Safety and effectiveness evaluation of patients with non-valvular atrial fibrillation treated with OACs: Comparison between NOACs and warfarin (CER3) (B0661120)

Statistical Analysis Plan (SAP)

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable (first version, no amendments).

2 INTRODUCTION

Note: in this document any text taken directly from the Non-Interventional (NI) study protocol is ***in italic.***

Atrial fibrillation (AF) is characterized by a rapid, irregular heartbeat which can cause blood to pool in the atria and increase the risk of the formation of blood clots. AF affects 0.6% to 1.6% of the general population and up to 14% in cardiovascular clinics in Japan[1-3]. AF can be categorized into three main categories based on patient characteristics: lone atrial fibrillation – AF in the absence of overt cardiovascular disease or precipitating illness[9]; non-valvular AF (NVAF) – presence of AF without concurrent rheumatic mitral valve disease or history of mitral valve repair or prosthetic heart valve; and secondary AF-AF that occurs in the setting of acute myocardial infarction (MI), cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia, or other acute pulmonary disease. Anticoagulation therapy is important to prevent thromboembolism in patients with NVAF. Warfarin, a vitamin K antagonist, is the first oral anticoagulant approved for the treatment and prevention of thromboembolism in Japan in 1962 and it had long been the only oral anticoagulant until the first non-vitamin K antagonist oral anticoagulants (NOACs), dabigatran, was introduced with approval for NVAF treatment in March 2011, followed by rivaroxaban in January 2012, apixaban in December 2012, and edoxaban in September 2014 in Japan.

Although randomized control trials (RCTs) aimed at head-to-head comparison with placebo or a reference drug may provide evidence of safety and efficacy of treatments at the highest level, there are potential limitations derived from a limited number of pre-selected patients and strict patient eligibility criteria with regard to age, comorbidities, and concomitant medications. Accordingly, these studies may not accurately represent what happens when drugs are used in general clinical practice. Recently, in order to overcome the drawbacks of RCTs and corroborate the evidence from RCTs, real-world evaluations of drugs have been conducted. As for anticoagulants, there are some studies that have evaluated safety and effectiveness of NOACs such as apixaban, dabigatran, and rivaroxaban in the real-world setting and the results were similar to those obtained from RCTs[4-7]. However, these studies are not sufficient, especially for effectiveness evaluation, and real-world data (RWD) specific to each country or region are also required. For example, Asian populations, including Japanese population, are known to be more

[redacted]

prone to intracranial hemorrhage when treated with warfarin[10]. Japan is a rapidly aging society with a large proportion of the population aged 75 years or older. Unfortunately, there have been few large-scale, real-world studies to investigate safety and effectiveness of NOACs in patients with NVAF receiving NOACs versus warfarin in Japan.

The objective of this study is to compare the risk of incidence of stroke and bleeding among patients with NVAF newly prescribed any of NOACs (apixaban, dabigatran, edoxaban or rivaroxaban), versus newly prescribed warfarin using a nation-wide administrative claims database.

This retrospective study is conducted voluntarily by Pfizer. This study will not be conducted as post-authorization safety study (PASS) [redacted] *according to the decision by the business process owner* [redacted].

3 STUDY DESIGN

This is a retrospective observational study using data from the MDV database (data set from March 1st, 2011 to December 31st, 2017). Among patients registered in the database patients are selected based on the inclusion and exclusion criteria (see blow). The first observed prescription of apixaban, dabigatran, edoxaban, rivaroxaban or warfarin is used to identify the patient's index date (date of the first prescription of any OACs is defined as "index date") and treatment cohort. Study measures include: (1) for safety evaluation: major bleeding and any bleeding; (2) for effectiveness evaluation: a composite of ischemic stroke, hemorrhagic stroke or SE.
The follow-up period is variable, and will begin on the next day of the index date and continue until the earliest of the following scenarios – occurrence of target outcome event (details available in Section 8.2); discontinuation of the index OAC; switching from the index OAC; withdrawal from the database.

4 STUDY POPULATION

Japanese OAC treatment-naïve NVAF patients with who were prescribed apixaban, dabigatran, edoxaban, rivaroxaban or warfarin. Further information on patient selection and enrolment and follow-up time periods are included in Subsections 7.2 of the protocol.

[redacted]

4.1 DATA SOURCE

The analysis will be based on administrative data from MDV Co. Ltd., a longitudinal database based on health insurance claims and medical records obtained from the hospitals in which the DPC payment system for utilization of both inpatient and outpatient hospital claims (percentage of inpatients is about 45%). The database provides claims data from 314 hospitals (as of June 2017) using the DPC system for medical service claims (21% of general hospitals but 55% of general beds in Japan is under the DPC system) including approximately 14 million patient data.

Treatment/cohort labels

- Apixaban Cohort: NVAF patients who initiated apixaban on the index date.
- Dabigatran cohort: NVAF patients who initiated dabigatran on the index date.
- Edoxaban Cohort: NVAF patients who initiated edoxaban 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

4.2 STUDY OBJECTIVES

The research questions:

1. *Are there any differences in the risk of major bleeding and any bleeding between NOACs and warfarin in the general practice settings in Japan?*
2. *Are there any differences in the risk of stroke/systemic embolism between NOACs and warfarin in the general practice settings in Japan?*

The primary objective *of the study compare both the risk of stroke/ SE and of bleeding events among patients with NVAF initiating treatment with one of NOACs (apixaban, dabigatran, edoxaban or rivaroxaban) versus warfarin.*

The secondary objectives *are*

1. *to compare the risk of major GI bleeding, any GI bleeding, and intracranial Hemorrhage between warfarin-initiators and NOAC-initiators*
2. *to compare the risk of ischemic stroke, hemorrhagic stroke or SE between warfarin-initiators and NOAC-initiators*

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5 INTERIM ANALYSES

Not applicable.

6 HYPOTHESES AND DECISION RULES

6.1 STATISTICAL HYPOTHESES

This study includes specific hypotheses to be tested. The null hypothesis for each objective is as follows:

Null: The risks of each of the following endpoints do not differ between NVAF patients treated with warfarin and patients treated with apixaban, dabigatran, edoxaban or rivaroxaban.

- Major Bleeding
- Composite of ischemic stroke, hemorrhagic stroke and systemic embolism
- Any bleeding

6.2 STATISTICAL DECISION RULES

All statistical tests will be performed at p=0.05 (two-sided) with no adjustment for multiplicity. Based on results of Japanese sub-population in confirmatory trials for NOACs, the required sample size to detect a significant difference in stroke/SE was calculated. The following sample size calculation is based on the significance level of 0.05 (two-sided) and power of 80%.

Desired Power	Hazard Ratio	Event Rate (Control)	Required Sample Size per Group
0.8	0.6	1.2 %/year	3,166
		1.6 %/year	2,378
		2.1 %/year	1,815
		2.6 %/year	1,469

[redacted]

Desired Power	Hazard Ratio	Event Rate (Control)	Required Sample Size per Group
	0.7	1.2 %/year	6,083
		1.6 %/year	4,570
		2.1 %/year	3,488
		2.6 %/year	2,823
	0.8	1.2 %/year	14,683
		1.6 %/year	11,031
		2.1 %/year	8,422
		2.6 %/year	6,817

7 ANALYSIS SETS/ POPULATIONS

This study uses data from the MDV database, which includes the data used for both inpatient and outpatient insurance claims by hospitals according to the Diagnosis Procedure Combination (DPC) procedure. Japanese OAC treatment-naïve NVAF patients with who were prescribed apixaban, edoxaban or warfarin. Further information on patient selection and enrolment and follow-up time periods are included in Subsections 7.2 of the protocol.

