Non-Interventional Study (NIS) Protocol

Document Number:	c37044336-01
BI Study Number:	1160-0308
BI Investigational Product(s):	Pradaxa
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)
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
Protocol version identifier:	1.0
Date of last version of protocol:	Not applicable
PASS:	Yes
EU PAS register number:	EUPAS41345
Active substance:	Dabigatran, warfarin, rivaroxaban
Medicinal product:	Pradaxa, Xarelto
Product reference:	1160
Procedure number:	Not applicable
Marketing authorisation holder(s):	[redacted]
Joint PASS:	No
Research question and objectives:	The study aims to evaluate the safety and effectiveness comparisons between warfarin, dabigatran, and rivaroxaban in routine clinical practice among Japanese NVAF patients with concomitant 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. **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.
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Date:	15 Nov 2021
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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
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
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 10th 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]	
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NIS	Non-Interventional Study
NOAC	Non-vitamin K Oral Anticoagulant
NVAF	Non-valvular Atrial Fibrillation
OAC	Oral Anticoagulation

PASS	Post-Authorization Safety Study
RE-LY	Randomized Evaluation of Long-term Anticoagulant Therapy
ROCKET-AF	The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
SAE	Serious Adverse Event
SD	Standard Deviation
SEAP	Statistical and Epidemiological Analysis Plan
SE	Systemic Embolism
s-IPTW	Stabilized Inverse Probability of Treatment Weighting
TIA	Transient Ischemic Attack

3. RESPONSIBLE PARTIES

BI NIS [redacted]

[redacted]

[redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: **Pradaxa, Xarelto**			
Name of active ingredient: **Dabigatran, warfarin, rivaroxaban**			
Protocol date: Nov. 15th, 2021	**Study number:** 1160-0308	**Version/Revision:** 1.0	**Version/Revision date:** NA
Title of study:	Comparative safety and effectiveness of warfarin, dabigatran, and rivaroxaban among Japanese patients with non-valvular atrial fibrillation (NVAF) and concomitant coronary artery disease (CAD)		
Rationale and background:	Atrial fibrillation (AF) is a common cardiac arrhythmia and is associated with 15-20% of all strokes [R96-0267], [R96-0252]. Among AF patients, the prevalence of concomitant coronary artery disease (CAD) is estimated to range from 17% to 46.5% [P17-09543], which can increase the risks of major bleeding, stroke, and mortality [R21-3491]. The management of AF is complicated by the presence of concomitant CAD when co-prescription of oral anticoagulation (OAC) with antiplatelet therapy is needed. Therefore, careful considerations are necessary in choosing antithrombotic therapies to balance the bleeding risk, stroke risk, and other thrombosis risks. Non-valvular atrial fibrillation (NVAF) is a subtype of AF. The 2020 European Society of Cardiology (ESC) Guidelines recommends non-vitamin K oral anticoagulant (NOAC) treatments over warfarin for eligible oral anticoagulant-naïve NVAF patients [P21-09613]. Dabigatran and rivaroxaban are the first two NOACs approved for thromboprophylaxis of AF, which are also the two widely used NOACs in Asia. According to RE-LY and ROCKET-AF, both dabigatran and rivaroxaban have shown at least equal efficacy compared to warfarin in the prevention of stroke/systemic embolism (SE), and dabigatran 110 mg bid demonstrates superiority over warfarin in major bleeding among NVAF patients [P09-11669], [R11-4223]. Further, post hoc or subgroup analyses of the two pivotal trials indicate consistent superiority in the safety profiles of NOACs versus warfarin among NVAF patients with concomitant CAD [P12-00109]. However, the current literature lacks comparative assessment of clinical outcomes among Asian NVAF patients with CAD who are managed with warfarin, dabigatran, or rivaroxaban in routine clinical practice. Given the increased risks of major bleeding and recurrent coronary events associated with CAD, it is necessary to evaluate the safety outcomes and net clinical benefits among Asian NVAF patients with concomitant CAD.		

