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. 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; 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. 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
prone to intracranial hemorrhage when treated with warfarin. 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) according to the decision by the business process owner.

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.
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
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%.

<table>
<thead>
<tr>
<th>Desired Power</th>
<th>Hazard Ratio</th>
<th>Event Rate (Control)</th>
<th>Required Sample Size per Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.8</td>
<td>0.6</td>
<td>1.2 %/year</td>
<td>3,166</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.6 %/year</td>
<td>2,378</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.1 %/year</td>
<td>1,815</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.6 %/year</td>
<td>1,469</td>
</tr>
</tbody>
</table>
### Desired Power

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>Event Rate (Control)</th>
<th>Required Sample Size per Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7</td>
<td>1.2 %/year</td>
<td>6,083</td>
</tr>
<tr>
<td></td>
<td>1.6 %/year</td>
<td>4,570</td>
</tr>
<tr>
<td></td>
<td>2.1 %/year</td>
<td>3,488</td>
</tr>
<tr>
<td></td>
<td>2.6 %/year</td>
<td>2,823</td>
</tr>
<tr>
<td>0.8</td>
<td>1.2 %/year</td>
<td>14,683</td>
</tr>
<tr>
<td></td>
<td>1.6 %/year</td>
<td>11,031</td>
</tr>
<tr>
<td></td>
<td>2.1 %/year</td>
<td>8,422</td>
</tr>
<tr>
<td></td>
<td>2.6 %/year</td>
<td>6,817</td>
</tr>
</tbody>
</table>

### 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
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.
## 8 ENDPOINTS AND COVARIATES

### 8.1 EFFICACY/ EFFECTIVENESS ENDPOINT(S)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Role</th>
<th>Operational definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SE (composite) event after index date</td>
<td>Outcome (primary endpoint)</td>
<td>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.</td>
</tr>
<tr>
<td>Ischemic stroke event after index date</td>
<td>Outcome (secondary endpoint)</td>
<td>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.</td>
</tr>
<tr>
<td>Hemorrhagic stroke event after index date</td>
<td>Outcome (secondary endpoint)</td>
<td>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.</td>
</tr>
<tr>
<td>SE event after index date</td>
<td>Outcome (secondary endpoint)</td>
<td>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”,</td>
</tr>
<tr>
<td>Variable</td>
<td>Role</td>
<td>Operational definition</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>“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.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 8.2 SAFETY ENDPOINTS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Role</th>
<th>Operational definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding event&lt;sup&gt;1&lt;/sup&gt; after index date</td>
<td>Outcome (primary endpoint)</td>
<td>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.</td>
</tr>
<tr>
<td>Any bleeding event&lt;sup&gt;2&lt;/sup&gt; after index date</td>
<td>Outcome (secondary endpoint)</td>
<td>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.</td>
</tr>
<tr>
<td>Major GI bleeding event after index date</td>
<td>Outcome (secondary endpoint)</td>
<td>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.</td>
</tr>
<tr>
<td>Any GI bleeding event after index date</td>
<td>Outcome (secondary endpoint)</td>
<td>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.</td>
</tr>
</tbody>
</table>
Outcome (secondary endpoint)

<table>
<thead>
<tr>
<th>Major intracranial hemorrhage event after index date</th>
<th>Outcome (secondary endpoint)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Any intracranial hemorrhage event after index date</th>
<th>Outcome (secondary endpoint)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

