NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Real-world Comparisons of Stroke, Major Bleeding, Myocardial Infarction, Acute Limb Ischemia and Death among Non-Valvular Atrial Fibrillation Patients Diagnosed With Coronary Artery Disease/Peripheral Arterial Disease who Initiated Oral Anticoagulation Therapies
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Research question and objectives	Aim 1: To compare the risk of myocardial infarction, stroke, acute limb ischemia, all-cause death and a composite of these endpoints among patients initiating OACs (warfarin, apixaban, rivaroxaban and dabigatran) Aim 2: To compare the risk of major bleeding, among patients initiating OACs Aim 3**:** To compare the risk of stroke and stroke/SE among patients initiating different OACs Aim 4: To compare healthcare resource utilization and costs among patients initiating OACs Aim 5: To compare the baseline demographic and clinical characteristics among patients initiating OACs.

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AF	Atrial Fibrillation
NVAF	Non-valvular Atrial Fibrillation
CCI	Charlson Comorbidity Index
CAD	Coronary Artery Disease
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
DOAC	Direct Oral Anticoagulant
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	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
ICD-9 CM	International Classification of Diseases – Clinical Modification, 9th Revision
PSM	Propensity Score Matching
MB	Major Bleeding
NDC	National Drug Code
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

2. RESPONSIBLE PARTIES

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ABSTRACT

Title: Real-world Comparisons of Stroke, Major Bleeding, Myocardial Infarction, Acute Limb Ischemia and Death among Non-Valvular Atrial Fibrillation Patients who Initiated Oral Anticoagulation Therapies

Version: 1.0
Date of Protocol: May 4, 2017

Rationale and background: Non-valvular atrial fibrillation (NVAF) has long been identified as a significant risk factor for disabling or fatal ischemic stroke and systemic embolism. There is a high prevalence of coronary artery disease (CAD) and peripheral arterial disease (PAD) among NVAF patients. In recent years, several new direct oral anticoagulants (DOACs) have been developed and these drugs were found to be at least as effective as warfarin to reduce stroke risk, and have lower or similar risk of bleeding in NVAF patients. These drugs do not require regular monitoring, without the inconvenience associated with warfarin. While there are clinical trials underway to evaluate the use of antithrombotic agents as secondary prevention among subpopulations, there is insufficient evidence in the real-world clinical setting regarding these new treatments in the high risk subpopulations of NVAF patients such as those with CAD or PAD; therefore, further research is necessary. Moreover, the clinical burden of NVAF is expected to double in the near future, with significant increases in morbidity and mortality. Understanding treatment outcomes among NVAF patients with CAD or PAD is critical to develop effective strategies to reduce the overall disease burden in this subpopulation. This study will evaluate the patient profiles, current antithrombotic patterns and real-world clinical outcomes among NVAF patients with CAD and/or PAD.

Objectives:

Aim 1: To compare the risk of myocardial infarction (MI), stroke, acute limb ischemia, all-cause death and a composite of these endpoints among patients initiating OACs (warfarin, apixaban, rivaroxaban and dabigatran).

Aim 2: To compare the risk of major bleeding among patients initiating OACs.

Aim 3: To compare the risk of stroke and stroke/SE among patients initiating OACs.

Aim 4: To compare healthcare resource use and costs among patients initiating different OACs.

Aim 5: To describe the baseline demographic and clinical characteristics among patients initiating OACs (warfarin, apixaban, rivaroxaban and dabigatran)

Study design: The study will be a longitudinal retrospective cohort analysis using the CMS fee-for-service (FFS) Medicare database. The study period will be from January 1, 2012

through December 31, 2014 or until the last date of the data cut available at the time of execution of the study. The study allows for a 12-month baseline period prior to the identification period that will be from January 1, 2013 through December 31, 2014 or until the last date of the data cut available at the time of execution of the study. For patients with a DOAC prescription, the first DOAC (apixaban, dabigatran, or rivaroxaban) prescription to occur during the identification period will be defined as the index event. For patients who were only prescribed warfarin and had no claims of DOACs, the date of first warfarin claim will be defined as the index date. In general, to avoid mixing the index event into the patient follow-up period, the follow-up period will begin 1 day after the index date.

Population: Elderly (≥65 years) NVAF patients diagnosed with CAD/PAD in the Medicare population, who were prescribed an OAC between January 1, 2013 and December 31, 2014 and had continuous health plan enrolment during their baseline and follow-up period will be included in the study. Patients will be followed 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 is earlier.

Variables: Demographic and clinical characteristics, clinical treatment patterns, economic outcomes, and clinical outcomes including major bleeding, MI, acute limb ischemia, stroke, stroke/SE, death and a composite of these endpoints will be determined and compared between OAC treatments among NVAF patients who were prescribed apixaban, dabigatran, rivaroxaban, or warfarin. Baseline demographic and clinical characteristics include: age, gender, geographic region, CCI score, $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores, prior bleed/stroke events, comorbid conditions and medication use. Baseline and follow-up healthcare resource utilization and costs will also be calculated.

Data sources: The study will be conducted using member enrollment, medical and pharmacy claims, from the Medicare database, a large national FFS claims database.

Study size: All eligible patients available for analysis will be included. Using the feasibility Major Adverse Cardiac Events (MACE) outcome rates of 6.2% and 14.3% per year for apixaban and warfarin users, respectively, a survival analysis of MACE would need 452 patients in each group. Using the feasibility major bleeding rate of 2.04% per year in the apixaban group and 4.3% per year in the warfarin group, a survival analysis of major bleeding would need 1,737 patients in each group. The sample size calculation used the assumptions of an alpha of 0.05, power of 80%, an accrual period (i.e. the time period when patients are identified until study end [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 assumes a uniform accrual and loss to follow-up during the identification period. To compute adjusted proportional HR in the PSM analysis, we will need robust variance estimation to be used and thus, the sample size presented here may be overestimated.

