with claims for liver disease in the baseline period.

Myocardial Infarction	Baseline characteristic and potential confounder	A flag was created for patients with claims for myocardial infarction in the baseline period.
Hospitalized Myocardial Infarction	Baseline characteristic and potential confounder	A flag was created for patients with claims for myocardial infarction during a hospitalization in the baseline period.
Dyspepsia or Stomach Discomfort	Baseline characteristic and potential confounder	A flag was created for patients with claims for dyspepsia or stomach discomfort in the baseline period.
Peripheral vascular disease	Baseline characteristic and potential confounder	A flag was created for patients with claims for peripheral vascular disease in the baseline period.
Transient Ischemic Attack	Baseline characteristic and potential confounder	A flag was created for patients with claims for transient ischemic attack in the baseline period.
Anemia and Coagulation defects	Baseline characteristic and potential confounder	A flag was created for patients with claims for anemia and coagulation defects in the baseline period.
Alcoholism	Baseline characteristic and potential confounder	A flag was created for patients with claims for alcoholism in the baseline period.
CAD only	Baseline characteristic and potential confounder	A flag was created for patients with claims for CAD only and no PAD in the baseline period.
PAD only	Baseline characteristic and potential confounder	A flag was created for patients with claims for PAD only and no CAD in the baseline period.
CAD and PAD	Baseline characteristic and potential confounder	A flag was created for patients with claims for CAD and PAD in the baseline period.
Coronary Bypass surgery (CABG)	Baseline characteristic and potential confounder	A flag was created for patients with claims for CABG. (See Protocol for codes)
Percutaneous Coronary Intervention (PCI)	Baseline characteristic and potential confounder	A flag was created for patients with claims for PCI.
Systolic Heart Failure	Baseline characteristic and potential confounder	A flag was created for patients with claims for systolic HF and combined systolic and diastolic HF.
Baseline Prior Bleed	Baseline characteristic and potential confounder	A flag was created for patients who had a bleeding-related claim during the baseline period.
Baseline Deyo-Charlson Comorbidity Index	Baseline characteristic and potential confounder	The Deyo-Charlson Comorbidity Index was created for the baseline period
Baseline $CHADS_2$	Baseline characteristic and potential confounder	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: 0, 1,2, $\geq$3
Baseline CHA_2DS_2-VASc Score	Baseline characteristic and potential confounder	The CHA_2DS_2VASc score was used to analyze the effect of stroke risk stratification on OAC

		use. The maximum score is 9. CHADS2-VASc scores: 0, 1,2, 3, ≥4
HAS-BLED Score	Baseline characteristic and potential confounder	HAS-BLED score was used to estimate the risk of MB for patients.
Anti-Platelet therapies	Baseline characteristic and potential confounder	A flag was created for patients with prescription fills for anti-platelet therapies (abciximab, anagrelide, cilostazol, clopidogrel, dipyridamole, eptifibatide, prasugrel, ticagrelor, ticlopidine and tirofiban).
Other Baseline Medications	Baseline characteristic and potential confounder	Flags was created for patients with prescription fills for angiotensin-converting enzyme inhibitor (ACE)/ angiotensin-receptor blocker (ARB), beta blocker, amiodarone, statin, proton pump inhibitor (PPI), H2-receptor antagonist, and NSAIDs.
Health Care Resource Utilization	Baseline characteristic and potential confounder	All-cause utilization variables were computed for inpatient, outpatient, ER, office, SNF, DME, HHA, hospice, and part D pharmacy claims.
Health care Costs	Baseline characteristic and potential confounder	Health care cost included total baseline all-cause costs and the components: inpatient, outpatient, ER, office, SNF, DME, HHA, hospice, and part D pharmacy.
DOAC Index dose	Baseline characteristic	Standard dose (apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg) and lower dose (apixaban 2.5 mg, dabigatran 75 mg, rivaroxaban 15 & 10 mg) based on dose of the initial prescription of DOAC was used.

[a]Baseline variables were evaluated using codes in any position (primary or secondary) unless noted otherwise; All codes can be viewed in the appendix attached at the end of the document.

Table 2. Descriptive Outcome Variables *

Variable	Role	Operational definition
Stroke	Outcome variable	Stroke was identified using hospital discharge records which had a stroke diagnosis code as the primary discharge diagnosis occurring anytime during the period of drug use or within 30 days from the last day of supply of treatment prescription. Stroke was a dichotomous variable that equals 1 if there was ≥1 stroke event during the follow-up period. Time to the first stroke event was calculated.
Stroke/SE	Outcome variable	Stroke/SE was identified using hospital discharge records which had a stroke/SE diagnosis code as the primary discharge diagnosis occurring anytime during the period of drug use or within 30 days from the last day of supply of treatment prescription. Stroke/SE was defined as a dichotomous variable that equals 1

Variable	Role	Operational definition
		if there was ≥1 stroke/SE event during the follow-up period. Time to the first stroke/SE event was calculated. The first stroke/SE event was stratified by ischemic stroke, hemorrhagic stroke, and SE.
Ischemic Stroke	Outcome variable	Ischemic stroke was identified using hospital discharge records which had a stroke diagnosis code as the primary discharge diagnosis occurring anytime during the period of drug use or within 30 days from the last day of supply of treatment prescription. Ischemic stroke was defined as a dichotomous variable that equals 1 if there was ≥ 1 stroke event during the follow-up period. Time to the first ischemic stroke event was calculated.
Myocardial Infarction (MI)	Outcome variable	MI events observed during follow-up were identified using hospital discharge records which had a MI diagnosis as the primary discharge diagnosis occurring any time during the follow-up period of drug use or within 30 days from the last day of supply of treatment prescription. MI event was defined as a dichotomous variable that equals 1 if there was ≥1 MI event during the follow-up period. Time to the first MI event was calculated.
Acute Limb Ischemia	Outcome variable	Acute limb ischemia event observed during follow-up was identified using hospital discharge records which had an acute limb ischemia diagnosis as the primary discharge diagnosis occurring anytime during the follow-up period of drug use or within 30 days from the last day of supply of treatment prescription. Acute limb ischemia event was defined as a dichotomous variable that equals 1 if there was ≥1 acute limb ischemia event during the follow-up period. Time to the first acute limb ischemia event was calculated.
All-cause Mortality	Outcome variable	Death occurring anytime during the follow-up period of drug use or within 30 days from the last day of supply of treatment prescription was identified. Death was defined as a dichotomous variable that equals 1 if there was a death event or 0, if otherwise. Time to the first death event was calculated.
Major Bleeding (MB)	Outcome variable	A MB event observed during follow-up was identified using hospital discharge records which had a MB diagnosis as the primary discharge diagnosis as listed by ICD-9-CM codes

Variable	Role	Operational definition
		occurring anytime during the follow-up period of drug use or within 30 days from the last day of supply of treatment prescription. Major bleeding event was a dichotomous variable that equals 1 if there was ≥ 1 bleeding event during the follow-up period. Time to the first MB event was calculated. Major bleeding was stratified by gastrointestinal (GI) bleeding, intracranial hemorrhage, and other bleeding.
MACE: Composite of MI, stroke and all-cause-death	Composite Outcome	A composite outcome of stroke, MI, and all-cause death was evaluated. The frequency and time to the first occurrence of stroke, MI, or all-cause death was calculated.
Composite of MI, ischemic stroke, acute limb ischemia and all-cause death	Composite Outcome	The frequency and time to the first occurrence of ischemic stroke, MI, acute limb ischemia, and all-cause death was calculated.
Composite of MI, ischemic stroke an all-cause death	Composite Outcome	The frequency and time to the first occurrence of MI, ischemic stroke, and all-cause death was calculated.
Follow-up All-cause Health Care Costs	Outcome	All-cause health care costs in the follow-up period were computed for inpatient, outpatient, ER, office, SNF, DME, HHA, hospice, and part D pharmacy costs. Costs were adjusted to 2014 US dollars using the CPI medical care component. Total medical and total health care costs were calculated per patient per month (PPPM).
Follow-up All-cause Health Care Utilization	Outcome	All-cause health utilization costs in the follow-up period were computed for inpatient, outpatient, ER, office, SNF, DME, HHA, hospice, and part D pharmacy claims.
First Major Bleeding-related Hospitalization Costs	Outcome	First MB-related hospitalization costs were defined as hospitalization costs associated with the first MB event in the follow-up period.
First Stroke/SE-related Hospitalization Costs	Outcome	First stroke/SE-related hospitalization costs were defined as hospitalization costs associated with the first stroke/SE event in the follow-up period.

Variable	Role	Operational definition
First Stroke/MI-related Hospitalization Costs	Outcome	First stroke/MI-related hospitalization costs were defined as hospitalization costs associated with the first stroke or MI event in the follow-up period.
Follow-up Bleeding-related Medical Costs	Outcome	Bleeding-related medical costs were defined as hospitalization costs associated with the first major bleed plus all subsequent bleeding costs occurring in the inpatient or outpatient setting (primary or secondary diagnosis).
Follow-up Stroke/SE-related Medical Costs	Outcome	All stroke/SE-related medical costs were defined as hospitalization costs associated with the first stroke/SE plus all subsequent stroke/SE costs occurring in the inpatient or outpatient setting (primary or secondary diagnosis
Follow-up Stroke or MI related Medical Costs	Outcome	All stroke/MI-related medical costs were defined as hospitalization costs associated with the first stroke or MI plus all subsequent stroke or MI costs occurring in the inpatient or outpatient setting (primary or secondary diagnosis)
Anti-Platelet therapies	Outcome variable	A flag was created for patients with prescription fills for anti-platelet therapies during the follow-up
Discontinuation	Treatment Pattern outcome	Percentage of patients who discontinued and time-to-index OAC discontinuation was reported.
Switch	Treatment Pattern outcome	Percentage of patients who switched to a non-index OAC and time-to-switch was reported.

***** All codes can be viewed in the protocol attached at the end of the document.

9.4. Data sources and measurement

100% CMS Medicare data was used for the purposes of this analysis. The following files were made use of in this study:

Medicare Inpatient Data

The inpatient claim file contains final action claims data submitted by inpatient hospital providers for reimbursement of facility costs. Some information contained in this file includes diagnosis (International Classification of Diseases, Ninth Revision, Clinical ICD-9-CM] diagnosis code, procedure (ICD-9 procedure code), diagnosis-related group (DRG), dates of service, reimbursement amount, hospital provider, and beneficiary demographic information. Each observation in this file is at the claim level.

Medicare Outpatient Data

The outpatient claim file contains final action claims data submitted by institutional outpatient providers. Examples of institutional outpatient providers include hospital outpatient departments, rural health clinics, renal dialysis facilities, outpatient rehabilitation facilities, comprehensive outpatient rehabilitation facilities, and community mental health centers. Some information contained in this file includes diagnosis and procedure (ICD-9-CM diagnosis, ICD-9 procedure, Centers for Medicare and Medicaid Service [CMS] Healthcare Common Procedure Coding System [HCPCS] codes), dates of service, reimbursement amount, outpatient provider number, revenue center codes, and beneficiary demographic information. Each observation in this file is at the claim level.

Medicare Part D Drug Events (PDE) Data

The PDE data contains prescription drug costs and payment data that enable CMS to make payments to the plans and otherwise administer Part D benefits. When a beneficiary fills a prescription under Medicare Part D, a prescription drug plan sponsor must submit a summary record to CMS. The PDE data are not the same as individual drug claim transactions, but are summary extracts using CMS-defined standard fields.

Skilled Nursing Facility (SNF) Research Identifiable File (RIF)

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

Home Health Agency (HHA) RIF

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

Hospice RIF

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

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

Durable Medical Equipment (DME) RIF

The DME file contains final action, FFS claims submitted by DME suppliers. This file includes: diagnosis (ICD-9-CM diagnosis), services provided (CMS Common Procedure Coding System [HCPCS] codes), dates of service, reimbursement amounts, DME provider number, and beneficiary demographic information.

Medicare Carrier File

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

Medicare Denominator File

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

Some information contained in this file includes the beneficiary's unique identifiers, state and county codes, ZIP codes, dates of birth, dates of death, sex, race, age, monthly entitlement indicators (A/B/both), reasons for entitlement, state buy-in indicators, and monthly managed care indicators (yes/no).

9.5. Bias

The limitation of this study was that the Medicare database does not uniformly capture over-the-counter medications, such as aspirin, which are used for stroke prevention in AF patients and could have an impact on the treatment outcomes of the anticoagulants being studied. Also, the Medicare database included only FFS patients. Furthermore, while claims data are extremely valuable for the efficient and effective examination of health care outcomes, treatment patterns, health care resource utilization, and costs, all claims databases have

certain inherent limitations because the claims are collected for the purpose of payment and not research. First, presence of a claim for a filled prescription did not indicate that the medication was consumed or that it was taken as prescribed. Second, medications filled over-the-counter or provided as samples by the physician were not observed in the claims data. Third, presence of a diagnosis code on a medical claim was not positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. Lastly, we did not have certain clinical information in the data to ascertain dose-specific selection criteria, such as body weight (in kilograms) or creatinine clearance values.

9.6. Study Size

The sample size was calculated for feasibility survival analysis comparing the differences in MACE and MB rates between apixaban and warfarin patients using an alpha of 0.05, power of 80%, an accrual period (identification period when patients are selected into the study until end of study [01JAN2013-31DEC2014]) of 2 years, and a loss of follow-up of 74% for the warfarin cohort and 50% for the apixaban cohort. This calculation assumed a uniform accrual and loss to follow-up during the identification period. Using the feasibility MACE outcome rates of 6.2% and 14.3% per year for apixaban and warfarin users, respectively, a Cox proportional hazards analysis of stroke would need 452 patients in each group. Using the feasibility MB rate of 2.04% per year for the apixaban cohort and 4.3% per year in the warfarin group, a Cox proportional hazards analysis of MB would require 1,737 patients in each group. The sample size and event rates were evaluated prior to proceeding with the analysis to determine if there is sufficient power.

9.7. Data transformation

Detailed methodology for data transformations, particularly complex transformations (eg, many raw variables used to derive an analytic variable), are documented in the Protocol. See embedded document at the end of the report.

9.8. Statistical methods

9.8.1. Main summary measures

Means, medians, and standard deviations were provided for continuous variables when performing descriptive analysis of continuous data. Numbers and percentages were provided for dichotomous and polychotomous variables when performing descriptive analysis of categorical data. Bivariate comparisons of baseline characteristics and outcomes measures were provided. Appropriate tests (eg, t-test, chi-square test) were used based on the distribution of the measure. The cumulative incidence rate for clinical outcomes (MB, MI, acute limb ischemia, stroke, and mortality) were 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 analysis.

9.8.2. Main statistical methods

The propensity score matching (PSM) technique was used to control for potential confounders when comparing the cohorts.[40] Each subject in the reference cohort was matched to a subject in the comparator cohort with the closest propensity score. The Nearest Neighbor method with or without replacement and with a caliper of 0.01 was used to select the matched samples. The radius, kernel, and mahalanobis stratified matching techniques were evaluated to find the one that best fits the data. The balance of covariates between treatment groups was determined using the absolute standardized difference of the mean ≤ 0.10

After PSM, no significant differences were expected among all pre-index measures between the patient cohorts, and the treatment effect calculated based on the matched population was considered to be the true effect. Covariates to be included in the logistic regression model included variables such as age (65-74 years, 75-79 years, and ≥80 years), gender, race, US geographic region, CCI score, socioeconomic status, Medicaid dual eligibility, low income subsidy, comorbidities (bleeding history, coronary heart failure, diabetes mellitus, hypertension, non-ESRD, liver disease, myocardial infarction, dyspepsia, non-stroke/SE peripheral disease, stroke/SE, transient ischemic attack, ESRD, anemia and coagulation defects and alcoholism) and other clinical characteristics such as baseline medications (amiodarone, beta blockers, h2 receptor antagonists, proton pump inhibitors, statins, anti-platelets and non-steroidal anti-inflammatory drugs) and procedures such as percutaneous coronary intervention and coronary bypass surgery..

Cox proportional models were fit to compare the time-to-MB, time-to-MACE, and other clinical outcomes among the apixaban, warfarin, rivaroxaban, and dabigatran cohorts. This model tested proportional hazards models on survival (or time-to-event) data via maximum likelihood with exponential, Weibull, and Gompertz distributions to be considered.

Generalized linear models (GLM) were applied for the multivariable analysis of health care costs among the warfarin, apixaban, dabigatran, and rivaroxaban cohorts. Since a large proportion of zeros exist in some health care cost variables (eg, major-bleeding costs, inpatient or ER costs), two-part models were implemented, in which the first part is a logistic regression of any service use, and the second part a GLM regression of cost, conditional on baseline demographics and clinical characteristics. Bootstrapping with the two-part model was conducted to generate the 95% confidence interval.

All data analysis was executed using statistical software STATA and SAS version 9.3/9.4

9.8.3. Missing values

None.

9.8.4. Sensitivity analyses

A sensitivity analysis was carried out by removing the one-year restriction on follow-up time.

9.8.5. Amendments to the statistical analysis plan

None.

9.9. Quality control

STATinMED Research's approach combined scientific rigor with accurate results. The company focuses on quality at each step of the process including, but not limited to, the following:

STATinMED Research incorporates sound scientific design and clinically rigorous review into its studies. To address the important research questions, STATinMED Research develops a detailed study protocol that includes definitions, codes, analyses, and table shells for the study. A member of the STATinMED Research clinical team is involved in reviewing the appropriateness and validity of the coding strategy and in identifying any issues that may be relevant but were not discussed during the proposal phase of the project. The protocol further provides STATinMED Research and Pfizer an opportunity to solidify the research questions and to address any potential gaps in information.

STATinMED Research believes that a study is only as good as the dataset created for analysis. Therefore, we generate the most accurate datasets by incorporating rigorous quality assurance checks during dataset construction. Several checks are used, including record-level verification of all data elements, double-programming of certain portions of the dataset, programming data edit checks, visual review of raw claims data against the constructed data elements, and review of the analysis to assess the validity of results. Twenty percent of a randomly-selected sample is subjected to such checks.

STATinMED Research analysis is performed by a statistician or senior analyst under the supervision of the project director. The project director reviews output for consistency with the analysis plan for quality and accuracy. Further, results were reviewed with Pfizer to establish that the results meet Pfizer's expectations.

The final deliverables produced by STATinMED Research receive internal review by a clinical consultant and/or by another senior researcher for quality and completeness.

9.10. Protection of human subjects

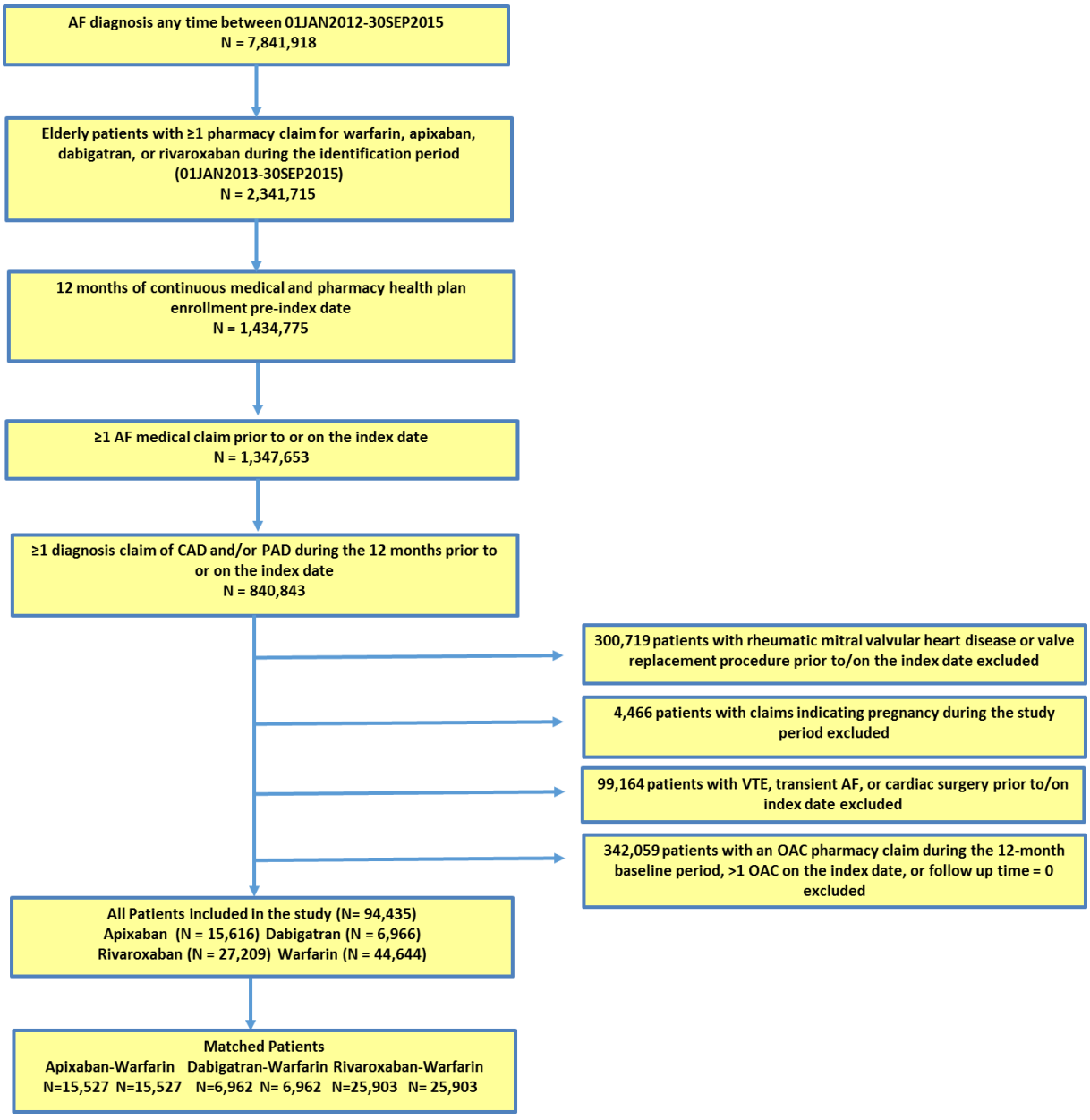
Not Applicable.

10. RESULTS

10.1. Participants

After applying all the selection criteria, a total of 94,435 patients were selected and included in the study (Figure 2). Among them, apixaban (N=15,616), dabigatran (N=6,966), rivaroxaban (N=27,209) and warfarin patients (N=44,644) were selected. After PSM, six pairs of matched cohorts were created – 15,527 pairs of apixaban-warfarin, 6,962 of dabigatran-warfarin, 25,903 of rivaroxaban-warfarin, 6,927 of apixaban-dabigatran, 15,611 of apixaban-rivaroxaban, and 6,966 pairs of dabigatran-rivaroxaban patients.

Figure 2. Patient Selection Flowchart



10.2. Descriptive data

Table 3 shows the patient demographic and clinical characteristics of apixaban, dabigatran, rivaroxaban, and warfarin users. Apixaban and warfarin patients (both with mean age 79 years) were older compared to dabigatran and rivaroxaban (both mean age 78 years) patients. All patients had similar gender distribution (55% men, 45% women). Overall, warfarin patients had higher CCI (4.3 vs 3.9, p<0.001), CHA_2DS_2-VaSc (2.9 vs 2.7, p<0.001), and HAS-BLED (3.7 vs 3.6, p<0.001) scores compared to apixaban patients.

Antiplatelet use was found to be lower in dabigatran (23.7% vs 28.2%), rivaroxaban (25.7% vs 28.2%) and warfarin patients (23.0% vs 28.2%) as compared to apixaban users (all p<0.001). Total mean baseline costs incurred were lower in the dabigatran group compared to apixaban ($2,129 vs $2,337; p<0.001); however, rivaroxaban ($2,409 vs $2,338; p=0.005) and warfarin costs ($2,990 vs $2,338; p<0.001) were higher compared to apixaban.