7.1 FULL ANALYSIS SET

All eligible patients for the study will be included in the analysis.

Inclusion criteria

Patients must meet all of the following criteria to be eligible for the study:

1. *Diagnosed with AF anytime in the baseline period or on the index date, also have definitive diagnosis of AF anytime in the baseline period, on the index date, or post-index period.*
2. *Prescribed one of the index OACs (apixaban, edoxaban, or warfarin) on or after the day of AF diagnosis. The first observed prescription will be used to identify the patient's index date and treatment cohort*
3. *No use of the any OACs during the baseline period (the 180 days before the index date)*
4. *Age of 18 years or older on the index date.*

Exclusion criteria

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

1. *Having a diagnosis of valvular atrial fibrillation, post-operative atrial fibrillation, rheumatic atrial fibrillation or mechanical-valvular atrial fibrillation during the baseline and post-index period*
2. *Having a cardiac surgery procedure record during the baseline period*

[redacted]

3. *Having a joint replacement procedure record during the baseline period*
4. *Having a procedure of prosthetic heart valve during the baseline period*
5. *Having a diagnosis of venous thromboembolism during the baseline period*
6. *Female patients with pregnancy during the follow-up period*
7. *Patients prescribed "off-label" doses of OACs (per Japanese package insert of each OAC) or patients treated with OAC but in "off-label" or "contraindicated" manners.*

7.2 SAFETY ANALYSIS SET

Bleeding events will be collected for this analysis. As mentioned above, bleeding will be investigated as safety-related primary endpoints. However, other adverse event, serious AE or non-serious AE will not be collected in this analysis because the dataset provided by MDV will not contain the AE-related information.

7.3 OTHER ANALYSIS SET

None.

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CCI [redacted]

8 ENDPOINTS AND COVARIATES

8.1 EFFICACY/ EFFECTIVENESS ENDPOINT(S)

Variable	Role	Operational definition
Stroke/SE (composite) event after index date	Outcome (primary endpoint)	Operational definition of Stroke and SE will follow the operational definition of Stroke event after index date and SE event after index date. Time to events will be defined as the number of days from the index date to the occurrence of the first stroke or SE.
Ischemic stroke event after index date	Outcome (secondary endpoint)	Ischemic stroke after index date not including the index date will be identified using hospital claims which had an ischemic stroke diagnosis code as the first listed ICD-10 diagnosis code (Appendix, Table 5). An event occurrence of ischemic stroke is defined as a case that “01: Disease name which input the most medical resources”, “02:Sub-disease name”, “11: Main disease name”, “21: Disease name behind hospitalization”, or “31: Disease name which input the second most medical resources” in DPC database. Time to ischemic stroke will be defined as the number of days from the index date to the occurrence of the first ischemic stroke.
Hemorrhagic stroke event after index date	Outcome (secondary endpoint)	Hemorrhagic stroke after index date not including the index date will be identified using hospital claims which had a hemorrhagic stroke diagnosis code as the first listed ICD-10 diagnosis code (Appendix, Table 5). An event occurrence of hemorrhagic stroke is defined as a case that “01: Disease name which input the most medical resources”, “02:Sub-disease name”, “11: Main disease name”, “21: Disease name behind hospitalization”, or “31: Disease name which input the second most medical resources” in DPC database. Time to hemorrhagic stroke will be defined as the number of days from the index date to the occurrence of the first hemorrhagic stroke.
SE event after index date	Outcome (secondary endpoint)	SE after index date not including the index date will be identified using hospital claims which had a SE diagnosis code as the first listed ICD-10 diagnosis code (Appendix, Table 5). An event occurrence of SE is defined as a case that “01: Disease name which input the most medical resources”, “02:Sub-disease name”,

[redacted]

Variable	Role	Operational definition
		"11: Main disease name", "21: Disease name behind hospitalization", or "31: Disease name which input the second most medical resources" in DPC database. Time to SE will be defined as the number of days from the index date to the occurrence of the first SE event.

8.2 SAFETY ENDPOINTS

Variable	Role	Operational definition
Major bleeding event[1] after index date	Outcome (primary endpoint)	Major bleeding after index date will be identified using hospital claims which had a bleeding diagnosis code as the first listed ICD-10 or disease code (Appendix, Table 7). An event occurrence of major bleeding is defined as a case that "21: Disease name behind hospitalization" in DPC database. Time-to-major bleeding will be defined as the number of days from the index date to the occurrence of the first major bleeding event.
Any bleeding event[2] after index date	Outcome (secondary endpoint)	Any bleeding after index date will be identified using hospital claims which had a bleeding diagnosis code as the first listed ICD-10 or disease code (Appendix, Table 7). Time-to-any bleeding will be defined as the number of days from the index date to the occurrence of the first any bleeding event.
Major GI bleeding event after index date	Outcome (secondary endpoint)	Major GI bleeding after index date will be identified using hospital claims which had a GI bleeding diagnosis code as the first listed ICD-10 or disease code (Appendix, Table 8). An event occurrence of major bleeding is defined as a case that "21: Disease name behind hospitalization" in DPC database. Time-to-major GI bleeding will be defined as the number of days from the index date to the occurrence of the first major GI bleeding event.
Any GI bleeding event after index date	Outcome (secondary endpoint)	Any GI bleeding after index date will be identified using hospital claims which had a GI bleeding diagnosis code as the first listed ICD-10 or disease code (Appendix-). Time-to-any GI bleeding will be defined as the number of days from the index date to the occurrence of the first any GI bleeding event.

[redacted]

Major intracranial hemorrhage event after index date	Outcome (secondary endpoint)	Intracranial hemorrhage after index date will be identified using hospital claims which had an intracranial hemorrhage diagnosis code as the first listed ICD-10 or disease code (Appendix-2). Time to major intracranial hemorrhage will be defined as the number of days from the index date to the occurrence of the first intracranial hemorrhage event.
Any intracranial hemorrhage event after index date	Outcome (secondary endpoint)	Intracranial hemorrhage after index date will be identified using hospital claims which had an intracranial hemorrhage diagnosis code as the first listed ICD-10 or disease code (Appendix-2). Time to any intracranial hemorrhage will be defined as the number of days from the index date to the occurrence of the first intracranial hemorrhage event.

[1,2] *Any bleeding will be defined based on definitions listed in Appendix-3. Among any bleeding events, bleeding events that requires hospitalization will be defined as "major bleeding".*

8.3 OTHER ENDPOINTS

None

8.4 COVARIATES

We will use demographic and clinical information available at the index date and baseline period of the initiation prescription for apixaban, edoxaban, and warfarin cohorts.