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Research question and objectives:	The study aims to make safety and effectiveness comparisons between warfarin, dabigatran, and rivaroxaban in routine clinical practice among Japanese NVAF patients with concomitant 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. **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.		
Study design:	This study will be a non-interventional study based on existing 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,		

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	respectively. Next, a sample size calculation using results from step one will be carried out to assess the of comparisons between Group 2 and Group 3. If feasible, comparisons will be made on the same outcomes as in step one.
Population:	The study period is from April 18th, 2011 to December 31st, 2020. Patients in the Japan [redacted] database during the study period will be identified based on the following in/exclusion criteria: Inclusion Criteria 1. ≥18 years of age 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, or undergo hemodialysis, or experience pregnancy during the study period 2. Initiate warfarin, dabigatran, rivaroxaban due to valvular AF, 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

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	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
Variables:	**<u>Exposure</u>**: Initiation of dabigatran, rivaroxaban, or warfarin during the study period (dosage and duration not restricted) **<u>Primary outcome</u>:** · Fatal or non-fatal major bleeding (defined as any blood transfusion and/or any hospitalization with associated bleeding) in all three patient groups **<u>Secondary outcome</u>:** · Composite outcome of stroke/systemic embolism (SE)/myocardial infarction (MI)/all-cause mortality (inpatient)/major bleeding/major gastrointestinal (GI) bleeding (hospitalization due to GI bleeding)/intracranial hemorrhage (ICH) in all three patient groups (the first occurrence of any of the component events counts as an event; this outcome indicates the net clinical benefit) **<u>Further outcomes</u>:** · Individual component of the composite outcome in all three patient groups **<u>Covariates (collected at baseline):</u>** <u>Demographic characteristics</u> · Age · Gender (male/female/other) <u>Ischemic and hematologic characteristics (if available)</u> · CHA2DS2-VASc score · HAS-BLED score

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Comorbidities (has at least 1 diagnosis before or on the index date during the look-back period)

- Heart failure (yes/no)
- Peripheral arterial disorder (yes/no)
- Hypertension (yes/no)
- Diabetes (yes/no)
- Prior stroke/transient ischemic attack (TIA)/SE (yes/no)
- Cerebrovascular disease (yes/no)
- Myocardial infarction (yes/no)
- Acute Coronary Syndrome (yes/no)
- Unstable angina (yes/no)
- Bleeding history (yes/no)
- Renal dysfunction (yes/no)
- Hepatic dysfunction (yes/no)
- Cancers (yes/no)
- Peptic ulcer disease (yes/no)
- Obesity (yes/no)

Baseline co-medication (had used the drug before or on the index date during the look-back period)

- Anti-platelet drugs (include aspirin, clopidogrel, ticagrelor, prasugrel) (yes/no)
- The number of anti-platelet drugs per prescription (single antiplatelet, dual antiplatelet, none)
- Antiplatelet use duration (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; measured from the first antiplatelet prescription to baseline)
- Nonsteroidal anti-inflammatory drugs (yes/no)
- Gastric secretion inhibitors (yes/no)
- Statins (yes/no)
- Heparins (yes/no)

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	• Proton pump inhibitor (yes/no) • Antihypertensive drugs (yes/no) Baseline medical procedures (underwent the procedure before or on the index date during the look-back period) • Cardioversion procedures (yes/no) • Ablation procedures (yes/no) • Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting (yes/no)		
Data sources:	The [redacted]) database is one of the largest databases in Japan, collecting data from over 400 acute care hospitals which account for 25% of emergency hospitals in Japan. The database contains comprehensive medical record data, blood test result data, insurance claims data, and pharmacy claims data, covering more than 35 million patients, 34% of whom are ≥ 65 years old. Each patient is assigned a specific identification number (ID) to which all inpatient and outpatient data are linked. The diagnosis is coded according to the 10th Revision of the International Classification of Diseases (ICD-10) codes or local disease codes.		
Expected Study size:	During the period from April 2011 to December 2020, there are roughly 17000, 11000, and 4000 NVAF adult patients with a medical history of CAD being respectively treated with either warfarin, rivaroxaban or dabigatran as the first OAC (defined as no history of OAC usage during the 12-month look-back period) within the [redacted] database. According to a published paper based on the [redacted] database, the mean (standard deviation, SD) treatment duration of different drugs among new user groups ranged from 265 (263.8) to 868 (725) days, with the dabigatran group exposed to the treatment the longest [P20-03503]. According to the same article, the major bleeding rate for AF patients is 1.5 per 100 patient-years. In comparison, AF patients with concomitant CAD are more likely to fall under high or medium/high risk categories of the HAS-BLED score, a predictor of bleeding complications among AF patients, thus increasing the event rate for		