Table 3. Baseline Descriptive Demographics and Clinical Characteristics

	Apixaban Cohort (Reference)		Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/ Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*
Sample Size	**15,616**		**6,966**				**27,209**				**44,644**			
Age	78.94	7.46	77.80	7.12	<.0001	15.51	78.15	7.33	<.0001	10.61	79.18	7.49	0.0004	3.31
65-74	5,032	32.22%	2,557	36.71%	<.0001	9.44	9,678	35.57%	<.0001	7.07	13,605	30.47%	<.0001	3.77
≥75	10,584	67.78%	4,409	63.29%	<.0001	9.44	17,531	64.43%	<.0001	7.07	31,039	69.53%	<.0001	3.77
75-79	3,375	21.61%	1,692	24.29%	<.0001	6.37	6,394	23.50%	<.0001	4.52	9,791	21.93%	0.4066	0.77
≥80	7,209	46.16%	2,717	39.00%	<.0001	14.52	11,137	40.93%	<.0001	10.57	21,248	47.59%	0.0021	2.87
Sex														
Male	8,452	54.12%	3,894	55.90%	0.0133	3.57	14,913	54.81%	0.1705	1.38	24,423	54.71%	0.2086	1.17
Female	7,164	45.88%	3,072	44.10%	0.0133	3.57	12,296	45.19%	0.1705	1.38	20,221	45.29%	0.2086	1.17
Race														
White	14,340	91.83%	6,252	89.75%	<.0001	7.19	24,666	90.65%	<.0001	4.16	40,431	90.56%	<.0001	4.47
Black	614	3.93%	334	4.79%	0.0028	4.22	1,080	3.97%	0.8484	0.19	2,437	5.46%	<.0001	7.22
Hispanic	175	1.12%	111	1.59%	0.0033	4.09	492	1.81%	<.0001	5.73	565	1.27%	0.1570	1.33
Other	487	3.12%	269	3.86%	0.0041	4.05	971	3.57%	0.0134	2.50	1,211	2.71%	0.0083	2.41
US Geographic Region														
Northeast	2,714	17.38%	1,391	19.97%	<.0001	6.65	4,818	17.71%	0.3911	0.86	9,417	21.09%	<.0001	9.43
Midwest	3,372	21.59%	1,685	24.19%	<.0001	6.18	6,237	22.92%	0.0015	3.20	14,014	31.39%	<.0001	22.34
South	7,068	45.26%	2,714	38.96%	<.0001	12.79	11,585	42.58%	<.0001	5.41	14,540	32.57%	<.0001	26.26
West	2,455	15.72%	1,157	16.61%	0.0926	2.41	4,513	16.59%	0.0195	2.35	6,633	14.86%	0.0094	2.40
Other	7	0.04%	19	0.27%	<.0001	5.73	56	0.21%	<.0001	4.55	40	0.09%	0.0845	1.73
SES Score														
Low	3,507	22.46%	1,721	24.71%	0.0002	5.30	6,249	22.97%	0.2268	1.21	9,590	21.48%	0.0109	2.36
Mid	4,170	26.70%	1,973	28.32%	0.0115	3.63	7,147	26.27%	0.3243	0.99	13,741	30.78%	<.0001	9.01
High	7,429	47.57%	3,060	43.93%	<.0001	7.32	12,892	47.38%	0.7023	0.38	20,031	44.87%	<.0001	5.43

	Apixaban Cohort (Reference)		Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/ Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*
Missing	510	3.27%	212	3.04%	0.3800	1.27	921	3.38%	0.5094	0.66	1,282	2.87%	0.0125	2.29
Medicaid dual-eligible	2,158	13.82%	1,248	17.92%	<.0001	11.23	4,663	17.14%	<.0001	9.18	7,859	17.60%	<.0001	10.41
Low-income subsidy	3,604	23.08%	1,731	24.85%	0.0038	4.15	6,467	23.77%	0.1056	1.63	10,545	23.62%	0.1696	1.28
Baseline Comorbidity														
Deyo-CCI score	3.85	2.60	3.64	2.49	<.0001	7.94	3.71	2.51	<.0001	5.40	4.32	2.75	<.0001	17.78
$CHADS_2$ Score	2.72	1.16	2.67	1.14	0.0021	4.42	2.65	1.15	<.0001	6.44	2.88	1.13	<.0001	13.37
0	196	1.26%	106	1.52%	0.1073	2.28	418	1.54%	0.0185	2.40	421	0.94%	0.0009	2.99
1	1,984	12.70%	872	12.52%	0.6962	0.56	3,688	13.55%	0.0126	2.52	4,067	9.11%	<.0001	11.55
2	4,730	30.29%	2,236	32.10%	0.0065	3.91	8,655	31.81%	0.0011	3.29	12,576	28.17%	<.0001	4.66
3+	8,706	55.75%	3,752	53.86%	0.0084	3.80	14,448	53.10%	<.0001	5.32	27,580	61.78%	<.0001	12.27
CHA_2DS_2-VASc Score	4.33	1.39	4.26	1.37	0.0004	5.09	4.25	1.38	<.0001	5.71	4.51	1.37	<.0001	13.00
0	0	0.00%	0	0.00%		0.00	0	0.00%		0.00	0	0.00%		0.00
1	123	0.79%	76	1.09%	0.0243	3.15	261	0.96%	0.0698	1.84	274	0.61%	0.0208	2.08
2	1,237	7.92%	541	7.77%	0.6894	0.58	2,322	8.53%	0.0271	2.23	2,431	5.45%	<.0001	9.93
3	3,040	19.47%	1,482	21.27%	0.0017	4.49	5,661	20.81%	0.0009	3.34	7,826	17.53%	<.0001	4.99
4+	11,216	71.82%	4,867	69.87%	0.0027	4.30	18,965	69.70%	<.0001	4.67	34,113	76.41%	<.0001	10.49
HAS-BLED Score	3.59	1.20	3.43	1.19	<.0001	13.11	3.53	1.18	<.0001	5.46	3.67	1.23	<.0001	6.42
0	0	0.00%	0	0.00%		0.00	0	0.00%		0.00	0	0.00%		0.00
1	283	1.81%	150	2.15%	0.0843	2.45	561	2.06%	0.0737	1.81	999	2.24%	0.0015	3.02
2	2,788	17.85%	1,518	21.79%	<.0001	9.89	5,030	18.49%	0.1026	1.64	7,197	16.12%	<.0001	4.62
3+	12,545	80.33%	5,298	76.06%	<.0001	10.38	21,618	79.45%	0.0286	2.20	36,448	81.64%	0.0003	3.33
Bleeding history	3,980	25.49%	1,640	23.54%	0.0018	4.52	7,037	25.86%	0.3914	0.86	13,828	30.97%	<.0001	12.21
Congestive Heart Failure	6,066	38.84%	2,661	38.20%	0.3580	1.33	10,193	37.46%	0.0045	2.85	20,694	46.35%	<.0001	15.23
Diabetes Mellitus	6,561	42.01%	3,155	45.29%	<.0001	6.61	11,528	42.37%	0.4756	0.72	21,169	47.42%	<.0001	10.88

	Apixaban Cohort (Reference)		Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/ Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*
Hypertension	14,811	94.85%	6,549	94.01%	0.0108	3.62	25,652	94.28%	0.0133	2.50	42,023	94.13%	0.0009	3.14
Non-ESRD	4,261	27.29%	1,588	22.80%	<.0001	10.38	6,573	24.16%	<.0001	7.16	13,305	29.80%	<.0001	5.57
Liver Disease	903	5.78%	379	5.44%	0.3053	1.49	1,639	6.02%	0.3092	1.02	2,767	6.20%	0.0617	1.75
Myocardial Infarction	2,329	14.91%	1,028	14.76%	0.7597	0.44	4,121	15.15%	0.5191	0.65	8,078	18.09%	<.0001	8.57
Dyspepsia or Stomach Discomfort	4,055	25.97%	1,633	23.44%	<.0001	5.86	6,962	25.59%	0.3867	0.87	11,420	25.58%	0.3409	0.88
Non-stroke/ SE Peripheral vascular disease	15,364	98.39%	6,861	98.49%	0.5538	0.86	26,708	98.16%	0.0846	1.75	43,798	98.11%	0.0237	2.14
Stroke/SE	2,582	16.53%	1,068	15.33%	0.0234	3.29	4,110	15.11%	<.0001	3.92	8,769	19.64%	<.0001	8.08
Transient ischemic attack	1,605	10.28%	629	9.03%	0.0037	4.23	2,557	9.40%	0.0031	2.96	4,236	9.49%	0.0041	2.65
Anemia and Coagulation Defects	5,866	37.56%	2,389	34.30%	<.0001	6.82	10,292	37.83%	0.5907	0.54	20,070	44.96%	<.0001	15.06
Alcoholism	28	0.18%	19	0.27%	0.1547	1.97	64	0.24%	0.2290	1.23	93	0.21%	0.4858	0.66
PAD only	1,936	12.40%	933	13.39%	0.0379	2.97	3,734	13.72%	<.0001	3.94	6,437	14.42%	<.0001	5.93
CAD only	9,546	61.13%	4,326	62.10%	0.1658	2.00	16,585	60.95%	0.7200	0.36	25,294	56.66%	<.0001	9.10
CAD and PAD	4,134	26.47%	1,707	24.50%	0.0018	4.52	6,890	25.32%	0.0088	2.63	12,913	28.92%	<.0001	5.48
Stroke within one 1 month of index date	357	2.29%	146	2.10%	0.3710	1.30	568	2.09%	0.1736	1.36	1,416	3.17%	<.0001	5.44
History of Hemorrhagic or lacunar stroke	1,963	12.57%	753	10.81%	0.0002	5.48	2,916	10.72%	<.0001	5.78	6,199	13.89%	<.0001	3.88
ESRD Renal Disease (Stage V CKD, ESRD, dialysis)	602	3.86%	260	3.73%	0.6570	0.64	881	3.24%	0.0008	3.34	4,042	9.05%	<.0001	21.28
Systolic HF or combined systolic and diastolic HF	1,873	11.99%	757	10.87%	0.0147	3.54	2,963	10.89%	0.0005	3.47	6,494	14.55%	<.0001	7.53
Hospitalized MI	1,030	6.60%	477	6.85%	0.4838	1.01	1,891	6.95%	0.1618	1.41	4,444	9.95%	<.0001	12.21

	Apixaban Cohort (Reference)		Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/ Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*
Baseline Medication Use														
ACEs/ARBs	9,976	63.88%	4,650	66.75%	<.0001	6.03	17,593	64.66%	0.1067	1.62	27,864	62.41%	0.0011	3.05
Amiodarone	2,465	15.79%	1,042	14.96%	0.1131	2.29	3,909	14.37%	<.0001	3.97	6,210	13.91%	<.0001	5.28
Beta blockers	9,626	61.64%	4,246	60.95%	0.3261	1.41	16,784	61.69%	0.9289	0.09	27,361	61.29%	0.4331	0.73
H2-receptor antagonists	1,347	8.63%	586	8.41%	0.5964	0.76	2,331	8.57%	0.8346	0.21	4,079	9.14%	0.0549	1.80
Proton pump inhibitors	5,779	37.01%	2,419	34.73%	0.0010	4.76	9,950	36.57%	0.3653	0.91	15,815	35.42%	0.0004	3.29
Statins	11,256	72.08%	4,785	68.69%	<.0001	7.43	18,888	69.42%	<.0001	5.85	30,244	67.74%	<.0001	9.46
Anti-platelets	4,400	28.18%	1,649	23.67%	<.0001	10.29	6,978	25.65%	<.0001	5.71	10,278	23.02%	<.0001	11.83
NSAIDs	3,802	24.35%	1,674	24.03%	0.6091	0.74	7,259	26.68%	<.0001	5.35	9,302	20.84%	<.0001	8.40
Baseline Procedures														
Coronary Bypass surgery	145	0.93%	100	1.44%	0.0007	4.69	336	1.23%	0.0038	2.96	1,178	2.64%	<.0001	12.95
PCI	328	2.10%	173	2.48%	0.0710	2.56	659	2.42%	0.0328	2.16	1,455	3.26%	<.0001	7.18
Index Dose*														
Low Dose	4,929	31.56%	1,690	24.26%	<.0001	16.33	7,639	28.08%	<.0001	7.63				
Standard Dose	10,693	68.47%	5,277	75.75%	<.0001	16.28	16,765	61.62%	<.0001	14.42				
Other Dose							2,862	10.52%						
Baseline All-cause Health Care Utilization														
Inpatient Admission Visit	7,798	49.94%	3,440	49.38%	0.4425	1.11	14,901	54.76%	<.0001	9.68	26,830	60.10%	<.0001	20.53
Outpatient Hospital Visit	14,017	89.76%	5,985	85.92%	<.0001	11.78	23,744	87.27%	<.0001	7.83	39,537	88.56%	<.0001	3.86
ER Visit	13,480	86.32%	5,850	83.98%	<.0001	6.59	23,157	85.11%	0.0006	3.47	38,902	87.14%	0.0092	2.41
Office Visit	15,509	99.31%	6,876	98.71%	<.0001	6.14	26,892	98.83%	<.0001	5.01	43,429	97.28%	<.0001	15.79
Pharmacy Claim	15,616	100.00%	6,966	100.00%		0.00	27,209	100.00%		0.00	44,644	100.00%		0.00
Durable Medical Equipment	7,280	46.62%	3,258	46.77%	0.8334	0.30	12,650	46.49%	0.8000	0.25	22,541	50.49%	<.0001	7.75
Skilled Nursing Facility Visits	1,995	12.78%	863	12.39%	0.4196	1.17	3,902	14.34%	<.0001	4.57	9,442	21.15%	<.0001	22.45

	Apixaban Cohort (Reference)		Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/ Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*
Home Health Agency Visits	3,183	20.38%	1,275	18.30%	0.0003	5.27	5,215	19.17%	0.0023	3.05	9,442	21.15%	0.0428	1.89
Hospice Visits	94	0.60%	51	0.73%	0.2580	1.60	263	0.97%	<.0001	4.13	561	1.26%	<.0001	6.83
# Inpatient Admissions (PPPM)	0.07	0.10	0.07	0.09	0.0792	2.54	0.07	0.10	<.0001	5.97	0.09	0.10	<.0001	19.11
# Outpatient Hospital Visits (PPPM)	0.53	0.59	0.46	0.54	<.0001	11.66	0.49	0.55	<.0001	7.83	0.66	0.72	<.0001	19.13
# of ER Visits (PPPM)	0.43	0.50	0.43	0.52	0.8996	0.18	0.44	0.51	0.2562	1.14	0.60	0.67	<.0001	28.84
# Office Visits (PPPM)	1.68	1.12	1.48	1.04	<.0001	18.62	1.58	1.11	<.0001	8.83	1.57	1.25	<.0001	8.90
# Pharmacy Visits (PPPM)	2.57	1.57	2.43	1.55	<.0001	9.25	2.49	1.60	<.0001	5.30	2.44	1.68	<.0001	8.21
# DME Visits (PPPM)	0.25	0.49	0.26	0.49	0.6661	0.62	0.25	0.48	0.0993	1.65	0.28	0.51	<.0001	5.61
# SNF Visits (PPPM)	0.03	0.11	0.03	0.10	0.4533	1.07	0.04	0.12	<.0001	4.80	0.06	0.14	<.0001	19.01
# HHA Visits (PPPM)	0.03	0.08	0.03	0.08	0.0595	2.71	0.03	0.08	0.0475	1.99	0.03	0.08	0.1700	1.28
# Hospice Visits (PPPM)	0.00	0.03	0.00	0.04	0.2117	1.88	0.00	0.04	0.0002	3.57	0.01	0.07	<.0001	7.53
Baseline All-cause Health Care Costs (PPPM)														
Inpatient Admission Costs	$849.06	1509.61	$808.34	1459.82	0.0555	2.74	$961.00	1612.34	<.0001	7.17	$1,329.16	2179.05	<.0001	25.61
Outpatient Costs (ER, Office, other)	$737.89	858.79	$609.91	700.77	<.0001	16.33	$662.02	797.54	<.0001	9.15	$761.00	1123.96	0.0078	2.31
ER Costs	$278.34	532.75	$254.04	469.59	0.0006	4.84	$253.88	459.56	<.0001	4.92	$362.20	755.39	<.0001	12.83
Office Visit Costs	$337.35	439.78	$290.67	366.61	<.0001	11.53	$328.37	510.97	0.0554	1.88	$313.12	562.32	<.0001	4.80
Prescription Costs	$362.98	655.75	$311.50	394.92	<.0001	9.51	$342.36	526.33	0.0008	3.47	$280.62	515.75	<.0001	13.96
DME Costs	$39.50	117.78	$43.12	119.51	0.0339	3.05	$41.49	157.54	0.1391	1.43	$49.81	179.49	<.0001	6.79
SNF Costs	$250.37	864.68	$258.67	891.80	0.5142	0.95	$303.42	984.24	<.0001	5.73	$452.47	1178.80	<.0001	19.55
HHA Costs	$91.57	254.29	$88.55	289.97	0.4528	1.11	$87.43	248.88	0.1019	1.65	$94.68	251.03	0.1877	1.23
Hospice Costs	$6.18	114.86	$9.09	157.22	0.1654	2.11	$12.07	192.87	<.0001	3.71	$22.07	273.93	<.0001	7.57

	Apixaban Cohort (Reference)		Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/ Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*
Other Costs (DME, SNF, HHA, Hospice)	$387.62	978.87	$399.43	1023.19	0.4171	1.18	$444.41	1107.03	<.0001	5.43	$619.03	1300.66	<.0001	20.10
Total Costs (inpatient, outpatient, other costs, part D pharmacy costs)	$2,337.55	2530.84	$2,129.18	2387.16	<.0001	8.47	$2,409.79	2624.48	0.0050	2.80	$2,989.80	3425.91	<.0001	21.66

10.3. Outcome data

Table 4 shows the descriptive outcomes among apixaban, dabigatran, rivaroxaban, and warfarin patients in the pre-matched population. Apixaban patients were found to have a shorter follow-up time (mean, median; 207.5, 140 days) as compared to dabigatran (248.3, 133 days), rivaroxaban (246.6, 144 days) and warfarin patients (239, 142 days). Within 1 year, all patients had a median follow-up time of 4 to 5 months.

The incidence of stroke/SE for apixaban, dabigatran, rivaroxaban, and warfarin was 1.13, 2.21, 1.47, and 2.48 per 100 person-years, respectively. Incidence of MB for apixaban, dabigatran, rivaroxaban, and warfarin was 4.9, 6.6, 9.5, and 9.7 per 100 person-years, respectively, of which GI bleeding was the most frequent outcome, ranging from 2.3 to 4.9 events per 100 person-years. Mortality rates for apixaban, dabigatran, rivaroxaban, and warfarin were 7.7, 8.5, 9.5 and 14.6 per 100 person-years, respectively. Composite endpoints were also evaluated; namely, incidence of MACE (stroke, MI, or ACM) for apixaban, dabigatran, rivaroxaban, and warfarin were 9.3, 10.7, 11.5 and 17.2 per 100 person-years, respectively.

Total health care costs incurred during follow-up for apixaban, dabigatran, rivaroxaban, and warfarin were $3,324; $3,367; $4,133; and $4,433 PPPM, respectively. MB-related medical costs for apixaban, dabigatran, rivaroxaban, and warfarin were $344, $468, $615, and $703 PPPM, respectively. A similar trend in lower costs for apixaban was seen among stroke/SE-related medical costs.

Table 4. Descriptive Clinical Outcomes

	Apixaban Cohort (Reference)		Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*
Sample Size	**15,616**		**6,966**				**27,209**				**44,644**			
Follow-up Time (days)	207.45	199.97	248.29	262.17	<.0001	17.52	246.63	256.21	<.0001	17.05	239.03	244.40	<.0001	14.14
minimum	1		1				1				1			
Q1	54		33				37				56			
median	140		133				144				142			
Q3	288		369				369				343			
maximum	975		1003				1003				1003			
Follow-up Time within 1 Year (days)	170.00	125.59	176.13	135.20	0.0013	4.70	177.89	135.97	<.0001	6.03	177.27	130.92	<.0001	5.67
minimum	1		1				1				1			
Q1	54		33				37				56			
median	140		133				144				142			
Q3	288		360				360				343			
maximum	360		360				360				360			
Discontinuation	7,414	47.48%	4,755	68.26%	<.0001	43.05	17,066	62.72%	<.0001	31.02	29,615	66.34%	<.0001	38.79
Time-to-Discontinuation	138.69	140.11	164.13	178.81	<.0001	15.84	162.66	177.29	<.0001	15.01	175.68	177.87	<.0001	23.11
Switch	363	2.32%	303	4.35%	<.0001	11.29	1,213	4.46%	<.0001	11.81				
Time-to-Switch	101.79	117.12	118.71	143.57	0.1007	12.91	128.62	150.30	0.0004	19.91				
Stroke within 1 Year of Index Date	78	0.50%	71	1.02%	<.0001	5.99	187	0.69%	0.0171	2.45	513	1.15%	<.0001	7.19
Time-to-Stroke (days) (among patients with stroke)	114.95	99.24	103.72	103.69	0.5005	11.07	118.51	94.87	0.7835	3.67	99.73	96.58	0.1969	15.54
Ischemic Stroke within One Year of the Index Date	63	0.40%	59	0.85%	<.0001	5.63	127	0.47%	0.3426	0.96	361	0.81%	<.0001	5.22
Time-to-ischemic stroke (days) (among patients with ischemic	106.94	100.45	96.20	99.04	0.5538	10.76	112.35	96.98	0.7206	5.49	95.59	97.57	0.3968	11.46

	Apixaban Cohort (Reference)		Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*
stroke)														
Stroke/SE within 1 Year of Index Date	83	0.53%	75	1.08%	<.0001	6.11	197	0.72%	0.0173	2.44	542	1.21%	<.0001	7.34
Hemorrhagic Stroke	15	0.10%	12	0.17%	0.1259	2.08	60	0.22%	0.0030	3.13	152	0.34%	<.0001	5.24
Ischemic Stroke	63	0.40%	59	0.85%	<.0001	5.63	127	0.47%	0.3426	0.96	361	0.81%	<.0001	5.22
Systemic Embolism	5	0.03%	4	0.06%	0.3770	1.20	11	0.04%	0.6647	0.44	30	0.07%	0.1163	1.58
Time-to-Stroke/SE (days) (among patients with stroke)	117.80	99.70	105.79	104.08	0.4602	11.78	117.91	94.61	0.9928	0.12	98.00	96.08	0.0825	20.22
Major Bleeding within 1 Year of Index Date	361	2.31%	224	3.22%	<.0001	5.52	1,268	4.66%	<.0001	12.83	2,104	4.71%	<.0001	13.07
Gastrointestinal Bleeding	187	1.20%	129	1.85%	0.0001	5.34	745	2.74%	<.0001	11.11	1,043	2.34%	<.0001	8.65
Intracranial Hemorrhage	41	0.26%	24	0.34%	0.2882	1.49	103	0.38%	0.0459	2.05	266	0.60%	<.0001	5.10
Other sites	161	1.03%	90	1.29%	0.0840	2.44	546	2.01%	<.0001	7.98	986	2.21%	<.0001	9.34
Time-to-MB (days) (among patients with Major Bleeding)	141.06	145.82	171.75	192.79	0.0414	17.96	158.60	176.33	0.0552	10.84	150.18	169.64	0.2848	5.77
Myocardial Infarction within 1 year of index date	101	0.65%	39	0.56%	0.4422	1.12	191	0.70%	0.5040	0.67	363	0.81%	0.0407	1.95
Time-to-MI (days) (among patients with MI)	120.70	102.51	125.36	109.88	0.8137	4.38	110.49	103.49	0.4217	9.91	103.52	99.52	0.1281	17.00
Acute Limb Ischemia (ALI) within 1 year of index date	4	0.03%	4	0.06%	0.2408	1.56	9	0.03%	0.6696	0.44	32	0.07%	0.0426	2.09
Time-to-ALI (days) (among patients with ALI)	193.75	93.65	142.50	120.11	0.5260	47.59	82.89	80.17	0.0506	127.18	71.00	79.82	0.0073	141.08
All-cause Mortality within 1 year of index date	655	4.19%	323	4.64%	0.1314	2.15	1,424	5.23%	<.0001	4.90	3,579	8.02%	<.0001	16.01
Time-to-death (among patients who died)	109.56	90.02	109.96	95.87	0.9497	0.42	105.91	94.26	0.4050	3.97	109.56	94.10	0.9997	0.002
Composite Outcomes within 1														