Data analysis: Means, medians, and standard deviations will be provided for continuous variables. Numbers and percentages will be provided for dichotomous and polychotomous variables. Bivariate comparisons of baseline characteristics and outcomes measures will be

provided. Appropriate tests (e.g., t-test, chi-square test) will be used based on the distribution of the measure. The cumulative incidence rate for clinical outcomes (major bleeding event, and stroke) will be calculated. Propensity score matching will be used to balance patient characteristics of the cohorts. Cox regression models will be used to evaluate the risk of clinical outcomes. Generalized linear models and two-part models will be used to compare health care costs between the OAC cohorts. Data analysis will be executed using statistical software SAS version 9.3/9.4.

3. AMENDMENTS AND UPDATES

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

4. MILESTONES

Milestones	Planned Completion Date
Completion of feasibility assessment	April 2017
Completion of protocol development	May 2017
Completion of main analysis for CAD/PAD	June 2017
Submit abstract for American College of Cardiology	October 2017
Manuscript Submission	August-September 2017

5. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) is a medical condition characterized by chaotic and irregular electrical activity in the upper chambers of the heart. It is the most common heart dysrhythmia diagnosed in the United States.[1] In 2010 there were an estimated 5.2 million cases of AF and the number of AF cases is projected to increase to 12.1 million cases in 2030.[2] AF prevalence has increased with an increasingly aging population in the United States and is expected to continue this trend substantially in the coming decades.[3]

AF increases the risk of stroke by five fold and is associated with 15-20% of all strokes.[4,5] In addition, strokes occurring among AF patients are deemed to be more severe – with lower discharge rate, higher risk of functional or neurological deficits and higher mortality rate.[6,7] With AF being more prevalent in the aging population, this cohort has a high likelihood of being diagnosed with coronary arterial disease (CAD).[8,9] In addition, previous literature has shown that the prevalence of CAD among AF diagnosed patients is quite high, ranging between 18-45%.[10,11,12,13,14] Additionally, a high prevalence of peripheral artery disease (PAD) has been found in AF diagnosed patients compared to non-AF patients.[15,16]

Previous study showed that patients diagnosed with CAD, in conjunction with AF, had an increased 10-year mortality rate as compared to those without AF (43% vs. 19%, $p<0.001$); in addition, AF was shown to be an independent predictor of all-cause mortality among CAD patients (adjusted HR: 1.45, 95% CI: 1.20-1.76).[17] AF and PAD have been found to be independently associated with increased stroke risk, heart failure-related hospitalization, and cardiovascular death; however, significant interaction effects of PAD and AF on these outcomes were not seen.[18] Therefore, CAD and PAD are two frequent comorbidities that are often presented in conjunction with AF to have a significant impact on outcomes such as stroke, myocardial infarction (MI) and death.

It is challenging to manage AF patients with CAD or PAD. Oral anticoagulants (OACs) have been used for stroke prevention of AF patients. Additionally, antiplatelet therapy has been used to prevent major cardiovascular events among patients with CAD or PAD.[19,20] For AF patients who have acute coronary syndrome (ACS) and/or are among those receiving a coronary stent, a short-term triple therapy of OAC, clopidogrel, and aspirin is recommended; on the other hand, monotherapy OAC is recommended for those AF patients without ACS/coronary stents.[21]Dual antiplatelet therapy (aspirin + $P2Y_{12}$ inhibitors) for primary prevention of stroke among NVAF, as an alternative to OACs, is therefore not recommended for patients without ACS or those not requiring revascularization techniques since it was shown to have similar risk of bleeding rates as OACs.[22,23,24,25]

In recent years, four direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, and edoxaban) have been approved for stroke prevention among patients with non-valvular atrial fibrillation (NVAF) in the United States (US). NVAF is the most common type of AF. In clinical trials, DOACs have been shown to be at least as safe and effective as warfarin with apixaban being the only DOAC showing superior efficacy and safety as compared to warfarin among patients with NVAF.[26,27,28] How DOACs perform among NVAF patients with CAD or PAD remains to be understood.

A comparative effectiveness study on NVAF patients with CAD or PAD who were treated with DOACs is important for identifying effective treatment regimen for this high-risk subpopulation. This protocol will examine the risk of stroke, MI, major bleeding, acute limb ischemia, all-cause mortality and composite outcomes (major adverse cardiac event(s) [MACE]: ischemic stroke, MI, and all-cause death; and MACE plus acute limb ischemia), stroke/SE, and healthcare resource utilization and costs among NVAF Medicare enrollees diagnosed with CAD/PAD and prescribed warfarin, dabigatran, rivaroxaban, and apixaban.

6. RESEARCH METHODS

The following aims will be addressed:

Aim 1: To compare the risk of MI, stroke, acute limb ischemia, all-cause death and a composite of these endpoints among patients initiating OACs.

Aim 2: To compare the risk of major bleeding among patients initiating OACs.

Aim 3: To compare the risk of stroke and stroke/SE among patients initiating OACs.