Variable	Role	Operational definition
Sex Category	Baseline characteristic	Dichotomous variable equals 1 if sex is male and 2 if female
Age	Baseline characteristic	Age (in years) at the index date
Physician specialty	Baseline characteristic	Dichotomous variable equals 1 if a physician specialty on the index date is categorized into a cardiac specialty and 0 if others. Following specialties will be categorized as the cardiac specialty: cardiology stroke, cardiovascular surgery, pediatric cardiology, neurosurgery, cardiovascular medicine, and neurology. If there are ≥1 specialties but including the cardiac specialty, the physician specialty will be regarded as the cardiac specialty.
Hospital size (<500 beds or not)	Baseline characteristic	Dichotomous variable equals 1 if hospital size on the index date is <500 beds and 0 if ≥500 beds.
Hospitalization status on index date	Baseline characteristic	Dichotomous variable equals 1 if hospitalization status is inpatient and 0 if outpatient.
$CHADS_2$	Baseline characteristic	$CHADS_2$ score will be calculated based on age and the presence of congestive heart failure, hypertension, diabetes, and stroke or TIA.

[redacted]

CHA_2DS_2-VASc	Baseline characteristic	CHA_2DS_2-VASc score will be calculated based on age and the presence of congestive heart failure, hypertension, diabetes, stroke or TIA, vascular disease and sex category.
PT-INR (Prothrombin time-international normalized ratio)	Baseline period	Continuous variable. * Only available for patients treated with warfarin
Heart failure diagnosis in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 diagnoses for heart failure ICD-10 or disease codes during the baseline period.
Coronary heart disease diagnosis in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 diagnoses for coronary heart disease ICD-10 or disease codes during the baseline period.
Peripheral arterial disorder diagnosis in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 diagnoses for peripheral arterial disorder ICD-10 or disease codes during the baseline period.
Myocardial infarction diagnosis in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 diagnoses for myocardial infarction ICD-10 or disease codes during the baseline period.
Hyperthyroidism or thyrotoxicosis in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 diagnoses for hyperthyroidism ICD-10 or disease codes during the baseline period.
Stroke, TIA or SE diagnosis in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 diagnoses for Stroke, TIA or systemic embolism ICD-10 or disease codes during the baseline period.
Renal dysfunction diagnosis in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 diagnoses for renal dysfunction ICD-10 or disease codes during the baseline period.
Liver dysfunction diagnosis in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 diagnoses for liver dysfunction ICD-10 or disease codes during the baseline period.
Bleeding diagnosis in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 diagnoses for bleeding ICD-10 or disease codes during the baseline period.
Hypertension diagnosis in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 diagnoses for hyper tension ICD-10 or disease codes during the baseline period.
Diabetes mellitus diagnosis in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 diagnoses for diabetes mellitus ICD-10 or disease codes during the baseline period.
Cancer diagnosis in baseline	Baseline period	Dichotomous variable equals 1 if there are ≥1 diagnoses for diabetes mellitus ICD-10 or disease codes during the baseline period.
Treated with antiplatelet drug in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 prescriptions of antiplatelet drug ATC or receipt codes during the baseline period.
Treated with NSAIDs in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 prescriptions of NSAIDs ATC or receipt codes during the baseline period.

[redacted]

Treated with gastric secretion inhibitor in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 prescriptions of gastric secretion inhibitor drug ATC or receipt codes during the baseline period.
Treated with statin-based drug in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 prescriptions of statin-based drug ATC or receipt codes during the baseline period.
Treated with anti-hypertensives in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 prescriptions of anti-hypertensive ATC or receipt codes during the baseline period.
Treated with anti-arrhythmics in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 prescriptions of anti-arrythmics ATC or receipt codes during the baseline period.
Treated with beta-blockers in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 prescriptions of beta-blockers ATC or receipt codes during the baseline period.
Treated with heparins in baseline	Baseline characteristic	Dichotomous variable equals 1 if there are ≥1 prescriptions of heparins ATC or receipt codes during the baseline period.
Cardioversion in baseline	Baseline characteristic	Dichotomous variable equals 1 if there is ≥1 operation of cardioversion receipt codes during the baseline period.

9 HANDLING OF MISSING VALUES

No imputation for missing data is planned.

10 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

10.1 STATISTICAL METHODS

10.1.1 Propensity Score Matching

In this study, matched cohorts (apixaban vs. warfarin, dabigatran versus warfarin, edoxaban vs. warfarin and rivaroxaban versus warfarin) will be created. Propensity scores will be estimated by unconditional logistic regression analyses that incorporate potential predictors of therapy as independent variables in the regression and cohort status as the outcome. The matching between warfarin group and each NOAC group (reference), 1:1 propensity score matching (PSM) method without replacement will be conducted. We will apply nearest neighbour method within caliper (width=0.2 times the standard deviation of the logit of the propensity score) matching technique. Standardized differences will be used to assess the balance of covariate between warfarin group and each NOAC group. If the standardized difference is less than 10%, the covariates are considered balanced. The following covariates will be included in the logistic regression:

- age on index date
- gender

[redacted]

- $CHADS_2$ score in baseline
- CHA_2DS_2-VASc score in baseline
- heart failure diagnosis in baseline
- coronary heart disease diagnosis in baseline
- peripheral arterial disorder diagnosis in baseline
- myocardial infarction diagnosis in baseline
- hyperthyroidism or thyrotoxicosis in baseline
- TIA diagnosis in baseline
- stroke or SE diagnosis in baseline
- renal dysfunction diagnosis in baseline
- liver dysfunction diagnosis in baseline
- bleeding diagnosis in baseline
- hypertension diagnosis in baseline
- diabetes mellitus diagnosis in baseline
- treated with antiplatelet drug in baseline
- treated with NSAIDs in baseline
- treated with gastric secretion inhibitor in baseline
- treated with statin-based drug in baseline
- treated with anti-hypertensives in baseline
- treated with anti-arrhythmics in baseline
- treated with beta-blockers in baseline
- treated with heparins in baseline
- cardioversion in baseline

The operational definitions for the above covariates are shown in the Section 6.4.

10.1.2 Inverse probability treatment weighting (IPTW)

As an alternative methods to a simple PSM (shown above), IPTW with stabilized weights will be used as a secondary analysis to balance patient characteristics between two groups[5-7].

Propensity score will be calculated by using a multinomial logistic model as mentioned above (see 10.1.1). However, if a treated patient has a very low propensity score, a very large weight can be created. Large weights can increase the variability of estimated treatment effect. In order to address this, the weights can be stabilized. Stabilized weights will be calculated by using a

$$\frac{\sum_{i=1}^{N_T} PS_i}{N_T} * \frac{1}{PS_i}$$

[redacted]

formula shown below, by multiplying the treatment and control weights by a constant, equal to the expected value of being in the treatment or comparison cohorts, respectively.

The distribution of the stabilized weight will be reviewed. If there are extreme outliers, the large weights could be set to a less extreme value (e.g. recoding all weights that are outside 5th and 95th percentile). If needed, truncation can be done after stabilizing the weights
After the weights are applied, the balance of the baseline covariates will be assessed.
First, the means and proportions of baseline variables are compared. The standardized difference compares the difference in means in units of the standard deviation. If the standardized difference is less than 10%, the covariates are considered balanced.