Note: 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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Role</th>
<th>Operational definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex Category</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if sex is male and 2 if female</td>
</tr>
<tr>
<td>Age</td>
<td>Baseline characteristic</td>
<td>Age (in years) at the index date</td>
</tr>
<tr>
<td>Physician specialty</td>
<td>Baseline characteristic</td>
<td>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.</td>
</tr>
<tr>
<td>Hospital size (&lt;500 beds or not)</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if hospital size on the index date is &lt;500 beds and 0 if ≥500 beds.</td>
</tr>
<tr>
<td>Hospitalization status on index date</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if hospitalization status is inpatient and 0 if outpatient.</td>
</tr>
<tr>
<td>CHADS&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Baseline characteristic</td>
<td>CHADS&lt;sub&gt;2&lt;/sub&gt; score will be calculated based on age and the presence of congestive heart failure, hypertension, diabetes, and stroke or TIA.</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Measurement</td>
<td>Description</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score</td>
<td>Baseline characteristic</td>
<td>CHA₂DS₂-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.</td>
</tr>
<tr>
<td>PT-INR (Prothrombin time-international normalized ratio)</td>
<td>Baseline period</td>
<td>Continuous variable.</td>
</tr>
<tr>
<td>* Only available for patients treated with warfarin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure diagnosis in baseline</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if there are ≥1 diagnoses for heart failure ICD-10 or disease codes during the baseline period.</td>
</tr>
<tr>
<td>Coronary heart disease diagnosis in baseline</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if there are ≥1 diagnoses for coronary heart disease ICD-10 or disease codes during the baseline period.</td>
</tr>
<tr>
<td>Peripheral arterial disorder diagnosis in baseline</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if there are ≥1 diagnoses for peripheral arterial disorder ICD-10 or disease codes during the baseline period.</td>
</tr>
<tr>
<td>Myocardial infarction diagnosis in baseline</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if there are ≥1 diagnoses for myocardial infarction ICD-10 or disease codes during the baseline period.</td>
</tr>
<tr>
<td>Hyperthyroidism or thyrotoxicosis in baseline</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if there are ≥1 diagnoses for hyperthyroidism ICD-10 or disease codes during the baseline period.</td>
</tr>
<tr>
<td>Stroke, TIA or SE diagnosis in baseline</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if there are ≥1 diagnoses for Stroke, TIA or systemic embolism ICD-10 or disease codes during the baseline period.</td>
</tr>
<tr>
<td>Renal dysfunction diagnosis in baseline</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if there are ≥1 diagnoses for renal dysfunction ICD-10 or disease codes during the baseline period.</td>
</tr>
<tr>
<td>Liver dysfunction diagnosis in baseline</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if there are ≥1 diagnoses for liver dysfunction ICD-10 or disease codes during the baseline period.</td>
</tr>
<tr>
<td>Bleeding diagnosis in baseline</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if there are ≥1 diagnoses for bleeding ICD-10 or disease codes during the baseline period.</td>
</tr>
<tr>
<td>Hypertension diagnosis in baseline</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if there are ≥1 diagnoses for hyper tension ICD-10 or disease codes during the baseline period.</td>
</tr>
<tr>
<td>Diabetes mellitus diagnosis in baseline</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if there are ≥1 diagnoses for diabetes mellitus ICD-10 or disease codes during the baseline period.</td>
</tr>
<tr>
<td>Cancer diagnosis in baseline</td>
<td>Baseline period</td>
<td>Dichotomous variable equals 1 if there are ≥1 diagnoses for diabetes mellitus ICD-10 or disease codes during the baseline period.</td>
</tr>
<tr>
<td>Treated with antiplatelet drug in baseline</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if there are ≥1 prescriptions of antiplatelet drug ATC or receipt codes during the baseline period.</td>
</tr>
<tr>
<td>Treated with NSAIDs in baseline</td>
<td>Baseline characteristic</td>
<td>Dichotomous variable equals 1 if there are ≥1 prescriptions of NSAIDs ATC or receipt codes during the baseline period.</td>
</tr>
</tbody>
</table>
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-arrhythmics 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
- CHADS\textsubscript{2} score in baseline
- CHA\textsubscript{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 method to a simple PSM (shown above), IPTW with stabilized weights will be used as a secondary analysis to balance patient characteristics between two groups\textsuperscript{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

\[
\sum_{i=1}^{n} \frac{1}{PS_i} \cdot \frac{N_t}{N_t - \frac{1}{PS_i}}
\]
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 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.
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.