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	major bleeding about 2-3 times [P09-11669], [R11-4223]. Therefore, the major bleeding rate is assumed to be rather 3-4.5 per 100 patient-years among Japanese AF+CAD patients in the [redacted] database. Furthermore, previous analysis concluded substantial superiority of dabigatran (HR=0.66, 95% CI 0.529-0.825) and rivaroxaban (HR=0.74, 95% CI 0.618-0.879) over warfarin in major bleeding among AF patients [P09-11669], [R11-4223]. The comparative rates of major bleeding between individual NOAC- and warfarin- treated patients should follow a similar trend among NVAF patients with concomitant CAD. For dabigatran vs. warfarin, if the HR is assumed to be 0.66 and the average exposure time to be 1 year per patient, an event rate of 3 per 100 patient-years with 80% power will require a total sample size of 6050 patients and 3025 patients for each arm; an event rate of 4.5 per 100 patient-years will require a total sample size of 4040 patients and 2020 patients for each arm. To be conservative, the lower bound is selected and therefore each arm needs around 3025 patients. Similarly, assuming the HR of rivaroxaban vs. warfarin is 0.74 and the average exposure time to be 1 year per patient, the lower-bound event rate of 3 per 100 patient-years with 80% power will require a total sample size of 9690 patients and 4845 patients for each arm. Additionally, to balance the baseline characteristics between groups, truncated Inverse Probability of Treatment Weighting (IPTW) will be applied and therefore sample loss is expected. In NOAC vs. warfarin comparisons, if the sample loss due to IPTW truncation is assumed to be 20%, the sample sizes for dabigatran and rivaroxaban groups need to be greater than 3781 and 6056 respectively, which can be satisfied by the database.		
Data analysis:	Descriptive analysis will be performed for describing patient demographic and clinical characteristics. Comparative analysis for		

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	primary and secondary outcomes will be conducted between treatment groups. The comparative analysis will follow a two-step approach. The first step will compare the baseline characteristics and clinical outcomes of individual NOAC (Dabigatran, Rivaroxaban) - versus warfarin-treated groups. To minimize potential confounding bias, the baseline characteristics of the individual NOAC groups will be balanced with the warfarin group using Stabilized Inverse Probability of Treatment Weighting (s-IPTW). Absolute standardized difference (ASD) will be used to measure balance of patient characteristics. A Cox proportional hazard regression model with the time since NOAC drug index date as the underlying timescale will be used to compute adjusted hazard ratios (aHRs) with 95% CIs. If substantial covariate imbalance between treatment group is noted, as assessed by a standardized difference >0.1, then outcome models will be further adjusted by covariates that are out of balance using multivariable Cox proportional hazards models. The second step will determine whether the patient characteristics are comparable between dabigatran and rivaroxaban treatment groups and whether there is the required sample size for comparisons between dabigatran- and rivaroxaban-treated groups. If the database can fulfil the sample size requirement, analysis will move forward for comparative analysis between the two NOAC groups. For each component outcome of all 3 groups, the event-free survival will be plotted with Kaplan-Meier curves after s-IPTW adjustments. A sensitivity analysis will be conducted for primary and secondary outcomes by using a conventional 1:1 propensity score matching method to assess the robustness of the s-IPTW model.
Milestones:	Protocol finalization: Sep. 2021 DMRP completion: Nov. 2021 Final report of study results: Dec. 2021