For continuous variables, the balance of the distribution is also assessed. The high-order movements and interactions between variables should be similar between treatment groups. The standardized difference is used to compare the mean of the square of continuous variables. Graphical comparisons of the distribution of continuous variables are completed. Side-by-side boxplots and empirical cumulative distribution functions are used to the compare the distribution of continuous covariates. The graphical approach can be subjective so a numerical method for comparing the distribution of continuous baseline covariates is also completed. Kolmogorov-Smirnov test allows a comparison of the distribution of a continuous variable between two independent groups.

10.1.3 Analysis of Time-to-Event Data

Time-to-endpoints will be summarized by OAC with the number and percentage of patients with event, and event rates. Event rates will be calculated as the number of patients with event per 100 patient-years at risk. In addition, total patient-years will be presented for each OAC.

Patients who experience a clinical endpoint event after the earlier of their discontinuation of the index OAC, switching from the index OAC, withdrawal from the database, or the end of intended follow-up period (i.e., two years after the index date as primary and one year for a sensitive analysis) will be censored.

Patients who do not experience a clinical endpoint event will be censored at the earlier of their discontinuation of the index OAC, switching from the index OAC or withdrawal from the database will be censored.

[redacted]

Propensity score matching

See above

Cox proportional hazards model

Cox proportional hazards model will be used to compare endpoints in each of the propensity-score-matched cohorts, with robust sandwich estimates to account for the clustering within matched sets. The Cox proportional hazards model will include only index OAC treatment as the independent variable if patient characteristics are balanced between groups based on standardized difference in components of the PS. If not balanced, the unbalanced variable will be also included to the model in addition to the index OAC treatment. The hazard ratios with corresponding 95% confidence intervals and p-values will be reported.

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[redacted]

Kaplan-Meier Method

For each endpoint, Kaplan-Meier curves will be plotted for the time from the index date to first event by index OAC treatment in each of the propensity-score-matched cohorts. The log-rank test is used for comparison between two curves.

10.1.4 Analysis of Continuous Data

Continuous data will be summarized using descriptive statistics, including the mean, standard deviation, median, first and third quartiles, and minimum and maximum. Baseline characteristics will be compared between patients treated with warfarin and patients treated with apixaban or

[redacted]

edoxaban using t-test or Mann-Whitney's U test depending on the distribution of the variables. In addition, standardized differences will be calculated for each variable.

10.1.5 Analysis of Categorical Data

Counts and percentages will be provided for dichotomous and polychotomous variables of baseline patient characteristics when performing descriptive analysis. Standardized differences will be calculated for each variable. For calculation of standardized differences, categorical variables will be converted into a set of binary indicators, one for each non-reference level of the variable and then a set of standardized differences defined[6]. In addition, the counts and percentages will be compared between patients treated with warfarin and patients treated with apixaban or edoxaban using chi-square tests.

10.1.6 Analyses of Efficacy/Effectiveness Endpoints

Propensity-Score-Matched Cohorts

For each propensity-score-matched cohort, a Cox proportional hazards model will be fit with the index OAC as a covariate. The hazard ratios with corresponding 95% confidence intervals and p-values will be reported. Kaplan-Meier estimates of time to the first event will be plotted. In addition, each endpoint will be summarized by the index OAC as described in the Section 8.1.

Matched cohorts by an IPTW method

For each matched cohort, a Cox proportional hazards model will be fit with the index OAC as a covariate. The hazard ratios with corresponding 95% confidence intervals and p-values will be reported. Kaplan-Meier estimates of time to first will be plotted. In addition, each endpoint will be summarized by the index OAC as described in the Section 8.1.

Pre-Matched Cohorts

Each endpoint will be summarized by the index OAC as described in the Section 8.1.

10.1.7 Analyses of Safety Endpoints

Propensity-Score-Matched Cohorts

For each propensity-score-matched cohort, a Cox proportional hazards model will be fit with the index OAC as a covariate. The hazard ratios with corresponding 95% confidence intervals and p-values will be reported for both any and major bleeding. Kaplan-Meier estimates of time to first

[redacted]

will be plotted. In addition, each endpoint will be summarized by the index OAC as described in the Section 8.2.

Matched cohorts by IPTW method

For each matched cohort, a Cox proportional hazards model will be fit with the index OAC as a covariate. The hazard ratios with corresponding 95% confidence intervals and p-values will be reported for both any and major bleeding. Kaplan-Meier estimates of time to first will be plotted. In addition, each endpoint will be summarized by the index OAC as described in the Section 8.2.

Pre-Matched Cohorts

Each endpoint will be summarized by the index OAC as described in the Section 8.2.

[redacted]

10.1.8 Summary of Analyses

Efficacy and safety analyses excluding descriptive summaries will be shown in the following table.

1) Propensity score matched cohorts

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
Major bleeding	**PS-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	safety, primary	NA	Cox proportional hazards model	Index OAC	No imputation
Major bleeding	**PS-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	safety, primary	NA	Plot of Kaplan-Meier Estimates		No imputation
Major bleeding	**PS-matched patients** ✓Warfarin vs. apixaban Cohorts ✓Warfarin vs. dabigatran Cohorts ✓Warfarin vs. edoxaban Cohorts ✓Warfarin vs. rivaroxaban Cohorts	safety, primary	NA	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Any bleeding	**PS-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts	safety, primary	NA	Cox proportional hazards model	Index OAC	No imputation

[redacted]

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
	✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts					
Any bleeding	**PS-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	safety, primary	NA	Plot of Kaplan-Meier Estimates		No imputation
Any bleeding	**PS-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	safety, primary	NA	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Major intracranial bleeding	**PS-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	Safety Secondary	NA	Cox proportional hazards model	Index OAC	No imputation
Major intracranial bleeding	**PS-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban	Safety Secondary	NA	Plot of Kaplan-Meier Estimates		No imputation

[redacted]

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
	Cohorts					
Major intracranial bleeding	**PS-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	Safety Secondary	NA	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Major GI bleeding	**PS-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	Safety Secondary	NA	Cox proportional hazards model	Index OAC	No imputation
Major GI bleeding	**PS-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	Safety Secondary	NA	Plot of Kaplan-Meier Estimates		No imputation
Major GI bleeding	**PS-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	Safety Secondary	NA	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Any GI bleeding	**PS-matched patients** ✓ Warfarin vs. apixaban	Safety Secondary	NA	Cox proportional hazards model	Index OAC	No imputation

[redacted]

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
	Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts					
Any GI bleeding	**PS-matched patients** ✓Warfarin vs. apixaban Cohorts ✓Warfarin vs. dabigatran Cohorts ✓Warfarin vs. edoxaban Cohorts ✓Warfarin vs. rivaroxaban Cohorts	Safety Secondary	NA	Plot of Kaplan-Meier Estimates		No imputation
Any GI bleeding	**PS-matched patients** ✓Warfarin vs. apixaban Cohorts ✓Warfarin vs. dabigatran Cohorts ✓Warfarin vs. edoxaban Cohorts ✓Warfarin vs. rivaroxaban Cohorts	Safety Secondary	NA	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Stroke/SE	**PS-matched patients** ✓Warfarin vs. apixaban Cohorts ✓Warfarin vs. dabigatran Cohorts ✓Warfarin vs. edoxaban Cohorts ✓Warfarin vs. rivaroxaban Cohorts	Effectiveness Primary	NA	Cox proportional hazards model	Index OAC	No imputation
Stroke/SE	**PS-matched patients** ✓Warfarin vs. apixaban Cohorts ✓Warfarin vs. dabigatran Cohorts	Effectiveness Primary	NA	Plot of Kaplan-Meier Estimates		No imputation