	Apixaban Cohort (Reference)		Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*
year of index date														
MACE (Stroke, MI or all-cause death)	791	5.07%	404	5.80%	0.0228	3.24	1,707	6.27%	<.0001	5.23	4,177	9.36%	<.0001	16.65
Time-to-first occurrence of either of MACE (among patients with MACE)	111.96	93.35	109.50	97.40	0.6719	2.57	106.11	94.93	0.1499	6.21	107.58	95.03	0.2334	4.65
Ischemic stroke, MI, ALI, or all-cause death	784	5.02%	401	5.76%	0.0220	3.26	1,676	6.16%	<.0001	4.96	4,126	9.24%	<.0001	16.46
Time-to-first-occurrence of either of the outcomes (among patients with either outcomes)	111.29	93.24	109.79	97.39	0.7965	1.57	105.53	94.83	0.1585	6.12	107.32	94.95	0.2821	4.22
Ischemic stroke, MI, or all-cause death	782	5.01%	399	5.73%	0.0248	3.20	1,670	6.14%	<.0001	4.93	4,100	9.18%	<.0001	16.32
Time-to-first-occurrence of either of the outcomes (among patients with either outcomes)	111.17	93.24	109.69	97.08	0.7993	1.55	105.64	94.86	0.1762	5.88	107.56	94.97	0.3282	3.84
Stroke Incidence Rate within 1 Year of Index Date (per 100 person-years)	1.06		2.09				1.39				2.35			
Stroke/SE Incidence Rate within 1 Year of Index Date (per 100 person-years)	1.13		2.21				1.47				2.48			
Hemorrhagic Stroke	0.20		0.35				0.45				0.69			
Ischemic Stroke	0.86		1.74				0.95				1.65			
Systemic Embolism	0.07		0.12				0.08				0.14			
Major Bleeding Incidence Rate within 1 year of index date (per 100 person-years)	4.92		6.58				9.49				9.66			
Gastrointestinal Bleeding	2.28		3.23				4.94				4.24			
Intracranial Hemorrhage	0.54		0.70				0.77				1.21			

	Apixaban Cohort (Reference)		Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*
Other sites	1.96		2.25				3.51				3.97			
Myocardial Infarction incidence rate within 1 year of index date (per 100 person-years)	1.37		1.15				1.42				1.66			
ALI incidence within 1 year of index date (per 100 person-years)	0.05		0.12				0.07				0.15			
All-cause Mortality incidence within 1 year of index date (per 100 person-years)	7.68		8.54				9.53				14.59			
Composite Outcomes within 1 year of index date														
MACE (Stroke, MI, all-cause death) incidence rate within 1 year of index date (per 100 person-years)	9.32		10.74				11.49				17.19			
(Ischemic stroke, MI, ALI or all-cause death) incidence within 1 year of index date (per 100 person-years)	9.24		10.66				11.28				16.98			
(Ischemic stroke, MI or all-cause death) incidence rate within one year of index date (per 100 person-years)	9.22		10.61				11.24				16.86			
Follow-up Medication Use														
Anti-platelets	1,325	8.48%	594	8.53%	0.9163	0.15	2,428	8.92%	0.1223	1.56	4,867	10.90%	<.0001	8.18
Cumulative days of supply for anti-platelets	124.21	95.39	127.12	108.87	0.5739	2.85	126.46	104.77	0.5043	2.25	140.75	108.18	<.0001	16.22
MPR (for patients with anti-platelets)	0.84	0.91	0.76	0.53	0.0191	10.45	0.83	0.99	0.7843	0.92	0.80	0.64	0.1760	4.58
Follow-up All-cause Health Care Utilization (PPPM)														

	Apixaban Cohort (Reference)		Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*
Inpatient Admission Visit	3,817	24.44%	1,926	27.65%	<.0001	7.31	8,185	30.08%	<.0001	12.69	14,961	33.51%	<.0001	20.09
Outpatient Hospital Visit	11,034	70.66%	4,829	69.32%	0.0426	2.92	19,290	70.90%	0.6030	0.52	34,880	78.13%	<.0001	17.18
ER Visit	7,468	47.82%	4,328	62.13%	<.0001	29.06	16,454	60.47%	<.0001	25.59	31,072	69.60%	<.0001	45.35
Office Visit	14,267	91.36%	6,274	90.07%	0.0017	4.46	24,534	90.17%	<.0001	4.12	40,133	89.90%	<.0001	5.03
Pharmacy Claim	14,970	95.86%	6,678	95.87%	0.9933	0.01	25,893	95.16%	0.0009	3.38	42,504	95.21%	0.0008	3.18
Durable Medical Equipment	5,706	36.54%	2,639	37.88%	0.0532	2.78	10,240	37.63%	0.0240	2.27	18,877	42.28%	<.0001	11.77
Skilled Nursing Facility Visits	911	5.83%	502	7.21%	<.0001	5.56	1,980	7.28%	<.0001	5.83	4,700	10.53%	<.0001	17.19
Home Health Agency Visits	2,487	15.93%	1,178	16.91%	0.0638	2.66	5,289	19.44%	<.0001	9.22	11,944	26.75%	<.0001	26.66
Hospice Visits	411	2.63%	207	2.97%	0.1485	2.06	990	3.64%	<.0001	5.78	2,158	4.83%	<.0001	11.63
# of Inpatient Admission Visits (PPPM)	0.10	0.34	0.11	0.39	0.0667	2.71	0.13	0.42	<.0001	7.71	0.15	0.45	<.0001	11.77
# of Outpatient Hospital Visits (PPPM)	0.68	0.98	0.66	0.98	0.1670	1.99	0.72	1.07	<.0001	3.89	1.39	1.68	<.0001	51.55
# of ER Visits (PPPM)	0.33	0.71	0.52	0.89	<.0001	23.41	0.51	0.93	<.0001	22.17	1.02	1.46	<.0001	60.01
# of Office Visits (PPPM)	1.90	1.62	1.81	1.61	<.0001	5.62	1.93	1.69	0.0343	2.11	2.55	2.18	<.0001	33.96
# of Pharmacy Visits (PPPM)	3.07	2.01	3.04	2.03	0.3441	1.36	3.13	2.16	0.0061	2.73	3.35	2.45	<.0001	12.72
# of DME Visits (PPPM)	0.31	0.64	0.31	0.62	0.5403	0.88	0.32	0.70	0.0316	2.13	0.37	0.71	<.0001	8.93
# of SNF Visits (PPPM)	0.03	0.19	0.04	0.33	0.0298	3.41	0.04	0.27	<.0001	5.51	0.06	0.27	<.0001	10.70
# of HHA Visits (PPPM)	0.06	0.30	0.06	0.22	0.9116	0.15	0.11	0.45	<.0001	12.20	0.13	0.43	<.0001	17.44
# of Hospice Visits (PPPM)	0.02	0.18	0.02	0.20	0.7266	0.51	0.03	0.25	<.0001	4.22	0.04	0.28	<.0001	6.52
Follow-up All-cause Health Care Costs (PPPM)														
Inpatient Admission Costs	$1,381.85	5497.04	$1,549.50	6808.10	0.0705	2.71	$1,904.76	7976.50	<.0001	7.63	$2,183.70	8070.15	<.0001	11.61
Outpatient Costs (ER, Office, and other)	$936.27	1796.05	$840.11	1475.11	<.0001	5.85	$976.48	1913.74	0.0295	2.17	$1,062.64	2085.34	<.0001	6.49
ER Costs	$247.60	945.42	$320.97	957.35	<.0001	7.71	$365.02	1353.29	<.0001	10.06	$443.02	1176.51	<.0001	18.31

	Apixaban Cohort (Reference)		Dabigatran Cohort				Rivaroxaban Cohort				Warfarin Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	P-value	Std Diff*
Office Visit Costs	$375.04	648.15	$362.79	640.46	0.1878	1.90	$389.62	759.13	0.0356	2.06	$404.28	1051.67	<.0001	3.35
DME Costs	$47.74	238.12	$49.96	243.76	0.5249	0.92	$56.09	299.78	0.0015	3.09	$65.61	338.11	<.0001	6.11
SNF Costs	$206.40	1448.42	$245.85	1666.35	0.0875	2.53	$284.79	1884.11	<.0001	4.67	$355.32	1877.42	<.0001	8.88
HHA Costs	$177.87	867.01	$171.61	633.18	0.5430	0.82	$330.38	1595.14	<.0001	11.88	$362.03	1405.13	<.0001	15.77
Hospice Costs	$42.77	394.30	$43.62	379.04	0.8779	0.22	$70.44	587.90	<.0001	5.53	$86.84	764.17	<.0001	7.25
Other Costs (DME, SNF, HHA, Hospice)	$474.78	1798.27	$511.04	1864.31	0.1724	1.98	$741.70	2587.95	<.0001	11.98	$869.80	2513.01	<.0001	18.08
Total Medical Costs	$2,792.90	6606.55	$2,900.65	7739.38	0.3128	1.50	$3,622.94	9127.22	<.0001	10.42	$4,116.14	9495.86	<.0001	16.18
Prescription Costs	$531.35	795.31	$465.88	536.89	<.0001	9.65	$509.96	679.63	0.0048	2.89	$316.69	669.80	<.0001	29.20
Total Health care Costs	$3,324.25	6657.99	$3,366.54	7758.47	0.6931	0.58	$4,132.90	9143.24	<.0001	10.11	$4,432.83	9540.01	<.0001	13.48
First Stroke/SE-related Hospitalization costs (PPPM)	$20.00	527.01	$47.45	723.19	0.0044	4.34	$31.05	630.43	0.0521	1.90	$73.26	1555.30	<.0001	4.59
Follow-up Stroke/SE-related Medical costs (PPPM) (Inpatient + Outpatient + ER + office + other costs)	$67.62	1096.47	$106.24	1364.82	0.0375	3.12	$106.16	1612.41	0.0033	2.80	$167.13	2091.13	<.0001	5.96
First Stroke/MI-related Hospitalization costs (PPPM)	$49.43	1025.26	$82.49	1122.87	0.0359	3.07	$83.29	1773.66	0.0123	2.34	$117.18	2095.15	<.0001	4.11
Follow Up Stroke/MI related Medical costs (PPPM)	$157.70	1761.99	$229.28	2449.94	0.0280	3.35	$234.91	3133.37	0.0011	3.04	$318.30	3169.55	<.0001	6.26
First Major Bleeding-related Hospitalization costs (PPPM)	$89.56	1270.80	$132.89	1780.39	0.0667	2.80	$154.83	1296.22	<.0001	5.09	$193.34	1999.84	<.0001	6.19
Follow-up Major Bleeding related Medical Costs (PPPM)	$344.01	2629.89	$468.07	4020.80	0.0183	3.65	$615.55	4526.28	<.0001	7.34	$703.22	4588.95	<.0001	9.60
First MI-related Hospitalization costs (PPPM)	$30.75	886.88	$36.40	865.39	0.6529	0.64	$54.77	1677.86	0.0528	1.79	$47.82	1469.30	0.0858	1.41
Follow-up MI-related Medical costs (PPPM)	$102.65	1447.05	$145.24	2220.93	0.1422	2.27	$154.12	2862.71	0.0136	2.27	$184.43	2572.67	<.0001	3.92

The unadjusted associations of cohort status by incidence of stroke/SE, MB and MACE was shown via Kaplan Meier curves in Appendix 3, Figures 1-5.

PSM Matching

After analyzing the unmatched baseline differences between the four cohorts, the following characteristics were matched including age (65-74 years, 75-79 years, and ≥80 years), gender, race, US geographic region, CCI score, socioeconomic status, Medicaid dual eligibility, low-income subsidy, comorbidities (bleeding history, coronary heart failure, diabetes mellitus, hypertension, non-ESRD, liver disease, myocardial infarction, dyspepsia, non-stroke/SE peripheral disease, stroke/SE, transient ischemic attack, ESRD, anemia and coagulation defects and alcoholism), baseline medications (amiodarone, beta blockers, h2 receptor antagonists, proton pump inhibitors, statins, ACE/ARBs, anti-platelets and non-steroidal anti-inflammatory drugs) and procedures such as percutaneous coronary intervention and coronary bypass surgery.

After matching, all variables that were included in the logistic model for PSM were well-balanced and resulted in 15,527 matched patient pairs of apixaban-warfarin; 6,962 pairs of dabigatran-warfarin; 25,903 pairs of rivaroxaban-warfarin; 6,962 pairs of apixaban-dabigatran; 15,611 pairs of apixaban-rivaroxaban and 6,966 pairs of dabigatran-rivaroxaban patients.

PSM-adjusted Baseline Characteristics

Table 5 shows the PSM matched baseline characteristics between apixaban, dabigatran, rivaroxaban, and warfarin patients.

Table 5a. Baseline Demographic and Clinical Characteristics in PSM Cohorts among DOACs vs Warfarin

	Apixaban Cohort		Warfarin Cohort				Dabigatran Cohort		Warfarin Cohort				Rivaroxaban Cohort		Warfarin Cohort			
	N/ Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
Sample Size	**15,527**		**15,527**				**6,962**		**6,962**				**25,903**		**25,903**			
Age	78.95	7.46	78.98	7.46	0.6985	0.44	77.81	7.12	78.17	7.32	0.0035	4.95	78.35	7.35	78.49	7.37	0.0272	1.94
65-74	4,987	32.12%	4,959	31.94%	0.7334	0.39	2,554	36.68%	2,497	35.87%	0.3150	1.70	8,885	34.30%	8,795	33.95%	0.4043	0.73
≥75	10,540	67.88%	10,568	68.06%	0.7334	0.39	4,408	63.32%	4,465	64.13%	0.3150	1.70	17,018	65.70%	17,108	66.05%	0.4043	0.73
75-79	3,362	21.65%	3,386	21.81%	0.7412	0.37	1,691	24.29%	1,649	23.69%	0.4045	1.41	6,067	23.42%	6,084	23.49%	0.8601	0.15
≥80	7,178	46.23%	7,182	46.25%	0.9637	0.05	2,717	39.03%	2,816	40.45%	0.0864	2.91	10,951	42.28%	11,024	42.56%	0.5164	0.57
Gender																		
Male	8,404	54.13%	8,526	54.91%	0.1644	1.58	3,891	55.89%	3,817	54.83%	0.2071	2.14	14,151	54.63%	14,289	55.16%	0.2230	1.07
Female	7,123	45.87%	7,001	45.09%	0.1644	1.58	3,071	44.11%	3,145	45.17%	0.2071	2.14	11,752	45.37%	11,614	44.84%	0.2230	1.07
Race																		
White	14,257	91.82%	14,255	91.81%	0.9670	0.05	6,249	89.76%	6,270	90.06%	0.5546	1.00	23,578	91.02%	23,580	91.03%	0.9755	0.03
Black	613	3.95%	615	3.96%	0.9536	0.07	334	4.80%	323	4.64%	0.6602	0.75	1,069	4.13%	1,084	4.18%	0.7412	0.29
Hispanic	175	1.13%	189	1.22%	0.4604	0.84	111	1.59%	107	1.54%	0.7848	0.46	402	1.55%	410	1.58%	0.7772	0.25
Other	482	3.10%	468	3.01%	0.6446	0.52	268	3.85%	262	3.76%	0.7904	0.45	854	3.30%	829	3.20%	0.5356	0.54
U.S. Geographic Region																		
Northeast	2,714	17.48%	2,709	17.45%	0.9404	0.08	1,391	19.98%	1,426	20.48%	0.4603	1.25	4,775	18.43%	4,790	18.49%	0.8651	0.15
North Central	3,372	21.72%	3,468	22.34%	0.1887	1.49	1,685	24.20%	1,764	25.34%	0.1209	2.63	6,230	24.05%	6,243	24.10%	0.8937	0.12
South	6,983	44.97%	6,908	44.49%	0.3920	0.97	2,714	38.98%	2,589	37.19%	0.0291	3.70	10,561	40.77%	10,590	40.88%	0.7955	0.23
West	2,451	15.79%	2,433	15.67%	0.7790	0.32	1,157	16.62%	1,175	16.88%	0.6829	0.69	4,302	16.61%	4,242	16.38%	0.4775	0.62
Other	7	0.05%	9	0.06%	0.6170	0.57	15	0.22%	8	0.11%	0.1441	2.48	35	0.14%	38	0.15%	0.7253	0.31

	Apixaban Cohort		Warfarin Cohort				Dabigatran Cohort		Warfarin Cohort				Rivaroxaban Cohort		Warfarin Cohort			
	N/ Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
SES Score																		
Low	3,494	22.50%	3,509	22.60%	0.8386	0.23	1,718	24.68%	1,732	24.88%	0.7835	0.47	5,905	22.80%	5,987	23.11%	0.3916	0.75
Mid	4,166	26.83%	4,254	27.40%	0.2613	1.27	1,973	28.34%	2,023	29.06%	0.3489	1.59	6,986	26.97%	6,970	26.91%	0.8741	0.14
High	7,361	47.41%	7,268	46.81%	0.2904	1.20	3,060	43.95%	2,994	43.00%	0.2592	1.91	12,166	46.97%	12,077	46.62%	0.4332	0.69
Missing	506	3.26%	496	3.19%	0.7481	0.36	211	3.03%	213	3.06%	0.9214	0.17	846	3.27%	869	3.35%	0.5722	0.50
Medicaid dual-eligible	2,155	13.88%	2,252	14.50%	0.1147	1.79	1,248	17.93%	1,257	18.06%	0.8426	0.34	4,396	16.97%	4,361	16.84%	0.6816	0.36
Low-income subsidy	3,596	23.16%	3,191	20.55%	<.0001	6.31	1,731	24.86%	1,682	24.16%	0.3344	1.64	6,113	23.62%	5,929	22.91%	0.0556	1.68
Baseline Comorbidity																		
Deyo-Charlson Comorbidity Index	3.86	2.60	3.87	2.59	0.5737	0.64	3.65	2.49	3.80	2.53	0.0003	6.14	3.77	2.52	3.78	2.53	0.6512	0.40
$CHADS_2$ Score	2.73	1.16	2.73	1.12	0.7049	0.43	2.67	1.14	2.71	1.11	0.0393	3.49	2.69	1.14	2.69	1.11	0.4284	0.70
0	196	1.26%	145	0.93%	0.0055	3.15	106	1.52%	74	1.06%	0.0164	4.07	392	1.51%	292	1.13%	0.0001	3.38
1	1,953	12.58%	1,729	11.14%	<.0001	4.46	871	12.51%	781	11.22%	0.0183	4.00	3,241	12.51%	3,012	11.63%	0.0020	2.71
2	4,695	30.24%	4,988	32.12%	0.0003	4.07	2,234	32.09%	2,258	32.43%	0.6635	0.74	8,152	31.47%	8,479	32.73%	0.0021	2.70
3+	8,683	55.92%	8,665	55.81%	0.8370	0.23	3,751	53.88%	3,849	55.29%	0.0953	2.83	14,118	54.50%	14,120	54.51%	0.9859	0.02
CHA_2DS_2-VASc Score	4.34	1.39	4.34	1.36	0.8525	0.21	4.26	1.37	4.32	1.34	0.0158	4.09	4.29	1.37	4.29	1.34	0.9330	0.07
0	0	0.00%	0	0.00%		0.00	0	0.00%	0	0.00%		0.00	0	0.00%	0	0.00%		0.00
1	123	0.79%	104	0.67%	0.2056	1.44	76	1.09%	40	0.57%	0.0008	5.69	244	0.94%	189	0.73%	0.0079	2.33
2	1,222	7.87%	1,052	6.78%	0.0002	4.20	541	7.77%	470	6.75%	0.0204	3.93	2,035	7.86%	1,809	6.98%	0.0002	3.33
3	3,007	19.37%	3,145	20.26%	0.0494	2.23	1,480	21.26%	1,445	20.76%	0.4665	1.23	5,260	20.31%	5,509	21.27%	0.0070	2.37
4+	11,175	71.97%	11,226	72.30%	0.5186	0.73	4,865	69.88%	5,007	71.92%	0.0081	4.49	18,364	70.90%	18,396	71.02%	0.7568	0.27

	Apixaban Cohort		Warfarin Cohort				Dabigatran Cohort		Warfarin Cohort				Rivaroxaban Cohort		Warfarin Cohort			
	N/ Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
HAS-BLED Score	3.59	1.20	3.58	1.20	0.7448	0.37	3.43	1.19	3.48	1.19	0.0226	3.86	3.53	1.19	3.53	1.19	0.5451	0.53
0	0	0.00%	0	0.00%		0.00	0	0.00%	0	0.00%		0.00	0	0.00%	0	0.00%		0.00
1	283	1.82%	295	1.90%	0.6144	0.57	150	2.15%	171	2.46%	0.2357	2.01	559	2.16%	530	2.05%	0.3744	0.78
2	2,785	17.94%	2,747	17.69%	0.5731	0.64	1,517	21.79%	1,324	19.02%	<.0001	6.88	4,855	18.74%	4,810	18.57%	0.6118	0.45
3+	12,459	80.24%	12,485	80.41%	0.7105	0.42	5,295	76.06%	5,467	78.53%	0.0005	5.90	20,489	79.10%	20,563	79.38%	0.4228	0.70
Bleeding history	3,976	25.61%	4,092	26.35%	0.1333	1.70	1,640	23.56%	1,780	25.57%	0.0058	4.67	6,853	26.46%	6,913	26.69%	0.5507	0.52
Congestive Heart Failure (CHF)	6,058	39.02%	6,097	39.27%	0.6502	0.51	2,661	38.22%	2,824	40.56%	0.0047	4.79	10,036	38.74%	10,073	38.89%	0.7387	0.29
Diabetes Mellitus	6,548	42.17%	6,612	42.58%	0.4624	0.83	3,152	45.27%	3,180	45.68%	0.6337	0.81	11,127	42.96%	11,173	43.13%	0.6831	0.36
Hypertension	14,722	94.82%	14,733	94.89%	0.7776	0.32	6,545	94.01%	6,538	93.91%	0.8033	0.42	24,393	94.17%	24,452	94.40%	0.2641	0.98
Non-ESRD	4,252	27.38%	4,223	27.20%	0.7118	0.42	1,588	22.81%	1,717	24.66%	0.0102	4.36	6,510	25.13%	6,544	25.26%	0.7308	0.30
Liver Disease	898	5.78%	932	6.00%	0.4126	0.93	378	5.43%	366	5.26%	0.6511	0.77	1,551	5.99%	1,566	6.05%	0.7817	0.24
Myocardial Infarction	2,323	14.96%	2,414	15.55%	0.1509	1.63	1,027	14.75%	1,065	15.30%	0.3674	1.53	3,994	15.42%	3,955	15.27%	0.6345	0.42
Dyspepsia or Stomach Discomfort	4,030	25.95%	4,058	26.14%	0.7173	0.41	1,632	23.44%	1,608	23.10%	0.6303	0.82	6,581	25.41%	6,555	25.31%	0.7929	0.23
Non-stroke/ SE Peripheral vascular disease	15,275	98.38%	15,277	98.39%	0.9283	0.10	6,857	98.49%	6,855	98.46%	0.8899	0.23	25,419	98.13%	25,428	98.17%	0.7693	0.26
Stroke/SE	2,579	16.61%	2,574	16.58%	0.9392	0.09	1,068	15.34%	1,093	15.70%	0.5585	0.99	4,050	15.64%	4,100	15.83%	0.5463	0.53
Transient ischemic attack	1,591	10.25%	1,583	10.20%	0.8809	0.17	629	9.03%	660	9.48%	0.3647	1.54	2,441	9.42%	2,453	9.47%	0.8569	0.16
Anemia and Coagulation	5,852	37.69%	6,008	38.69%	0.0684	2.07	2,388	34.30%	2,558	36.74%	0.0026	5.10	9,980	38.53%	9,981	38.53%	0.9928	0.01