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1				
2				

6. MILESTONES

Milestone	Planned Date
Protocol finalization	Sep. 2021
DMRP	Oct. 2021
Final report of study results:	Dec. 2021

7. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) is a common cardiac arrhythmia and is associated with 15-20% of all strokes [R96-0267], [R96-0252]. Among AF patients, the prevalence of concomitant coronary artery disease (CAD) is estimated to range from 17% to 46.5% [P17-09543], which can increase the risks of major bleeding, stroke, and mortality [R21-3491]. The management of AF is complicated by the presence of concomitant CAD when co-prescription of oral anticoagulation (OAC) with antiplatelet therapy is needed. Therefore, careful considerations are necessary in choosing antithrombotic therapies to balance the bleeding risk, stroke risk, and other thrombosis risks.

Non-valvular atrial fibrillation (NVAF) is a subtype of AF. The 2020 European Society of Cardiology (ESC) Guidelines recommends non-vitamin K oral anticoagulant (NOAC) treatments over warfarin for eligible oral anticoagulant-naïve NVAF patients [P21-09613]. Dabigatran and rivaroxaban are the first two NOACs approved for thromboprophylaxis of AF, which are also the two widely used NOACs in Asia. According to RE-LY and ROCKET-AF, both dabigatran and rivaroxaban have shown at least equal efficacy compared to warfarin in the prevention of stroke/systemic embolism (SE), and dabigatran 110 mg bid demonstrates superiority over warfarin in major bleeding among NVAF patients [P09-11669], [R11-4223]. Further, post hoc or subgroup analyses of the two pivotal trials indicate consistent superiority in the safety profiles of NOACs versus warfarin among NVAF patients with concomitant CAD [P12-00109]. However, the current literature lacks comparative assessment of clinical outcomes among Asian NVAF patients with CAD who are managed with warfarin, dabigatran, or rivaroxaban in routine clinical practice. Given the increased risks of major bleeding and recurrent coronary events associated with CAD, it is necessary to evaluate the safety outcomes and net clinical benefits among Asian NVAF patients with concomitant CAD.

8. RESEARCH QUESTION AND OBJECTIVES

The study aims to make safety and effectiveness comparisons between warfarin, dabigatran, and rivaroxaban in routine clinical practice among Japanese NVAF patients with concomitant 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. Specifically, the composite outcome will be used to indicate net clinical benefits.

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.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This study will be a non-interventional cohort study based on existing 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.

9.2 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.

Follow-Up Period: the period starting from the cohort entry date (first prescription of the drug of interest) and ending at the earliest occurrence of the following:

- 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 (discontinuation date defined as 45 days after the expected refill date)
- Switching to another OAC, if the index OAC is discontinued and another OAC is started within 45 days of the expected refill date of the index OAC
- Loss of follow-up
- 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)
- Death (except for analyses for the composite outcome and all-cause mortality as a component outcome)
- End of study period

The notion of enrollment is not defined in [redacted] Therefore, a proxy enrolment criterion defined as start of enrolment = date of first inpatient/outpatient encounter; end of enrolment = date of last inpatient/outpatient encounter will be used. “Enrolment” herein will refer to this proxy enrolment measure. For entry into the study population, patients will be required to have had at least 365 days of enrollment prior to the cohort entry date.

9.2.1 Study Sites

The study will be based on existing data from the [redacted] database, which covers all insurance types and a large population size (9.4). Thus, selection bias can be minimized.

9.2.2 Study population

The target population of the study are Japanese NVAF patients with concomitant CAD, who are prescribed with dabigatran, rivaroxaban, or warfarin. The source population of the study are Japanese patients in the Japan [redacted]) database during the study period, which is from April 18th, 2011 to December 31st, 2020. The study population will be selected based on the following in/exclusion criteria:

Inclusion Criteria

1. ≥18 years of age
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, or undergo hemodialysis, or experience pregnancy during the study period
2. Initiate warfarin, dabigatran, rivaroxaban due to valvular AF, 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

9.2.3 Study visits

This is a non-interventional study based on existing data, hence not applicable.