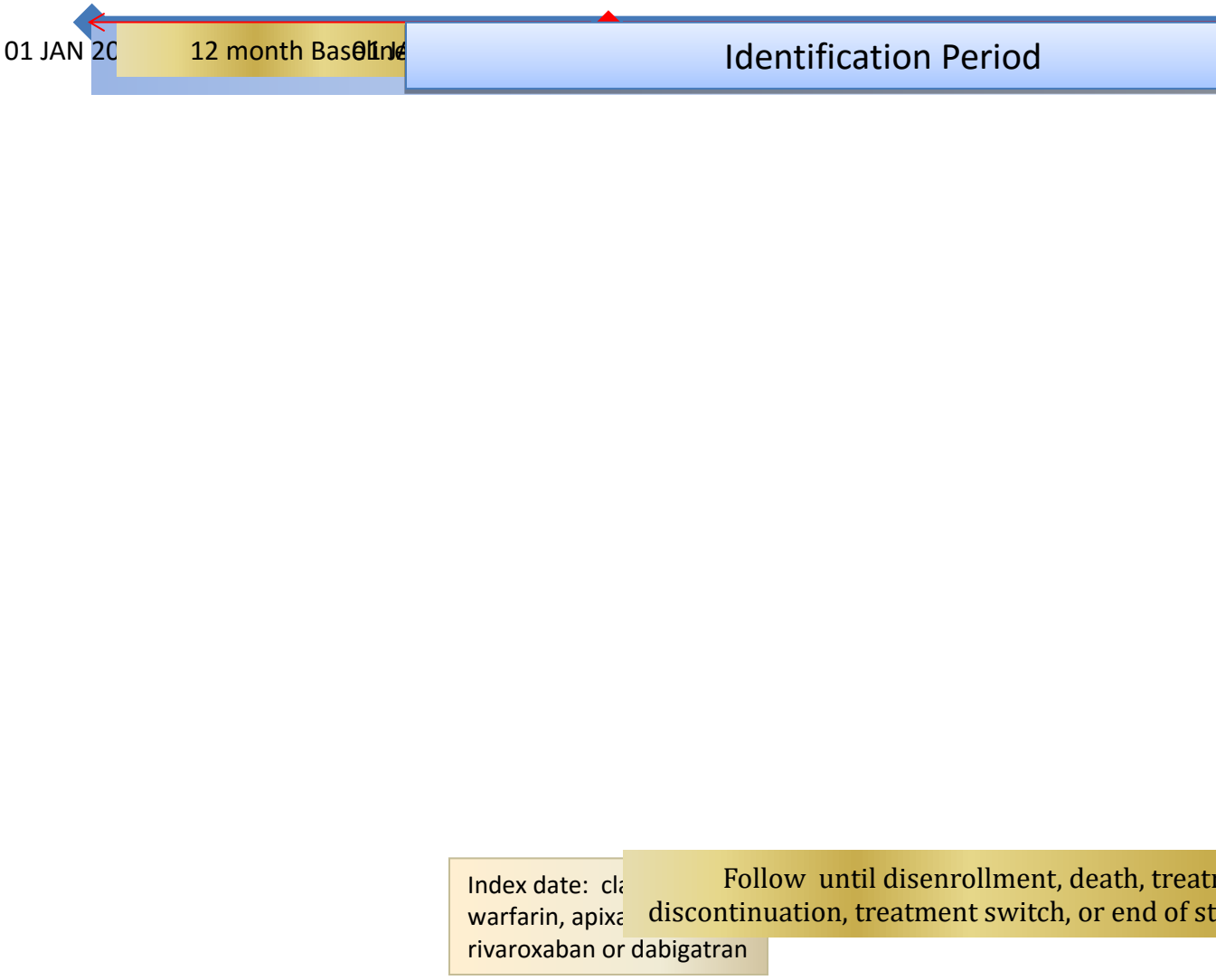
Aim 4: To compare healthcare resource utilization and costs among patients initiating OACs.

Aim 5: To compare the baseline demographic and clinical characteristics among patients initiating OACs.

6.1. Study design

The study will be a longitudinal retrospective cohort analysis using the 100% CMS Medicare fee-for-service (FFS) database. Demographics, clinical characteristics, clinical outcomes (including stroke, SE, MI, major bleeding, acute limb ischemia, all-cause mortality, ischemic stroke, and composite outcomes (MACE, MACE plus acute limb ischemia), and economic outcomes will be determined and compared among NVAF patients who were prescribed warfarin, apixaban, dabigatran, or rivaroxaban. The study period will be from January 1, 2012 through December 31, 2014 or until the last date of the data cut available at the time of execution of the study. The study allows for a 12-month baseline period prior to the identification period (January 1, 2013 through December 31, 2014, or until the last date of the data cut available at the time of execution of the study). For patients with a DOAC prescription, the date of the earliest DOAC prescription (apixaban, dabigatran or rivaroxaban) to occur during the identification period (index event) will be defined as the index date. For patients who were only prescribed warfarin and had no DOAC claims, the first warfarin claim during the identification period will be defined as the index date.

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



6.2. Setting

Adult patients who were prescribed OACs will be selected from the Medicare database between January 1, 2013 and December 31, 2014 or until the last date of the data cut available at the time of execution of the study. For patients with a DOAC prescription, the first DOAC (apixaban, dabigatran, or rivaroxaban) prescription to occur during this period will be defined as the index event. For patients who were only prescribed warfarin and had no claims of DOACs, the date of first warfarin claim will be defined as the index date. Patients will be required to have an AF diagnosis before or on the index date as well as continuous health plan enrolment for 12 months prior to and on the index date (baseline period) to ensure that the patients' complete medical history is available. In addition, patients will be required to be at least 65 years on the index date. Patients will be assessed from the day after the index date until the earliest of the following dates: 30 days after the date of

discontinuation, switch, death, end of study period, or end of continuous medical and pharmacy enrollment, whichever is earlier.

