# STATISTICAL AND EPIDEMIOLOGICAL ANALYSIS PLAN (SEAP) FOR NON-INTERVENTIONAL STUDIES (NIS)



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| **Title:** | Statistical and Epidemiological Analysis Plan (SEAP) for post-authorization safety study (PASS) to assess the safety and effectiveness of warfarin, dabigatran, and rivaroxaban among Japanese patients with non-valvular atrial fibrillation and concomitant coronary artery disease |
| **Brief lay title:** | A study based on Japanese medical records that looks at bleeding events in people with atrial fibrillation and coronary artery disease who start taking either dabigatran, rivaroxaban, or warfarin |
| **SEAP version identifier:** | 1.0 |
| **Date of last version of SEAP:** | Not applicable |
| **NIS Statistician** [SEAP author] | [redacted] |
| **NIS** [redacted] [SEAP reviewer] | [redacted] |
| **NIS Data** [redacted] [SEAP reviewer] | [redacted] |
| | |

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# 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| BI | Boehringer Ingelheim |
| CI | Confidence Interval |
| IQR | Interquartile range |
| NIS | Non-interventional study |
| SEAP | Statistical and epidemiological analysis plan |
| DMRP | Data management and review plan |
| AE | Adverse Event |
| AF | Atrial Fibrillation |
| ASD | Absolute Standardized Difference |
| CA | Competent Authority |
| CAD | Coronary Artery Disease |
| CCDS | Company Core Data Sheet |
| CHA2DS2-VASc | Congestive heart failure, Hypertension, Age ⩾ 75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female) |
| CI | Confidence Interval |
| CML | Local Clinical Monitor |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CTP | Clinical Trial Protocol |
| DMRP | Data Management and Review Plan |
| DCP | Diagnosis Procedure Combination |
| eCRF | Electronic Case Report Form |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| EMA | European Medicines Agency |
| ESC | European Society of Cardiology |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GEP | Good Epidemiological Practice |
| GI | Gastrointestinal |
| GPP | Good Pharmacoepidemiology Practice |
| GVP | Good Pharmacovigilance Practices |
| HAS-BLED | Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs/alcohol concomitantly |
| HR | Hazard Ratio |
| IB | Investigator's Brochure |
| ICD-10 | The 10$^{th}$ Revision of the International Classification of Diseases |
| ICH | Intracranial Hemorrhage |
| ID | Identification Number |

| | |
|---|---|
| IEC | Independent Ethics Committee |
| IPTW | Inverse Probability of Treatment Weighting |
| IRB | Institutional Review Board |
| MAH | Marketing Authorization Holder |
| [redacted] | [redacted] |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial Infarction |
| NIS | Non-Interventional Study |
| NOAC | Non-vitamin K Oral Anticoagulant |
| NVAF | Non-valvular Atrial Fibrillation |
| SE | Systemic Embolism |
| VAF | Valvular Atrial Fibrillation |
| ESRD | End-stage renal disease |
| OAC | Oral Anticoagulation |

# 3. RESPONSIBLE PARTIES

NIS Statistician [SEAP author] : [redacted]

SEAP reviewers are:

- BI NIS [redacted] [SEAP reviewer] (in all cases) : [redacted]
- NIS Data [redacted] [SEAP reviewer] (in all cases): [redacted]
- RWE CoE [SEAP reviewer] (for all globally initiated studies and for local studies) involving BI products and Global NIS not involving BI products: [redacted]
- TM Epi [SEAP reviewer] (When BI NIS [redacted] is not TM Epi; in all cases): [redacted]

# 4. PURPOSE AND SCOPE

SEAP reviewers are expected to be familiar with the NIS protocol entitled "Comparative safety and effectiveness of warfarin, dabigatran, and rivaroxaban among Japanese patients with non-valvular atrial fibrillation (NVAF) and concomitant coronary artery disease (CAD)" version 1.0 dated 15 November 2021 unless otherwise stated.

The SEAP addresses the details of the implementation of this study. In the SEAP, you can find the detailed definitions on how to identify each of the index medication cohorts, detailed data analysis plan such as the inverse probability of treatment weighting (IPTW), propensity score matching and main analysis plan.

# 5. AMENDMENTS AND UPDATES

None

# 6. RESEARCH QUESTION AND OBJECTIVE

This non-interventional cohort study using data from large Japan clinical database to access the safety and effectiveness of oral anticoagulants among patients with non-valvular atrial fibrillation (NVAF) and concomitant coronary artery disease (CAD).

**Primary objective:**
To compare the risk of major bleeding between dabigatran and warfarin, and between rivaroxaban and warfarin, among Japanese NVAF patients with concomitant CAD.

**Secondary objective:**
To compare the net clinical benefits of dabigatran vs. warfarin, and rivaroxaban vs. warfarin, among Japanese NVAF patients with concomitant CAD. The net clinical benefits are defined as free of composite outcome of stroke/SE/MI/all-cause mortality (inpatient)/major bleeding/major GI bleeding (hospitalization due to GI bleeding)/ICH.

**Further objective:**
If the required sample size can be fulfilled and the baseline characteristics are balanced between dabigatran and rivaroxaban groups after IPTW adjustment, to compare the safety and net clinical benefits of dabigatran vs rivaroxaban among Japanese NVAF patients with concomitant CAD.

# 7. RESEARCH METHODS

## 7.1 STUDY DESIGN

This study will be a non-interventional cohort study based on existing data, the [redacted]) database. It contains comprehensive medical record data, blood test result data and insurance claims data. Patients meeting the in/exclusion criteria will be selected and will be defined as 3 patient groups:

Group 1: new users of warfarin
Group 2: new users of dabigatran
Group 3: new users of rivaroxaban

Comparative analyses of the study will follow a two-step approach. In the first step, the primary and secondary outcomes, as well as baseline characteristics, will be compared between Group 1&2 and Group 1&3, respectively.

The second step will utilize the estimated results from step one, which are HRs of major bleeding events between Group 1&2 and between Group 1&3 among NVAF patients with concomitant CAD, to carry out a more accurate sample size calculation to compare dabigatran versus rivaroxaban. If feasible, comparisons will be made on the same outcomes as in step one.

## 7.2 SETTING

Study Period: the entire time period that includes the look-back period, the cohort entry date (drug index date), and follow-up period for the study population. The study period will be from April 18th, 2011 (start of data collection) to December 31st, 2020 (end of data collection).