[redacted]

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
	✓Warfarin vs. edoxaban Cohorts ✓Warfarin vs. rivaroxaban Cohorts					
Stroke/SE	**PS-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	Effectiveness Primary	NA	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
CCI [redacted]						

[redacted]

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

[redacted]

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI [redacted]						

2) IPTW-matched cohorts

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
Major bleeding	**IPTW-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	safety, primary	NA	Cox proportional hazards model	Index OAC	No imputation
Major bleeding	**IPTW-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	safety, primary	NA	Plot of Kaplan-Meier Estimates		No imputation
Major bleeding	**IPTW-matched patients** ✓Warfarin vs. apixaban Cohorts ✓Warfarin vs. dabigatran Cohorts ✓Warfarin vs. edoxaban Cohorts ✓Warfarin vs. rivaroxaban Cohorts	safety, primary	NA	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Any bleeding	**IPTW-matched patients** ✓ Warfarin vs. apixaban	safety, primary	NA	Cox proportional hazards model	Index OAC	No imputation

[redacted]

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
	Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts					
Any bleeding	**IPTW-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	safety, primary	NA	Plot of Kaplan-Meier Estimates		No imputation
Any bleeding	**IPTW-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	safety, primary	NA	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Major intracranial bleeding	**IPTW-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	Safety Secondary	NA	Cox proportional hazards model	Index OAC	No imputation
Major intracranial bleeding	**IPTW-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts	Safety Secondary	NA	Plot of Kaplan-Meier Estimates		No imputation

[redacted]

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
	✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts					
Major intracranial bleeding	**IPTW-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	Safety Secondary	NA	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Major GI bleeding	**IPTW-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	Safety Secondary	NA	Cox proportional hazards model	Index OAC	No imputation
Major GI bleeding	**IPTW-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	Safety Secondary	NA	Plot of Kaplan-Meier Estimates		No imputation
Major GI bleeding	**IPTW-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban	Safety Secondary	NA	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation

[redacted]

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
	Cohorts					
Any GI bleeding	**IPTW-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	Safety Secondary	NA	Cox proportional hazards model	Index OAC	No imputation
Any GI bleeding	**IPTW-matched patients** ✓Warfarin vs. apixaban Cohorts ✓Warfarin vs. dabigatran Cohorts ✓Warfarin vs. edoxaban Cohorts ✓Warfarin vs. rivaroxaban Cohorts	Safety Secondary	NA	Plot of Kaplan-Meier Estimates		No imputation
Any GI bleeding	**IPTW-matched patients** ✓Warfarin vs. apixaban Cohorts ✓Warfarin vs. dabigatran Cohorts ✓Warfarin vs. edoxaban Cohorts ✓Warfarin vs. rivaroxaban Cohorts	Safety Secondary	NA	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
Stroke/SE	**IPTW-matched patients** ✓Warfarin vs. apixaban Cohorts ✓Warfarin vs. dabigatran Cohorts ✓Warfarin vs. edoxaban Cohorts ✓Warfarin vs. rivaroxaban Cohorts	Effectiveness Primary	NA	Cox proportional hazards model	Index OAC	No imputation
Stroke/SE	**IPTW-matched patients** ✓Warfarin vs. apixaban	Effectiveness Primary	NA	Plot of Kaplan-Meier Estimates		No imputation

[redacted]

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
	Cohorts ✓Warfarin vs. dabigatran Cohorts ✓Warfarin vs. edoxaban Cohorts ✓Warfarin vs. rivaroxaban Cohorts					
Stroke/SE	**IPTW-matched patients** ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts	Effectiveness Primary	NA	Incidence rate (per 100 patient-year) (no statistical comparison)		No imputation
CCI [redacted]						

[redacted]

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

[redacted]

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

[redacted]

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
CCI						

[redacted]

11 LIST OF TABLES AND TABLE SHELLS

A list of tables and table shells will be prepared separately.

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12 REFERENCES

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7. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. *Value Health* 2010;**13**:273-277.

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Appendix-1: List of ICD-10 Codes

Variable Used in Study	ICD-10 Code*	Additional rules on Data Extraction
Atrial fibrillation	I48	
Post-operative atrial fibrillation	8847772	Standard disease code
Valvular atrial fibrillation	8846941	Standard disease code
Rheumatic atrial fibrillation	I05	
	I06	
	I07	
	I08	
	I09	
Mechanical-valvular atrial fibrillation	T820	
Hyperthyroidism or thyrotoxicosis	E05	
Heart failure	I110	
	I500	
	I501	Exclude cardiac asthma
	I509	
Hypertension	H350	Include only hypertensive retinopathy and hypertensive neuroretinopathy
	I10	
	I110	
	I119	
	I120	
	I129	Include only hypertensive renal disease, hypertensive nephropathy and hypertensive nephrosclerosis
	I150	
Diabetes	E10	
	E11	
	E12	
	E13	
	E14	
Hemorrhage stroke	I60	
	I61	
	I62	Exclude non-traumatic extradural haemorrhage
Ischemic stroke	I63	
	3489032	standard disease code

[redacted]

	4371003	
	4379014	
	3448002	
	3448028	
	3489029	
	3489035	
	4379006	
TIA	H340	
	G450	
	G451	
	G458	
	G459	
Systemic embolism	I740	Include only abdominal aortic embolism
	I741	Include only aortic embolism
	I742	Include only acute arterial occlusive disease of arteries of upper extremities
	I743	Include only femoral arterial occlusion and acute arterial occlusive disease of arteries of lower extremities
	I744	
	I745	Include only iliac artery embolism
	I748	Include only hepatic artery embolism
	I749	Include only thromboembolism, embolic infarction, aortic embolism
Peripheral vascular disorder	I702	Include only atherosclerosis and arteriosclerosis obliterans
	I709	
	I731	Include only Buerger's disease
	I739	Exclude peripheral circulatory failure, cerebrovascular spasm, and angiospasm pf the extremities
	I742	
	I743	
	I745	
	I748	Include only subclavian artery stenosis
Aortic plaque	4400011	Standard disease code
	8837393	Standard disease code
Coronary artery disease	I200	
	I201	
	I208	
	I209	

[redacted]

	I210	
	I211	
	I212	
	I213	
	I214	
	I240	
	I241	
	I248	
	I251	
	I252	Exclude calcification of coronary artery
	I255	
	I258	Exclude coronary arteritis
	I259	
Myocardial infarction	I200	Exclude intermediate angina syndrome, preinfarction syndrome, initial arbeits angina, intermediate coronary syndrome
	I210	
	I211	
	I212	
	I214	
	I240	
	I241	Exclude Dressler syndrome
Renal dysfunction	I120	
	I129	
	I139	
	N003	
	N009	
	N032	
	N033	
	N039	
	N040	
	N044	
	N049	
	N052	
	N055	
	N058	
	N059	
	N170	
	N171	
	N172	