6.2.1. Inclusion criteria

Patients will be included in the study if they:

a) had ≥1 pharmacy claim for apixaban, dabigatran, rivaroxaban or warfarin during the identification period (01JAN2013-31DEC2014). For patients with a DOAC prescription, the first DOAC (apixaban, dabigatran, or rivaroxaban) pharmacy claim date during the identification period will be designated as the index date. The first warfarin prescription date will be designated as the index date for patients who were only prescribed 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 ICD-9-CM code in Appendix, 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.

6.2.2. Exclusion criteria

Patients will be 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 1.

Follow Up:

The follow-up period will be defined as the time period between the day after the index date and end of study period (31-December-2014 or last date of the last data cut available at the time of execution of the study). Patients will be followed 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 is earlier.

To assess first major bleeding, stroke/SE, MI, acute limb ischemia or death event, patient will be censored at first occurrence of either event occurring anytime during period on 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 is earlier.

Discontinuation:

Discontinuation will be defined as no evidence of index OAC prescription for 30 days from the last day of days' supply of last filled prescription.[29,30] The date of discontinuation will be the last day of days' supply of last filled prescription. The follow-up will be censored at 30 days after the index drug discontinuation date.

Switch

Atrial fibrillation patients that receive a prescription for an OAC (warfarin, apixaban, dabigatran or rivaroxaban) other than the index OAC drug prescription during the follow-up period will be considered switchers if this OAC prescription is within ± 30 days of last days' supply. The follow-up will be censored at the switching of the index drug.

6.1.3. Cohorts

After applying the inclusion and exclusion criteria, eligible patients will be 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.

6.3. Variables

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

Variable	Role	Operational definition
Age	Baseline characteristic and potential confounder	Age will be 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 will be created for female beneficiaries and reported as a percentage.
US Geographic Region	Baseline characteristic and potential confounder	The United States will be divided into five regions: Northeast, South, North Central, West and Other. Geographic region will be captured

		from enrollment data.
Prior Stroke/SE	Baseline characteristic and potential confounder	A flag will be created for patients who had a stroke/SE claim during the baseline period. (See Table, Appendix 1 for codes)
Ischemic Stroke	Baseline characteristics and potential confounder	A flag will be created for patients who had an ischemic stroke (primary inpatient discharge codes) claim 1 month prior to index date during the baseline period. (See Table 1, Appendix 1 for codes)
Hemorrhagic stroke	Baseline characteristic and potential confounder	A flag will be created for patients who had a hemorrhagic stroke (primary inpatient discharge codes) claim 1 month prior to index date during the baseline period (See Table 1, Appendix 1 for codes)
Lacunar stroke	Baseline characteristic and potential confounder	A flag will be created for patients who had a lacunar stroke claim during the baseline period (See Table 1, Appendix 1 for codes)
Congestive Heart Failure	Baseline characteristic and potential confounder	A flag will be created for patients with claims for congestive heart failure in the baseline period. (See Table 1, Appendix 1 for codes)
Diabetes	Baseline characteristic and potential confounder	A flag will be created for patients with claims for diabetes in the baseline period. (See Table 1, Appendix 1 for codes)
Hypertension	Baseline characteristic and potential confounder	A flag will be created for patients with claims for hypertension in the baseline period. (See Table 1, Appendix 1 for codes)
Renal Disease	Baseline characteristic and potential confounder	A flag will be created for patients with claims for renal disease in the baseline period. A flag for chronic kidney disease stage V, ESRD or dialysis will be created in baseline period. (See Table 1, Appendix 1 for codes)
Liver Disease	Baseline characteristic and potential confounder	A flag will be created for patients with claims for liver disease in the baseline period. (See Table 1, Appendix 1 for codes)
Myocardial Infarction	Baseline characteristic and potential confounder	A flag will be created for patients with claims for myocardial infarction in the baseline period. (See Table 1, Appendix 1 for codes).
Hospitalized Myocardial Infarction	Baseline characteristic and potential confounder	A flag will be created for patients with claims for myocardial infarction during a hospitalization in the baseline period. (See Table 1, Appendix 1 for codes).
Dyspepsia or Stomach Discomfort	Baseline characteristic and potential confounder	A flag will be created for patients with claims for dyspepsia or stomach discomfort in the baseline period. (See Table 1, Appendix 1 for codes)
Non-stroke/SE	Baseline characteristic	A flag will be created for patients with claims