Patient Selection Period: the time period for which patients are eligible to enter the cohort, which is from April 18th, 2012 to December 31st, 2020.

Cohort Entry Date: The drug index date, defined as the first date of prescription for dabigatran, rivaroxaban, or warfarin during the patient selection period.

Look-back Period: the 365-day period that ends 1 day prior to the cohort entry date. The earliest start date of the look-back period is April 18th, 2011.

Loss of follow-up: the last data point available in the database during the study period.

### 7.2.1 Follow up period

The follow up period starts from cohort entry date (first prescription of the drug of interest) and ends at the earliest date of the following dates:

- Discontinuation date of index OAC.

Discontinuation of the index OAC, defined as a continuous gap of 45 days or more between the expected refill date and the actual refill date. The discontinuation date is defined as 45 days after the expected refill date. The codes for index OAC are listed in Annex 1.

- Date of switching to another OAC.
  If the index OAC is discontinued, the date of switching to another OAC was the first prescription date of another OAC within 45 days of the expected refill date of the index OAC. The codes of another OAC are the codes in Annex 1 excluding codes of the index OAC.
- Loss of follow-up date.
  The date of the last inpatient/outpatient encounter during period starting from index OAC date and ending on December 31st, 2020.
- Date of the first occurrence of outcomes of interest (for primary outcome: major bleeding; for secondary outcome: the onset of the first occurring component event; for further outcomes: the respective onset of component events) during period starting from index OAC date and ending on December 31st, 2020.
- Date of death during period starting from index OAC date and ending on December 31st, 2020.
- End of study period date (December 31st, 2020).

## 7.3 STUDY POPULATION

The target population of the study are Japanese NVAF patients with concomitant CAD, who are prescribed with dabigatran, rivaroxaban, or warfarin. The study population will be selected based on the following in/exclusion criteria:

Inclusion Criteria

1. ≥18 years of age on index date
2. Has one year of look-back period prior to the index date (defined as the first date of prescription for dabigatran, rivaroxaban, or warfarin during the study period)
3. New users of warfarin, dabigatran, and rivaroxaban, defined as patients without historic use of any oral anticoagulants during the look-back period
4. Has at least 1 diagnosis of NVAF during the look-back period prior to or on the index date
5. Has at least 1 diagnosis of CAD during the look-back period prior to or on the index date

Exclusion Criteria

1. Diagnosed with end-stage renal disease (ESRD), or undergo hemodialysis, or experience pregnancy during the study period
2. Initiate warfarin, dabigatran, rivaroxaban due to valvular AF (VAF), AF associated with mechanical valve malfunction or mechanical complication of heart valve prosthesis, or rheumatic AF
3. Underwent joint replacement procedures or diagnosed with venous thromboembolism during the look-back period prior to or on the index date
4. Prescribed with more than 1 OAC on the index date

5. Prescribed with more than 2 anti-platelet drugs per prescription (triple or quadruple anti-platelet use), or prescribed with any anti-platelet injection
6. Patients with missing or ambiguous age or sex information

The codes for OAC are listed in Annex 1 and codes to select study population (in/exclusion criteria) are listed in Annex 2.

NVAF during the look-back period prior to or on the index date is defined as patients had diagnosis of AF and had no diagnosis of VAF during the specific period.

Pregnancy during the study period is defined as patients had any of the following:

- Confirmed diagnosis of pregnancy in the study period.
- In FF1 data (discharge summary data), the admission date was within the study period, and returned true for the pregnancy flag or the number of weeks of pregnancy at the time of hospitalization greater than 0 or the number of weeks of pregnancy at the time of delivery greater than 0.
- Medical treatment of pregnancy in the study period.

AF associated with mechanical valve malfunction or mechanical complication of heart valve prosthesis is defined as a record with diagnosis of AF and diagnosis of mechanical valve malfunction or mechanical complication of heart valve prosthesis.

Rheumatic AF is defined as a record with diagnosis of AF and diagnosis of rheumatic heart disease.

## 7.4 STUDY VISITS

Not applicable.

# 8. VARIABLES

Study variables are explained the study protocol section 9.3. you can find operational definitions below:

## 8.1 EXPOSURES

Respectively for Group 1 (new users of warfarin), group 2 (new users of dabigatran), and group 3 (new users of rivaroxaban), the first prescribed dates of warfarin, dabigatran and rivaroxaban during the study period were selected as the index date, and the patients did not have any OAC prescription during the look back period. The [redacted] Receipt Code of warfarin, dabigatran and rivaroxaban are in Annex 1.

## 8.2 OUTCOMES

### 8.2.1 Primary outcomes

Operational definition of fatal or non-fatal major bleeding is the first new confirmed diagnosis of

- blood transfusion (inpatient or outpatient)
  OR
- bleeding of inpatient (non-DPC hospital)
  OR
- bleeding of inpatient (DPC hospital) with “disease name behind this hospitalization” (“dpcdiseasesegment”=21)

during the follow up period. The ICD-10 diagnosis codes of blood transfusion and bleeding are in Annex 3.

### 8.2.2 Secondary outcomes

Operational definition of composite outcome of stroke/SE/MI/all-cause mortality (inpatient) /major bleeding/major GI bleeding (hospitalization due to GI bleeding)/ICH is the first new confirmed diagnosis of

- Stroke/SE/MI/ Major bleeding (defined as primary outcome)/ICH
  OR
- Major GI bleeding (hospitalization due to GI bleeding)
  OR
- All-cause mortality (inpatient)

during the follow up period. The ICD-10 diagnosis codes of stroke, SE, MI, major bleeding, ICH, major GI bleeding and death are in Annex 3.

Major GI bleeding (hospitalization due to GI bleeding) is the first new confirmed diagnosis of major GI bleeding in inpatient claims from non-DPC hospital or inpatient claims with “disease name behind this hospitalization” (“dpcdiseasesegment”=21) from DPC hospital.

All-cause mortality (inpatient) is:

- Death of discharge status
  OR
- Died within 24 hours of admission in FF1 data (discharge summary data)
  OR
- Confirmed diagnosis of death in inpatient claims.

[redacted]

## 8.3 COVARIATES

Please check section 9.3.3. of the study protocol. List of covariates and operational definitions are added to Annex 4.

The HAS-BLED score is calculated as the total points of the following elements (1 point per element) during the baseline period including the index date.