	Apixaban Cohort		Warfarin Cohort				Dabigatran Cohort		Warfarin Cohort				Rivaroxaban Cohort		Warfarin Cohort			
	N/ Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
Defects																		
Alcoholism	28	0.18%	31	0.20%	0.6958	0.44	19	0.27%	19	0.27%	1.0000	0.00	57	0.22%	59	0.23%	0.8525	0.16
CAD and PAD	4,113	26.49%	4,260	27.44%	0.0601	2.13	1,707	24.52%	1,898	27.26%	0.0002	6.27	6,608	25.51%	6,792	26.22%	0.0649	1.62
PAD only	1,928	12.42%	2,119	13.65%	0.0013	3.65	933	13.40%	993	14.26%	0.1408	2.50	3,610	13.94%	3,695	14.26%	0.2833	0.94
CAD only	9,486	61.09%	9,148	58.92%	<.0001	4.44	4,322	62.08%	4,071	58.47%	<.0001	7.37	15,685	60.55%	15,416	59.51%	0.0158	2.12
Stroke within one 1 month of index date	357	2.30%	425	2.74%	0.0138	2.80	146	2.10%	197	2.83%	0.0053	4.73	564	2.18%	705	2.72%	<.0001	3.52
History of Hemorrhagic or lacunar stroke	1,961	12.63%	1,831	11.79%	0.0243	2.56	753	10.82%	781	11.22%	0.4485	1.28	2,873	11.09%	2,946	11.37%	0.3098	0.89
ESRD Renal Disease (Stage V CKD, ESRD, or dialysis)	602	3.88%	658	4.24%	0.1073	1.83	260	3.73%	279	4.01%	0.4039	1.41	881	3.40%	979	3.78%	0.0207	2.03
Systolic HF or combined systolic and diastolic HF	1,870	12.04%	1,877	12.09%	0.9029	0.14	757	10.87%	861	12.37%	0.0060	4.66	2,919	11.27%	3,098	11.96%	0.0141	2.16
Hospitalized MI	1,028	6.62%	1,218	7.84%	<.0001	4.73	477	6.85%	544	7.81%	0.0294	3.69	1,856	7.17%	1,993	7.69%	0.0217	2.02
Baseline Medication Use																		
ACEs/ARBs	9,917	63.87%	9,906	63.80%	0.8966	0.15	4,646	66.73%	4,607	66.17%	0.4839	1.19	16,645	64.26%	16,644	64.26%	0.9927	0.01
Amiodarone	2,428	15.64%	2,452	15.79%	0.7082	0.42	1,040	14.94%	1,029	14.78%	0.7933	0.44	3,633	14.03%	3,656	14.11%	0.7713	0.26
Beta blockers	9,562	61.58%	9,504	61.21%	0.4990	0.77	4,244	60.96%	4,269	61.32%	0.6638	0.74	15,928	61.49%	15,917	61.45%	0.9209	0.09
H2-receptor antagonists	1,338	8.62%	1,368	8.81%	0.5461	0.69	584	8.39%	618	8.88%	0.3049	1.74	2,225	8.59%	2,218	8.56%	0.9125	0.10

	Apixaban Cohort		Warfarin Cohort				Dabigatran Cohort		Warfarin Cohort				Rivaroxaban Cohort		Warfarin Cohort			
	N/ Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
Proton pump inhibitors	5,727	36.88%	5,741	36.97%	0.8692	0.19	2,417	34.72%	2,443	35.09%	0.6439	0.78	9,312	35.95%	9,345	36.08%	0.7626	0.27
Statins	11,174	71.96%	11,222	72.27%	0.5436	0.69	4,783	68.70%	4,720	67.80%	0.2514	1.94	17,836	68.86%	17,863	68.96%	0.7977	0.23
Anti-platelets	4,322	27.84%	4,299	27.69%	0.7707	0.33	1,647	23.66%	1,723	24.75%	0.1326	2.55	6,388	24.66%	6,423	24.80%	0.7215	0.31
NSAIDs	3,757	24.20%	3,757	24.20%	1.0000	0.00	1,671	24.00%	1,679	24.12%	0.8740	0.27	6,521	25.17%	6,568	25.36%	0.6346	0.42
Baseline Procedures																		
Coronary Bypass Surgery	145	0.93%	174	1.12%	0.1027	1.85	100	1.44%	112	1.61%	0.4063	1.41	336	1.30%	351	1.36%	0.5645	0.51
Percutaneous Coronary Intervention	328	2.11%	345	2.22%	0.5076	0.75	173	2.48%	179	2.57%	0.7460	0.55	651	2.51%	672	2.59%	0.5586	0.51
Index Dose*																		
Low Dose	4,909	31.62%					1,690	24.27%					7,414	28.62%				
Standard Dose	10,624	68.42%					5,273	75.74%					15,794	60.97%				
Other Dose													2,749	10.61%				
Baseline All-cause Health care Utilization																		
Inpatient Admission Visit	7,766	50.02%	8,527	54.92%	<.0001	9.83	3,439	49.40%	3,765	54.08%	<.0001	9.38	14,407	55.62%	14,205	54.84%	0.0743	1.57
Outpatient Hospital Visit	13,942	89.79%	13,525	87.11%	<.0001	8.41	5,983	85.94%	6,057	87.00%	0.0667	3.11	22,664	87.50%	22,592	87.22%	0.3412	0.84
ER Visit	13,410	86.37%	13,317	85.77%	0.1275	1.73	5,848	84.00%	5,951	85.48%	0.0152	4.11	22,098	85.31%	22,208	85.74%	0.1696	1.21
Office Visit	15,420	99.31%	15,141	97.51%	<.0001	14.41	6,872	98.71%	6,768	97.21%	<.0001	10.58	25,595	98.81%	25,217	97.35%	<.0001	10.65
Pharmacy Claim	15,527	100.00%	15,527	100.00%		0.00	6,962	100.00%	6,962	100.00%		0.00	25,903	100.00%	25,903	100.00%		0.00

	Apixaban Cohort		Warfarin Cohort				Dabigatran Cohort		Warfarin Cohort				Rivaroxaban Cohort		Warfarin Cohort			
	N/ Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
Durable Medical Equipment	7,251	46.70%	7,435	47.88%	0.0365	2.37	3,256	46.77%	3,392	48.72%	0.0210	3.91	12,133	46.84%	12,511	48.30%	0.0009	2.92
Skilled Nursing Facility Visits	1,993	12.84%	2,668	17.18%	<.0001	12.19	863	12.40%	1,162	16.69%	<.0001	12.20	3,845	14.84%	4,413	17.04%	<.0001	5.99
Home Health Agency Visits	3,175	20.45%	2,879	18.54%	<.0001	4.81	1,275	18.31%	1,211	17.39%	0.1567	2.40	5,067	19.56%	4,766	18.40%	0.0007	2.96
Hospice Visits	94	0.61%	162	1.04%	<.0001	4.84	51	0.73%	83	1.19%	0.0055	4.71	260	1.00%	294	1.14%	0.1464	1.28
# of Inpatient Admission Visits (PPPM)	0.07	0.10	0.08	0.10	<.0001	7.74	0.07	0.09	0.07	0.10	<.0001	8.06	0.08	0.10	0.08	0.10	0.8971	0.11
# of ER Visits (PPPM)	0.43	0.50	0.54	0.62	<.0001	18.79	0.43	0.52	0.55	0.63	<.0001	20.43	0.44	0.51	0.54	0.62	<.0001	18.44
# of Office Visits (PPPM)	1.68	1.12	1.57	1.18	<.0001	9.58	1.48	1.04	1.51	1.15	0.0531	3.28	1.58	1.11	1.56	1.20	0.0131	2.18
# of Pharmacy Visits (PPPM)	2.57	1.57	2.42	1.60	<.0001	9.59	2.43	1.55	2.42	1.67	0.7158	0.62	2.48	1.61	2.42	1.65	<.0001	3.93
# of DME Visits (PPPM)	0.25	0.49	0.26	0.49	0.7579	0.35	0.26	0.49	0.26	0.49	0.5340	1.05	0.25	0.49	0.26	0.49	0.0030	2.61
# of SNF Visits (PPPM)	0.03	0.11	0.04	0.13	<.0001	10.52	0.03	0.10	0.04	0.13	<.0001	10.79	0.04	0.12	0.04	0.12	<.0001	3.59
# of HHA Visits (PPPM)	0.03	0.08	0.03	0.08	0.0027	3.40	0.03	0.08	0.03	0.08	0.0442	3.41	0.03	0.08	0.03	0.08	0.0024	2.67
# of Hospice Visits (PPPM)	0.00	0.03	0.00	0.06	<.0001	6.18	0.00	0.04	0.01	0.06	0.0018	5.28	0.00	0.04	0.01	0.06	0.0001	3.40
Baseline All-cause Health Care Costs (PPPM)																		

	Apixaban Cohort		Warfarin Cohort				Dabigatran Cohort		Warfarin Cohort				Rivaroxaban Cohort		Warfarin Cohort			
	N/ Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
Inpatient Admission Costs	$851.91	1512.58	$1,081.35	1977.52	<.0001	13.03	$808.63	1460.13	$1,060.61	1941.30	<.0001	14.67	$984.67	1633.36	$1,073.65	1869.58	<.0001	5.07
Outpatient Costs (ER, Office, and other)	$737.36	858.68	$680.46	899.78	<.0001	6.47	$610.12	700.91	$660.79	859.22	0.0001	6.46	$662.76	802.59	$674.31	945.74	0.1339	1.32
ER Costs	$278.11	532.38	$301.91	596.25	0.0002	4.21	$254.14	469.70	$293.85	552.21	<.0001	7.75	$255.46	463.64	$296.50	622.56	<.0001	7.48
Office Visit Costs	$337.50	440.59	$301.07	474.54	<.0001	7.96	$290.74	366.70	$289.64	466.09	0.8767	0.26	$328.02	514.99	$300.77	510.10	<.0001	5.32
Prescription Costs	$363.33	657.34	$272.38	491.96	<.0001	15.67	$311.58	395.00	$275.77	468.79	<.0001	8.26	$338.92	519.33	$273.23	483.93	<.0001	13.09
DME Costs	$39.61	118.03	$44.01	126.08	0.0015	3.60	$43.14	119.54	$46.08	239.55	0.3602	1.55	$42.10	160.29	$46.40	193.19	0.0058	2.42
SNF Costs	$251.61	866.84	$364.49	1064.25	<.0001	11.63	$258.82	892.03	$348.46	1046.34	<.0001	9.22	$315.06	1001.19	$345.23	1013.49	0.0007	3.00
HHA Costs	$91.91	254.81	$83.57	242.03	0.0031	3.35	$88.60	290.05	$77.36	234.38	0.0119	4.26	$89.15	250.94	$81.83	235.04	0.0006	3.01
Hospice Costs	$6.21	115.19	$19.03	263.37	<.0001	6.31	$9.09	157.26	$20.25	263.94	0.0025	5.14	$12.54	197.06	$19.83	261.06	0.0003	3.15
Other Costs (DME, SNF, HHA, Hospice)	$389.34	981.17	$511.10	1178.58	<.0001	11.23	$399.65	1023.44	$492.14	1179.02	<.0001	8.38	$458.85	1125.22	$493.29	1142.68	0.0005	3.04
Total Costs	$2,341.95	2535.69	$2,545.30	3044.99	<.0001	7.26	$2,129.98	2387.60	$2,489.31	2991.76	<.0001	13.28	$2,445.20	2655.42	$2,514.48	2936.93	0.0049	2.47

Table 5b. Baseline Demographic and Clinical Characteristics in PSM Cohorts among DOACs vs. DOACs

	Apixaban Cohort (Reference)		Dabigatran Cohort				Apixaban Cohort (Reference)		Rivaroxaban Cohort				Dabigatran Cohort (Reference)		Rivaroxaban Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
Sample Size	**6,927**		**6,927**				**15,611**		**15,611**				**6,966**		**6,966**			
Age	77.98	7.38	77.83	7.12	0.2041	2.16	78.93	7.46	78.70	7.37	0.0061	3.10	77.80	7.12	78.06	7.33	0.0371	3.53
65-74	2,539	36.65%	2,532	36.55%	0.9017	0.21	5,032	32.23%	5,083	32.56%	0.5374	0.70	2,557	36.71%	2,501	35.90%	0.3238	1.67
≥75	4,388	63.35%	4,395	63.45%	0.9017	0.21	10,579	67.77%	10,528	67.44%	0.5374	0.70	4,409	63.29%	4,465	64.10%	0.3238	1.67
75-79	1,736	25.06%	1,685	24.33%	0.3150	1.71	3,374	21.61%	3,457	22.14%	0.2559	1.29	1,692	24.29%	1,670	23.97%	0.6631	0.74
≥80	2,652	38.28%	2,710	39.12%	0.3117	1.72	7,205	46.15%	7,071	45.29%	0.1279	1.72	2,717	39.00%	2,795	40.12%	0.1766	2.29
Sex																		
Male	3,900	56.30%	3,873	55.91%	0.6439	0.79	8,451	54.13%	8,453	54.15%	0.9819	0.03	3,894	55.90%	3,890	55.84%	0.9456	0.12
Female	3,027	43.70%	3,054	44.09%	0.6439	0.79	7,160	45.87%	7,158	45.85%	0.9819	0.03	3,072	44.10%	3,076	44.16%	0.9456	0.12
Race																		
White	6,224	89.85%	6,229	89.92%	0.8880	0.24	14,336	91.83%	14,306	91.64%	0.5375	0.70	6,252	89.75%	6,312	90.61%	0.0876	2.89
Black	336	4.85%	326	4.71%	0.6904	0.68	614	3.93%	589	3.77%	0.4623	0.83	334	4.79%	280	4.02%	0.0258	3.78
Hispanic	99	1.43%	109	1.57%	0.4848	1.19	174	1.11%	196	1.26%	0.2499	1.30	111	1.59%	107	1.54%	0.7848	0.46
Other	268	3.87%	263	3.80%	0.8249	0.38	487	3.12%	520	3.33%	0.2905	1.20	269	3.86%	267	3.83%	0.9298	0.15
US Geographic Region																		
Northeast	1,400	20.21%	1,376	19.86%	0.6105	0.87	2,714	17.39%	2,741	17.56%	0.6874	0.46	1,391	19.97%	1,332	19.12%	0.2075	2.14
North Central	1,681	24.27%	1,678	24.22%	0.9526	0.10	3,372	21.60%	3,310	21.20%	0.3923	0.97	1,685	24.19%	1,583	22.72%	0.0414	3.46
South	2,626	37.91%	2,712	39.15%	0.1333	2.55	7,064	45.25%	7,023	44.99%	0.6410	0.53	2,714	38.96%	2,828	40.60%	0.0485	3.34
West	1,215	17.54%	1,156	16.69%	0.1832	2.26	2,455	15.73%	2,531	16.21%	0.2403	1.33	1,157	16.61%	1,208	17.34%	0.2498	1.95
Other	5	0.07%	5	0.07%	1.0000	0.00	6	0.04%	6	0.04%	1.0000	0.00	19	0.27%	15	0.22%	0.4922	1.16

	Apixaban Cohort (Reference)		Dabigatran Cohort				Apixaban Cohort (Reference)		Rivaroxaban Cohort				Dabigatran Cohort (Reference)		Rivaroxaban Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
SES Score																		
Low	1,680	24.25%	1,705	24.61%	0.6211	0.84	3,505	22.45%	3,550	22.74%	0.5426	0.69	1,721	24.71%	1,671	23.99%	0.3236	1.67
Mid	1,983	28.63%	1,962	28.32%	0.6926	0.67	4,168	26.70%	4,136	26.49%	0.6819	0.46	1,973	28.32%	1,879	26.97%	0.0750	3.02
High	3,063	44.22%	3,053	44.07%	0.8641	0.29	7,428	47.58%	7,405	47.43%	0.7944	0.30	3,060	43.93%	3,188	45.77%	0.0292	3.70
Missing	201	2.90%	207	2.99%	0.7630	0.51	510	3.27%	520	3.33%	0.7514	0.36	212	3.04%	228	3.27%	0.4383	1.31
Medicaid dual-eligible	1,231	17.77%	1,228	17.73%	0.9468	0.11	2,157	13.82%	2,274	14.57%	0.0578	2.15	1,248	17.92%	1,208	17.34%	0.3738	1.51
Low-income subsidy	1,841	26.58%	1,710	24.69%	0.0108	4.33	3,602	23.07%	3,369	21.58%	0.0015	3.58	1,731	24.85%	1,652	23.72%	0.1185	2.64
Baseline Comorbidity																		
Deyo-CCI score	3.59	2.46	3.65	2.49	0.2204	2.08	3.85	2.59	3.83	2.55	0.4998	0.76	3.64	2.49	3.68	2.45	0.3495	1.59
$CHADS_2$ Score	2.67	1.16	2.67	1.14	0.7782	0.48	2.72	1.16	2.71	1.15	0.4418	0.87	2.67	1.14	2.67	1.16	0.6684	0.73
0	111	1.60%	106	1.53%	0.7323	0.58	196	1.26%	219	1.40%	0.2557	1.29	106	1.52%	123	1.77%	0.2573	1.92
1	931	13.44%	871	12.57%	0.1297	2.58	1,984	12.71%	1,926	12.34%	0.3213	1.12	872	12.52%	924	13.26%	0.1886	2.23
2	2,154	31.10%	2,218	32.02%	0.2420	1.99	4,728	30.29%	4,774	30.58%	0.5715	0.64	2,236	32.10%	2,192	31.47%	0.4234	1.36
3+	3,731	53.86%	3,732	53.88%	0.9864	0.03	8,703	55.75%	8,692	55.68%	0.9003	0.14	3,752	53.86%	3,727	53.50%	0.6710	0.72
CHA_2DS_2-VASc Score	4.25	1.39	4.26	1.37	0.5335	1.06	4.33	1.39	4.32	1.38	0.4662	0.82	4.26	1.37	4.26	1.38	0.7768	0.48
0	0	0.00%	0	0.00%		0.00	0	0.00%	0	0.00%		0.00	0	0.00%	0	0.00%		0.00
1	75	1.08%	76	1.10%	0.9348	0.14	123	0.79%	134	0.86%	0.4908	0.78	76	1.09%	73	1.05%	0.8048	0.42
2	606	8.75%	541	7.81%	0.0451	3.41	1,237	7.92%	1,234	7.90%	0.9499	0.07	541	7.77%	603	8.66%	0.0557	3.24
3	1,422	20.53%	1,473	21.26%	0.2865	1.81	3,040	19.47%	3,022	19.36%	0.7968	0.29	1,482	21.27%	1,448	20.79%	0.4797	1.20
4+	4,824	69.64%	4,837	69.83%	0.8100	0.41	11,211	71.81%	11,221	71.88%	0.8999	0.14	4,867	69.87%	4,842	69.51%	0.6449	0.78

	Apixaban Cohort (Reference)		Dabigatran Cohort				Apixaban Cohort (Reference)		Rivaroxaban Cohort				Dabigatran Cohort (Reference)		Rivaroxaban Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
HAS-BLED Score	3.42	1.18	3.43	1.19	0.3570	1.57	3.59	1.20	3.57	1.18	0.1098	1.81	3.43	1.19	3.48	1.17	0.0139	4.17
0	0	0.00%	0	0.00%		0.00	0	0.00%	0	0.00%		0.00	0	0.00%	0	0.00%		0.00
1	171	2.47%	150	2.17%	0.2357	2.02	283	1.81%	306	1.96%	0.3387	1.08	150	2.15%	154	2.21%	0.8166	0.39
2	1,475	21.29%	1,508	21.77%	0.4952	1.16	2,788	17.86%	2,763	17.70%	0.7113	0.42	1,518	21.79%	1,348	19.35%	0.0004	6.04
3+	5,281	76.24%	5,269	76.06%	0.8109	0.41	12,540	80.33%	12,542	80.34%	0.9773	0.03	5,298	76.06%	5,464	78.44%	0.0008	5.69
Bleeding history	1,641	23.69%	1,627	23.49%	0.7794	0.48	3,979	25.49%	4,034	25.84%	0.4761	0.81	1,640	23.54%	1,716	24.63%	0.1321	2.55
Congestive Heart Failure (CHF)	2,591	37.40%	2,649	38.24%	0.3096	1.73	6,063	38.84%	5,989	38.36%	0.3897	0.97	2,661	38.20%	2,665	38.26%	0.9444	0.12
Diabetes Mellitus	3,186	45.99%	3,122	45.07%	0.2749	1.86	6,558	42.01%	6,581	42.16%	0.7920	0.30	3,155	45.29%	3,073	44.11%	0.1623	2.37
Hypertension	6,502	93.86%	6,510	93.98%	0.7760	0.48	14,806	94.84%	14,782	94.69%	0.5419	0.69	6,549	94.01%	6,546	93.97%	0.9148	0.18
Non-ESRD	1,558	22.49%	1,582	22.84%	0.6262	0.83	4,258	27.28%	4,162	26.66%	0.2209	1.39	1,588	22.80%	1,628	23.37%	0.4213	1.36
Liver Disease	375	5.41%	376	5.43%	0.9701	0.06	903	5.78%	913	5.85%	0.8089	0.27	379	5.44%	402	5.77%	0.3969	1.44
Myocardial Infarction	986	14.23%	1,022	14.75%	0.3850	1.48	2,329	14.92%	2,310	14.80%	0.7624	0.34	1,028	14.76%	1,036	14.87%	0.8487	0.32
Dyspepsia or Stomach Discomfort	1,588	22.92%	1,623	23.43%	0.4810	1.20	4,052	25.96%	4,030	25.82%	0.7762	0.32	1,633	23.44%	1,735	24.91%	0.0435	3.42
Non-stroke/ SE Peripheral vascular disease	6,831	98.61%	6,822	98.48%	0.5225	1.09	15,359	98.39%	15,350	98.33%	0.6887	0.45	6,861	98.49%	6,847	98.29%	0.3457	1.60
Stroke/SE	1,081	15.61%	1,060	15.30%	0.6216	0.84	2,578	16.51%	2,551	16.34%	0.6800	0.47	1,068	15.33%	1,076	15.45%	0.8510	0.32
Transient ischemic attack	630	9.09%	628	9.07%	0.9528	0.10	1,604	10.27%	1,617	10.36%	0.8089	0.27	629	9.03%	640	9.19%	0.7460	0.55

	Apixaban Cohort (Reference)		Dabigatran Cohort				Apixaban Cohort (Reference)		Rivaroxaban Cohort				Dabigatran Cohort (Reference)		Rivaroxaban Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
Anemia and Coagulation Defects	2,356	34.01%	2,374	34.27%	0.7471	0.55	5,863	37.56%	5,834	37.37%	0.7346	0.38	2,389	34.30%	2,512	36.06%	0.0291	3.70
Alcoholism	22	0.32%	18	0.26%	0.5265	1.08	28	0.18%	30	0.19%	0.7927	0.30	19	0.27%	21	0.30%	0.7515	0.54
CAD and PAD	1,693	24.44%	1,695	24.47%	0.9685	0.07	4,132	26.47%	4,008	25.67%	0.1099	1.81	1,707	24.50%	1,733	24.88%	0.6095	0.87
PAD only	888	12.82%	927	13.38%	0.3261	1.67	1,935	12.40%	2,121	13.59%	0.0017	3.54	933	13.39%	1,053	15.12%	0.0036	4.93
CAD only	4,346	62.74%	4,305	62.15%	0.4720	1.22	9,544	61.14%	9,482	60.74%	0.4720	0.81	4,326	62.10%	4,180	60.01%	0.0112	4.30
Stroke within one 1 month of index date	154	2.22%	146	2.11%	0.6405	0.79	357	2.29%	359	2.30%	0.9397	0.09	146	2.10%	144	2.07%	0.9055	0.20
History of Hemorrhagic or lacunar stroke	803	11.59%	747	10.78%	0.1312	2.56	1,960	12.56%	1,836	11.76%	0.0318	2.43	753	10.81%	743	10.67%	0.7844	0.46
ESRD Renal Disease	245	3.54%	259	3.74%	0.5253	1.08	601	3.85%	593	3.80%	0.8134	0.27	260	3.73%	248	3.56%	0.5875	0.92
Systolic HF or combined systolic and diastolic HF	835	12.05%	755	10.90%	0.0330	3.62	1,873	12.00%	1,794	11.49%	0.1649	1.57	757	10.87%	767	11.01%	0.7861	0.46
Hospitalized MI	461	6.66%	474	6.84%	0.6597	0.75	1,030	6.60%	1,042	6.67%	0.7850	0.31	477	6.85%	478	6.86%	0.9733	0.06
Baseline Medication Use																		
ACE/ARB	4,635	66.91%	4,618	66.67%	0.7591	0.52	9,976	63.90%	10,051	64.38%	0.3761	1.00	4,650	66.75%	4,556	65.40%	0.0925	2.85
Amiodarone	1,040	15.01%	1,038	14.98%	0.9620	0.08	2,461	15.76%	2,402	15.39%	0.3572	1.04	1,042	14.96%	1,029	14.77%	0.7569	0.52
Beta blockers	4,164	60.11%	4,223	60.96%	0.3051	1.74	9,621	61.63%	9,576	61.34%	0.6007	0.59	4,246	60.95%	4,233	60.77%	0.8215	0.38
H2-receptor antagonist	572	8.26%	576	8.32%	0.9019	0.21	1,347	8.63%	1,333	8.54%	0.7773	0.32	586	8.41%	573	8.23%	0.6900	0.68