Peripheral vascular disease	and potential confounder	for peripheral vascular disease in the baseline period. (See Table 1, Appendix 1 for codes)
Transient Ischemic Attack	Baseline characteristic and potential confounder	A flag will be created for patients with claims for transient ischemic attack in the baseline period. (See Table 1, Appendix 1 for codes)
Anemia and Coagulation defects	Baseline characteristic and potential confounder	A flag will be created for patients with claims for anemia and coagulation defects in the baseline period. (See Table 1, Appendix 1 for codes)
Alcoholism	Baseline characteristic and potential confounder	A flag will be created for patients with claims for alcoholism in the baseline period (See Table 1, Appendix 1 for codes)
CAD only	Baseline characteristic and potential confounder	A flag will be created for patients with claims for CAD only and no PAD in the baseline period. (See Table 1, Appendix 1 for codes)
PAD only	Baseline characteristic and potential confounder	A flag will be created for patients with claims for PAD only and no CAD in the baseline period. (See Table 1, Appendix 1 for codes)
CAD and PAD	Baseline characteristic and potential confounder	A flag will be created for patients with claims for CAD and PAD in the baseline period. (See Table 1, Appendix 1 for codes)
Coronary Bypass surgery (CABG)	Baseline characteristic and potential confounder	A flag will be created for patients with claims for CABG. (See Table 1, Appendix 1 for codes)
Percutaneous Coronary Intervention (PCI)	Baseline characteristic and potential confounder	A flag will be created for patients with claims for PCI. (See Table 1, Appendix 1 for codes)
Systolic Heart Failure	Baseline characteristic and potential confounder	A flag will be created for patients with claims for systolic HF and combined systolic and diastolic HF. (See Table 1, Appendix 1 for codes)
Baseline Prior Bleed	Baseline characteristic and potential confounder	A flag will be created for patients who had a bleeding-related claim during the baseline period. (See Table 2, Appendix 1 for codes)
Baseline Deyo-Charlson Comorbidity Index	Baseline characteristic and potential confounder	The Deyo-Charlson Comorbidity Index will be created for the baseline period (See Table 3, Appendix 1 for codes)
Baseline $CHADS_2$	Baseline characteristic and potential confounder	The $CHADS_2$ score will be used to analyze the effect of stroke risk stratification on OAC use. The maximum score is 6. $CHADS_2$ scores: 0, 1,2, ≥3 (See Table 4, Appendix 1 for codes)
Baseline CHA_2DS_2-VASc Score	Baseline characteristic and potential confounder	The CHA_2DS_2VASc score will be 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 (See Table 5, Appendix 1 for codes)
HAS-BLED Score	Baseline characteristic	HAS-BLED score will be used to estimate the

	and potential confounder	risk of major bleeding for patients (See Table 6, Appendix 1 for codes)
Anti-Platelet therapies	Baseline characteristic and potential confounder	A flag will be created for patients with prescription fills for anti-platelet therapies (abciximab, anagrelide, cilostazol, clopidogrel, dipyridamole, eptifibatide, prasugrel, ticagrelor, ticlopidine and tirofiban). (See Table 7, Appendix 1 for codes)
Other Baseline Medications	Baseline characteristic and potential confounder	Flags will be 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.
Healthcare Resource Utilization	Baseline characteristic and potential confounder	All-cause utilization variables will be computed for inpatient, outpatient, ER, office, SNF, DME, HHA, hospice, and part D pharmacy claims.
Healthcare Costs	Baseline characteristic and potential confounder	Healthcare cost will include 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 mg) based on dose of the initial prescription of DOAC

[a] Baseline variables will be evaluated using codes in any position (primary or secondary) unless noted otherwise

Table 2. Descriptive Outcome Variables in the CAD/PAD Population

Variable	Role	Operational definition
Stroke	Outcome variable	Stroke will be 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 will be a dichotomous variable that equals 1 if there is ≥ 1 stroke event during the follow-up period. Time to the first stroke event will be calculated. (See Table 1, Appendix 1 for codes)
Stroke/SE	Outcome variable	Stroke/SE will be 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 will

		be a dichotomous variable that equals 1 if there is ≥ 1 stroke/SE event during the follow-up period. Time to the first stroke/SE event will be calculated. The first stroke/SE event will be stratified by ischemic stroke, hemorrhagic stroke, and SE. (See Table 1, Appendix 1 for codes)
Ischemic Stroke	Outcome variable	Ischemic stroke will be 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 will be a dichotomous variable that equals 1 if there is ≥ 1 stroke event during the follow-up period. Time to the first stroke event will be calculated. (See Table 1, Appendix 1 for codes)
Myocardial Infarction	Outcome variable	MI events observed during follow-up will be identified using hospital discharge records which had a MI 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. MI event will be a dichotomous variable that equals 1 if there is ≥ 1 MI event during the follow-up period. Time to the first MI event will be calculated. (See Table 1, Appendix 1 for codes)
Acute Limb Ischemia	Outcome variable	Acute limb ischemia event observed during follow-up will be 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 will be a dichotomous variable that equals 1 if there is ≥ 1 acute limb ischemia event during the follow-up period. Time to the first acute limb ischemia event will be calculated (See Table 1, Appendix 1 for codes)
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 will be identified. Death will be a dichotomous variable that equals 1 if there is a death event or 0, if otherwise. Time to the first death event will be calculated.
Major Bleeding	Outcome variable	A major bleeding event observed during follow-up will be identified using hospital discharge records which had a major bleeding diagnosis as

		the primary discharge diagnosis as listed by ICD-9-CM diagnosis 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 will be a dichotomous variable that equals 1 if there is ≥ 1 bleeding event during the follow-up period. Time to the first major bleeding event will be calculated. Major bleeding will be stratified by gastrointestinal bleeding, intracranial hemorrhage and other bleeding. (See Tables 1 and 2, Appendix 1 for codes)
MACE	Composite Outcome	A composite outcome of stroke, MI, and all-cause death will be evaluated. The frequency and time to the first occurrence of stroke, MI, or all-cause death will be calculated
MACE plus Acute Limb Ischemia	Composite Outcome	The frequency and time to the first occurrence of ischemic stroke, MI, acute limb ischemia, and all-cause death will be calculated
Follow-up All-cause Health Care Costs	Outcome	All-cause health care costs in the follow-up period will be computed for inpatient, outpatient, ER, office, SNF, DME, HHA, hospice, and part D pharmacy costs. Costs will be adjusted to 2014 U.S. dollars using the CPI medical care component. Total medical and total health care costs will be calculated per patient per month (PPPM).
Follow-up All-cause Health Care Utilization	Outcome	All-cause health utilizatione costs in the follow-up period will be computed for inpatient, outpatient, ER, office, SNF, DME, HHA, hospice, and part D pharmacy claims.
First Major Bleeding-related Hospitalization Costs	Outcome	First major bleeding-related hospitalization costs will be defined as hospitalization costs associated with the first major bleeding event in the follow-up period.
First Stroke/SE-related Hospitalization Costs	Outcome	First stroke/SE-related hospitalization costs will be defined as hospitalization costs associated with the first stroke/SE event in the follow-up period.
First Stroke/MI-related Hospitalization Costs	Outcome	First stroke/MI-related hospitalization costs will be defined as hospitalization costs associated with the first stroke or MI event in the follow-up period.
Follow-up Bleeding	Outcome	Bleeding-related medical costs will be defined as