- Confirmed diagnosis of hypertension
- Dialysis-dependent kidney disease including confirmed diagnosis of hepatic dysfunction or confirmed diagnosis of renal dysfunction or on hemodialysis treatment
  OR
  Confirmed diagnosis of cirrhosis
  OR
  Renal transplant
  OR
  Serum creatinine > 200 m mol/L
  OR
  ALP > 3x upper limit (1050 IU/L) or ALT > 3x upper limit (132 IU/L) or AST > 3x upper limit (114 IU/L)
  OR
  Bilirubin > 2x upper limit (2.4 mg/dL)
- Confirmed diagnosis of stroke
- Confirmed diagnosis of bleeding history
- Age calculated as of index date > 65 years old
- Confirmed diagnosis of excessive alcohol use
  OR
  on treatment of excessive alcohol use
  OR
  on antiplatelet drugs or non-steroidal anti-inflammatory drug

The CHA2DS2-VASc score is calculated as the total points of the following elements during the baseline period including the index date.

- Confirmed diagnosis of congestive heart failure (1 point)
- Hypertension (1 point) including confirmed diagnosis of hypertension or on any anti-hypertensive medications
- Age calculated as of index date ≥ 75 years old (2 points)

- Diabetes Mellitus (1 point) including confirmed diagnosis of diabetes mellitus or on any anti-hyperglycemia agents or on any insulin treatment
- Confirmed diagnosis of stroke (2 points)
- Vascular disease including confirmed diagnoses of MI or peripheral arterial disorder (1 point)
- Age between 65 and 74 (1 point)
- Female (1 point)

The code used to define the elements of HAS-BLED score and CHA2DS2-VASc score are in Annex 4.

# 9. DATA SOURCES

Please check section 9.4 of the study protocol.

# 10. DATA MANAGEMENT AND SOFTWARE/TOOLS

Data is stored using the secured Instant Health Data (IHD) platform (https://www.bhei.com/product). The database is accessed through a user and password system. All study details are addressed either in the protocol, SEAP, or DMRP.

## 10.1 SOFTWARE/TOOLS

The cohort selection, exposure, outcomes, and covariates derivation will be conducted in IHD platform and the data analysis will be run in BI internal server using SAS software 9.4 (SAS Institute, Inc., Cary, NC) or R Studio 3.5.2.

## 10.2 HANDLING OF MISSING VALUES

The absence of a code for a condition will be interpreted as an absence of the event. If a study variable is totally missing from a database, it is excluded from the analysis of the pooled data.

If a variable is missing for only some of the patients a missing data category will be added and utilized in the analysis.

## 10.3 HANDLING OF INCONSISTENCIES IN DATA AND OUTLIERS

For lab values, distribution of each variable will be assessed. The extreme outliers will be treated as missing values, approaches to handling missing values are described in the previous section.

# 11. DATA ANALYSIS

Please check section 9.7 of the study protocol

## 11.1 MAIN ANALYSIS

During the first step of the comparative analysis, the baseline characteristics of the individual NOAC groups will be balanced with the warfarin group to account for potential confounding effects through an inverse probability of treatment weighting (IPTW) method. A multinomial logistic regression model will be used to estimate the generalized propensity score (GPS). The treatment membership (warfarin, dabigatran and rivaroxaban) is the dependent variable and all the covariate variables listed in Annex 4 except for "Anti-platelet drugs" and "The number of anti-platelet drugs per prescription" are independent variables in the multinomial logistic regression model, as the two variables can be fully derived from the variable "Anti-platelet use duration". For each patient, we will obtain the estimated GPS vector with components of the probabilities of receiving each treatment (warfarin, dabigatran and rivaroxaban) through the multinomial logistic regression model.

The stabilized IPTW (s-IPTW) will be used to deal with the inflation of type I error and extremely large weight when using regular IPTW. The s-IPTW is calculated as

$$w_i = \frac{\Pr(T = k)}{\Pr(T = k|X = x_i)}$$

for the $i$th patient, where $T$ is the treatment membership and $x_i$ is the covariates of this patient. The denominator is the $k$th component of GPS vector of the $i$th patient who was actually in treatment group $k$ and the numerator is the marginal probability of receiving treatment $k$[R22-1420].

The GPS distributions (density curves, boxplots) of each treatment will be used to examine GPS overlap between the treatment groups. Patients outside of the common support or overlap area for any component of the GPS vector are removed from the analysis. The area of common support is formed by defining boundaries for each component $k$, $k = 1, 2, 3$ of the GPS vector [R22-1419]:

$$Pr(T = k|x)^{low} = \max[\min(Pr(T = k|x, T = 1)), \min(Pr(T = k|x, T = 2)), \min(Pr(T = k|x, T = 3))]$$