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
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
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.
## 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

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<th>Outcome</th>
<th>Analysis Set</th>
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<th>Subgroups</th>
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<th>Covariates/Strata</th>
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<td>Cox proportional hazards model</td>
<td>Index OAC</td>
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*PS-matched patients* refers to propensity score-matched patients.**
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- Warfarin vs. dabigatran Cohorts
- Warfarin vs. edoxaban Cohorts
- Warfarin vs. rivaroxaban Cohorts
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**Outcome** | **Analysis Set** | **Supports Protocol Objective Number** | **Subgroups** | **Statistical Method** | **Covariates/Strata** | **Missing Data** |
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Stroke/SE | ✓ Warfarin vs. apixaban Cohorts ✓ Warfarin vs. dabigatran Cohorts ✓ Warfarin vs. edoxaban Cohorts ✓ Warfarin vs. rivaroxaban Cohorts |  |  |  |  |  |
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Outcome Analysis Set Supports Protocol Objective Number Subgroups Statistical Method Covariates/Strata Missing Data

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### Outcome Analysis Set Supports Protocol Objective Number

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#### 2) IPTW-matched cohorts

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11 LIST OF TABLES AND TABLE SHELLS

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

12 REFERENCES


Appendix-1: List of ICD-10 Codes

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**Systemic embolism**

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**Peripheral vascular disorder**

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ICD-10, International Statistical Classification of Diseases and Related Health Problems
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14 APPENDIX-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 (bleeding)" or (ecchymoma)"

Group B: Disease name includes (bleeding)" or (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.

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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
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<th>ICD-10</th>
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<td>P519</td>
<td>Umbilical haemorrhage of newborn, unspecified</td>
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<td>P523</td>
<td>Unspecified intraventricular (nontraumatic) haemorrhage of fetus and newborn</td>
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<td>Intracerebral (nontraumatic) haemorrhage of fetus and newborn</td>
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<td>Other intracranial (nontraumatic) haemorrhages of fetus and newborn</td>
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<td>Intracranial (nontraumatic) haemorrhage of fetus and newborn, unspecified</td>
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<td>Neonatal haematemesis</td>
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<td>P542</td>
<td>Neonatal rectal haemorrhage</td>
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<td>P543</td>
<td>Other neonatal gastrointestinal haemorrhage</td>
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<td>P544</td>
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<td>Neonatal jaundice due to bleeding</td>
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<td>Haemorrhage from throat</td>
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<td>Superficial injury of lip and oral cavity</td>
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<td>Traumatic subarachnoid haemorrhage</td>
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<td>Other intracranial injuries</td>
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<td>Other specified injuries of head</td>
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<td>Other and unspecified superficial injuries of throat</td>
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<td>Other and unspecified injuries of cervical spinal cord</td>
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<td>Other and unspecified injuries of thoracic spinal cord</td>
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<td>S272</td>
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<td>S279</td>
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<td>Contusion of external genital organs</td>
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<td>Other injury of lumbar genital organs</td>
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<td>Injury of liver or gallbladder</td>
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<td>Injury of other intra-spinal cord</td>
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<td>Other superficial injuries of shoulder and upper arm</td>
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<td>Contusion of thigh</td>
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<td>Contusion of knee</td>
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<td>S801</td>
<td>Contusion of other and unspecified parts of lower leg</td>
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<td>Contusion of toe(s) without damage to nail</td>
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ICD-10, International Statistical Classification of Diseases and Related Health Problems
### 15 APPENDIX-4: EFFECTIVENESS ENDPOINTS

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<td>I61</td>
<td>Exclude non-traumatic extradural haemorrhage</td>
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<th>Disease</th>
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<td>Include only abdominal aortic embolism</td>
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<td>I741</td>
<td>Include only aortic embolism</td>
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<td>I742</td>
<td>Include only acute arterial occlusive disease of arteries of upper extremities</td>
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<td>I743</td>
<td>Include only femoral arterial occlusion and acute arterial occlusive disease of arteries of lower extremities</td>
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<td>I744</td>
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<td>I745</td>
<td>Include only iliac artery embolism</td>
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<td>I748</td>
<td>Include only hepatic artery embolism</td>
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<td>I749</td>
<td>Include only thromboembolism, embolic infarction, aortic embolism</td>
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<td>I748</td>
<td>Include only subclavian artery stenosis</td>
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### 16 APPENDIX-5: SAFETY ENDPOINTS

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<td>Subarachnoid haemorrhage from anterior communicating artery</td>
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<td>Subarachnoid haemorrhage from posterior communicating artery</td>
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<td>Subarachnoid haemorrhage from intracranial artery, unspecified</td>
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<td>Other subarachnoid haemorrhage</td>
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