related Medical Costs		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 will be 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 will be 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 will be 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 will be reported.
Switch	Treatment Pattern outcome	Percentage of patients who switched to a non-index OAC and time-to-switch will be reported.

6.4. Sub-group and Sensitivity Analyses

Given enough sample size

, subgroup analysis and/or sensitivity analysis will be considered, including the following but not limited to:

- **Type of CAD and PAD:** PAD only, CAD only, CAD and PAD;
- **Baseline characteristics**: Congestive heart failure, systolic heart failure, MI, etc;
- **Anti-Platelet therapy use**: Baseline anti-platelet use; follow-up concurrent - antiplatelet use, where anti-platelet use may be included as a time-dependent variable. Patients on DOACs and anti-platelet use may also be tested as an interaction; and
- **Dose**: Sub-group analysis among standard and low doses for each of the comparators may be evaluated.

6.5. Data source

100% CMS Medicare data will be used for the purposes of this analysis. The following files will be 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 will 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).

All Medicare files described above can be linked by de-identified patient ID, and will be included in the same CMS access request. Data are collected on an ongoing basis with the files constructed on an annual basis. It does not contain data on all beneficiaries ever entitled to Medicare. The file contains data only for beneficiaries who were entitled during the year of the data. These data are available annually in May of the current year for the previous year.

6.6. Study size

The sample size was calculated for survival analysis comparing the differences in MACE outcome and major bleeding 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 assumes 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 major bleeding 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 major bleeding would require 1,737 patients in each group. The sample size and event rates will be evaluated prior to proceeding with the analysis to determine if there is sufficient power

6.7. Data management

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

6.8. Data analysis

Means, medians, and standard deviations will be provided for continuous variables when performing descriptive analysis of continuous data. Numbers and percentages will be provided for dichotomous and polychotomous variables when performing descriptive analysis of categorical data. Bivariate comparisons of baseline characteristics and outcomes measures will be provided. Appropriate tests (eg, t-test, chi-square test) will be used based on the distribution of the measure. The cumulative incidence rate for clinical outcomes (major bleeding, MI, acute limb ischemia, stroke and mortality) will be calculated. The incidence rate will be calculated as the number of patients who experience the event divided by the observed time at risk. An unadjusted Kaplan Meier curve will be drawn to illustrate time-to-event analysis.

The propensity score matching (PSM) technique will be used to control for potential confounders when comparing the cohorts.[31] Each subject in the reference cohort will be 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 will be used to select the matched samples. The radius, kernel, and mahalanobis stratified matching techniques will also be evaluated to find the one that best fits the data. The balance of covariates between treatment groups will be determined using the absolute standardize difference of the mean ≤ 0.10

After PSM, no significant differences are expected among all pre-index measures between the patient cohorts, and the treatment effect calculated based on the matched population is considered to be the true effect. PSM with a different ratio (1:2 or 1:3) can also be considered if the matched sample size using a ratio of 1:1 is too small. Covariates to be included in the

logistic regression model will include variables such as age, geographic region, CCI score, comorbidities and other clinical characteristics such as bleeding history, renal disease etc. The final lists of variables to be used in the model will be discussed and determined during analysis development, after reviewing the pre-matched descriptive tables and post-matched pre-index measures.

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

A generalized linear model (GLM) will be applied for the multivariable analysis of healthcare costs among the warfarin, apixaban, dabigatran, and rivaroxaban cohorts. Since a large proportion of zeros usually exist in health care cost variables (e.g., major-bleeding costs, inpatient or ER costs), two-part models may also be 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 will be conducted to generate the 95% confidence interval.

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

6.9. Quality control

Data in Medicare Databases are collected periodically in an electronic format. Medicare employs a number of subsequent quality assurance procedures and undertakes routine audits to ensure the quality of information. The data analysis follows our good data analysis practices which have been demonstrated in many past research studies and publications. The analysis is also inspected with at least two independent researchers for quality control purposes.

6.10. Strengths and Limitations of the research methods

A key strength is that retrospective observational analyses provide a better understanding about the study population in real-world clinical practice and complimentary information to controlled clinical trials. Retrospective observational studies also allow evaluation of patients who are often under-represented in clinical trials, such as those with comorbidities and the elderly. Since prescribing patterns in the real-world can be complex, the retrospective analysis provides a comprehensive picture of how medications are used by clinicians in routine practice. In addition, the Medicare claims databases include all medical and pharmacy claims of patients and allow for longitudinal analysis of a nationally representative sample. Many of the medications being studied are relatively new to market and this database captures the utilization of these new drugs. The limitation of this study is that the Medicare databases do not uniformly capture over-the-counter medications, such as aspirin, which have also been 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 includes only FFS (fee-for-service) 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 does 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 will not be observed in the claims data. Third, presence of a diagnosis code on a medical claim is not positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease.