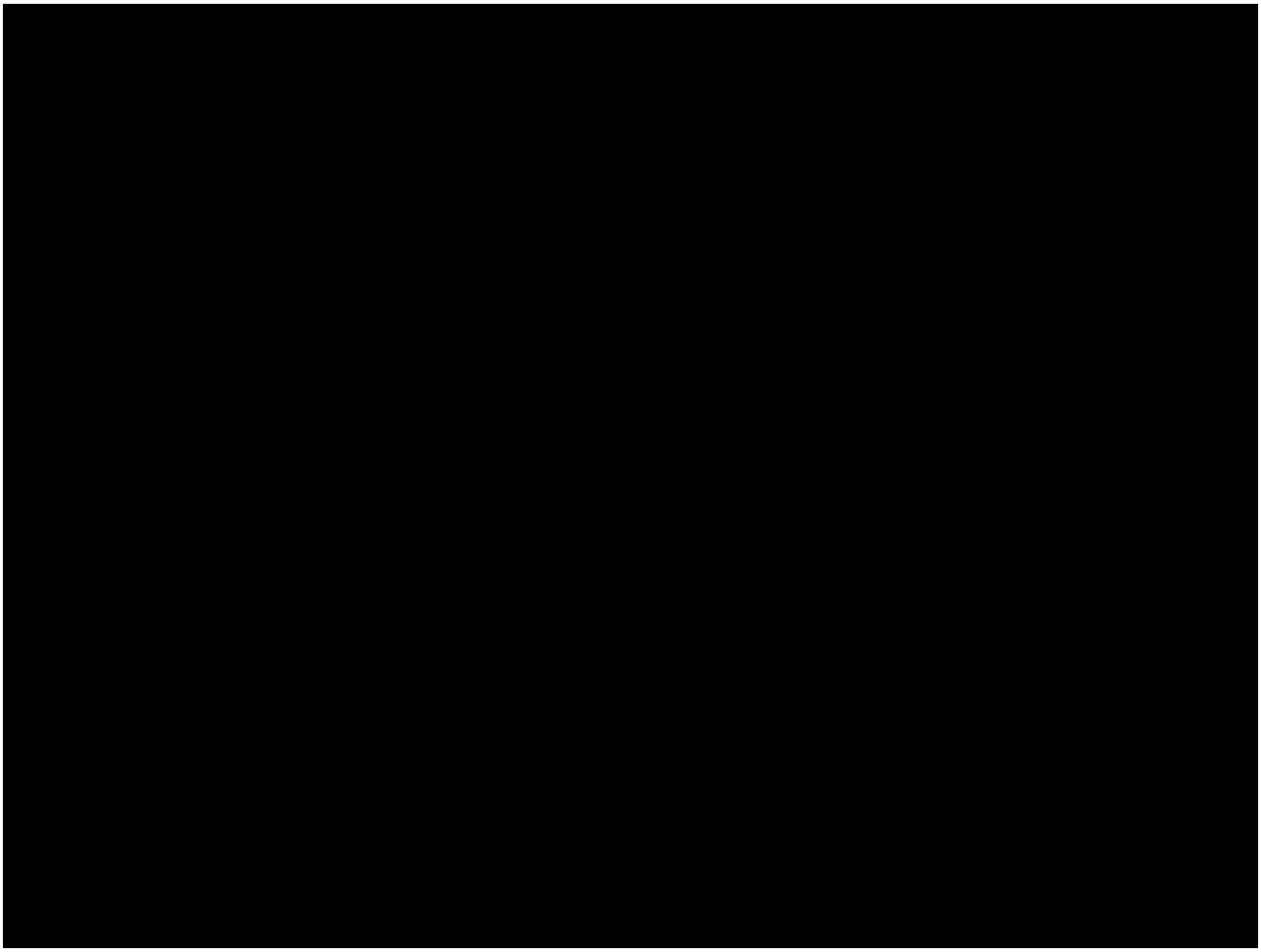
$$Pr(T = k|x)^{high} = \min[\max(Pr(T = k|x, T = 1)), \max(Pr(T = k|x, T = 2)), \max(Pr(T = k|x, T = 3))]$$

The distributions of s-IPTW for each treatment group will be examined, the mean s-IPTW is expected to be close to 1. Weight truncation based on the distributions of s-IPTW will be applied if there are extremely high s-IPTW.

The baseline demographics, risk factors, and clinical characteristics will be compared between the treatment groups (dabigatran vs warfarin, rivaroxaban vs warfarin, dabigatran vs rivaroxaban) using the absolute standardized difference (ASD) pre- and post- s-IPTW to assess the balance of these confounders. A covariate will be considered well balanced if the ASD is below 0.1.

A Cox proportional hazard regression model with s-IPTW will be used to estimate adjusted hazard ratios (aHRs) of treatments (dabigatran vs warfarin, rivaroxaban vs warfarin) and their 95% CIs on primary, secondary, and further outcomes. The treatment membership is the independent variable in the model. A patient will be censored if discontinuation of the index OAC or switching to another OAC or death or loss to follow-up occurred before outcome event. If substantial covariate imbalance between treatment group is noted assessed by a standardized difference >0.1, then the Cox proportional hazard model will be further adjusted by including covariates that are out of balance in the model. A robust sandwich variance estimation of the treatment effect estimates will be used to account for the fact that the pseudo-population size is inflated or deflated relative to the original population and that weights are estimated [P21-02302].

A sensitivity analysis will be performed by restricting the follow-up period to 3 years for Cox regression models on primary and secondary outcomes.



### 11.3 SAFETY ANALYSIS

Please check section 9.7.3 of the study protocol

## 12. QUALITY CONTROL

Please check section 9.8 of the study protocol

## 13. REFERENCES

### 13.1 PUBLISHED REFERENCES


| | |
|---|---|
| R22-1420 | Masahiro Sugihara. Survival analysis using inverse probability of treatment weighted methods based on the generalized propensity score. Pharmaceutical Statistics 2010; 9: 21-34 |
| R22-1419 | Lopez MJ, Gutman R. Estimation of causal effects with multiple treatments: a review and new ideas. Statist. Sci. 2017; 32(3): 432-454 |
| P21-02302 | Rishi J Desai, Jessica M Franklin. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. BMJ 2019; 367:l5657 |


### 13.2 UNPUBLISHED REFERENCES

Not applicable.

## ANNEX 1. LIST OF [redacted] RECEIPT CODE FOR OAC

| OAC | [redacted] Receipt Code | Description |
|---|---|---|
| Warfarin | 610450012 | Warfarin K Tablets 1mg [B01A0] |
| | 610460002 | Arefarin Tablets 1mg [B01A0] |
| | 610462024 | Warfarin Potassium Tablets 0.5mg (HD) [B01A0] |
| | 610462025 | Warfarin Potassium Tablets 2mg (HD) [B01A0] |
| | 610463227 | Warfarin Potassium Tablets 0.5mg [B01A0] |
| | 610463228 | Warfarin Potassium Tablets 2mg [B01A0] |
| | 613330001 | Warfarin Potassium Tablets 1mg [B01A0] |
| | 613330002 | Warfarin Potassium Tablets 5mg [B01A0] |
| | 613330003 | Warfarin Tablets 1mg [B01A0] |
| | 613330004 | Warfarin Tablets 5mg [B01A0] |
| | 620000731 | Warfarin Potassium Tablets 1mg (HD) [B01A0] |
| | 620002332 | Warfarin Tablets 0.5mg [B01A0] |
| | 620002472 | Warlin Tablets 0.5mg [B01A0] |
| | 620002473 | Warlin Tablets 1mg [B01A0] |
| | 620811502 | Warfarin K Tablets 1mg (F) [B01A0] |
| | 620811503 | Warfarin K Tablets 1mg (NISSIN) [B01A0] |