[redacted]

	N178	
	N179	
	N189	
	N19	Exclude renal anemia, afunctional kidney, and alimentary proteinuria
Liver dysfunction	B150	
	B159	
	B162	
	B169	
	B171	
	B172	
	B178	
	B181	
	B182	
	B189	
	B199	
	K700	
	K701	
	K703	
	K709	
	K716	
	K720	
	K721	
	K729	
	K730	
	K732	
	K738	
	K739	
	K740	
	K741	
	K743	
	K744	
	K745	
	K746	
	K750	
	K751	
	K754	
	K759	
	K760	
	K761	
	K762	

[redacted]

	K763	
	K766	
	K767	
	K768	
	K769	
Cancer	C00	
	C01	
	C02	
	C03	
	C04	
	C05	
	C06	
	C07	
	C08	
	C09	
	C10	
	C11	
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	C40	

[redacted]

	C41	
	C43	
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[redacted]

	C84	
	C85	
	C88	
	C90	
	C91	
	C92	
	C93	
	C94	
	C95	
	C96	
	C97	
	D00	
	D01	
	D02	
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[redacted]

	D31	
	D32	
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	D36	
	D37	
	D38	
	D39	
	D40	
	D41	
	D42	
	D43	
	D44	
	D45	
	D46	
	D48	

ICD-10, International Statistical Classification of Diseases and Related Health Problems
*: 7-digit numbers not beginning with alphabets are the standard disease code instead of ICD-10 code.

[redacted]

13 APPENDEX-2: LIST OF PROCEDURES CODES

Procedure	Procedure Code
Cardiac surgery	150138210
	150138310
	150138410
	150138510
	150359210
	150138710
	150140510
	150140610
	150140710
	150139010
	150140810
	150318010
	150317810
	150318110
	150331450
	150331550
	150331950
	150332050
	150317910
	150318210
	150140010
	150139210
	150153910
	150374910
	150375010
	150375110
	150260350
	150284310
	150359310
	150263310
	150375210
	150375310
	150375410
	160107550
	150139810
	150139910
	150318310
	150145710

[redacted]

Procedure	Procedure Code
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	150145910
	150146010
	150318410
	150318510
	150302770
	150143010
	150143110
	150331650
	150332150
	150318710
	150319010
	150319310
	150318810
	150319110
	150319410
	150328750
	150328850
	150331750
	150331850
	150332250
	150332350
	150318910
	150319210
	150319510
	150318610
	150141010
	150279510
	150279610
	150141410
	150141610
	150369950
	150141710
	150359470
	150143610
	150260050
	150143710
	150143810
	150141510

[redacted]

Procedure	Procedure Code
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	150375770
	150319610
	150292910
	150139310
	150140910
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	150244910
	150245010
	150359510
	150359610
	150381150
	150381250
	150381350
	150381450
	150150010
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	150381850
	150381950
	150150110
	150382050
	150245110
	150245210
	150375870
	150375970
	150376070
	150141210
	150301310
	150267850
	150319710
	150151810
	150376110

[redacted]

Procedure	Procedure Code
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	150138810
	150151910
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	150346410
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	150144110
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	150142710
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	150376310
	150143250
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	150143550
	150283250
	150283350
	150283450
	150283550
	150144910
	150139610
	150142410
	150141810
	150141910
	150320610
	150142050
	150142110
	150142210

[redacted]

Procedure	Procedure Code
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	150142810
	150144010
	150320710
	150144210
	150144550
	150147410
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	150146910
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	150321310
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	150139510
	150330010
	150147010
	150330110
	150376570
	150321410
	150321510
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	150147310
	150145650
	150141310
	150321810
	150321610

[redacted]

Procedure	Procedure Code
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	150321710
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	150330310
	150376770
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	150330410
	150145510
	150302870
	150145410
	150322010
	150322110
	150144310
	150147250
	150346610
	150144810
	150253810
	150253910
	150275610
	150346710
	150262810
	150303310
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	150140110
	150140210
	150140410
	150346910
	150347010
	150303210
	150322210
	150275210
	150275310
	150336910
	150337010
	150360010
	150148010
	150148110
	150147610

[redacted]

Procedure	Procedure Code
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	150147870
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	150275870
	150262910
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	150266210
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	150303510
	150360110
	150360210
	150360310
	150360410
	150303610
	150303710
	150322410
	150322610
Ablation	150346710
	150262810
	150303310
	150346870
	150370050
Electrical defibrillation	140051410
	140010310
	140055010
	150275210
	150275310
	150336910
	150337010
	150370550
Heart valve prosthesis implantation surgery	150141410
	150141610
	150141710

[redacted]

Procedure	Procedure Code
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	150369950
	150331950
	150332050
	150332150
	150328850
	150332250
	150332350
	150141510
	150375570
	150375670
	150375770
	150244910
	150359510
	150381150
	150381250
	150359710
	150359810
	150381650
	150381750
	150283450

[redacted]

14 APPENDEX-3: LIST OF ANY BLEEDING

Procedure for definition of “any bleeding”

Step 1. To extracted the following group A or group B from MDV data base.

Group A: ICD-10 name includes [redacted] (bleeding)” or [redacted] (ecchymoma)”

Group B: Disease name includes [redacted] (bleeding)” or [redacted] (ecchymoma)”

Step 2. To select disease names considered to be relevant to side effect of OAC individually from disease names excluded in Step 1.

Step 3. To exclude disease names which are not considered to be relevant to side effect of OAC from the disease names included in Step 1.

ICD-10	ICD10Name
A162	Tuberculosis of lung, without mention of bacteriological or histological confirmation
A165	Tuberculous pleurisy, without mention of bacteriological or histological confirmation
B303	Acute epidemic haemorrhagic conjunctivitis (enteroviral)
D500	Iron deficiency anaemia secondary to blood loss (chronic)
D62	Acute posthaemorrhagic anaemia
D66	Hereditary factor VIII deficiency
D683	Haemorrhagic disorder due to circulating anticoagulants
D698	Other specified haemorrhagic conditions
D699	Haemorrhagic condition, unspecified
E078	Other specified disorders of thyroid
E274	Other and unspecified adrenocortical insufficiency
G361	Acute and subacute haemorrhagic leukoencephalitis [Hurst]
G951	Vascular myelopathies
G968	Other specified disorders of central nervous system
H052	Exophthalmic conditions
H113	Conjunctival haemorrhage
H168	Other keratitis
H208	Other iridocyclitis
H210	Hyphaema
H313	Choroidal haemorrhage and rupture
H350	Background retinopathy and retinal vascular changes
H356	Retinal haemorrhage
H357	Separation of retinal layers
H405	Glaucoma secondary to other eye disorders
H431	Vitreous haemorrhage

[redacted]