6.11. Other aspects

Not Applicable

7. PROTECTION OF HUMAN SUBJECTS

7.1. Patient Information and Consent

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

7.2. Patient Withdrawal

Not Applicable

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

IRB/IEC review is not required.

7.4. Ethical Conduct of the Study

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

8. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

9. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

10. COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer/BMS product, Pfizer/BMS should be informed immediately.

In addition, the investigator will inform Pfizer/BMS immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

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11. LIST OF TABLES

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APPENDIX 1. LIST OF RELEVANT ICD-9-CM DIAGNOSIS, CPT, HCPCS CODES

VARIABLE DEFINITIONS

DISEASE DEFINITIONS

Table 1. Variable Definitions Based on ICD-9, CPT and/or HCPCS Codes

Diagnosis	ICD-9 Code
Selection Criteria	
Atrial fibrillation	427.31
Valvular Heart Disease	394.0, 394.1, 394.2, 394.9, 396.0, 396.1, 396.8, 396.9, 424.0, 745.xx
VTE	DVT: ICD-9-CM codes: 451-453, 671.3, 671.4, 671.9; or PE: ICD-9-CM codes 415.1, 673.2, 673.8
Transient Atrial Fibrillation (Heart valve replacement/transplant, pericarditis, hyperthyroidism and thyrotoxicity	Heart valve replacement/transplant: V422, V433, 35.05-35.09, 35.20-35.28, 35.97 Pericarditis: 006.8, 017.9, 036.41, 074.21, 093.81, 098.83, 115.93, 390, 391, 392.0, 393, 411.0, 420.90, 420.91, 420.99, 423.0, 423.1, 423.2, 423.8, 423.9 Hyperthyroidism and Thyrotoxicity: 242.0, 242.1, 242.2, 242.3, 242.4, 242.8, 242.9
Pregnancy	630-679, V22, V23, V24, V27, V28, V61.6, V61.7, 792.3, 796.5; ICD-9-CM procedure codes:72-75.99 HCPCS codes: 59000-59350, 76801-76828, 83661-83664
Baseline Covariates	
Prior Stroke/SE	430.xx-432.xx, 433.x1, 434.x1, 436, 444.x, 445.x

Congestive Heart Failure (CHF)	428.xx
Diabetes Mellitus	250, 357.2, 362.0, 366.41
Hypertension	362.11, 401, 402, 403, 404, 405
Renal Disease	403, 404, 580-586
Chronic Kidney Disease, Stage V and ESRD	585.5, 585.6
Liver Disease	570-573
Myocardial Infarction	410, 411
Dyspepsia or Stomach Discomfort	787.1: Heartburn 789.0: Abdominal Pain 789.4: Abdominal Rigidity 789.6: Abdominal Tenderness 536.8: Dyspepsia
Non-Stroke/SE Peripheral Vascular Disease	412, 413, 414, 440, 441, 442, 443
Transient ischemic attack **(**TIA**)**	435
Coronary artery disease	410-414
Peripheral artery disease	443.8, 443.9, 440
Anemia and Coagulation Defects	280.xx-286.xx
Lacunar Stroke	434.91
Systolic Heart Failure	428.2x, 428.4x
Alcoholism	303.xx, 305.0x, V11.3x
CABG	ICD-9-CM Procedure Codes: 36.10-36.17, 36.19; CPT: 33510-33514, 33516-33519, 33521-33523, 33530, 33533-33536; HCPCS: S2205-S2209;

PCI	ICD-9-CM Procedure code: 00.66, 36.03, 36.04, 36.06, 36.07, 36.09, 17.55; CPT: 92980, 92981, 92982, 92984, 92995, 92996; HCPCS: G0290, G0291
Dialysis Codes	
ICD-9-CM Diagnosis	996.56, 996.68, 458.21, V45.11, V56.0-V56.2, V56.32, V56.8
ICD-9-CM Procedure	38.95, 39.27, 39.42, 39.43, 39.95, 54.98
CPT	49420, 49421, 90935, 90937, 90939, 90940, 90945, 90947, 93990, 99512, 36145, 36800, 36832-36833, 36810, 36815, 36831-833, 36838
HCPCS	A4653, A4671-73, A4719-A4726, A4728, A4760, A4765, A4766, A4860, A4880, A4900-01, A4905, A4674/80/90, A4700, A4705-A4709, A4712, A4714, A4730/40/50/55/70/74/80/90, A4800, A4801-A4802, A4820/50/70/90, A4918, A4919, A4929, E1600, E1610, E1615, E1620, E1625, E1635, E1636, E1630, E1632, E1634, E1638, E1640, E1510, E1520, E1530, E1540, E1550, E1560, E1575, E1580, E1590, E1592, E1594
Outcomes	
Major Gastrointestinal bleeding event	456.0, 456.20, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x Procedure Code: 44.43
Major Intracranial Hemorrhage (ICH)	430, 431, 432.0, 432.1, 432.9, , 852.0x, 852.2x, 852.4x, 853.0x,