| | | |
|---|---|---|
| | 620811507 | Warfarin K Tablets 1mg (TEVA) [B01A0] |
| | 620811510 | Warfarin K Tablets 1mg (TOWA) [B01A0] |
| | 620811511 | Warfarin K Tablets 1mg (NP) [B01A0] |
| | 621480504 | Warfarin K Tablets 0.5mg (TEVA) [B01A0] |
| | 621480506 | Warfarin K Tablets 0.5mg (TOWA) [B01A0] |
| | 621480507 | Warfarin K Tablets 0.5mg (NP) [B01A0] |
| | 621480604 | Warfarin K Tablets 2mg (NP) [B01A0] |
| | 621938101 | Warfarin K Fine Granules 0.2% (NS) [B01A0] |
| | 621940901 | Warfarin K Fine Granules 0.2% (YD) [B01A0] |
| | 622122601 | Warfarin Granules 0.2% [B01A0] |
| Dabigatran | 622043301 | Prazaxa Capsules 75mg [B01E0] |
| | 622043401 | Prazaxa Capsules 110mg [B01E0] |
| Rivaroxaban | 622068301 | Xarelto Tablets 10mg [B01F0] |
| | 622068401 | Xarelto Tablets 15mg [B01F0] |
| | 622449101 | Xarelto Fine Granules Packet 10mg [B01F0] |
| | 622449201 | Xarelto Fine Granules Packet 15mg [B01F0] |
| | 622829001 | Xarelto OD Tablets 10mg [B01F0] |
| | 622829101 | Xarelto OD Tablets 15mg [B01F0] |
| Apixaban | 622224901 | Eliquis Tablets 2.5mg [B01F0] |
| | 622225001 | Eliquis Tablets 5mg [B01F0] |
| Edoxaban | 622080901 | Lixiana Tablets 15mg [B01F0] |
| | 622576001 | Lixiana OD Tablets 15mg [B01F0] |
| | 622081001 | Lixiana Tablets 30mg [B01F0] |
| | 622576101 | Lixiana OD Tablets 30mg [B01F0] |
| | 622375201 | Lixiana Tablets 60mg [B01F0] |
| | 622576201 | Lixiana OD Tablets 60mg [B01F0] |

# ANNEX 2. CODE USED TO CREATE STUDY POPULATION

DIGNOSIS CODE:

| **Indication** | **ICD-10/[redacted] disease code** | **Description** |
|---|---|---|
| AF | I48 | Atrial fibrillation and flutter |
| | I48.0 | Paroxysmal atrial fibrillation |
| | I48.1 | Persistent atrial fibrillation |
| | I48.2 | Chronic atrial fibrillation |
| | I48.3 | Typical atrial flutter |
| | I48.4 | Atypical atrial flutter |
| | I48.9 | Atrial fibrillation and atrial flutter, unspecified |
| VAF | 8846941 | valvular atrial fibrillation |

| | | |
|---|---|---|
| CAD | 4140014 | coronary artery disease |
| | 8831577 | coronary artery heart disease |
| | I20 | Angina pectoris |
| | I20.0 | Unstable angina |
| | I20.1 | Angina pectoris with documented spasm |
| | I20.8 | Other forms of angina pectoris |
| | I20.9 | Angina pectoris, unspecified |
| | I21 | Acute myocardial infarction |
| | I21.0 | Acute transmural myocardial infarction of anterior wall |
| | I21.1 | Acute transmural myocardial infarction of inferior wall |
| | I21.2 | Acute transmural myocardial infarction of other sites |
| | I21.3 | Acute transmural myocardial infarction of unspecified site |
| | I21.4 | Acute subendocardial myocardial infarction |
| | I21.9 | Acute myocardial infarction, unspecified |
| | I22 | Subsequent myocardial infarction |
| | I22.0 | Subsequent myocardial infarction of anterior wall |
| | I22.1 | Subsequent myocardial infarction of inferior wall |
| | I22.8 | Subsequent myocardial infarction of other sites |
| | I22.9 | Subsequent myocardial infarction of unspecified site |
| | I23 | Certain current complications following acute myocardial infarction |
| | I23.0 | Haemopericardium as current complication following acute myocardial infarction |
| | I23.1 | Atrial septal defect as current complication following acute myocardial infarction |
| | I23.2 | Ventricular septal defect as current complication following acute myocardial infarction |
| | I23.3 | Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction |
| | I23.4 | Rupture of chordae tendineae as current complication following acute myocardial infarction |
| | I23.5 | Rupture of papillary muscle as current complication following acute myocardial infarction |
| | I23.6 | Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction |
| | I23.8 | Other current complications following acute myocardial infarction |
| | I24 | Other acute ischaemic heart diseases |
| | I24.0 | Coronary thrombosis not resulting in myocardial infarction |
| | I24.1 | Dressler syndrome |
| | I24.8 | Other forms of acute ischaemic heart disease |
| | I24.9 | Acute ischaemic heart disease, unspecified |
| | I25 | Chronic ischaemic heart disease |

| | | |
|---|---|---|
| | I25.0 | Atherosclerotic cardiovascular disease, so described |
| | I25.1 | Atherosclerotic heart disease |
| | I25.2 | Old myocardial infarction |
| | I25.3 | Aneurysm of heart |
| | I25.4 | Coronary artery aneurysm and dissection |
| | I25.5 | Ischaemic cardiomyopathy |
| | I25.6 | Silent myocardial ischaemia |
| | I25.8 | Other forms of chronic ischaemic heart disease |
| | I25.9 | Chronic ischaemic heart disease, unspecified |
| ESRD | N16.5 | Renal tubulo-interstitial disorders in transplant rejection |
| | N18.5 | Chronic kidney disease, stage 5 |
| | T82.4 | Mechanical complication of vascular dialysis catheter |
| | T86.1 | Kidney transplant failure and rejection |
| | Y60.2 | Unintentional cut, puncture, perforation or haemorrhage during surgical and medical care during kidney dialysis or other perfusion |
| | Y61.2 | Foreign object accidentally left in body during surgical and medical care during kidney dialysis or other perfusion |
| | Y62.2 | Failure of sterile precautions during surgical and medical care during kidney dialysis or other perfusion |
| | Y84.1 | Kidney dialysis as the cause of abnormal reaction of the patient, or of later complication, without mention of misadventure at the time of the procedure |
| | Z49 | Care involving dialysis |
| | Z49.0 | Preparatory care for dialysis |
| | Z49.1 | Extracorporeal dialysis |
| | Z49.2 | Other dialysis |
| | Z49 | Care involving dialysis |
| | Z94.0 | Kidney transplant status |
| | Z99.2 | Dependence on renal dialysis |
| mechanical valve malfunction or mechanical complication of heart valve prosthesis | T82 | Complications of cardiac and vascular prosthetic devices, implants and grafts |
| | T82.0 | Mechanical complication of heart valve prosthesis |
| | T82.1 | Mechanical complication of cardiac electronic device |
| | T82.2 | Mechanical complication of coronary artery bypass and valve grafts |
| | T82.3 | Mechanical complication of other vascular grafts |
| | T82.4 | Mechanical complication of vascular dialysis catheter |
| | T82.5 | Mechanical complication of other cardiac and vascular devices and implants |
| | T82.6 | Infection and inflammatory reaction due to cardiac valve prosthesis |
| | T82.7 | Infection and inflammatory reaction due to other cardiac and vascular devices, implants and grafts |
| | T82.8 | Other specified complications of cardiac and vascular prosthetic devices, implants and grafts |