9.2.4 Study discontinuation

This is a non-interventional study based on existing data, hence not applicable.

9.3 VARIABLES

9.3.1 Exposures

Exposure:
Respectively for Group 1, 2, and 3, the initiation of warfarin, dabigatran, or rivaroxaban during the study period (dosage and duration are not restricted).

The exposure is measured through drug prescription records, which is recorded as [redacted] Receipt Code. In the [redacted] database, information pertinent to exposure records include the date of dispensing, drug quantity, dose, number of days of prescription supply, and prescriber.

9.3.2 Outcomes

Outcomes are recorded with the 10th Revision of the International Classification of Diseases (ICD-10) codes. In the [redacted] database, information related to outcomes include the date of occurrence, the number of events, and the severity. All outcomes are incident events after the index date.

9.3.2.1 Primary outcomes

Primary outcome:
- Fatal or non-fatal major bleeding (defined as any blood transfusion and/or any hospitalization with associated bleeding) in all three patient groups

9.3.2.2 Secondary outcomes

Secondary outcome:
- Composite outcome of stroke/SE/MI/all-cause mortality (inpatient) /major bleeding/major GI bleeding (hospitalization due to GI bleeding)/ICH in all three patient groups (the first occurrence of any of the component events counts as an event; this outcome indicates the net clinical benefit)

[redacted]

9.3.3 Covariates

Covariates are recorded with the 10th Revision of the International Classification of Diseases (ICD-10) codes for disease diagnosis and [redacted] Receipt Code for medications.

Covariates (collected at baseline):

Demographic characteristics
- Age
- Gender (male/female/other)

Ischemic and hematologic characteristics (if available)
- CHA2DS2-VASc score
- HAS-BLED score

Comorbidities (has at least 1 diagnosis before or on the index date during the look-back period)

- Heart failure (yes/no)
- Peripheral arterial disorder (yes/no)
- Hypertension (yes/no)
- Diabetes (yes/no)
- Prior stroke/transient ischemic attack (TIA)/SE (yes/no)
- Cerebrovascular disease (yes/no)
- Myocardial infarction (yes/no)
- Acute Coronary Syndrome (yes/no)
- Unstable angina (yes/no)
- Bleeding history (yes/no)
- Renal dysfunction (yes/no)
- Hepatic dysfunction (yes/no)
- Cancers (yes/no)
- Peptic ulcer disease (yes/no)
- Obesity (yes/no)

Baseline co-medication (had used the drug before or on the index date during the look-back period)

- Anti-platelet drugs (include aspirin, clopidogrel, ticagrelor, prasugrel) (yes/no)
- The number of anti-platelet drugs per prescription (single antiplatelet, dual antiplatelet, none)
- Antiplatelet use duration (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; measured from the first antiplatelet prescription to baseline)
- Nonsteroidal anti-inflammatory drugs (yes/no)
- Gastric secretion inhibitors (yes/no)
- Statins (yes/no)
- Heparins (yes/no)
- Proton pump inhibitor (yes/no)
- Antihypertensive drugs (yes/no)

Baseline medical procedures (underwent the procedure before or on the index date during the look-back period)

- Cardioversion procedures (yes/no)
- Ablation procedures (yes/no)
- Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting (yes/no)

9.4 DATA SOURCES

The [redacted]) database is one of the largest databases in Japan, collecting data from over 400 acute care hospitals which account for 25% of emergency hospitals in Japan. The database contains comprehensive medical record data,

blood test result data, insurance claims data, and pharmacy claims data, covering more than 35 million patients, 34% of whom are ≥ 65 years old. Each patient is assigned a specific identification number (ID) to which all inpatient and outpatient data are linked. The diagnosis is coded according to the 10th Revision of the International Classification of Diseases (ICD-10) codes or local disease codes.
The distribution of demographic characteristics, including age and sex, of patients registered in the [redacted] database is very similar to the distribution of these characteristics of patients visiting hospitals in Japan.