Major Other hemorrhage	285.1, 360.43, 362.43, 362.81, 363.61, 363.62, 363.72, 364.41, 372.72, 374.81, 376.32, 377.42, 379.23, 423.0x, 596.7x, 599.7x, 602.1x, 620.1, 621.4, 626.2, 626.5, 626.7, 626.8, 626.9, 719.1x, 782.7, 784.7, 784.8, 786.3x, 958.2, 997.02, 998.11 Procedure codes: 99.04
Hemorrhagic Stroke	430.xx-432.xx. Cases will be excluded if traumatic brain injury (ICD-9: 800-804, 850-854) was present during hospitalization.
Ischemic Stroke	433.x1, 434.x1, 436
Systemic Embolism	444.x, 445.x
Acute Limb Ischemia	459.89, 459.9, 444.0, 444.22, 444.81, 444.21
Myocardial Infarction	410.xx

BLEEDING CODES

Table 2: ICD-9-Codes

Category	**ICD-9 Code(s)**
Gastrointestinal	ICD-9: 455.2, 455.5, 455.8, 456.0x, 456.2x, 459.0x, 530.21, 530.7x, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3x, 569.85, 569.86, 578.xx, 784.8 CPT: 43227, 43255, 43501, 44366, 44378, 44391, 45317, 45334, 45382, 46614 ICD-9 procedure: 44.43, 44.44, 44.49
Intracranial	430.xx, 431.xx, 432..xx, 852.xx, 853.xx, 854.xx

Other	Blood Transfusions HCPCS Codes: C1010, C1016, C1018, C1020, C1021, C9504, C9505, P9010, P9011, P9016, P9021, P9022, P9038, P9039, P9040, P9051, P9054, P9056, P9057, P9058, S3906 ICD-9: 99.03, 99.04 Facility Revenue Codes: 381, 382 336.1, 360.43, 362.43, 362.81, 363.72, 364.41, 363.61, 363.62, 377.42, 379.23, 423.x, 719.1x, 997.02, CPT: , 32658, 33020, 47350-47362, 65815, 65930 285.1, 376.32, 459.0x, 568.81, 573.8, 593.81, 596.7x, 599.7x, 790.01, 864.01, 865.01, 866.01, 958.2, 998.11 078.6, 246.3, 372.72, 374.81, 380.31, 602.1, 620.7, 621.4x, 623.6, 626.2, 640.xx, 641.9x, 666.10, 784.7x , 784.8x, 786.3 CPT codes: 30901, 30903, 30905, 31238, 42970 ICD-9: 21.01, 21.07

CHARLSON COMORBIDITY INDEX CODES

Table 3: Charlson Comorbidity Index

Comorbidity	ICD-9 Codes	Charlson Weight
Myocardial Infarction	410, 411	1
Congestive Heart Failure	402.x1, 404.x1, 404.x3, 428.xx	1
Peripheral vascular disease	412, 413, 414, 440, 441, 442, 443, 444, 445	1
Cerebrovascular disease	430-433, 435	1
Dementia	290, 291, 294	1
Chronic obstructive pulmonary disease	491-493	1

Rheumatologic disease	710, 714, 725	1
Peptic ulcer disease	531-534	1
Mild liver disease	571, 573	1
Diabetes	250 (excluding 250.4-250.6)	1
Hemiplegia or paraplegia	342, 434, 436, 437	2
Moderate or severe renal disease	403, 404, 580-586	2
Diabetes + complications	250.4-250.6	2
Malignancy	200, 202, 203	2
Moderate/severe liver disease	070, 570, 572	3
Metastatic solid tumor	196-199	6
AIDS	042-044	6

CHADS2 SCORE CODES

Table 4: $CHADS_2$-Score

$CHADS_2$	**ICD-9 Codes**
Congestive Heart Failure	402.x1, 404.x1, 404.x3, 428.xx
Hypertension	362.11, 401, 402, 403, 404, 405
Age≥ 75 years	-
Diabetes mellitus	250, 357.2, 362.0, 366.41
History of Stroke or Transient Ischemic Attack	433.x1, 434.x1, 436, 437.1, 437.9 362.34, 435

CHA2DS2-VASC SCORE CODES

Table 5: CHA_2DS_2-VASC Score Algorithm

CHA_2DS_2 –VASc	**ICD-9 Codes**
Congestive Heart Failure	402.x1, 404.x1, 404.x3, 428.xx
Hypertension	362.11, 401, 402, 403, 404, 405

Age≥ 75 years	-
Diabetes mellitus	250, 357.2, 362.0, 366.41
History of Stroke or Transient Ischemic Attack	433.x1, 434.x1, 436, 437.1, 437.9 362.34, 435
Vascular Disease	410, 411
Age 65-75 years	-
Sex Category	-

HAS-BLED SCORE

Table 6: HAS-BLED Score

HAS-BLED	ICD-9 Codes	Points Algorithm
Hypertension	401.xx-405.xx	1 point
Abnormal kidney and/or liver function:	Kidney: 580.xx-589.xx Liver: 570.xx-573.xx	1 point each
Stroke	History of stroke V12.54, 433.xx-435.xx	1 point
Bleeding	Baseline bleeding and 280.xx-286.xx	1 point
Labile INR	Not measurable.	Not applicable
Elderly	65+ years	1 point for age 65 or older
Alcohol/ Drug Therapy	303.xx, 305.0x, V11.3x	1 point

	Antiplatelets administered (abciximab, anagrelide HCL, aspirin, aspirin/dipyridamole, cilostazol, clopidogrel, dipyridamole, eptifibatide, prasugrel, ticagrelor, ticlopidine, tirofiban) NSAIDs administered (bromfenac, celecoxib, diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, lansoprazole/naproxen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tolmetin)	1 point

ANNEX 1. ADDITIONAL INFORMATION

Not Applicable