ICD-10	ICD10Name
H448	Other disorders of globe
H470	Disorders of optic nerve, not elsewhere classified
H603	Other infective otitis externa
H669	Otitis media, unspecified
H738	Other specified disorders of tympanic membrane
H922	Otorrhagia
I213	Acute transmural myocardial infarction of unspecified site
I230	Haemopericardium as current complication following acute myocardial infarction
I312	Haemopericardium, not elsewhere classified
I600	Subarachnoid haemorrhage from carotid siphon and bifurcation
I601	Subarachnoid haemorrhage from middle cerebral artery
I602	Subarachnoid haemorrhage from anterior communicating artery
I603	Subarachnoid haemorrhage from posterior communicating artery
I604	Subarachnoid haemorrhage from basilar artery
I605	Subarachnoid haemorrhage from vertebral artery
I606	Subarachnoid haemorrhage from other intracranial arteries
I607	Subarachnoid haemorrhage from intracranial artery, unspecified
I608	Other subarachnoid haemorrhage
I609	Subarachnoid haemorrhage, unspecified
I610	Intracerebral haemorrhage in hemisphere, subcortical
I611	Intracerebral haemorrhage in hemisphere, cortical
I613	Intracerebral haemorrhage in brain stem
I614	Intracerebral haemorrhage in cerebellum
I615	Intracerebral haemorrhage, intraventricular
I616	Intracerebral haemorrhage, multiple localized
I618	Other intracerebral haemorrhage
I619	Intracerebral haemorrhage, unspecified
I620	Subdural haemorrhage (acute)(nontraumatic)
I621	Nontraumatic extradural haemorrhage
I629	Intracranial haemorrhage (nontraumatic), unspecified
I638	Other cerebral infarction
I690	Sequelae of subarachnoid haemorrhage
I691	Sequelae of intracerebral haemorrhage
I780	Hereditary haemorrhagic telangiectasia
I788	Other diseases of capillaries
I841	Internal hemorrhoid with other complications
I844	External hemorrhoid with other complications
I848	Unspecified hemorrhoid with other complications
I850	Oesophageal varices with bleeding
I864	Gastric varices
J041	Acute tracheitis

[redacted]

ICD-10	ICD10Name
J339	Nasal polyp, unspecified
J90	Pleural effusion, not elsewhere classified
J942	Haemothorax
J950	Tracheostomy malfunction
K049	Other and unspecified diseases of pulp and periapical tissues
K068	Other specified disorders of gingiva and edentulous alveolar ridge
K121	Other forms of stomatitis
K137	Other and unspecified lesions of oral mucosa
K148	Other diseases of tongue
K226	Gastro-oesophageal laceration-haemorrhage syndrome
K228	Other specified diseases of oesophagus
K250	Acute with haemorrhage
K252	Gastric ulcer, Acute with both haemorrhage and perforation
K254	Gastric ulcer, Chronic or unspecified with haemorrhage
K256	Gastric ulcer, Chronic or unspecified with both haemorrhage and perforation
K260	Duodenal ulcer, Acute with haemorrhage
K262	Duodenal ulcer, Acute with both haemorrhage and perforation
K264	Duodenal ulcer, Chronic or unspecified with haemorrhage
K266	Duodenal ulcer, Chronic or unspecified with both haemorrhage and perforation
K270	Acute duodenal tumor with haemorrhage
K284	Gastrojejunal ulcer, Chronic or unspecified with haemorrhage
K290	Acute haemorrhagic gastritis
K571	Diverticular disease of small intestine without perforation or abscess
K573	Diverticular disease of large intestine without perforation or abscess
K625	Haemorrhage of anus and rectum
K661	Haemoperitoneum
K762	Central haemorrhagic necrosis of liver
K768	Other specified diseases of liver
K85	Acute pancreatitis
K920	Haematemesis
K921	Melaena
K922	Gastrointestinal haemorrhage, unspecified
L508	Other urticaria
M250	Haemarthrosis
N029	Recurrent and persistent haematuria, Unspecified
N288	Other specified disorders of kidney and ureter
N300	Acute cystitis
N304	Irradiation cystitis
N309	Cystitis, unspecified
N328	Other specified disorders of bladder

[redacted]

ICD-10	ICD10Name
N368	Other specified disorders of urethra
N421	Congestion and haemorrhage of prostate
N488	Other specified disorders of penis
N501	Vascular disorders of male genital organs
N645	Other signs and symptoms in breast
N830	Follicular cyst of ovary
N831	Corpus luteum cyst
N836	Haematosalpinx
N837	Haematoma of broad ligament
N838	Other noninflammatory disorders of ovary, fallopian tube and broad ligament
N898	Other specified noninflammatory disorders of vagina
N908	Other specified noninflammatory disorders of vulva and perineum
N921	Excessive and frequent menstruation with irregular cycle
N922	Excessive menstruation at puberty
N923	Ovulation bleeding
N924	Excessive bleeding in the premenopausal period
N930	Postcoital and contact bleeding
N938	Other specified abnormal uterine and vaginal bleeding
N939	Abnormal uterine and vaginal bleeding, unspecified
N950	Postmenopausal bleeding
O208	Other haemorrhage in early pregnancy
O209	Haemorrhage in early pregnancy, unspecified
O441	Placenta praevia with haemorrhage
O469	Antepartum haemorrhage, unspecified
O679	Intrapartum haemorrhage, unspecified
O695	Labour and delivery complicated by vascular lesion of cord
O717	Obstetric haematoma of pelvis
O720	Third-stage haemorrhage
O721	Other immediate postpartum haemorrhage
O722	Delayed and secondary postpartum haemorrhage
O901	Disruption of perineal obstetric wound
O902	Haematoma of obstetric wound
P021	Fetus and newborn affected by other forms of placental separation and haemorrhage
P100	Subdural haemorrhage due to birth injury
P101	Cerebral haemorrhage due to birth injury
P102	Intraventricular haemorrhage due to birth injury
P103	Subarachnoid haemorrhage due to birth injury
P109	Unspecified intracranial laceration and haemorrhage due to birth injury
P120	Cephalhaematoma due to birth injury
P269	Unspecified pulmonary haemorrhage originating in the perinatal period

[redacted]

ICD-10	ICD10Name
P510	Massive umbilical haemorrhage of newborn
P519	Umbilical haemorrhage of newborn, unspecified
P523	Unspecified intraventricular (nontraumatic) haemorrhage of fetus and newborn
P524	Intracerebral (nontraumatic) haemorrhage of fetus and newborn
P528	Other intracranial (nontraumatic) haemorrhages of fetus and newborn
P529	Intracranial (nontraumatic) haemorrhage of fetus and newborn, unspecified
P540	Neonatal haematemesis
P542	Neonatal rectal haemorrhage
P543	Other neonatal gastrointestinal haemorrhage
P544	Neonatal adrenal haemorrhage
P545	Neonatal cutaneous haemorrhage
P546	Neonatal vaginal haemorrhage
P549	Neonatal haemorrhage, unspecified
P580	Neonatal jaundice due to bruising
P581	Neonatal jaundice due to bleeding
R040	Epistaxis
R041	Haemorrhage from throat
R042	Haemoptysis
R048	Haemorrhage from other sites in respiratory passages
R049	Haemorrhage from respiratory passages, unspecified
R18	Ascites
R195	Other faecal abnormalities
R233	Spontaneous ecchymoses
R31	Unspecified haematuria
R571	Hypovolaemic shock
R58	Haemorrhage, not elsewhere classified
S000	Superficial injury of scalp
S001	Contusion of eyelid and periocular area
S002	Other superficial injuries of eyelid and periocular area
S003	Superficial injury of nose
S004	Superficial injury of ear
S005	Superficial injury of lip and oral cavity
S007	Multiple superficial injuries of head
S008	Superficial injury of other parts of head
S013	Open wound of ear
S019	Open wound of head, part unspecified
S050	Injury of conjunctiva and corneal abrasion without mention of foreign body
S051	Contusion of eyeball and orbital tissues
S063	Focal brain injury