	Apixaban Cohort (Reference)		Dabigatran Cohort				Apixaban Cohort (Reference)		Rivaroxaban Cohort				Dabigatran Cohort (Reference)		Rivaroxaban Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
Proton pump inhibitor	2,354	33.98%	2,407	34.75%	0.3431	1.61	5,776	37.00%	5,674	36.35%	0.2310	1.36	2,419	34.73%	2,529	36.30%	0.0515	3.30
Statins	4,768	68.83%	4,767	68.82%	0.9854	0.03	11,252	72.08%	11,207	71.79%	0.5709	0.64	4,785	68.69%	4,767	68.43%	0.7426	0.56
Anti-platelets	1,597	23.05%	1,642	23.70%	0.3664	1.53	4,396	28.16%	4,299	27.54%	0.2207	1.39	1,649	23.67%	1,761	25.28%	0.0273	3.74
NSAIDs	1,604	23.16%	1,662	23.99%	0.2457	1.97	3,801	24.35%	3,866	24.76%	0.3927	0.97	1,674	24.03%	1,780	25.55%	0.0375	3.52
Baseline Procedures																		
Coronary Bypass surgery	84	1.21%	95	1.37%	0.4079	1.41	145	0.93%	157	1.01%	0.4878	0.79	100	1.44%	85	1.22%	0.2669	1.88
Percutaneous Coronary Intervention	175	2.53%	172	2.48%	0.8704	0.28	328	2.10%	322	2.06%	0.8120	0.27	173	2.48%	181	2.60%	0.6667	0.73
Index Dose*																		
Low Dose	1,888	27.26%	1,685	24.33%	<.0001	6.70	4,926	31.55%	4,675	29.95%	0.0021	3.48	1,690	24.26%	1,912	27.45%	<.0001	7.28
Standard Dose	5,039	72.74%	5,243	75.69%	<.0001	6.74	10,691	68.48%	9,338	59.82%	<.0001	18.15	5,277	75.75%	4,370	62.73%	<.0001	28.50
Other Dose						0.00	0	0.00%	1,627	10.42%	<.0001	48.24	0	0.00%	693	9.95%	<.0001	47.00
Baseline All-cause Health care Utilization																		
Inpatient Admission Visit	3,256	47.00%	3,423	49.42%	0.0045	4.83	7,795	49.93%	8,644	55.37%	<.0001	10.91	3,440	49.38%	3,801	54.57%	<.0001	10.39
Outpatient Hospital Visit	6,175	89.14%	5,954	85.95%	<.0001	9.67	14,013	89.76%	13,643	87.39%	<.0001	7.46	5,985	85.92%	6,077	87.24%	0.0222	3.87
ER Visit	5,921	85.48%	5,820	84.02%	0.0170	4.06	13,476	86.32%	13,304	85.22%	0.0053	3.15	5,850	83.98%	5,916	84.93%	0.1228	2.61
Office Visit	6,872	99.21%	6,837	98.70%	0.0035	4.97	15,504	99.31%	15,433	98.86%	<.0001	4.78	6,876	98.71%	6,881	98.78%	0.7037	0.64

	Apixaban Cohort (Reference)		Dabigatran Cohort				Apixaban Cohort (Reference)		Rivaroxaban Cohort				Dabigatran Cohort (Reference)		Rivaroxaban Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
Pharmacy Claim	6,927	100.00%	6,927	100.00%		0.00	15,611	100.00%	15,611	100.00%		0.00	6,966	100.00%	6,966	100.00%		0.00
Durable Medical Equipment	3,238	46.74%	3,236	46.72%	0.9728	0.06	7,277	46.61%	7,310	46.83%	0.7082	0.42	3,258	46.77%	3,265	46.87%	0.9054	0.20
Skilled Nursing Facility Visits	811	11.71%	859	12.40%	0.2104	2.13	1,994	12.77%	2,272	14.55%	<.0001	5.19	863	12.39%	1,005	14.43%	0.0004	5.98
Home Health Agency Visits	1,250	18.05%	1,267	18.29%	0.7080	0.64	3,182	20.38%	3,097	19.84%	0.2301	1.36	1,275	18.30%	1,334	19.15%	0.2001	2.17
Hospice Visits	38	0.55%	51	0.74%	0.1668	2.35	94	0.60%	154	0.99%	0.0001	4.33	51	0.73%	70	1.00%	0.0828	2.94
# of Inpatient Admission Visits (PPPM)	0.06	0.09	0.07	0.09	0.0344	3.59	0.07	0.10	0.08	0.10	<.0001	7.59	0.07	0.09	0.07	0.09	<.0001	7.60
# of ER Visits (PPPM)	0.42	0.51	0.43	0.52	0.3549	1.57	0.43	0.50	0.44	0.52	0.1331	1.70	0.43	0.52	0.42	0.48	0.5892	0.92
# of Office Visits (PPPM)	1.61	1.09	1.48	1.04	<.0001	12.24	1.68	1.12	1.60	1.13	<.0001	6.85	1.48	1.04	1.54	1.10	0.0008	5.70
# of Pharmacy Visits (PPPM)	2.53	1.59	2.43	1.55	0.0002	6.35	2.57	1.57	2.49	1.56	<.0001	5.21	2.43	1.55	2.44	1.57	0.6821	0.69
# of DME Visits (PPPM)	0.25	0.48	0.26	0.49	0.4807	1.20	0.25	0.49	0.25	0.48	0.2088	1.42	0.26	0.49	0.25	0.48	0.3131	1.71
# of SNF Visits (PPPM)	0.03	0.11	0.03	0.10	0.4460	1.30	0.03	0.11	0.04	0.12	<.0001	4.86	0.03	0.10	0.04	0.11	0.0007	5.74
# of HHA Visits (PPPM)	0.03	0.08	0.03	0.08	0.0678	3.10	0.03	0.08	0.03	0.08	0.4781	0.80	0.03	0.08	0.03	0.08	0.6596	0.75
# of Hospice Visits (PPPM)	0.00	0.02	0.00	0.04	0.0798	2.98	0.00	0.03	0.00	0.04	0.0036	3.30	0.00	0.04	0.00	0.05	0.2606	1.91
Baseline All-cause Health care Costs																		

	Apixaban Cohort (Reference)		Dabigatran Cohort				Apixaban Cohort (Reference)		Rivaroxaban Cohort				Dabigatran Cohort (Reference)		Rivaroxaban Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
(PPPM)																		
Inpatient Admission Costs	$795.85	1493.99	$808.40	1461.45	0.6171	0.85	$848.79	1509.41	$968.90	1619.75	<.0001	7.67	$808.34	1459.82	$957.77	1569.60	<.0001	9.86
Outpatient Costs (ER, Office, and other)	$699.49	823.77	$610.72	702.09	<.0001	11.60	$737.90	858.90	$671.73	811.88	<.0001	7.92	$609.91	700.77	$642.82	778.27	0.0088	4.44
ER Costs	$270.36	532.05	$254.37	470.42	0.0610	3.18	$278.35	532.81	$257.81	470.71	0.0003	4.09	$254.04	469.59	$248.10	437.68	0.4398	1.31
Office Visit Costs	$314.92	400.50	$291.17	367.40	0.0003	6.18	$337.35	439.84	$333.50	511.77	0.4763	0.81	$290.67	366.61	$319.46	520.14	0.0002	6.40
Prescription Costs	$350.42	615.71	$311.58	395.44	<.0001	7.51	$363.02	655.84	$333.81	475.17	<.0001	5.10	$311.50	394.92	$330.99	483.74	0.0092	4.41
DME Costs	$39.05	120.92	$43.21	119.77	0.0420	3.46	$39.51	117.80	$43.07	169.22	0.0311	2.44	$43.12	119.51	$40.57	110.49	0.1907	2.22
SNF Costs	$230.71	841.60	$259.37	893.64	0.0520	3.30	$250.36	864.76	$307.36	991.87	<.0001	6.13	$258.67	891.80	$304.68	995.30	0.0041	4.87
HHA Costs	$79.34	230.35	$88.69	290.55	0.0360	3.56	$91.55	254.27	$89.77	251.60	0.5329	0.71	$88.55	289.97	$86.59	240.99	0.6645	0.73
Hospice Costs	$5.14	92.03	$9.14	157.66	0.0684	3.10	$6.18	114.88	$11.74	193.61	0.0020	3.49	$9.09	157.22	$12.29	200.67	0.2948	1.78
Other Costs (DME, SNF, HHA, Hospice)	$354.24	945.46	$400.40	1025.30	0.0059	4.68	$387.61	978.92	$451.94	1118.91	<.0001	6.12	$399.43	1023.19	$444.12	1106.83	0.0133	4.19
Total Costs	$2,200.00	2444.04	$2,131.10	2391.06	0.0935	2.85	$2,337.32	2530.93	$2,426.38	2630.53	0.0023	3.45	$2,129.18	2387.16	$2,375.70	2571.08	<.0001	9.94

PSM Outcomes

DOACs vs Warfarin

Compared to warfarin, the incidence of stroke/SE was lower for dabigatran (2.2 vs 2.5 per 100 person-years), rivaroxaban (1.5 vs. 2.1 per 100 person-years) and apixaban (1.1 vs 2.3 per 100 person-years). Compared to warfarin, dabigatran (6.6 vs 7.4) and apixaban (5.0 vs 8.4) had a lower incidence of MB per 100 person-years. All-cause mortality was lower among dabigatran (8.5 vs 11.1), rivaroxaban (9.9 vs 11.5) and apixaban (7.7 vs 12.3) compared to warfarin. Composite endpoints were also evaluated; namely, incidence of MACE (stroke, MI, or mortality) was shown to be lower in dabigatran (10.8 vs 13.5 per 100 person-years), rivaroxaban (11.9 vs 13.8 per 100 person-years) and apixaban (9.3 vs 14.6 per 100 person-years) compared to warfarin.

Total health care costs were lower for dabigatran ($3,368 vs $3,900; p<0.001) and apixaban ($3,328 vs $3,951; p<0.001) but higher for rivaroxaban ($4,174 vs $3,849; p<0.001) compared to warfarin. Compared to warfarin, MB-related medical costs were lower for apixaban ($346 vs $588; p<0.001). Also, stroke/SE related medical costs were lower for apixaban ($158 vs $282; p<0.001) compared to warfarin.

DOACs vs. DOACs

Compared to apixaban, the incidence of stroke/SE was higher for dabigatran (2.2 vs 0.98 per 100 person-years) and rivaroxaban (1.63 vs 1.13 per 100 person-years). Dabigatran had a higher incidence of stroke/SE compared to rivaroxaban (2.2 vs 1.7). Among the types of stroke, ischemic stroke was the most common. Compared to apixaban, dabigatran (6.61 vs. 4.41) and rivaroxaban (9.84 vs 4.92) had a higher incidence of MB per 100 person-years. Dabigatran had a lower incidence of MB compared to rivaroxaban (6.6 vs 9.8) of which GI bleeding was the most frequent bleeding event. All-cause mortality was higher among dabigatran (6.4 vs 8.5) and rivaroxaban (7.7 vs 10.2) compared to apixaban. Dabigatran had a lower incidence of mortality compared to rivaroxaban (8.5 vs 10.2 per 100 person-years). The incidence of MACE was shown to be higher in dabigatran (8.0 vs 10.7 per 100 person-years) and rivaroxaban (9.3 vs 12.1 per 100 person-years) compared to apixaban. Dabigatran had lower incidence of MACE compared to rivaroxaban (10.7 vs 12.2 per 100 person-years).

Total health care costs incurred during follow-up were higher for rivaroxaban ($4,095 vs $3,324; p<0.001) vs apixaban, and patients with dabigatran use incurred lower costs compared to rivaroxaban ($3,367 vs $4,275; p<0.001). Compared to apixaban, MB-related medical costs were higher for dabigatran ($470 vs $321; p=0.009) and rivaroxaban patients ($601 vs $344, p<0.001); costs were lower for dabigatran patients when compared to rivaroxaban ($468 vs $643; p=0.017).

Table 6a. Outcomes in the Propensity Score Matched Cohorts for DOACs vs Warfarin

	Apixaban Cohort		Warfarin Cohort				Dabigatran Cohort		Warfarin Cohort				Rivaroxaban Cohort		Warfarin Cohort			
	N/Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/ Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/ Mean	%/ SD	N/ Mean	%/ SD	P-value	Std Diff*
Sample Size	**15,527**		**15,527**				**6,962**		**6,962**				**25,903**		**25,903**			
Follow-up Time (days)	207.45	199.89	245.68	247.33			248.39	262.21	246.29	247.31			245.44	255.75	245.82	248.49		
minimum	1		1				1		1				1		1			
Q1	54		58				33		59				36		58			
median	140		151				133		151				143		149			
Q3	288		358				369		359				367		356			
maximum	975		1,003				1003		1,003				1003		1,003			
Follow-up Time within 1 Year (days)	170.03	125.61	181.08	131.26			176.18	135.21	181.38	131.40			177.20	135.93	180.61	131.50		
minimum	1		1				1		1				1		1			
Q1	54		58				33		59				36		58			
median	140		151				133		151				143		149			
Q3	288		358				360		359				360		356			
maximum	360		360				360		360				360		360			
Discontinuation	7,376	47.50%	10,303	66.36%			4,752	68.26%	4,635	66.58%			16,249	62.73%	17,345	66.96%		
Time-to-Discontinuation	138.78	140.24	180.11	180.23			164.20	178.85	175.58	174.92			161.73	176.51	179.30	180.87		
Switch	363	2.34%					303	4.35%					1,164	4.49%				
Time-to-Switch	101.79	117.12					118.71	143.57					127.05	148.01				
Stroke within 1 Year of Index Date	77	0.50%	169	1.09%			71	1.02%	85	1.22%			183	0.71%	260	1.00%		
Time-to-Stroke (days) (among patients with stroke)	114.39	99.77	94.75	96.29			103.72	103.69	103.46	103.51			119.26	94.92	93.83	91.46		
Ischemic Stroke within 1 Year of Index Date	62	0.40%	124	0.80%			59	0.85%	63	0.90%			125	0.48%	189	0.73%		
Time-to-ischemic stroke (days) (among patients with ischemic stroke)	106.11	101.06	95.89	98.86			96.20	99.04	99.94	105.90			113.52	97.31	88.81	92.25		

	Apixaban Cohort		Warfarin Cohort				Dabigatran Cohort		Warfarin Cohort				Rivaroxaban Cohort		Warfarin Cohort			
	N/Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/ Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/ Mean	%/ SD	N/ Mean	%/ SD	P-value	Std Diff*
Stroke/SE within 1 Year of Index Date	82	0.53%	179	1.15%			75	1.08%	88	1.26%			193	0.75%	272	1.05%		
Hemorrhagic Stroke	15	0.10%	45	0.29%			12	0.17%	22	0.32%			58	0.22%	71	0.27%		
Ischemic Stroke	62	0.40%	124	0.80%			59	0.85%	63	0.90%			125	0.48%	189	0.73%		
Systemic Embolism	5	0.03%	10	0.06%			4	0.06%	3	0.04%			11	0.04%	13	0.05%		
Time-to-Stroke/SE (days) (among patients with stroke)	117.30	100.21	92.61	95.15			105.79	104.08	107.72	105.48			118.60	94.65	92.66	91.64		
Major Bleeding within One Year of the Index Date	361	2.32%	650	4.19%			224	3.22%	258	3.71%			1,226	4.73%	1,077	4.16%		
Gastrointestinal Bleeding	187	1.20%	333	2.14%			129	1.85%	113	1.62%			724	2.80%	523	2.02%		
Intracranial Hemorrhage	41	0.26%	76	0.49%			24	0.34%	39	0.56%			96	0.37%	131	0.51%		
Other sites	161	1.04%	299	1.93%			90	1.29%	129	1.85%			529	2.04%	526	2.03%		
Time-to-MB (days) (among patients with Major Bleeding)	141.06	145.82	161.62	179.07			171.75	192.79	156.10	174.61			157.99	176.17	155.16	177.34		
Myocardial Infarction within 1 year of index date	99	0.64%	110	0.71%			39	0.56%	52	0.75%			182	0.70%	183	0.71%		
Time-to-MI (days) (among patients with MI)	121.92	102.95	96.66	94.97			125.36	109.88	104.06	101.07			107.69	102.23	100.12	99.45		
ALI within 1 year of index date	4	0.03%	11	0.07%			4	0.06%	3	0.04%			9	0.03%	13	0.05%		
Time-to-ALI (days) (among patients with ALI)	193.75	93.65	56.73	62.41			142.50	120.11	228.33	106.88			82.89	80.17	68.92	91.68		
All-cause Mortality within 1 year of index date	653	4.21%	1,070	6.89%			323	4.64%	433	6.22%			1,400	5.40%	1,663	6.42%		
Time-to-death (among patients who died)	109.64	90.14	110.95	95.24			109.96	95.87	111.34	96.71			105.27	93.97	112.27	95.64		
Composite Outcomes																		

	Apixaban Cohort		Warfarin Cohort				Dabigatran Cohort		Warfarin Cohort				Rivaroxaban Cohort			Warfarin Cohort		
	N/Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/ Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/ Mean	%/ SD	N/ Mean	%/ SD	P-value	Std Diff*
within 1 year of index date																		
MACE (Stroke, MI or all-cause death)	786	5.06%	1,263	8.13%			404	5.80%	524	7.53%			1,672	6.45%	1,976	7.63%		
Time-to-first occurrence of either of MACE (among patients with MACE)	112.10	93.55	108.06	95.95			109.50	97.40	109.23	97.47			105.35	94.48	108.72	95.82		
Ischemic stroke, MI, ALI or all-cause death	779	5.02%	1,249	8.04%			401	5.76%	517	7.43%			1,643	6.34%	1,949	7.52%		
Time-to-first-occurrence of either outcomes (among patients with either outcomes)	111.43	93.45	107.68	95.82			109.79	97.39	109.89	97.86			104.77	94.38	108.50	95.85		
Ischemic stroke, MI, or all-cause death	777	5.00%	1,239	7.98%			399	5.73%	514	7.38%			1,637	6.32%	1,939	7.49%		
Time-to-first-occurrence of either of the outcomes (among patients with either outcomes)	111.31	93.45	108.14	95.92			109.69	97.08	109.20	97.49			104.88	94.40	108.71	95.80		
Stroke Incidence Rate within 1 Year of the Index Date (per 100 person-years)	1.05		2.17				2.10		2.45				1.44		2.02			
Stroke/SE Incidence Rate within 1 Year of Index Date (per 100 person-years)	1.12		2.30				2.22		2.54				1.52		2.11			
Hemorrhagic Stroke	0.20		0.58				0.35		0.69				0.46		0.55			
Ischemic Stroke	0.85		1.59				1.74		1.84				0.99		1.47			
Systemic Embolism	0.07		0.13				0.12		0.09				0.09		0.10			
Major Bleeding Incidence Rate within 1 year of index date (per 100 person-years)	4.95		8.38				6.59		7.42				9.69		8.38			

	Apixaban Cohort		Warfarin Cohort				Dabigatran Cohort		Warfarin Cohort				Rivaroxaban Cohort		Warfarin Cohort			
	N/Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/ Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/ Mean	%/ SD	N/ Mean	%/ SD	P-value	Std Diff*
Gastrointestinal Bleeding	2.29		3.73				3.23		2.85				5.08		3.54			
Intracranial Hemorrhage	0.55		0.97				0.71		1.12				0.75		1.01			
Other sites	1.98		3.28				2.25		3.17				3.59		3.53			
Myocardial Infarction incidence rate within 1 year of index date (per 100 person-years)	1.35		1.41				1.15		1.49				1.44		1.42			
Acute Limb Ischemia incidence rate within 1 year of index date (per 100 person-years)	0.05		0.14				0.12		0.09				0.07		0.10			
All-cause Mortality incidence rate within 1 year of index date (per 100 person-years)	7.70		12.29				8.54		11.08				9.88		11.48			
Composite Outcomes within 1 year of index date																		
MACE (Stroke, MI or all-cause death) incidence rate within 1 year of index date (per 100 person-years)	9.32		14.64				10.75		13.54				11.86		13.76			
(Ischemic stroke, MI, ALI or all-cause death) incidence rate within one year of index date (per 100 person-years)	9.23		14.48				10.66		13.35				11.66		13.57			
(Ischemic stroke, MI or all-cause death) incidence rate within one year of index date (per 100 person years)	9.21		14.36				10.61		13.27				11.61		13.49			
Follow-up Medication Use																		

	Apixaban Cohort		Warfarin Cohort				Dabigatran Cohort		Warfarin Cohort				Rivaroxaban Cohort		Warfarin Cohort			
	N/Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/ Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/ Mean	%/ SD	N/ Mean	%/ SD	P-value	Std Diff*
Anti-platelets	1,302	8.39%	1,920	12.37%			594	8.53%	785	11.28%			2,246	8.67%	2,957	11.42%		
cumulative days of supply for anti-platelets	124.52	95.65	142.39	108.40			127.12	108.87	150.22	107.33			125.28	104.67	144.78	109.36		
MPR (for patients with anti-platelets)	0.84	0.91	0.80	0.67			0.76	0.53	0.79	0.58			0.83	1.00	0.80	0.63		
Follow-up All-cause Health Care Utilization (PPPM)																		
Inpatient Admission Visit	3,796	24.45%	4,892	31.51%	<.0001	15.77	1,926	27.66%	2,149	30.87%	<.0001	7.04	7,861	30.35%	7,965	30.75%	0.3212	0.87
ER Visit	7,432	47.87%	10,524	67.78%	<.0001	41.17	4,327	62.15%	4,710	67.65%	<.0001	11.54	15,696	60.60%	17,550	67.75%	<.0001	14.97
Office Visit	14,189	91.38%	14,056	90.53%	0.0085	2.99	6,271	90.07%	6,261	89.93%	0.7775	0.48	23,344	90.12%	23,389	90.29%	0.5059	0.58
Pharmacy Claim	14,887	95.88%	14,830	95.51%	0.1110	1.81	6,675	95.88%	6,628	95.20%	0.0537	3.27	24,637	95.11%	24,725	95.45%	0.0682	1.60
Durable Medical Equipment (DME)	5,686	36.62%	6,235	40.16%	<.0001	7.27	2,638	37.89%	2,910	41.80%	<.0001	7.99	9,791	37.80%	10,461	40.39%	<.0001	5.30
Skilled Nursing Facility (SNF) Visits	910	5.86%	1,409	9.07%	<.0001	12.25	502	7.21%	644	9.25%	<.0001	7.43	1,941	7.49%	2,311	8.92%	<.0001	5.21
Home Health Agency (HHA) Visits	2,479	15.97%	3,841	24.74%	<.0001	21.92	1,178	16.92%	1,629	23.40%	<.0001	16.20	5,099	19.68%	6,321	24.40%	<.0001	11.40
Hospice Visits	411	2.65%	646	4.16%	<.0001	8.35	207	2.97%	255	3.66%	0.0231	3.85	973	3.76%	1,052	4.06%	0.0733	1.57
# of Inpatient Admission Visits (PPPM)	0.10	0.34	0.13	0.44	<.0001	8.03	0.11	0.39	0.13	0.45	0.0039	4.89	0.13	0.42	0.13	0.40	0.0452	1.76
# of Outpatient Hospital Visits (PPPM)	0.68	0.98	1.25	1.60	<.0001	43.29	0.66	0.98	1.29	1.59	<.0001	47.68	0.72	1.08	1.26	1.59	<.0001	39.50
# of ER Visits (PPPM)	0.33	0.72	0.91	1.38	<.0001	52.61	0.52	0.89	0.93	1.38	<.0001	35.94	0.52	0.94	0.92	1.37	<.0001	34.22
# of Office Visits (PPPM)	1.90	1.63	2.56	2.12	<.0001	34.92	1.81	1.61	2.47	2.09	<.0001	35.58	1.94	1.69	2.51	2.10	<.0001	30.34
# of Pharmacy Visits (PPPM)	3.07	2.02	3.25	2.31	<.0001	8.32	3.04	2.03	3.25	2.38	<.0001	9.21	3.13	2.18	3.25	2.36	<.0001	5.22
# of DME Visits (PPPM)	0.31	0.64	0.33	0.67	0.0013	3.66	0.31	0.62	0.34	0.66	0.0328	3.62	0.32	0.70	0.34	0.68	0.0497	1.72
# of SNF Visits (PPPM)	0.03	0.20	0.05	0.23	<.0001	6.62	0.04	0.33	0.05	0.26	0.0240	3.83	0.05	0.27	0.05	0.24	0.9398	0.07