| | | |
|---|---|---|
| | T82.9 | Unspecified complication of cardiac and vascular prosthetic device, implant and graft |
| Rheumatic heart disease | I09 | Other rheumatic heart diseases |
| | I09.0 | Rheumatic myocarditis |
| | I09.1 | Rheumatic diseases of endocardium, valve unspecified |
| | I09.2 | Chronic rheumatic pericarditis |
| | I09.8 | Other specified rheumatic heart diseases |
| | I09.9 | Rheumatic heart disease, unspecified |
| Venous thromboembolism | I26 | Pulmonary embolism |
| | I26.0 | Pulmonary embolism with mention of acute cor pulmonale |
| | I26.9 | Pulmonary embolism without mention of acute cor pulmonale |
| | I80.2 | Phlebitis and thrombophlebitis of other deep vessels of lower extremities |
| Pregnancy | codes presented in the following excel file:  1160-0308 diagnosis_pregnancy.: | |

PROCEDURE CODE:

| **Procedure** | **Kubun code** | **Description** |
|---|---|---|
| Hemodialysis | C102 | Home self-peritoneal irrigation guidance management fee |
| | C102-2 | Home hemodialysis frequent time guidance management |
| | C155 | Automated peritoneal irrigation equipment add-on fee |
| | J038-2 | Continuous mild blood filtration |
| | J038-21 | Impaired people add-on fee (continuous mild hemofiltration) |
| | J038-22 | Impaired people add-on fee (continuous mild hemofiltration) |
| | K635-3 | Catheter intraabdominal placement for continuous ambulatory peritoneal dialysis |
| Joint replacement | K082-21 | Artificial joint removal (knee) |
| | K082-22 | Artificial joint removal (foot) |
| | K082-23 | Artificial joint removal (finger) |
| | K082-31 | Artificial joint reimplantation add-on fee (knee) |
| | K082-32 | Artificial joint reimplantation add-on fee (foot) |
| | K082-33 | Artificial joint reimplantation add-on fee (finger) |
| | K082-4 | Total joint replacement of autologous costal bone and cartilage |
| | K082-5 | Total artificial talus replacement |
| | K082-6 | Hip prosthesis sliding surface exchange |
| | K083 | Direct traction using steel codes, and others |
| | K083-2 | Arthrodesis for clubfoot using foot plate and pinch bar |
| Pregnancy | K890 | Tuboplasty (tubo-ovarian transplant, tubal bypass procedure and others) |

| | | |
|---|---|---|
| | K890-2 | Falloposcopic tuboplasty |
| | K890-3 | Laparoscopic salpingoplasty |
| | K891 | Hysterocervicotomy during delivery (including suture) |
| | K892 | Vaginal breech delivery |
| | K893 | Aspiration delivery |
| | K8941 | Outlet/low forceps delivery |
| | K8942 | Middle forceps delivery |
| | K895 | Perineal/vulvar incision and suturing (during delivery) |
| | K8961 | Perineal/vaginal tear suturing (during delivery) (with involvement of the muscular layer) |
| | K8962 | Perineal/vaginal tear suturing (during delivery) (with involvement of the anal) |
| | K8963 | Perineal/vaginal tear suturing (during delivery) (up to vaginal fornix) |
| | K8964 | Suturing of perineal/vaginal tear (associated with rectal tear) (during delivery) |
| | K897 | Endocervical tear suturing (during delivery) |
| | K8981 | Caesarean delivery (emergency cesarean section) |
| | K8982 | Cesarean section (selective cesarean section) |
| | K8983 | Complication add-on fee (hysterotomy) |

MEDICATION CODE:

| **Medication** | [redacted] **Receipt Code** | **Description** |
|---|---|---|
| Anti-platelet injection | 620004669 | Shiphnos I.V.Injection 10mg 0.5%2mL [C01D0] |
| | 620008786 | Agilease I.V.Injection 10mg 0.5%2mL [C01D0] |
| | 620008891 | Tohmol I.V.Injection 10mg 0.5%2mL [C01D0] |
| | 620008931 | Persantin I.V.Injection 10mg 0.5%2mL [C01D0] |
| | 620330301 | Dipyridamole I.V.Injection 10mg (ISEI) 0.5%2mL [C01D0] |
| | 620330502 | Dipyridamole I.V.Injection 10mg (NICHIIKO) 0.5%2mL [C01D0] |
| | 642170001 | Agilease Injection 0.5%2mL [C01D0] |
| | 642170008 | Tohmol Injection 0.5%2mL [C01D0] |
| | 642170009 | Persantin Injection 0.5%2mL [C01D0] |
| Anti-platelet Drug | codes presented in the following excel file:  1160-0308 Anti-platelet drug.xlsx | |