9.5 STUDY SIZE

During the period from April 2011 to December 2020, there are roughly 17000, 11000, and 4000 NVAF adult patients with a medical history of CAD being respectively treated with either warfarin, rivaroxaban or dabigatran as the first OAC (defined as no history of OAC usage during the 12-month look-back period) within the [redacted] database.

According to a published paper based on the [redacted] database, the mean (standard deviation, SD) treatment duration of different drugs among new user groups ranged from 265 (263.8) to 868 (725) days, with the dabigatran group exposed to the treatment the longest [P20-03503]. According to the same article, the major bleeding rate for AF patients is 1.5 per 100 patient-years. In comparison, AF patients with concomitant CAD are more likely to fall under high or medium/high risk categories of the HAS-BLED score, a predictor of bleeding complications among AF patients, thus increasing the event rate for major bleeding about 2-3 times [P09-11669], [R11-4223]. Therefore, the major bleeding rate is assumed to be rather 3-4.5 per 100 patient-years among Japanese AF+CAD patients in the [redacted] database. Furthermore, previous analysis concluded substantial superiority of dabigatran (HR=0.66, 95% CI 0.529-0.825) and rivaroxaban (HR=0.74, 95% CI 0.618-0.879) over warfarin in major bleeding among AF patients [P09-11669], [R11-4223]. The comparative rates of major bleeding between individual NOAC- and warfarin- treated patients should follow a similar trend among NVAF patients with concomitant CAD.

For dabigatran vs. warfarin, if the HR is assumed to be 0.66 and the average exposure time to be 1 year per patient, an event rate of 3 per 100 patient-years with 80% power will require a total sample size of 6050 patients and 3025 patients for each arm; an event rate of 4.5 per 100 patient-years will require a total sample size of 4040 patients and 2020 patients for each arm. To be conservative, the lower bound is selected and therefore each arm needs around 3025 patients.

Similarly, assuming the HR of rivaroxaban vs. warfarin is 0.74 and the average exposure time to be 1 year per patient, the lower-bound event rate of 3 per 100 patient-years with 80% power will require a total sample size of 9690 patients and 4845 patients for each arm.

Additionally, to balance the baseline characteristics between groups, truncated Inverse Probability of Treatment Weighting (IPTW) will be applied and therefore sample loss is expected. In NOAC vs. warfarin comparisons, if the sample loss due to IPTW truncation is assumed to be 20%, the sample sizes for dabigatran and rivaroxaban groups need to be greater than 3781 and 6056 respectively, which can be satisfied by the database.

9.6 DATA MANAGEMENT

The data management plan is summarized below. Full details of the data management plan are documented in a separate NIS-Data Management and Review Plan (NIS-DMRP).
The data will be managed by BI. Source code of data management and data analyses will be kept for inspection at least for five years after publication of the results.

9.7 DATA ANALYSIS

For the purpose of this study, analyses will be conducted using [redacted] from [redacted] and SAS statistical software (version 9.3 or higher).

Descriptive analysis will be performed for describing patient demographic and clinical characteristics. For categorical variables, the frequency (n) and percentage (%) of patients under each category will be calculated. For continuous variables, the mean, median, standard deviations, interquartile range and minimum and maximum will be summarized.
In comparative analysis, the number of patients, number of events, number of person-years, incidence rate, and incidence proportion will be reported for all outcomes. Incidence rate of each outcome for each treatment group will be reported as the number of events (counts the first event per patient) divided by the total number of person-years at risk during follow-up. In addition, the incidence proportion of each outcome for each treatment group will be reported as the number of events (counts the first event per patient) divided by the total number of patients at risk.
Incidence rate of each outcome for each treatment group will be reported as the main descriptive statistics.

Table shells are attached as Annex 3.

9.7.1 Main analysis

Comparative analysis for primary and secondary outcomes will be conducted between treatment groups. The comparative analysis will follow a two-step approach. The first step will compare the baseline characteristics and clinical outcomes of individual NOAC (Dabigatran, Rivaroxaban) -versus warfarin-treated groups.