	Apixaban Cohort		Warfarin Cohort				Dabigatran Cohort		Warfarin Cohort				Rivaroxaban Cohort		Warfarin Cohort			
	N/Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/ Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/ Mean	%/ SD	N/ Mean	%/ SD	P-value	Std Diff*
# of HHA Visits (PPPM)	0.06	0.30	0.12	0.39	<.0001	15.26	0.06	0.22	0.11	0.40	<.0001	15.56	0.11	0.46	0.12	0.43	0.0326	1.88
# of Hospice Visits (PPPM)	0.02	0.18	0.03	0.27	0.0007	3.85	0.02	0.20	0.02	0.19	0.1417	2.49	0.03	0.25	0.03	0.23	0.3180	0.88
Follow-up All-cause Health Care Costs (PPPM)																		
Inpatient Admission Costs	$1,385.59	5509.35	$1,930.92	8218.79	<.0001	7.79	$1,550.39	6809.95	$1,892.48	7040.66	0.0036	4.94	$1,932.27	8070.10	$1,822.50	7396.24	0.1065	1.42
Outpatient Costs (ER, Office, and other)	$933.44	1779.91	$958.34	1742.68	0.2129	1.41	$840.52	1475.43	$938.08	1594.41	0.0002	6.35	$973.66	1909.90	$945.12	1749.34	0.0761	1.56
ER Costs	$247.12	944.50	$375.47	1063.54	<.0001	12.76	$321.15	957.59	$374.90	951.33	0.0009	5.63	$365.25	1358.88	$371.77	1081.46	0.5456	0.53
Office Visit Costs	$374.70	645.53	$388.83	783.81	0.0829	1.97	$362.94	640.61	$373.00	717.84	0.3832	1.48	$389.19	758.65	$383.51	812.79	0.4103	0.72
DME Costs	$47.90	238.75	$56.66	268.10	0.0024	3.45	$49.99	243.83	$60.44	316.27	0.0289	3.70	$56.71	304.76	$60.30	339.18	0.2055	1.11
SNF Costs	$207.43	1452.38	$299.71	1751.70	<.0001	5.74	$245.99	1666.82	$321.75	1803.68	0.0101	4.36	$296.73	1927.77	$301.63	1760.81	0.7629	0.27
HHA Costs	$178.54	869.16	$336.35	1306.88	<.0001	14.22	$171.71	633.35	$322.03	1269.91	<.0001	14.98	$334.06	1611.81	$345.07	1490.39	0.4194	0.71
Hospice Costs	$43.02	395.41	$69.33	641.89	<.0001	4.94	$43.65	379.15	$59.18	608.31	0.0707	3.06	$73.02	599.95	$71.24	597.41	0.7355	0.30
Other Costs (DME, SNF, HHA, Hospice)	$476.89	1802.95	$762.06	2334.49	<.0001	13.67	$511.33	1864.80	$763.40	2330.71	<.0001	11.94	$760.52	2633.01	$778.23	2440.54	0.4271	0.70
Total Medical Costs	$2,795.91	6614.35	$3,651.32	9348.09	<.0001	10.56	$2,902.25	7741.31	$3,593.96	8372.50	<.0001	8.58	$3,666.45	9232.04	$3,545.85	8656.45	0.1251	1.35
Prescription Costs	$532.11	797.22	$299.64	612.31	<.0001	32.71	$466.05	536.99	$305.57	585.03	<.0001	28.58	$507.60	676.41	$303.24	638.10	<.0001	31.08
Total Health Care Costs	$3,328.02	6666.00	$3,950.96	9378.23	<.0001	7.66	$3,368.30	7760.35	$3,899.53	8408.04	0.0001	6.57	$4,174.05	9246.54	$3,849.09	8699.86	<.0001	3.62
First Stroke/SE-related Hospitalization costs	$20.02	528.39	$68.88	1245.79	<.0001	5.11	$47.47	723.40	$81.78	1835.60	0.1468	2.46	$32.15	643.81	$60.62	1168.01	0.0006	3.02
Follow Up Stroke/SE-related Medical costs	$67.90	1099.53	$144.01	1707.74	<.0001	5.30	$106.30	1365.21	$159.61	2281.28	0.0943	2.84	$109.87	1646.26	$140.27	1725.07	0.0402	1.80
First Stroke/MI-related Hospitalization costs	$49.16	1027.04	$110.18	1579.66	<.0001	4.58	$82.53	1123.19	$117.28	1942.67	0.1964	2.19	$86.39	1816.44	$93.36	1371.64	0.6224	0.43
Follow Up Stroke/MI related Medical costs	$157.97	1766.33	$281.63	2846.22	<.0001	5.22	$229.41	2450.63	$279.42	2787.83	0.2610	1.91	$241.25	3185.33	$254.32	2488.63	0.6026	0.46
First Major Bleeding-related Hospitalization	$90.07	1274.41	$151.94	1516.48	<.0001	4.42	$132.97	1780.90	$138.43	1322.83	0.8372	0.35	$157.73	1313.10	$149.08	1432.71	0.4738	0.63

	Apixaban Cohort		Warfarin Cohort				Dabigatran Cohort		Warfarin Cohort				Rivaroxaban Cohort		Warfarin Cohort			
	N/Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/ Mean	%/SD	N/ Mean	%/SD	P-value	Std Diff*	N/ Mean	%/ SD	N/ Mean	%/ SD	P-value	Std Diff*
costs																		
Follow Up Major Bleeding related Medical Costs	$345.88	2637.28	$587.77	4494.16	<.0001	6.56	$468.34	4021.93	$595.85	3905.37	0.0577	3.22	$628.71	4596.43	$568.60	3881.68	0.1078	1.41
First MI-related Hospitalization costs	$30.46	888.15	$42.24	983.46	0.2679	1.26	$36.42	865.64	$36.46	649.35	0.9972	0.01	$56.90	1719.06	$35.10	780.56	0.0632	1.63
Follow Up MI-related Medical costs	$102.71	1450.40	$175.81	2490.83	0.0016	3.59	$145.33	2221.56	$140.77	1714.04	0.8921	0.23	$157.20	2906.47	$140.79	1979.34	0.4525	0.66

Table 6b. Outcomes in the Propensity Score Matched Cohorts for DOACs vs DOACs

	Apixaban Cohort		Dabigatran Cohort				Apixaban Cohort		Rivaroxaban Cohort				Dabigatran Cohort			Rivaroxaban Cohort		
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
Sample Size	**6,927**		**6,927**				**15,611**		**15,611**				**6,966**		**6,966**			
Follow-up Time (days)	209.30	201.79	248.67	262.29			207.42	199.96	248.41	257.66			248.29	262.17	245.94	256.06		
minimum	1		1				1		1				1		1			
Q1	55		33				54		38				33		37			
median	140		134				140		146				133		144			
Q3	292		369				288		376				369		364			
maximum	962		1,003				975		1,002				1003		1,002			
Follow-up Time within 1 Year (days)	170.86	125.72	176.35	135.21			169.98	125.57	178.58	136.12			176.13	135.20	177.51	135.69		
minimum	1		1				1		1				1		1			
Q1	55		33				54		38				33		37			
median	140		134				140		146				133		144			
Q3	292		360				288		360				360		360			
maximum	360		360				360		360				360		360			
Discontinuation	3,312	47.81%	4,728	68.25%			7,411	47.47%	9,710	62.20%			4,755	68.26%	4,360	62.59%		
Time-to-Discontinuation	138.11	139.45	164.54	179.11			138.60	140.00	164.04	177.80			164.13	178.81	161.86	174.99		
Switch	153	2.21%	303	4.37%			363	2.33%	686	4.39%			303	4.35%	303	4.35%		
Time-to-Switch	98.67	109.26	118.71	143.57			101.79	117.12	127.19	148.29			118.71	143.57	138.23	165.37		
Stroke within 1 Year of Index Date	29	0.42%	71	1.02%			78	0.50%	119	0.76%			71	1.02%	55	0.79%		
Time-to-Stroke (days) (among patients with stroke)	118.86	103.85	103.72	103.69			114.95	99.24	117.88	97.67			103.72	103.69	116.13	88.17		
Ischemic Stroke within 1 Year of Index Date	26	0.38%	59	0.85%			63	0.40%	81	0.52%			59	0.85%	41	0.59%		

	Apixaban Cohort		Dabigatran Cohort				Apixaban Cohort		Rivaroxaban Cohort				Dabigatran Cohort			Rivaroxaban Cohort		
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
Time-to-ischemic stroke (days) (among patients with ischemic stroke)	114.15	105.86	96.20	99.04			106.94	100.45	104.01	98.22			96.20	99.04	109.10	91.15		
Stroke/SE within 1 Year of Index Date	32	0.46%	75	1.08%			83	0.53%	126	0.81%			75	1.08%	58	0.83%		
Hemorrhagic Stroke	3	0.04%	12	0.17%			15	0.10%	38	0.24%			12	0.17%	14	0.20%		
Ischemic Stroke	26	0.38%	59	0.85%			63	0.40%	81	0.52%			59	0.85%	41	0.59%		
Systemic Embolism	3	0.04%	4	0.06%			5	0.03%	8	0.05%			4	0.06%	3	0.04%		
Time-to-Stroke/SE (days) (among patients with stroke)	120.97	102.93	105.79	104.08			117.80	99.70	116.22	96.62			105.79	104.08	110.60	89.08		
Major Bleeding within 1 Year of Index Date	144	2.08%	224	3.23%			361	2.31%	757	4.85%			224	3.22%	334	4.79%		
Gastrointestinal (GI) Bleeding	79	1.14%	129	1.86%			187	1.20%	459	2.94%			129	1.85%	190	2.73%		
Intracranial Hemorrhage (ICH)	17	0.25%	24	0.35%			41	0.26%	62	0.40%			24	0.34%	22	0.32%		
Other sites	58	0.84%	90	1.30%			161	1.03%	306	1.96%			90	1.29%	150	2.15%		
Time-to-MB (days) (among patients with Major Bleeding)	133.46	138.38	171.75	192.79			141.06	145.82	157.12	172.98			171.75	192.79	157.40	176.83		
Myocardial Infarction within 1 year of index date	41	0.59%	39	0.56%			101	0.65%	102	0.65%			39	0.56%	44	0.63%		
Time-to-MI (days) (among patients with MI)	117.98	85.71	125.36	109.88			120.70	102.51	114.46	107.70			125.36	109.88	113.05	93.76		
ALI within 1 year of index date	2	0.03%	4	0.06%			4	0.03%	7	0.04%			4	0.06%	3	0.04%		
Time-to-ALI (days) (among patients with ALI)	194.00	91.92	142.50	120.11			193.75	93.65	81.14	79.79			142.50	120.11	9.33	4.16		

	Apixaban Cohort		Dabigatran Cohort			Apixaban Cohort		Rivaroxaban Cohort			Dabigatran Cohort			Rivaroxaban Cohort			
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
All-cause Mortality within 1 year of index date	244	3.52%	321	4.63%			653	4.18%	875	5.61%			323	4.64%	389	5.58%		
Time-to-death (among patients who died)	108.19	88.46	109.58	95.21			109.31	89.64	105.45	94.53			109.96	95.87	104.92	98.28		
Composite Outcomes within 1 year of index date																		
MACE (Stroke, MI, or all-cause death)	301	4.35%	402	5.80%			789	5.05%	1,034	6.62%			404	5.80%	465	6.68%		
Time-to-first occurrence of either of MACE (among patients with MACE)	110.89	90.15	109.20	96.88			111.76	93.06	105.63	95.46			109.50	97.40	104.87	95.42		
Ischemic stroke, MI, ALI or all-cause death	300	4.33%	399	5.76%			782	5.01%	1,019	6.53%			401	5.76%	457	6.56%		
Time-to-first-occurrence of either of the outcomes (among patients with either outcomes)	110.59	90.27	109.49	96.87			111.08	92.95	104.76	95.06			109.79	97.39	103.34	95.63		
Ischemic stroke, MI, or all-cause death	299	4.32%	397	5.73%			780	5.00%	1,013	6.49%			399	5.73%	455	6.53%		
Time-to-first-occurrence of either of the outcomes (among patients with either outcomes)	110.22	90.07	109.39	96.55			110.96	92.95	104.85	95.15			109.69	97.08	103.93	95.54		
Stroke Incidence Rate within 1 Year of Index Date (per 100 person-years)	0.88		2.10				1.06		1.54				2.10		1.61			
Stroke/SE Incidence Rate within 1 Year of the Index Date (per 100 person-years)	0.98		2.22				1.13		1.63				2.21		1.70			

	Apixaban Cohort		Dabigatran Cohort				Apixaban Cohort		Rivaroxaban Cohort				Dabigatran Cohort			Rivaroxaban Cohort		
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
Hemorrhagic Stroke	0.09		0.35				0.20		0.49				0.35		0.41			
Ischemic Stroke	0.79		1.74				0.86		1.05				1.74		1.23			
Systemic Embolism	0.09		0.12				0.07		0.10				0.12		0.09			
Major Bleeding Incidence within 1 year of index date (per 100 person-years)	4.41		6.61				4.92		9.84				6.59		9.78			
Gastrointestinal Bleeding	2.11		3.24				2.28		5.27				3.23		4.96			
Intracranial Hemorrhage	0.52		0.71				0.54		0.80				0.71		0.64			
Other sites	1.65		2.25				1.97		3.42				2.25		3.86			
Myocardial Infarction incidence rate within 1 year of index date (per 100 person years)	1.25		1.15				1.37		1.32				1.15		1.29			
Acute Limb Ischemia incidence rate within one year of index date (per 100 person-years)	0.06		0.12				0.05		0.09				0.12		0.09			
All-cause Mortality incidence rate within one year of index date (per 100 person-years)	6.42		8.53				7.66		10.18				8.54		10.18			
Composite Outcomes within one year of index date																		
MACE (Stroke, MI, or all-cause death) incidence rate within 1 year of index date (per 100 person-years)	7.96		10.74				9.30		12.09				10.74		12.24			

	Apixaban Cohort		Dabigatran Cohort				Apixaban Cohort		Rivaroxaban Cohort				Dabigatran Cohort			Rivaroxaban Cohort		
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
(Ischemic stroke, MI, ALI, or all-cause death) incidence rate within 1 year of index date (per 100 person-years)	7.93		10.66				9.22		11.91				10.66		12.03			
(Ischemic stroke, MI, or all-cause death) incidence rate within 1 year of index date (per 100 person-years)	7.90		10.60				9.20		11.84				10.61		11.97			
Follow-up Medication Use																		
Anti-platelets	534	7.71%	590	8.52%			1,324	8.48%	1,464	9.38%			594	8.53%	630	9.04%		
Cumulative days of supply for anti-platelets	119.87	91.43	127.06	108.84			124.28	95.39	124.83	102.96			127.12	108.87	131.57	108.08		
MPR (for patients with anti-platelets)	0.81	0.71	0.76	0.53			0.84	0.91	0.83	1.07			0.76	0.53	0.86	1.12		
Follow-up All-cause Health Care Utilization (PPPM)																		
Inpatient Admission Visit	1,627	23.49%	1,917	27.67%	<.0001	9.61	3,813	24.43%	4,826	30.91%	<.0001	14.54	1,926	27.65%	2,124	30.49%	0.0002	6.26
Outpatient Hospital Visit	4,912	70.91%	4,808	69.41%	0.0535	3.28	11,030	70.66%	11,129	71.29%	0.2171	1.40	4,829	69.32%	4,943	70.96%	0.0348	3.58
ER Visit	3,339	48.20%	4,309	62.21%	<.0001	28.44	7,464	47.81%	9,505	60.89%	<.0001	26.48	4,328	62.13%	4,218	60.55%	0.0557	3.24
Office Visit	6,304	91.01%	6,241	90.10%	0.0673	3.11	14,262	91.36%	14,116	90.42%	0.0041	3.25	6,274	90.07%	6,304	90.50%	0.3909	1.45
Pharmacy Claim	6,624	95.63%	6,641	95.87%	0.4741	1.22	14,965	95.86%	14,843	95.08%	0.0009	3.76	6,678	95.87%	6,637	95.28%	0.0913	2.86
Durable Medical Equipment (DME)	2,551	36.83%	2,628	37.94%	0.1763	2.30	5,703	36.53%	5,916	37.90%	0.0126	2.82	2,639	37.88%	2,664	38.24%	0.6627	0.74
Skilled Nursing Facility (SNF) Visits	371	5.36%	499	7.20%	<.0001	7.62	910	5.83%	1,159	7.42%	<.0001	6.42	502	7.21%	537	7.71%	0.2590	1.91
Home Health Agency (HHA) Visits	1,007	14.54%	1,172	16.92%	0.0001	6.55	2,485	15.92%	3,102	19.87%	<.0001	10.32	1,178	16.91%	1,380	19.81%	<.0001	7.49

	Apixaban Cohort		Dabigatran Cohort			Apixaban Cohort		Rivaroxaban Cohort				Dabigatran Cohort			Rivaroxaban Cohort		
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
Hospice Visits	156	2.25%	206	2.97%	0.0077	4.53	411	2.63%	607	3.89%	<.0001	7.07	207	2.97%	253	3.63%	0.0292	3.70
# of Inpatient Admission Visits (PPPM)	0.10	0.33	0.11	0.39	0.0127	4.24	0.10	0.34	0.13	0.41	<.0001	8.26	0.11	0.39	0.14	0.42	0.0003	6.17
# of Outpatient Hospital Visits (PPPM)	0.68	0.97	0.66	0.98	0.2847	1.82	0.68	0.98	0.72	1.08	0.0004	4.02	0.66	0.98	0.72	1.05	0.0003	6.10
# of ER Visits (PPPM)	0.34	0.77	0.52	0.89	<.0001	21.34	0.33	0.71	0.51	0.95	<.0001	22.16	0.52	0.89	0.51	0.93	0.9407	0.13
# of Office Visits (PPPM)	1.85	1.64	1.81	1.62	0.1146	2.68	1.90	1.62	1.96	1.71	0.0017	3.55	1.81	1.61	1.93	1.69	<.0001	7.21
# of Pharmacy Visits (PPPM)	3.03	2.01	3.04	2.03	0.7914	0.45	3.07	2.01	3.14	2.14	0.0029	3.37	3.04	2.03	3.10	2.16	0.0793	2.97
# of DME Visits (PPPM)	0.30	0.62	0.31	0.62	0.2815	1.83	0.31	0.64	0.32	0.70	0.0452	2.27	0.31	0.62	0.33	0.69	0.2196	2.08
# of SNF Visits (PPPM)	0.03	0.18	0.04	0.33	0.0082	4.49	0.03	0.19	0.05	0.29	<.0001	6.00	0.04	0.33	0.05	0.26	0.1724	2.31
# of HHA Visits (PPPM)	0.06	0.31	0.06	0.22	0.2234	2.07	0.06	0.30	0.11	0.47	<.0001	12.43	0.06	0.22	0.11	0.44	<.0001	12.64
# of Hospice Visits (PPPM)	0.02	0.16	0.02	0.20	0.3633	1.54	0.02	0.18	0.03	0.26	<.0001	5.17	0.02	0.20	0.03	0.32	0.0013	5.44
Follow-up All-cause Health Care Costs (PPPM)																		
Inpatient Admission Costs	$1,327.57	5452.54	$1,552.68	6823.55	0.0320	3.64	$1,381.62	5497.81	$1,847.21	7417.55	<.0001	7.13	$1,549.50	6808.10	$2,024.36	8364.72	0.0002	6.23
Outpatient Costs (ER, Office, and other)	$912.76	1649.83	$842.24	1478.54	0.0081	4.50	$936.25	1796.21	$979.50	1863.76	0.0368	2.36	$840.11	1475.11	$981.05	1910.01	<.0001	8.26
ER Costs	$249.77	992.19	$321.81	959.69	<.0001	7.38	$247.57	945.55	$363.62	1170.23	<.0001	10.91	$320.97	957.35	$373.55	1275.15	0.0059	4.66
Office Visit Costs	$362.43	620.01	$363.67	641.97	0.9082	0.20	$374.97	648.11	$395.53	758.00	0.0100	2.91	$362.79	640.46	$385.70	723.13	0.0478	3.35
DME Costs	$48.47	278.56	$50.16	244.40	0.7041	0.65	$47.74	238.16	$56.56	317.16	0.0055	3.14	$49.96	243.76	$55.67	211.91	0.1396	2.50
SNF Costs	$190.63	1420.34	$243.02	1651.14	0.0453	3.40	$206.36	1448.60	$295.14	1852.95	<.0001	5.34	$245.85	1666.35	$321.06	2004.92	0.0161	4.08
HHA Costs	$163.39	907.60	$172.01	634.50	0.5172	1.10	$177.91	867.15	$334.05	1627.85	<.0001	11.97	$171.61	633.18	$315.14	1448.77	<.0001	12.84
Hospice Costs	$37.77	389.28	$43.84	380.09	0.3534	1.58	$42.79	394.36	$75.86	607.41	<.0001	6.46	$43.62	379.04	$72.53	603.37	0.0007	5.74
Other Costs (DME, SNF, HHA, Hospice)	$440.25	1805.66	$509.03	1851.46	0.0269	3.76	$474.80	1798.53	$761.61	2577.84	<.0001	12.90	$511.04	1864.31	$764.41	2588.88	<.0001	11.23

	Apixaban Cohort		Dabigatran Cohort				Apixaban Cohort		Rivaroxaban Cohort				Dabigatran Cohort			Rivaroxaban Cohort		
	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*	N/Mean	%/SD	N/Mean	%/SD	P-value	Std Diff*
Total Medical Costs	$2,680.58	6593.82	$2,903.94	7746.22	0.0677	3.11	$2,792.67	6607.41	$3,588.32	8667.33	<.0001	10.32	$2,900.65	7739.38	$3,769.82	9465.05	<.0001	10.05
Prescription Costs	$522.17	755.63	$466.13	536.77	<.0001	8.55	$531.39	795.43	$507.01	662.07	0.0033	3.33	$465.88	536.89	$504.85	625.35	<.0001	6.69
Total Health Care Costs	$3,202.75	6637.53	$3,370.07	7764.89	0.1728	2.32	$3,324.06	6658.86	$4,095.33	8676.59	<.0001	9.97	$3,366.54	7758.47	$4,274.67	9467.88	<.0001	10.49
First Stroke/SE-related Hospitalization costs	$16.25	348.07	$47.71	725.21	0.0011	5.53	$20.00	527.09	$34.28	624.36	0.0291	2.47	$47.45	723.19	$47.60	945.22	0.9912	0.02
Follow Up Stroke/SE-related Medical costs	$78.99	1343.99	$106.83	1368.64	0.2270	2.05	$67.64	1096.65	$113.61	1497.32	0.0020	3.50	$106.24	1364.82	$127.13	1651.09	0.4156	1.38
First Stroke/MI-related Hospitalization costs	$31.19	565.24	$82.95	1126.01	0.0006	5.81	$49.45	1025.42	$74.79	1258.30	0.0511	2.21	$82.49	1122.87	$74.28	1089.92	0.6617	0.74
Follow-up Stroke/MI related Medical costs	$139.33	1699.25	$230.57	2456.76	0.0110	4.32	$157.75	1762.27	$211.39	2198.77	0.0174	2.69	$229.28	2449.94	$246.67	3749.42	0.7459	0.55
First Major Bleeding-related Hospitalization costs	$92.71	1534.64	$133.64	1785.37	0.1480	2.46	$89.59	1271.00	$152.20	1187.32	<.0001	5.09	$132.89	1780.39	$169.42	1513.96	0.1921	2.21
Follow-up Major Bleeding related Medical Costs	$320.97	2593.62	$470.28	4031.90	0.0095	4.40	$344.00	2630.27	$601.00	4093.58	<.0001	7.47	$468.07	4020.80	$643.22	4641.09	0.0173	4.03
First MI-related Hospitalization costs	$17.50	473.00	$36.60	867.82	0.1077	2.73	$30.76	887.02	$44.84	1142.68	0.2240	1.38	$36.40	865.39	$32.17	688.46	0.7496	0.54
Follow-up MI-related Medical costs	$79.94	1191.84	$146.06	2227.15	0.0294	3.70	$102.69	1447.28	$122.69	1804.08	0.2799	1.22	$145.24	2220.93	$148.97	3508.12	0.9404	0.13

Kaplan Meier curves were generated to show the cumulative incidence of stroke/SE, MB, and MACE among each pair of matched cohorts (Appendix 3, Figures 6A-8F).