[redacted]

ICD-10	ICD10Name
S064	Epidural haemorrhage
S065	Traumatic subdural haemorrhage
S066	Traumatic subarachnoid haemorrhage
S068	Other intracranial injuries
S098	Other specified injuries of head
S100	Contusion of throat
S101	Other and unspecified superficial injuries of throat
S141	Other and unspecified injuries of cervical spinal cord
S241	Other and unspecified injuries of thoracic spinal cord
S271	Traumatic haemothorax
S272	Traumatic haemopneumothorax
S278	Injury of other specified intrathoracic organs
S279	Injury of unspecified intrathoracic organ
S301	Contusion of abdominal wall
S302	Contusion of external genital organs
S341	Other injury of lumbar spinal cord
S361	Injury of liver or gallbladder
S368	Injury of other intra-abdominal organs
S369	Injury of unspecified intra-abdominal organ
S370	Injury of kidney
S378	Injury of other pelvic organs
S390	Injury of muscle and tendon of abdomen, lower back and pelvis
S400	Contusion of shoulder and upper arm
S408	Other superficial injuries of shoulder and upper arm
S500	Contusion of elbow
S501	Contusion of other and unspecified parts of forearm
S600	Contusion of finger(s) without damage to nail
S601	Contusion of finger(s) with damage to nail
S701	Contusion of thigh
S800	Contusion of knee
S801	Contusion of other and unspecified parts of lower leg
S901	Contusion of toe(s) without damage to nail
S902	Contusion of toe(s) with damage to nail
T009	Multiple superficial injuries, unspecified
T060	Injuries of brain and cranial nerves with injuries of nerves and spinal cord at neck level
T090	Superficial injury of trunk, level unspecified
T093	Injury of spinal cord, level unspecified
T140	Superficial injury of unspecified body region
T144	Injury of nerve(s) of unspecified body region
T145	Injury of blood vessel(s) of unspecified body region
T146	Injury of muscles and tendons of unspecified body region

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ICD-10	ICD10Name
T794	Traumatic shock
T810	Haemorrhage and haematoma complicating a procedure, not elsewhere classified
T811	Shock during or resulting from a procedure, not elsewhere classified
T876	Other and unspecified complications of amputation stump
T905	Sequelae of intracranial injury
	Subgaleal hemorrhage
	Intracranial hemorrhage

ICD-10, International Statistical Classification of Diseases and Related Health Problems

[redacted]

15 APPENDIX-4: EFFECTIVENESS ENDPOINTS

Disease	*ICD10 code*	*Standard disease code*	*Note*
Hemorrhage stroke	I60		
	I61		
	I62		Exclude non-traumatic extradural haemorrhage

Disease	*ICD10 code*	*Standard disease code*	*Note*
Ischemic stroke	I63		
		3489032	
		4371003	
		4379014	
		3448002	
		3448028	
		3489029	
		3489035	
		4379006	

Disease	*ICD10 code*	*Standard disease code*	*Note*
TIA	H340		
	G450		
	G451		
	G458		
	G459		

Disease	*ICD10 code*	*Standard disease code*	*Note*
Systemic embolism	I740		Include only abdominal aortic embolism
	I741		Include only aortic embolism
	I742		Include only acute arterial occlusive disease of arteries of upper extremities
	I743		Include only femoral arterial occlusion and acute arterial occlusive disease of arteries of lower extremities
	I744		
	I745		Include only iliac artery embolism
	I748		Include only hepatic artery embolism
	I749		Include only thromboembolism, embolic infarction, aortic embolism
	I748		Include only subclavian artery stenosis

[redacted]

16 APPENDIX-5: SAFETY ENDPOINTS

Disease	*ICD10 code*	*Standard disease code*	*Note*
Intracranial bleeding	I600		Subarachnoid haemorrhage from carotid siphon and bifurcation
	I601		Subarachnoid haemorrhage from middle cerebral artery
	I602		Subarachnoid haemorrhage from anterior communicating artery
	I603		Subarachnoid haemorrhage from posterior communicating artery
	I604		Subarachnoid haemorrhage from basilar artery
	I605		Subarachnoid haemorrhage from vertebral artery
	I606		Subarachnoid haemorrhage from other intracranial arteries
	I607		Subarachnoid haemorrhage from intracranial artery, unspecified
	I608		Other subarachnoid haemorrhage
	I609		Subarachnoid haemorrhage, unspecified
	I610		Intracerebral haemorrhage in hemisphere, subcortical
	I611		Intracerebral haemorrhage in hemisphere, cortical
	I613		Intracerebral haemorrhage in brain stem
	I614		Intracerebral haemorrhage in cerebellum
	I615		Intracerebral haemorrhage, intraventricular
	I616		Intracerebral haemorrhage, multiple localized
	I618		Other intracerebral haemorrhage
	I619		Intracerebral haemorrhage, unspecified
	I620		Subdural haemorrhage (acute)(nontraumatic)
	I621		Nontraumatic extradural haemorrhage
	I629		Intracranial haemorrhage (nontraumatic), unspecified
	I690		Sequelae of subarachnoid haemorrhage
	I691		Sequelae of intracerebral haemorrhage
	S064		Epidural haemorrhage
	S065		Traumatic subdural haemorrhage
	S066		Traumatic subarachnoid haemorrhage
	S068		Other intracranial injuries

Disease	*ICD10 code*	*Standard disease code*	*Note*
GI bleeding	I850		Oesophageal varices with bleeding
	K226		Gastro-oesophageal laceration-haemorrhage syndrome
	K228		Other specified diseases of oesophagus
	K250		Acute with haemorrhage
	K252		Gastric ulcer, Acute with both haemorrhage and perforation
	K254		Gastric ulcer, Chronic or unspecified with haemorrhage
	K256		Gastric ulcer, Chronic or unspecified with both haemorrhage and perforation
	K260		Duodenal ulcer, Acute with haemorrhage
	K262		Duodenal ulcer, Acute with both haemorrhage and perforation
	K264		Duodenal ulcer, Chronic or unspecified with haemorrhage
	K266		Duodenal ulcer, Chronic or unspecified with both haemorrhage and perforation
	K270		Acute duodenal tumor with haemorrhage
	K284		Gastrojejunal ulcer, Chronic or unspecified with haemorrhage

[redacted]

	K290	Acute haemorrhagic gastritis
	K625	Haemorrhage of anus and rectum
	K920	Haematemesis
	K921	Melaena
	K922	Gastrointestinal haemorrhage, unspecified

CCI

[redacted]

[redacted]