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. Propensity scores will be calculated based on multinomial logistic regressions, with all covariates being incorporated. Next, an inverse probability of treatment weighting (IPTW) method will be applied using the calculated propensity score to avoid sample size inflation and to ensure appropriate estimation of variances. Yet, the IPTW estimates can be heavily influenced by large weights, thus destabilizing the results. To increase the robustness of the model, weight truncation will be applied once the distribution of propensity score is available. The distribution of propensity scores will be described, based on which the cut-off points of weight estimates will be chosen. Lastly, the calculated stabilized IPTW (s-IPTW) estimates will be applied to obtain two comparative pairs of individual NOAC vs. warfarin groups, for which the baseline demographics, risk factors, and clinical characteristics will be compared

using the absolute standardized difference (ASD) pre- and post- IPTW to assess the balance and model robustness. A covariate (baseline demographics, risk factors, clinical characteristics) will be considered well balanced if the ASD is below 0.1.

A Cox proportional hazard regression model with the time since NOAC drug index date as the underlying timescale will be used to compute adjusted hazard ratios (aHRs) with 95% CIs. If substantial covariate imbalance between treatment group is noted assessed by a standardized difference >0.1, then outcome models will be further adjusted by covariates that are out of balance using multivariable Cox proportional hazards models.

The second step will determine whether the patient characteristics are comparable between dabigatran and rivaroxaban treatment groups and whether there is the required sample size for comparisons between dabigatran- and rivaroxaban-treated groups. If the database can fulfil the sample size requirement, analysis will move forward for comparative analysis between the two NOAC groups.

For each component outcome of all 3 groups, the event-free survival will be plotted with Kaplan-Meier curves after s-IPTW adjustments.

[redacted]

9.7.3 Safety Analysis

Please refer to the other analysis sections.

9.8 QUALITY CONTROL

The quality control, review, and monitoring plan are summarized below. Greater details are documented in the NIS-DMRP.

The study will strictly follow BI NIS SOP, PASS SOP and any other relevant SOPs. In addition, this study will follow key elements of the Guideline for Good Pharmacoepidemiology Practices (GPP) and Good Pharmacovigilance Practice (GVP). The statistical analytic approach will be reviewed/repeated by a second analyst. The study report will be reviewed, approved and archived per BI SOP.

Whenever possible, validated algorithm will be used for variables, including exposure, outcomes, and covariates, to minimize misclassification and information bias.

One Analyst from [redacted] will build measures (variables) for cohort inclusion, exposures, outcomes and covariates. All measures created, cohorts developed, statistical analyses implemented, and tables output will undergo quality control review performed by at least 1 additional Analyst from [redacted].

Quality controls include checks for the validity and logical content of codes and checks for missing values and variables.
The Analyst from BI assigned to the study will perform a cross-review of the different tables of results.

In order to control for potential inconsistencies and errors, all variables will be tabulated. The distribution of each variable will be examined. Extreme observations with values larger than ± 3 standard deviations (SD) will be examined as potential outliers and consequently excluded from the dataset.

9.9 LIMITATIONS OF THE RESEARCH METHODS

This is a non-interventional study based on existing data. The data do not include vital signs or laboratory test results (e.g. blood pressure, international normalized ratio values, renal function parameters). Therefore, the study may be subject to potential residual confounding due to the absence of certain key data.
Further, the [redacted] database contains around 23% of emergency care hospitals in Japan, which does not form a fully closed healthcare system and therefore could lead to information bias.
Additionally, the mortality is only known for hospitalized patients during hospitalization, thus resulting in inaccurate estimates of the mortality rate.
Due to the above reasons, the study results might not be generalizable to the entire AF patient population in Japan.

9.10 OTHER ASPECTS

Not Applicable.

9.10.1 Data quality assurance

The quality assurance auditor will have access to the investigator's study-related files and correspondence of this study.

9.10.2 Study records

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at BI.

9.10.2.2 Direct access to source data and documents

All source documents must be available at all times for review by BI, IRB/IEC, auditor and inspection by health authorities.