10.4. Main results

DOACs vs Warfarin

Apixaban was associated with a 52% lower rate of stroke/SE (hazard ratio [HR]: 0.48, 95% confidence interval [CI]: 0.37-0.62) and a 34% lower rate of MB (HR: 0.66, 95% CI: 0.58-0.75) compared to warfarin within 1 year of treatment initiation. In addition, apixaban patients had a 37% lower rate of stroke/MI/ACM (HR; 0.63, 95% CI: 0.58-0.69) and ACM (HR: 0.62, 95% CI: 0.56-0.69) compared to warfarin.

Compared to warfarin, dabigatran was associated with a non-statistically significant lower rate of stroke/SE (HR: 0.87, 95% CI: 0.64-1.19) and MB (HR: 0.85, 95% CI: 0.71-1.02). Compared to warfarin, dabigatran use was associated with lower rates of stroke/MI/ACM (HR: 0.79, 95% CI: 0.70-0.90), which were driven by all-cause mortality (HR: 0.77, 95% CI: 0.67-0.89).

Compared to warfarin, rivaroxaban was associated with a lower rate of stroke/SE (HR: 0.72, 95% CI: 0.60-0.89) driven by ischemic stroke. Rivaroxaban use was associated with a significantly higher rate of MB (HR: 1.14; 95% CI: 1.05-1.23) compared to warfarin, driven by GI bleeding. Rivaroxaban patients were found to have a 13% lower rate of stroke/MI/ACM (HR: 0.87, 95% CI: 0.81-0.92) and a 14% lower rate of ACM (HR: 0.86, 95% CI: 0.81-0.93).

Figure 3. Incidence and Hazard Rates of stroke/SE, MB, and MACE Comparing Apixaban vs Warfarin

Outcomes	Apixaban	Warfarin (Reference)	Hazard Ratio (95% CI)	P-value
	Incidence per 100 person-years			
Stroke/SE	1.1	2.3	0.48 (0.37-0.62)	<0.001
MB	5.0	8.4	0.66 (0.58-0.75)	<0.001
ACM	7.7	12.3	0.62 (0.56-0.69)	<0.001
Stroke/MI/ACM	9.3	14.6	0.63 (0.58-0.69)	<0.001
Stroke/MI/ACM/RV	9.9	15.6	0.63 (0.58-0.69)	<0.001

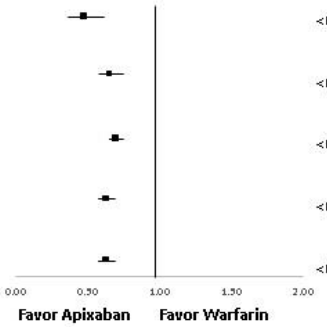


Figure 4. Incidence and Hazard Rates of stroke/SE, MB, and MACE Comparing Dabigatran vs Warfarin

Outcomes	Dabigatran	Warfarin (Reference)	Hazard Ratio (95% CI)	P-value
	Incidence per 100 person-years			
Stroke/SE	2.2	2.5	0.87 (0.64-1.19)	0.377
MB	6.6	7.4	0.85 (0.71-1.02)	0.077
ACM	8.5	11.1	0.77 (0.67-0.89)	<0.001
Stroke/MI/ACM	10.8	13.5	0.79 (0.70-0.90)	<0.001
Stroke/MI/ACM/RV	11.6	14.5	0.80 (0.71-0.91)	<0.001

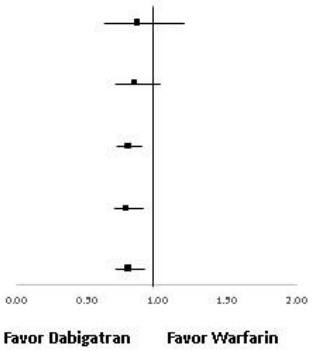
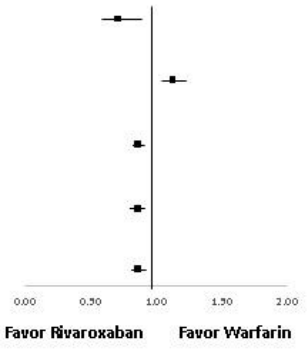


Figure 5. Incidence and Hazard Rates of stroke/SE, MB and MACE Comparing Rivaroxaban vs Warfarin

Outcomes	Rivaroxaban	Warfarin (Reference)	Hazard Ratio (95% CI)	P-value
	Incidence per 100 person-years			
Stroke/SE	1.5	2.1	0.72 (0.60-0.89)	<0.001
MB	9.7	8.4	1.14 (1.05-1.23)	0.002
ACM	9.9	11.5	0.86 (0.81-0.93)	<0.001
Stroke/MI/ACM	11.9	13.8	0.87 (0.81-0.92)	<0.001
Stroke/MI/ACM/RV	12.8	14.8	0.87 (0.82-0.93)	<0.001



DOACs v. DOACs

Apixaban was associated with a 56% lower rate of stroke/SE (hazard ratio [HR]: 0.44, 95% confidence interval [CI]: 0.29-0.66) and a 23% lower rate of MB (HR: 0.77, 95% CI: 0.62-0.95) compared to dabigatran within 1 year of treatment initiation. In addition, apixaban patients had a 27% lower rate of stroke/MI/ACM (HR; 0.73, 95% CI: 0.63-0.85) and ACM (HR: 0.74, 95% CI: 0.63-0.88) compared to dabigatran. Compared to rivaroxaban, apixaban was associated with a significantly lower rate of stroke/SE (HR: 0.69, 95% CI: 0.52-0.91) and MB (HR: 0.55, 95% CI: 0.49-0.63). In addition, compared to rivaroxaban, apixaban was associated with a lower rate of stroke/MI/ACM (HR: 0.76, 95% CI: 0.69-0.83), which were driven by all-cause mortality (HR: 0.74, 95% CI: 0.67-0.82). Compared to rivaroxaban, dabigatran was associated with a lower rate of MB (HR: 0.68; 95% CI: 0.58-0.81), driven by GI bleeding. Dabigatran patients were found to have a 16% lower rate of ACM (HR: 0.84, 95% CI: 0.73-0.98).

Figure 6. Incidence and Hazard Rates of stroke/SE, MB, and MACE Comparing Apixaban vs Dabigatran

Outcomes	Apixaban	Dabigatran (Reference)	Hazard Ratio (95% CI)	P-value
	Incidence per100 person-years			
Stroke/SE	1.0	2.2	0.44 (0.29-0.66)	<0.001
MB	4.4	6.6	0.77 (0.62-0.95)	0.016
ACM	6.4	8.5	0.74 (0.63-0.88)	<0.001
Stroke/MI/ACM	8.0	10.7	0.73 (0.63-0.85)	<0.001
Stroke/MI/ACM/RV	8.4	11.6	0.72 (0.63-0.83)	<0.001

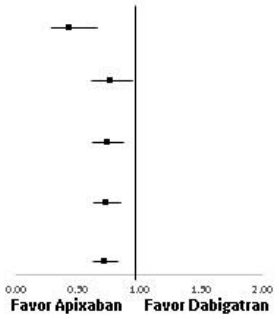


Figure 7. Incidence and Hazard Rates of stroke/SE, MB, and MACE Comparing Apixaban vs Rivaroxaban

Outcomes	Apixaban	Rivaroxaban (Reference)	Hazard Ratio (95% CI)	P-value
	Incidence per100 person-years			
Stroke/SE	1.1	1.6	0.69 (0.52-0.91)	<0.001
MB	4.9	9.8	0.55 (0.49-0.63)	0.008
ACM	7.7	10.2	0.74 (0.67-0.82)	<0.001
Stroke/MI/ACM	9.3	12.1	0.76 (0.69-0.83)	<0.001
Stroke/MI/ACM/RV	9.9	13.0	0.75 (0.69-0.82)	<0.001

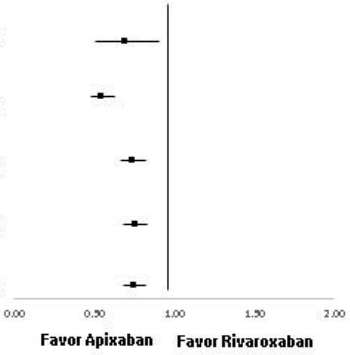
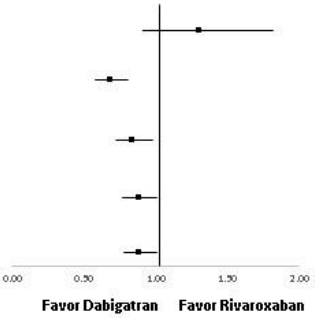


Figure 8. Incidence and Hazard Rates of stroke/SE, MB, and MACE Comparing Dabigatran vs. Rivaroxaban

Outcomes	Dabigatran	Rivaroxaban (Reference)	Hazard Ratio (95% CI)	P-value
	Incidence per100 person-years			
Stroke/SE	2.2	1.7	1.30 (0.92-1.82)	0.138
MB	6.6	9.8	0.68 (0.58-0.81)	<0.001
ACM	8.5	10.2	0.84 (0.73-0.98)	0.023
Stroke/MI/ACM	10.7	12.2	0.88 (0.77-1.01)	0.065
Stroke/MI/ACM/RV	11.6	13.3	0.88 (0.78-1.01)	0.061



GLM Cost Models

Compared to warfarin, apixaban was associated with lower total health care costs (mean, $3,328 vs $3,951, p<0.001).

Compared to rivaroxaban, apixaban was associated with lower total health care costs (mean, $3,324 vs $4,095; p<0.001). Compared to dabigatran, apixaban had lower inpatient costs ($1,328 vs $1,553; p=0.031), but had similar total health care costs ($3,203 vs $3,370; p=0.172)

Follow-up MB-related total medical costs were significantly lower for apixaban compared to warfarin, dabigatran, and rivaroxaban. Specifically, compared to warfarin, apixaban accrued lower costs by $242 (mean, $346 vs $588; p<0.001); compared to dabigatran, apixaban accrued lower costs by $149 (mean, $321 vs $470; p=0.009); compared to rivaroxaban, apixaban accrued lower costs by $257 (mean, $344 vs $601; p<0.001).

Table 7a. Health care Costs in Propensity Score Matched Cohorts Among Apixaban vs Warfarin

	Apixaban Cohort	Warfarin Cohort	Difference between Marginal Effects	P-Value
	Marginal Effect	Marginal Effect		
Inpatient Admission Costs	$1,386	$1,931	$545	<.0001
Outpatient Costs (ER, Office, and other)	$933	$958	$25	0.214
Other Costs (DME, SNF, HHA, Hospice)	$477	$762	$285	<.0001
Total Medical Costs	$2,796	$3,651	$855	<.0001
Prescription Costs	$532	$300	-$232	<.0001
Total Health Care Costs	$3,328	$3,951	$623	<.0001

Table 7b. Health care Costs in Propensity Score Matched Cohorts Among Apixaban vs. Dabigatran and Apixaban vs. Rivaroxaban

	Apixaban Cohort	Dabigatran Cohort	Difference between Marginal Effects	P-Value		Apixaban Cohort	Rivaroxaban Cohort	Difference between Marginal Effects	P-Value
	Marginal Effect	Marginal Effect				Marginal Effect	Marginal Effect		
Inpatient Admission Costs	$1,328	$1,553	$225	0.031		$1,382	$1,847	$466	<.0001
Outpatient Costs (ER, Office, and other)	$913	$842	-$71	0.008		$936	$979	$43	0.037
Other Costs (DME, SNF, HHA, Hospice)	$440	$509	$69	0.028		$475	$762	$287	<.0001
Total Medical Costs	$2,681	$2,904	$223	0.067		$2,793	$3,588	$796	<.0001
Prescription Costs	$522	$466	-$56	<.0001		$531	$507	-$24	0.0030
Total Health Care Costs	$3,203	$3,370	$167	0.172		$3,324	$4,095	$771	<.0001

Table 7c. Major Bleeding and Stroke/SE Costs for PSM-adjusted Apixaban vs Warfarin Patients

	Apixaban Cohort	Warfarin Cohort	Difference between Marginal Effects (95% CI)	P-Value
	Marginal Effect (95% Confidence interval)	Marginal Effect (95% Confidence interval)		
Two-Part Model				
Follow-up Major Bleeding-related Medical Costs (PPPM)	$346 (95% CI: $305-$387)	$588 (95% CI: $517-$658)	$242 (95% CI: $161-$322)	<.0001
Follow-up Stroke/SE-related Medical Costs (PPPM)	$68 (95% CI: $50-$86)	$144 (95% CI: $117-$170)	$76 (95% CI: $45-$107)	<.0001
Follow-up MI-related Medical Costs (PPPM)	$103 (95% CI: $81-$125)	$176 (95% CI: $138-$219)	$73 (95% CI: $28-$118)	0.0010
Follow-up Revascularization-related Medical Costs (PPPM)	$65 (95% CI: $45-$87)	$71 (95% CI: $51-$94)	$6 (95% CI: $-23-$35)	0.6970

Table 7d. Major Bleeding and Stroke/SE Costs for PSM-adjusted Apixaban vs Dabigatran and vs Rivaroxaban Patients

	Apixaban Cohort	Dabigatran Cohort	Difference between Marginal Effects (95% CI)	P-Value		Apixaban Cohort	Rivaroxaban Cohort	Difference between Marginal Effects (95% CI)	P-Value
	Marginal Effect (95% CI)	Marginal Effect (95% CI)				Marginal Effect (95% CI)	Marginal Effect (95% CI)		
Two-Part Model									
Follow-up Major Bleeding-related Medical Costs (PPPM)	$321 (95% CI: $257-$385)	$470 (95% CI: $377-$563)	$149 (95% CI: $37-$261)	0.009		$344 (95% CI: $303-$385)	$601 (95% CI: $537-$665)	$257 (95% CI: $180-$334)	<.0001
Follow-up Stroke/SE-related Medical Costs (PPPM)	$79 (95% CI: $46-$112)	$107 (95% CI: $75-$139)	$28 (95% CI: -$18-$73.6)	0.232		$68 (95% CI: $51-$84)	$114 (95% CI: $91-$137)	$46 (95% CI: $18-$73)	0.001
Follow-up MI-related Medical Costs (PPPM)	$80 (95% CI: $52-$108)	$146 (95% CI: $93-$199)	$66 (95% CI: $5-$128)	0.035		$103 (95% CI: $80-$126)	$123 (95% CI: $95-$150)	$20 (95% CI: -$15-$55)	0.268

	Apixaban Cohort	Dabigatran Cohort	Difference between Marginal Effects (95% CI)	P-Value	Apixaban Cohort	Rivaroxaban Cohort	Difference between Marginal Effects (95% CI)	P-Value
	Marginal Effect (95% CI)	Marginal Effect (95% CI)			Marginal Effect (95% CI)	Marginal Effect (95% CI)		
Follow-up Revascularization-related Medical Costs (PPPM)	$49 (95% CI: $25-$74)	$114 (95% CI: $70-$158)	$64 (95% CI: $14-$115)	0.012	$66 (95% CI: $46-$87)	$96 (95% CI: $70-$125)	$30 (95% CI: -$4-$65)	0.084

Other analyses

CAD/PAD Interaction Analysis

Compared to warfarin, apixaban was associated with a lower rate of MACE at CAD only (HR: 0.57; 95% CI: 0.50-0.66), PAD only (HR: 0.60; 95% CI: 0.47-0.76), and CAD and PAD levels (HR: 0.74; 95% CI: 0.64-0.85; $p_{interaction}$=0.030).

Compared to warfarin, rivaroxaban was associated with lower rate of stroke/SE at CAD and PAD (HR: 0.55; 95% CI: 0.40-0.76), CAD only (HR: 0.99; 95% CI: 0.76-1.29), and PAD only levels (HR: 0.53; 95% CI: 0.34-0.83; $p_{interaction}$=0.007). Difference MB rates were observed for CAD and PAD (HR: 0.98; 95% CI: 0.85-1.14), CAD only (HR: 1.22; 95% CI: 1.09-1.36) and PAD only (HR: 1.27; 95% CI: 1.01-1.60; $p_{interaction}$=0.041). Likewise, rivaroxaban was associated with lower rates for MACE as well for all types of CAD/PAD ($p_{interaction}$=0.06).

No significant associations were observed for CAD/PAD interaction variables for DOAC vs. DOAC comparisons.

Table 8. Cox Model Comparison of Patients with DOAC vs Warfarin and DOAC vs DOAC Use, by CAD/PAD Type

DOACs vs Warfarin						
	Apixaban vs Warfarin[1]	P-value*	Dabigatran vs. Warfarin[2]	P-value*	Rivaroxaban vs Warfarin	P-value*
CAD/PAD Type						
Stroke/SE						
Both CAD & PAD	0.51 (0.33-0.77)		0.60 (0.34-1.07)		0.55(0.40-0.76)	
CAD only	0.49 (0.33-0.73)	0.902	0.89 (0.58-1.37)	**0.079**	0.99(0.76-1.29)	**0.007**
PAD only	0.43 (0.23-0.81)		1.9 (0.84-4.32)		0.53(0.34-0.83)	
Major Bleeding						
Both CAD & PAD	0.75 (0.61-0.94)		0.78(0.57-1.05)		0.98(0.85-1.14)	
CAD only	0.62 (0.52-0.75)	0.377	0.87(0.67-1.12)	0.600	1.22(1.09-1.36)	**0.041**
PAD only	0.61 (0.43-0.88)		1.05(0.64-1.72)		1.27(1.01-1.60)	
Stroke/MI/ACM						
Both CAD & PAD	0.74 (0.64-0.85)		0.90(0.73-1.12)		0.88 (0.79-0.98)	
CAD only	0.57 (0.50-0.66)	**0.0302**	0.77(0.64-0.93)	0.575	0.91(0.83-1.00)	**0.056**
PAD only	0.60 (0.47-0.76)		0.82(0.58-1.16)		0.72(0.61-0.85)	

DOACs vs DOACs						
	Apixaban vs Dabigatran[3]	P value*	Apixaban vs Rivaroxaban	P value*	Dabigatran vs Rivaroxaban[4]	P value*
CAD/PAD Type						
Stroke/SE						
Both CAD & PAD	0.76 (0.38-1.53)		0.84 (0.53-1.35)		1.32 (0.66-2.65)	
CAD only	0.33 (0.18-0.62)		0.58 (0.39-0.86)		1.12 (0.71-1.76)	
PAD only	0.32 (0.12-0.87)	0.173	0.75 (0.37-1.50)	0.479	2.15 (0.95-4.87)	0.395
Major Bleeding						
Both CAD & PAD	0.84 (0.59-1.20)		0.63 (0.51-0.78)		0.74 (0.54-1.02)	
CAD only	0.74 (0.55-1.00)		0.53 (0.44-0.62)		0.64 (0.51-0.80)	
PAD only	0.60 (0.34-1.06)	0.595	0.48 (0.34-0.68)	0.297	0.81 (0.52-1.26)	0.568
Stroke/MI/ACM						
Both CAD & PAD	0.78 (0.61-0.99)		0.80 (0.69-0.93)		0.94 (0.75-1.18)	
CAD only	0.68 (0.55-0.85)		0.68 (0.59-0.78)		0.81 (0.67-0.98)	
PAD only	0.76 (0.51-1.14)	0.725	0.94 (0.72-1.16)	0.06	1.08 (0.76-1.55)	0.303

1. Female sex was controlled for in the model.

2. Age, CHF, and anemia and coagulation defects was controlled for in the model.

3. Transient ischemic attack was controlled for in the model.

4. Age, non-ESRD, anemia, and coagulation defects were controlled for in the model.

Description of the unadjusted baseline and outcomes results stratified by CAD and PAD, CAD only and PAD only can be viewed in the Appendix 3, Tables 1 and 2.

Dose Subgroup Analysis

Both apixaban 2.5mg and 5mg were associated with a lower rate of stroke/SE, MB, and stroke/MI/ACM compared to warfarin (all p<0.001). Dabigatran 150 mg patients had a non-statistically significant lower rate of stroke/SE (HR: 0.81; 95% CI: 0.54-1.21) while dabigatran 75 mg patients had a non-statistically significant higher rate of stroke/SE (HR: 1.35; 95% CI: 0.80-2.29) compared to warfarin. Dabigatran 150 mg was associated with a lower rate of MB (HR: 0.80; 95% CI: 0.65-1.00) and stroke/MI/ACM (HR: 0.72; 95% CI: 0.61-0.85) while dabigatran 75 mg had a non-statistically significant lower rate of MB (HR: 0.81; 95% CI: 0.60-1.09) and stroke/MI/ACM (HR: 0.81; 95% CI: 0.66-1.00) compared to warfarin.

Rivaroxaban 10/15mg was associated with a non-statistically significant lower rate of stroke/SE (HR: 0.81; 95% CI: 0.62-1.06) and non-statistically significant higher rate of stroke/MI/ACM (HR: 1.01; 95% CI: 0.93-1.11,) while rivaroxaban 20mg was associated with a significantly lower rate of stroke/SE (HR: 0.54; 95% CI: 0.42-0.68) and stroke/MI/ACM (HR: 0.71; 95% CI: 0.65-0.78) compared to warfarin. Both rivaroxaban 20 mg (HR:1.17 95% CI: 1.04-1.30) and 10/15mg (HR: 1.25; 95% CI: 1.10-1.41) were associated with a higher rate of MB compared to warfarin.

Compared to standard-dose dabigatran (150 mg), standard-dose apixaban (5 mg) was associated with lower rate of MB (HR: 0.75; 95% CI: 0.58-0.98; p=0.031). Similar results were seen with low doses (apixaban 2.5 mg; dabigatran 75 mg) as well (HR: 0.57; 95% CI: 0.38-0.86; p=0.007). Compared to standard-dose rivaroxaban (20 mg), apixaban had a lower rate of MB (HR: 0.58; 95% CI: 0.49-0.68; p<0.001). Similar findings were seen with low-dose (rivaroxaban 10 or 15 mg; apixaban 2.5 mg) as well (HR: 0.51; 95% CI: 0.42-0.63; p<0.001). In addition, there was a lower rate of MACE as well in standard- (HR: 0.72; 95% CI: 0.63-0.82; p<0.001) and low-dose apixaban compared to rivaroxaban (HR: 0.83; 95% CI: 0.73-0.95; p=0.006). Low-dose dabigatran patients were associated with higher rate of stroke/SE compared to rivaroxaban (HR: 3.43; 95% CI: 1.64-7.16; p=0.001).