# ANNEX 3. CODE USED FOR OUTCOMES

| **Indication** | **ICD-10 code** | **Description** |
|---|---|---|

| | | |
|---|---|---|
| Blood transfusion | K92.0 | Haematemesis |
| Bleeding | D50 | Iron deficiency anaemia |
| | D50.0 | Iron deficiency anaemia secondary to blood loss (chronic) |
| | D50.1 | Sideropenic dysphagia |
| | D50.8 | Other iron deficiency anaemias |
| | D50.9 | Iron deficiency anaemia, unspecified |
| | D62 | Acute posthaemorrhagic anaemia |
| | D64.9 | Anaemia, unspecified |
| | H35.6 | Retinal haemorrhage |
| | I31.2 | Haemopericardium, not elsewhere classified |
| | I60 | Subarachnoid haemorrhage |
| | I60.0 | Subarachnoid haemorrhage from carotid siphon and bifurcation |
| | I60.1 | Subarachnoid haemorrhage from middle cerebral artery |
| | I60.2 | Subarachnoid haemorrhage from anterior communicating artery |
| | I60.3 | Subarachnoid haemorrhage from posterior communicating artery |
| | I60.4 | Subarachnoid haemorrhage from basilar artery |
| | I60.5 | Subarachnoid haemorrhage from vertebral artery |
| | I60.6 | Subarachnoid haemorrhage from other intracranial arteries |
| | I60.7 | Subarachnoid haemorrhage from intracranial artery, unspecified |
| | I60.8 | Other subarachnoid haemorrhage |
| | I60.9 | Subarachnoid haemorrhage, unspecified |
| | I61 | Intracerebral haemorrhage |
| | I61.0 | Intracerebral haemorrhage in hemisphere, subcortical |
| | I61.1 | Intracerebral haemorrhage in hemisphere, cortical |
| | I61.2 | Intracerebral haemorrhage in hemisphere, unspecified |
| | I61.3 | Intracerebral haemorrhage in brain stem |
| | I61.4 | Intracerebral haemorrhage in cerebellum |
| | I61.5 | Intracerebral haemorrhage, intraventricular |
| | I61.6 | Intracerebral haemorrhage, multiple localized |
| | I61.8 | Other intracerebral haemorrhage |
| | I61.9 | Intracerebral haemorrhage, unspecified |
| | K92.2 | Gastrointestinal haemorrhage, unspecified |
| | M25.0 | Haemarthrosis |
| | M25.00 | Haemarthrosis, multiple sites |
| | M25.01 | Haemarthrosis, shoulder region |
| | M25.02 | Haemarthrosis, upper arm |
| | M25.03 | Haemarthrosis, forearm |
| | M25.04 | Haemarthrosis, hand |
| | M25.05 | Haemarthrosis, pelvic region and thigh |
| | M25.06 | Haemarthrosis, lower leg |

| | | |
|---|---|---|
| | M25.07 | Haemarthrosis, ankle and foot |
| | M25.08 | Haemarthrosis, other |
| | M25.09 | Haemarthrosis, site unspecified |
| | N92.0 | Excessive and frequent menstruation with regular cycle |
| | R04 | Haemorrhage from respiratory passages |
| | R04.0 | Epistaxis |
| | R04.1 | Haemorrhage from throat |
| | R04.2 | Haemoptysis |
| | R04.8 | Haemorrhage from other sites in respiratory passages |
| | R04.9 | Haemorrhage from respiratory passages, unspecified |
| | R31 | Unspecified haematuria |
| | R58 | Haemorrhage, not elsewhere classified |
| Stroke/SE/MI/ICH/Maj or GI bleeding/Death | codes presented in the following excel file:  1160-0308 stroke_SE_MI_GI_ICH_ | |

# ANNEX 4. STUDY COVARIATES

| N | Category | Variables | Definition |
|---|---|---|---|
| 1 | Demographic characteristics | Age | - By year (calculated on index date) |
| | | Gender | - Male, Female |
| 2 | Ischemic and hematologic characteristics | CHA2DS2-VASc score | Codes used to define elements of CHA2DS2-VASc score in the following excel file:  11600308 CHA2DS2_VASc.xlsx |
| | | HAS-BLED score | Codes used to define elements of HAS- BLED score in the following excel file:  1160-0308 HASBLED.xlsx |
| 3 | Comorbidities | Heart failure | ICD-10 diagnosis codes presented in the following excel file: |
| | | Peripheral arterial disorder | |
| | | Hypertension | |
| | | Diabetes | |

| | | | |
|---|---|---|---|
| | | Prior stroke/transient ischemic attack (TIA)/SE<br>Cerebrovascular disease<br>Myocardial infarction<br>Acute Coronary Syndrome<br>Unstable angina<br>Bleeding history<br>Renal dysfunction<br>Hepatic dysfunction<br>Cancers<br>Peptic ulcer disease<br>Obesity |  <br>1160-0308 Comorbidities.xlsx |
| 4 | Co-medications | Anti-platelet drugs<br>The number of anti-platelet drugs per prescription<br>Anti-platelet use duration<br>Nonsteroidal anti-inflammatory drugs<br>Gastric secretion inhibitors<br>Statins<br>Heparins<br>Proton pump inhibitor<br>Antihypertensive drugs | Anti-platelet drugs include aspirin, clopidogrel, ticagrelor and prasugrel. The number of anti-platelet drugs is the number of anti-platelet drugs prescribed on the earliest prescription date before or on the index date during the look back period. Anti-platelet use duration is based on the number of days from the earliest anti-platelet prescription date to the index date. [redacted] Receipt codes presented in the following excel file:<br>  <br>1160-0308 Comedication.xlsx |
| 5 | Medical procedures | Cardioversion procedures<br>Ablation procedures<br>Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting | [redacted] Receipt codes presented in the following excel file:<br>  <br>1160-0308 Medical procedure.xlsx |

# ANNEX 5. ANALYSIS TABLE SHELLS

Note：Table 1, Table 2a, and Table 3 are shown here to exemplify; please find the complete table shells in the attached excel file below


Safety comparisons between OACs among

**Table 1. Patient Flow Diagram**

| | Dabigatran | Rivaroxaban | Warfarin |
|---|---|---|---|
| Total number of patients [redacted] database 2008-04-01 - 2020-12-31 | | | |
| Patients prescribed with index drug in selection period | | | |
| Patients older than 18 years old at drug index date | | | |
| Have at least 1y look-back prior drug index date | | | |
| New user of Dabigatran or Rivaroxaban or Warfarin, i.e, patients without historic use of any oral anticoagulants during the look-back period | | | |
| Have at least 1 diagnosis of NVAF during the look-back period prior to or on the index date | | | |
| Have at least 1 diagnosis of CAD during the look-back period prior to or on the index date | | | |
| Excluded because of Diagnosis of end-stage renal disease, or undergo hemodialysis, or experience pregnancy during the study period | | | |
| Excluded because of Initiation of warfarin, dabigatran, rivaroxaban due to valvular AF, AF associated with mechanical valve malfunction or mechanical complication of heart valve prosthesis, or rheumatic AF | | | |

| | | | |
|---|---|---|---|
| Excluded because Underwent joint replacement procedures or diagnosed with venous thromboembolism during the look-back period prior to or on the index date | | | |
| Excluded because of Prescription with more than 1 OAC on the index date | | | |
| Excluded because of Triple or Quadruple Antiplatelet Use or Antiplatelet Injection | | | |
| Excluded because Patients with missing or ambiguous age or sex information | | | |
| Final cohort | | - | |

**Table 2a. Baseline Characteristics Comparisons – Dabigatran vs. Warfarin**

| | Crude | | | s-IPTWAdjusted | | | PS-matched | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Dabigatran | Warfarin | Abs. Std. Dif | Dabigatran | Warfarin | Abs.Std.Dif | Dabigatran | Warfarin | Abs.Std.Dif |
| **Age** | | | | | | | | | |
| …mean (sd) | | | | | | | | | |
| …median [IQR] | | | | | | | | | |
| …Min-Max | | | | | | | | | |
| **Gender** | | | | | | | | | |
| …1 - Male; n (%) | | | | | | | | | |
| …2 - Female; n (%) | | | | | | | | | |
| **CHA2DS2-VASc score** | | | | | | | | | |
| …mean (sd) | | | | | | | | | |
| …median [IQR] | | | | | | | | | |
| …Min-Max | | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| HAS-BLED score | | | | | | | | | |
| ···mean(sd) | | | | | | | | | |
| ···median[IQR] | | | | | | | | | |
| ···Min-Max | | | | | | | | | |
| **Heart failure; n (%)** | | | | | | | | | |
| **Peripheral arterial disorder; n (%)** | | | | | | | | | |
| **Hypertension; n (%)** | | | | | | | | | |
| **Diabetes; n (%)** | | | | | | | | | |
| **Prior stroke/transient ischemic attack (TIA)/SE; n (%)** | | | | | | | | | |
| **Myocardial infarction; n (%)** | | | | | | | | | |
| **Acute Coronary Syndrome; n (%)** | | | | | | | | | |
| **Unstable angina; n (%)** | | | | | | | | | |
| **Bleeding history; n (%)** | | | | | | | | | |
| **Renal dysfunction; n (%)** | | | | | | | | | |
| **Hepatic dysfunction; n (%)** | | | | | | | | | |
| **Cancers; n (%)** | | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Peptic ulcer disease; n (%)** | | | | | | | | | |
| **Cerebrovascular disease; n (%)** | | | | | | | | | |
| **Obesity; n (%)** | | | | | | | | | |
| **Anti-platelet drugs (include aspirin, clopidogrel, ticagrelor, prasugrel); n (%)** | | | | | | | | | |
| **The number of anti-platelet drugs per prescription (single antiplatelet, dual antiplatelet, none); n (%)** | | | | | | | | | |
| single antiplatelet; | | | | | | | | | |
| dual antiplatelet; | | | | | | | | | |
| none; | | | | | | | | | |
| **Antiplatelet use duration; n (%)** | | | | | | | | | |
| Single Antiplatelet Use: 6 months to 1 year | | | | | | | | | |
| Single Antiplatelet | | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Use: 1 month to 6 months | | | | | | | | | |
| Single Antiplatelet Use: <1 month | | | | | | | | | |
| Dual Antiplatelet Use: 6 months to 1 year | | | | | | | | | |
| Dual Antiplatelet Use: 1 month to 6 months | | | | | | | | | |
| Dual Antiplatelet Use: <1 month | | | | | | | | | |
| None | | | | | | | | | |
| **Nonsteroidal anti-inflammatory drugs; n (%)** | | | | | | | | | |
| **Gastric secretion inhibitors; n (%)** | | | | | | | | | |
| **Statins; n (%)** | | | | | | | | | |
| **Heparins; n (%)** | | | | | | | | | |
| **Proton pump inhibitor; n (%)** | | | | | | | | | |
| **Antihypertensive drugs; n (%)** | | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Cardioversion procedures; n (%)** | | | | | | | | | |
| **Ablation procedures; n (%)** | | | | | | | | | |
| **Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting; n (%)** | | | | | | | | | |

**Table 3. Rates and Risks of Fatal/Non-fatal Major Bleeding**

| | Comparison 1 | | Comparison 2 | | Comparison 3* | |
|---|---|---|---|---|---|---|
| | Dabigatran | Warfarin | Rivaroxaban | Warfarin | Dabigatran | Rivaroxaban |
| *Rate* | | | | | | |
| *Crude* | | | | | | |
| Number of patients | | | | | | |
| Number of events | | | | | | |
| Number of person-years | | | | | | |
| | | | | | | |
| Incidence Rate per 1,000 person-years (95% CI) | | | | | | |
| Incidence Proportion (n (%)) | | | | | | |
| *s-IPTW adjusted* | | | | | | |
| Number of patients | | | | | | |
| Number of events | | | | | | |
| Number of person-years | | | | | | |
| Incidence Rate per 1,000 person-years (95% CI) | | | | | | |
| Incidence Proportion (n (%)) | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| *PS-matched* | | | | | | |
| Number of patients | | | | | | |
| Number of events | | | | | | |
| Number of person-years | | | | | | |
| Incidence Rate per 1,000 person-years (95% CI) | | | | | | |
| Incidence Proportion (n (%)) | | | | | | |
| ***Hazard ratios*** | | | | | | |
| s-IPTWAdjusted Hazard Ratio (95% CI, p value) | | | | | | |
| PS Matched Hazard Ratio (95% CI, p value) | | | | | | |

*Note: comparison 3 will be conducted if sample size is sufficient (see section 9.5 of protocol)

# ANNEX 6. REVIEWERS AND APPROVAL SIGNATURES

The NIS SEAP must be sent for review to the following individuals **prior to approval**.

| Reviewer | NIS involving BI product(s) | NIS not involving BI product(s) | |
|---|---|---|---|
| | | Global NIS | Local NIS |
| NIS Lead | X | X | X |
| Global TM Epi* | X | X | X |
| NIS Data Manager | X | X | X |
| RWE CoE | X | X | |

** When BI NIS lead is not TM Epi*

**Study Title:** Comparative safety and effectiveness of warfarin, dabigatran, and rivaroxaban among Japanese patients with non-valvular atrial fibrillation (NVAF) and concomitant coronary artery disease (CAD)

**Study Number: 1160.0308**

**Protocol Version: V1.0**

**I herewith certify that I agree to the content of the study SEAP and to all documents referenced in the study SEAP.**

Position: Name/Date: Signature: _____

Position: Name/Date: Signature: _____

Position: Name/Date: Signature: _____

Position: Name/Date: Signature: _____