Table 9. Incidence and Hazard Ratios of Outcomes for Patients prescribed Standard- and Reduced-dose DOACs vs Warfarin and DOACs vs DOACs

Standard Dose	Incidence per 100 person-years		Hazard Ratio (95% CI)	p-value	Reduced Dose	Incidence per 100 person-years		Hazard Ratio (95% CI)	p-value
	Apixaban	Warfarin				Apixaban	Warfarin		
Stroke/SE	0.9	2.3	0.38 (0.27-0.54)	<0.001	Stroke/SE	1.70	2.80	0.58(0.39-0.86)	0.007
MB	4.4	7.4	0.67 (0.56-0.78)	<0.001	MB	6.20	10.90	0.61(0.50-0.75)	<0.001
Stroke/MI/ACM	6.2	12.80	0.48 (0.42-0.54)	<0.001	Stroke/MI/ACM	16.50	20.40	0.79 (0.69-0.89)	<0.001
	Dabigatran	Warfarin				Dabigatran	Warfarin		
Stroke/SE	1.6	2.00	0.81(0.54-1.21)	0.304	Stroke/SE	4.30	3.10	1.35 (0.80-2.29)	0.263
MB	5.7	7.0	0.80 (0.65-1.00)	0.047	MB	9.50	12.00	0.81(0.60-1.09)	0.167
Stroke/MI/ACM	8.30	11.70	0.72 (0.61-0.85)	<0.001	Stroke/MI/ACM	18.90	21.70	0.81 (0.66-1.00)	0.050
	Rivaroxaban	Warfarin				Rivaroxaban	Warfarin		
Stroke/SE	1.2	2.2	0.54 (0.42-0.68)	<0.001	Stroke/SE	2.10	2.60	0.81(0.62-1.06)	0.12
MB	8.2	7.0	1.17 (1.04-1.30)	0.007	MB	12.50	9.80	1.25(1.10-1.41)	<0.001
Stroke/MI/ACM	8.20	11.80	0.71 (0.65-0.78)	<0.001	Stroke/MI/ACM	18.20	17.60	1.01 (0.93-1.11)	0.790

Standard Dose	Incidence per 100 person-years		Hazard Ratio (95% CI)	p-value	Reduced Dose	Incidence per 100 person-years		Hazard Ratio (95% CI)	p-value
	Apixaban	Dabigatran				Apixaban	Dabigatran		
Stroke/SE	0.96	1.57	0.61 (0.36-1.01)	0.054	Stroke/SE	2.3	4.3	0.53 (0.30-0.95)	0.034
MB	3.70	5.70	0.75 (0.58-0.98)	0.031	MB	5	9.6	0.57 (0.38-0.86)	0.007
Stroke/MI/ACM	6.10	8.30	0.72 (0.60-0.88)	0.001	Stroke/MI/ACM	15.7	19	0.82 (0.65-1.03)	0.082
	Apixaban	Rivaroxaban				Apixaban	Rivaroxaban		
Stroke/SE	0.91	1.30	0.72 (0.50-1.05)	0.085	Stroke/SE	1.7	2.2	0.73 (0.48-1.12)	0.154
MB	4.30	8.30	0.58 (0.49-0.68)	<0.001	MB	6.2	13.2	0.51 (0.42-0.63)	<0.001
Stroke/MI/ACM	6.20	8.40	0.72 (0.63-0.82)	<0.001	Stroke/MI/ACM	16.4	19.5	0.83 (0.73-0.95)	0.006
	Dabigatran	Rivaroxaban				Dabigatran	Rivaroxaban		
Stroke/SE	1.60	1.30	1.30 (0.83-2.04)	0.254	Stroke/SE	4.4	1.3	3.43 (1.64-7.16)	0.001
MB	5.70	8.00	0.68 (0.55-0.83)	<0.001	MB	9.6	10.4	1.09 (0.79-1.51)	0.611
Stroke/MI/ACM	8.40	8.10	1.03 (0.87-1.23)	0.247	Stroke/MI/ACM	18.8	18.8	1.03 (0.82-1.28)	0.818

Descriptive baseline and outcomes characteristics for pre-matched low- and standard-dose patients in the CAD/PAD population can be viewed in Appendix 3, Tables 3 and 4; PSM matched baseline and outcomes characteristics for low-dose patients can be viewed in Appendix 3, Tables 5 and 6; PSM matched baseline and outcomes characteristics for standard-dose patients can be viewed in Appendix 3, Tables 7 and 8.

Sensitivity Analysis

A sensitivity analysis was carried out to evaluate the association of apixaban, dabigatran, rivaroxaban and warfarin on rates of stroke/SE, MB, and MACE after removing the 1-year restriction on the follow-up period.

Our findings were very similar to the main analysis. Of note, apixaban was associated with lower rate of stroke/SE compared to warfarin (HR: 0.48; 95% CI: 0.35-0.66); dabigatran had a 19% lower rate of MACE compared to warfarin (HR: 0.79; 95% CI: 0.70-0.89); however, as opposed to the main analysis results, rivaroxaban had a similar rate of stroke/SE compared to warfarin (HR: 0.92; 95% CI: 0.74-1.15).

Compared to dabigatran and rivaroxaban, apixaban had a lower rate of stroke/SE, MB, and MACE (p<0.001). Compared to rivaroxaban, dabigatran had similar rate of stroke/SE (HR: 1.17; 95% CI: 0.80-1.72; p=0.420), but lower rates of MB (HR: 0.69; 95% CI: 0.57-0.85; p<0.001) and MACE (HR: 0.88; 95% CI: 0.78-0.99; p=0.031).

Table 10. Hazard Rates for stroke/SE, MB, and MACE Outcomes After Removing the 1-Year Restriction on Follow-up Period (Sensitivity Analysis)

Outcomes	Hazard Ratio (95% CI)	p-value
DOACs vs Warfarin		
Apixaban vs Warfarin		
Stroke/SE	0.48 (0.35-0.66)	<0.001
MB	0.59 (0.50-0.69)	<0.001
Stroke/MI/ACM	0.65 (0.59-0.70)	<0.001
Dabigatran vs Warfarin		
Stroke/SE	0.89 (0.62-1.27)	0.514
MB	0.96 (0.77-1.19)	0.733
Stroke/MI/ACM	0.79 (0.70-0.89)	<0.001
Rivaroxaban vs Warfarin		
Stroke/SE	0.92 (0.74-1.15)	0.452
MB	1.19 (1.08-1.31)	<0.001
Stroke/MI/ACM	0.87 (0.82-0.92)	<0.001
DOACs vs. DOACs		

Outcomes	Hazard Ratio (95% CI)	p-value
Apixaban vs Dabigatran		
Stroke/SE	0.36 (0.22-0.60)	<0.001
MB	0.63 (0.49-0.81)	<0.001
Stroke/MI/ACM	0.74 (0.65-0.85)	<0.001
Apixaban vs Rivaroxaban		
Stroke/SE	0.58 (0.42-0.82)	0.002
MB	0.49 (0.42-0.57)	<0.001
Stroke/MI/ACM	0.77 (0.71-0.84)	<0.001
Dabigatran vs Rivaroxaban		
Stroke/SE	1.17 (0.80-1.72)	0.416
MB	0.69 (0.57-0.85)	<0.001
Stroke/MI/ACM	0.88 (0.78-0.99)	0.031

Note: Descriptive outcomes after removal of one-year restriction on follow-up can be viewed in Appendix 3, Table 9.

The results tables can also be accessed in the embedded Excel file below.


Final Tables

10.5. Adverse events / adverse reactions

Not applicable.

11. DISCUSSION

11.1. Key results

This study was a retrospective analysis of NVAF patients co-diagnosed with CAD/PAD in the Medicare database. Compared to warfarin, apixaban had lower rates of stroke/SE, MB, and MACE; dabigatran had lower rates of mortality, and MACE; rivaroxaban had lower rates of stroke/SE, mortality, and MACE – but showed higher MB rates compared to warfarin. On the other hand, apixaban showed lower rates of stroke/SE, MB, mortality, and MACE composite endpoint, compared to dabigatran and rivaroxaban, respectively. In addition, compared to rivaroxaban, dabigatran had a 32% lower rate of MB in the current sample.

Sub-analysis carried out by CAD/PAD type resulted in significant interaction between CAD/PAD type and MACE (p=0.030 for interaction) comparing apixaban vs warfarin. Dabigatran vs warfarin showed significant interaction between stroke/SE and CAD/PAD type (p=0.079 for interaction), and rivaroxaban versus warfarin showed significant

interaction with CAD/PAD type for stroke/SE (p=0.007), MB (p=0.041), and MACE (p=0.06). On analyzing DOACs vs DOACs, we observed that no significant interaction was observed between CAD/PAD type and outcomes of interest.

Our costs analyses revealed that compared to warfarin, apixaban was associated with lower total health care costs, with a cost reduction of $623 PPPM. Compared to rivaroxaban, apixaban was associated with a cost reduction of $771 PPPM. In addition, MB-related medical costs were significantly lower for apixaban, as compared to warfarin, dabigatran, and rivaroxaban, ranging from $150-$260 PPPM in cost differential.

11.2. Limitations

This study has several limitations. Most importantly, although all cohorts were matched using propensity scores, there may have been residual confounding due to unmeasured variables such as over-the-counter use of aspirin and dose change(s) in warfarin treatment. Moreover, only associations can be inferred from this retrospective observational study—not causations. Medicare data does not provide granularity in the data (ie, laboratory test result values); specifically, creatinine clearance, international normalized ratio values, and time in therapeutic range information are not available. Since this was a claims analysis, variables were defined using ICD-9-CM diagnosis and procedure, CPT, HCPCS, and NDC codes; therefore, coding errors and lack of clinical accuracy may have introduced bias in the study. PSM was conducted to match each of the OAC cohorts; thus, the results are not comparable across matched cohorts. For example, the apixaban-warfarin cohort was older, and had higher HAS-BLED scores compared to the dabigatran-warfarin and rivaroxaban-warfarin matched cohorts.

Next, there are design differences between clinical trials and "real-world" settings; subsequently, many factors may lead to disparity in findings between these settings.[41] The stringent criteria and controlled environment under which patients are chosen, as opposed to claims-based studies which apply more relaxed selection criteria, yield a much larger sample size for analysis. Also, outcomes in this claims analysis were based on patient claims, and in trials they were adjudicated. Moreover, the ineffective management of warfarin patients that are better controlled in the trial environment may be a reason for the increase in outcome events in the claims studies. In addition, we do not know if patients were appropriately dose-adjusted according to clinical factors since creatinine clearance and body weight are not available in the data. If doses are reduced inappropriately, there could be worse clinical outcomes.[42]

11.3. Interpretation

The current analysis suggested that apixaban patients had a 52% lower rate of stroke/SE and a 34% lower rate of MB compared with warfarin patients, which were similar to the safety

and efficacy findings between apixaban and warfarin in the ARISTOTLE trial.[21] Patients in the ARISTOTLE trial were further examined as ad-hoc analyses by stratifying patients with versus without CAD and with versus without PAD. In the ARISTOTLE trial, the effect of apixaban versus warfarin on stroke/SE (interaction p=0.52) and MB (interaction p =0.58) was similar among patients with and without PAD.[35] Apixaban was associated with a lower rate of stroke/SE (interaction p-value=0.11) and MB (interaction p-value=0.17) among patients with and without CAD compared to warfarin.[36] Dosage was not evaluated in the ad-hoc CAD and PAD studies but in the main ARISTOTLE trial there was no significant interaction for dosage and stroke/SE or MB.[21] Our study found that among CAD/PAD patients co-diagnosed with NVAF, apixaban use showed consistent results of lower stroke/SE, MB, and stroke/MI/ACM rates among those prescribed a standard dose and reduced dose versus warfarin.

A post-hoc analysis using data of the ROCKET AF study showed that patients with PAD had a significantly higher risk of MB with rivaroxaban versus warfarin, whereas those without PAD had a similar risk of MB (interaction p=0.037) while the risk of stroke/SE was similar for patients with and without PAD (p=0.84).[34]

In a post-hoc analysis of the RE-LY trial data, both 110 mg and 150 mg dabigatran were associated with similar risks of stroke/SE and MB compared to warfarin among patients with prior CAD or MI.[37] Additionally, reduced-dose dabigatran (110mg dabigatran) treatment had similar rates of stroke/SE (p=0.45) and MB rates (p=0.35) compared to warfarin.[37] Although 110mg dabigatran is not approved in the United States, the current reduced-dose analysis (75mg dabigatran) showed that the rates of stroke/SE and MB were not significantly different between patients prescribed dabigatran and warfarin. These ad-hoc analyses evaluated NVAF patients with and without CAD/PAD; however, the estimates were based on a relatively small sample size. Our current analysis provides a much larger CAD/PAD population among the NVAF cohort.

Beyond randomized controlled trials, studies (such as real-world studies) have not explored DOACs vs DOACs extensively in the past. A recent observational study among NVAF patients leveraging data from the Humana database compared apixaban to dabigatran and rivaroxaban. The study results showed that apixaban had lower rates of any stroke/SE (HR; 0.72, p=0.003) and any MB (HR: 0.51, p<0.001) compared to rivaroxaban. However, no statistically significant differences were found between apixaban and dabigatran, in terms of stroke/SE and MB. On the contrary, in our analysis, apixaban was shown to have lower rates of stroke/SE and MB, compared to dabigatran as well. Dabigatran and rivaroxaban have both been evaluated in comparison to warfarin, as part of randomized controlled trials, sub-group analyses within trials, and few real-world studies.[19,28,43,44] The majority of the evidence supports that dabigatran and rivaroxaban are significantly efficacious and safer as compared

to warfarin. The current literature is devoid of evaluation of apixaban with other DOACs. The current assessment adds important evidence of real-world evaluations in the NVAF literature. We compared clinical endpoints comparing apixaban vs. dabigatran, apixaban vs. rivaroxaban, as well as dabigatran vs. rivaroxaban. Apixaban was found to have a 56% lower adjusted risk for stroke/SE compared to dabigatran and a 31% lower risk of stroke/SE compared to rivaroxaban. Compared to dabigatran and rivaroxaban, apixaban showed a similar risk reduction for the stroke/MI/ACM outcome of around 24% and 27%, respectively. However, findings in our study suggest that apixaban is clinically effective when compared to dabigatran and rivaroxaban and clinical trials comparing DOACs versus DOACs are warranted.

Based on this large Medicare enrolled NVAF and CAD/PAD patient population, our analysis suggested that compared to warfarin, apixaban and rivaroxaban were associated with lower risk of stroke/SE, while apixaban and dabigatran were associated with lower risk of MB. Apixaban was found to be more efficacious compared to dabigatran and rivaroxaban, while dabigatran was found to be safer than rivaroxaban.

One of the main strengths of this study is the large sample size and sufficient statistical power necessary to evaluate both effectiveness and safety. Based on this large Medicare-enrolled NVAF and CAD/PAD patient population, our analysis suggests that compared to warfarin, apixaban, and rivaroxaban use were associated with lower risk of stroke/SE. Apixaban was associated with lower risk of MB, whereas rivaroxaban was associated with a higher risk of MB when compared to warfarin. Results from sensitivity analyses were relatively consistent with our main findings.

12. CONCLUSIONS

In this large Medicare population, NVAF patients co-diagnosed with coronary artery disease and/or peripheral arterial disease were evaluated. This observational study analysis revealed that when compared to warfarin, apixaban was associated with a lower rate of stroke/systemic embolism, MB, all-cause mortality, and composite outcomes; dabigatran was associated with a lower rate of all-cause mortality and composite outcomes; rivaroxaban was associated with a lower rate of stroke/systemic embolism, all-cause mortality, and composite outcomes, and higher rate of MB compared to warfarin. In addition, compared to dabigatran and rivaroxaban, apixaban showed lower rates of stroke/SE, MB, and MACE composite outcome; compared to rivaroxaban, dabigatran had lower rate of MB and all-cause mortality but no differences in stroke/SE rates. Our findings from this observational analysis provide important insights regarding the use of oral anticoagulation therapy among patients diagnosed with atrial fibrillation and coronary artery disease/peripheral artery disease in a real-word setting and may help physicians in the decision-making process when treating this high-risk group of patients.

13. APPENDICES

Appendix 1: ***Refer to CT24-GSOP-RF29 NI Study Report Signatures.***

Appendix 2: Protocol attached as an object in the report.

Appendix 3: Supplemental Tables and Figures

Table 1. Baseline Characteristics Stratified by CAD only, PAD only and CAD and PAD after PSM (Medicare)

Table 2. Outcomes Characteristics Stratified by CAD only, PAD only and CAD and PAD after PSM

Table 3. Baseline Characteristics for low and standard dose patients

Table 4. Outcomes for low and standard dose patients

Table 5. PSM-Matched Baseline Characteristics for Low dose

Table 6. PSM-Matched Outcomes Characteristics for Low dose

Table 7. PSM-Matched Baseline Characteristics for Standard dose

Table 8. PSM-Matched Outcome Characteristics for Standard Dose

List of Figures

Figure 1. Unadjusted Kaplan Meier curve for incidence of stroke/SE

Figure 2. Unadjusted Kaplan Meier curve for incidence of Major Bleeding

14. REFERENCES

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

2 Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the US adult population. *Am J Cardiol*. 2013;112(18):1142-7.

3 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med*. 1987;147(9):1561-4.

4 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. *Stroke*. 1991;22(8): 983-8.

5 Jørgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. *Stroke*. 1996;27(10):1765-9.

6 Lamassa M, Di Carlo A, Pracucci G, et al. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project). *Stroke*. 2001;32(2):392-8.

7 Crijns HJ, Van Gelder IC, Van Gilst WH, Hillege H, Gosselink AM, Lie KI. Serial antiarrhythmic drug treatment to maintain sinus rhythm after electrical cardioversion for chronic atrial fibrillation or atrial flutter. *Am J Cardiol*.1991;68(4):335-41.

8 The AFFIRM Investigators. Baseline characteristics of patients with atrial fibrillation: The AFFIRM Study. *Am Heart J*. 2002;143(6):991-1001.

9 Lip GY, Beevers DG. ABC of atrial fibrillation. history, epidemiology, and importance of atrial fibrillation. *BMJ*. 1995;311(7016):1361-3.

10 Krahn AD, Manfreda J, Tate RB, Mathewson FA, Cuddy TE. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. *Am J Med*. 1995;98(5):476-84.

11 Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med*. 2009;360(7):668-78.

12 Kralev S, Schneider K, Lang S, Süselbeck T, Borggrefe M. Incidence and severity of coronary artery disease in patients with atrial fibrillation undergoing first-time coronary angiography. *PLoS One*. 2011;6(9):e24964.

[13] Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994;271(11):840-4.

[14] Vedovati MC, Becattini C, Agnelli G. Combined oral anticoagulants and antiplatelets: benefits and risks. *Intern Emerg Med*. 2010;5(4):281-90.

[15] Violi F, Lip GY, Basili S. Peripheral artery disease and atrial fibrillation: a potentially dangerous combination. *Intern Emerg Med*. 2011;7(3):213-8.

[16] Violi F, Daví G, Hiatt W, et al. Prevalence of peripheral artery disease by abnormal ankle-brachial index in atrial fibrillation. *J Am Coll Cardiol*. 2013;62(23):2255-6.

[17] Lin YS, Tung TH, Wang J, et al. Peripheral arterial disease and atrial fibrillation and risk of stroke, heart failure hospitalization and cardiovascular death: a nationwide cohort study. *Int J Cardiol*. 2016;203:204-11.

[18] Marte T, Saely CH, Schmid F, Koch L, Drexel H. Effectiveness of atrial fibrillation as an independent predictor of death and coronary events in patients having coronary angiography. *Am J Cardiol*. 2009;103(1):36-40.

[19] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-51.

[20] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883-91.

[21] Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981-92.

[22] Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093-104.

[23] Lauffenburger JC, Farley JF, Gehi AK, Rhoney DH, Brookhart MA, Fang G. Effectiveness and safety of dabigatran and warfarin in real-world US patients with non-valvular atrial fibrillation: a retrospective cohort study. *J Am Heart Assoc*. 2015;4(4):e001798.

[24] Lip GY, Keshishian A, Kamble S, et al. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. a propensity score matched analysis. *Thromb Haemost*. 2016;116(5):975-86.

[25] Villines TC, Schnee J, Fraeman K, et al. A comparison of the safety and effectiveness of dabigatran and warfarin in non-valvular atrial fibrillation patients in a large healthcare system. *Thromb Haemost*. 2015;114(6):1290-8.

[26] Laliberté F, Cloutier M, Nelson WW, et al. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. *Curr Med Res Opin*. 2014;30(7):1317-25.

[27] Noseworthy PA, Yao X, Abraham NS, Sangaralingham LR, McBane RD, Shah ND. Direct comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in nonvalvular atrial fibrillation. *Chest*. 2016;150(6):1302-12.

[28] Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *J Am Heart Assoc*. 2016;5(6):e003725.

[29] Bai Y, Deng H, Shantsila A, Lip GYH. Rivaroxaban versus dabigatran or warfarin in real-world studies of stroke prevention in atrial fibrillation. *Stroke*. 2017;48(4):970-6.

[30] Bai Y, Shi XB, Ma CS, Lip GYH. Meta-Analysis of effectiveness and safety of oral anticoagulants in atrial fibrillation with focus on apixaban. *Am J Cardiol*. 2017;120(9):1689-95.

[31] Ntaios G, Papavasileiou V, Makaritsis K, Vemmos K, Michel P, Lip GYH. Real-world setting comparison of nonvitamin-K antagonist oral anticoagulants versus vitamin-K antagonists for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. *Stroke*. 2017;48(9)2494-503.

[32] Deitelzweig S, Farmer C, Luo X, et al. Risk of major bleeding in patients with non-valvular atrial fibrillation treated with oral anticoagulants: a systematic review of real-world observational studies. *Curr Med Res Opin*. 2017;33(9):1583-94.

[33] Li XS, Deitelzweig S, Keshishian A, et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in "real-world" clinical practice. a propensity-matched analysis of 76,940 patients. *Thromb Haemost*. 2017;117(6):1072-82.

[34] Jones WS, Hellkamp AS, Halperin J, et al. Efficacy and safety of rivaroxaban compared with warfarin in patients with peripheral artery disease and non-valvular atrial fibrillation: insights from ROCKET AF. *Eur Heart J*. 2014;35(4):242-9.

[35] Hu PT, Lopes RD, Stevens SR, et al. Efficacy and safety of apixaban compared with warfarin in patients with atrial fibrillation and peripheral artery disease: insights from the ARISTOTLE trial. *J Am Heart Assoc*. 2017;6(1):e004699.

[36] Bahit MC, Lopes RD, Wojdyla DM, et al. Apixaban in patients with atrial fibrillation and prior coronary artery disease: insights from the ARISTOTLE trial. *Int J Cardiol*. 2013;170(2):215-20.

[37] Hohnloser SH, Oldgren J, Yang S, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial. *Circulation*.2012;125(5):669-76.

[38] Pan X, Kachroo S, Liu JXC, et al. Real-world discontinuation among early users of apixaban, dabigatran, rivaroxaban or warfarin among atrial fibrillation patients newly initiated on anticoagulation therapy: tell of first 200 days. *Eur Heart J*. 2014;35(Abstract Supplement):897.

[39] Teutsch C, Huisman MV, Lip GYH, et al. Persistence with dabigatran therapy for stroke prevention in patients with non-valvular atrial fibrillation: The Gloria-AF Registry. *Blood*. 2016;128(22):2616.

[40] Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41-55.

[41] Freedman B, Lip GY. "Unreal world" or "real world" data in oral anticoagulant treatment of atrial fibrillation. *Thromb Haemost*. 2016;116(4):587-9.

[42] Steinberg BA, Shrader P, Thomas L, et al. Off-label dosing of non-vitamin K antagonist oral anticoagulations and adverse outcomes: the ORBIT-AF II Registry. *J Am Coll Cardiol*. 2016;68(24):2597-604.

[43] Mahaffey KW, Wojdyla D, Hankey GJ, White HD, Nessel CC, Piccini JP, Patel MR, Berkowitz SD, Becker RC, Halperin JL, Singer DE. Clinical Outcomes With Rivaroxaban in Patients Transitioned From Vitamin K Antagonist Therapy: A Subgroup Analysis of a Randomized Trial. *Ann Internal Med*. 2013;158(12):861-8.

[44] Wang SV, Franklin JM, Glynn RJ, Schneeweiss S, Eddings W, Gagne JJ. Prediction of rates of thromboembolic and major bleeding outcomes with dabigatran or warfarin among patients with atrial fibrillation: new initiator cohort study. *BMJ Open*. 2016;353:i2607.