9.10.3 Protocol deviations

The investigators or sub-investigators will not develop or implement any deviation or change to the protocol without prior review by BI.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, Guidelines for Good Pharmacoepidemiology Practice (GPP), and the relevant BI Standard Operating Procedures (SOPs).

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This NIS will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Only anonymized data will be used in the study. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

Collection of AEs
This study is a non-interventional study based on secondary data without involving review or analysis of any individual patient level data. The data is extracted and analyzed in an aggregate manner. Therefore, from safety information collecting perspective, no AE/ADR collection & reporting of individual case safety reports is required. .

11.2 REPORTING TO HEALTH AUTHORITIES

Based on current guidelines from the International Society for Pharmacoepidemiology [R11-4318] and the European Medicines Agency (EMA) [R16-4913], non-interventional studies conducted using health care records do not require expedited reporting of suspected adverse events/reactions. Specifically, as stated in section VI.C.1.2.1 of GVP, Module VI – Management and Reporting of Adverse Reactions to Medicinal Products, for non-interventional study designs, which are based on use of secondary data, reporting of adverse reactions is not required.
This study is a non-interventional study based on secondary data, which will not involve individual medical record review. Therefore, no AE/ADR collection of this study will be performed and reported to Chinese regulatory authorities.
This study is classified as a PASS, and the study report will be reported to health authorities according to local regulations. The study results will also be reflected in the PSURs.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

BI intends to use data from this study to prepare peer-reviewed publications and other scientific communications such as abstracts, posters, and podiums presentations.

The final report of the study result is planned in December 2021. Results of this PASS will be disclosed on encepp.eu and ClinicalTrials.gov.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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[R96-0252] Wolf, P. A., Abbott, R. D., & Kannel, W. B. (1991). Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. Stroke, 22(8), 983–988. https://doi.org/10.1161/01.str.22.8.983

[P17-09543] Michniewicz E, Mlodawska E, Lopatowska P, Tomaszuk-Kazberuk A, Malyszko J. Patients with atrial fibrillation and coronary artery disease - Double trouble. Adv Med Sci. 2018 Mar;63(1):30-35. doi: 10.1016/j.advms.2017.06.005. Epub 2017 Aug 14. PMID: 28818746.

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[R11-4223] Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91. doi: 10.1056/NEJMoa1009638. Epub 2011 Aug 10. PMID: 21830957.

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[R11-4318] ISPE. (April 2007). Guidelines for good pharmacoepidemiology practices (GPP).International Society for Pharmacoepidemiology. http://www.pharmacoepi.org/resources/guidelines_08027.cfm (access date: 9 October 2021)

[R16-4913] European Medicines Agency (EMA). (8 September 2014). Guideline on good pharmacovigilance practices (GVP): module VI - management and reporting of adverse reactions to medicinal products (rev 1). European Medicines Agency (EMA). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf (access date: 9 October 2021)

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1			

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

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)

EU PAS Register® number: EUPAS41345

Study reference number (if applicable): 1160-0308

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6.0
1.1.2 End of data collection[2]	☒	☐	☐	6.0
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	6.0
1.1.5 Registration in the EU PAS Register®	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	6.0

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.0
2.1.2 The objective(s) of the study?	☒	☐	☐	8.0
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	8.0
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	8.0

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.3.2

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11.0

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2.2
4.2.2 Age and sex	☒	☐	☐	9.2.2
4.2.3 Country of origin	☒	☐	☐	9.2.2
4.2.4 Disease/indication	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7.1
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.8

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	9.7.2

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.2

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.10.1
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5.0

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12.0
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.0

Comments:

Name of the main author of the protocol: [redacted]

Date: 2021/11/15

Signature: [redacted]

ANNEX 3. 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 betv

Table 1. Patient Flow Diagram

	Excluded	Total
Total number of patients MDV database 2008-04-01 - 2020-12-31		
Total number of patients MDV database in study period 2011-04-01 - 2020-12-31		
Patients prescribed with Dabigatran, or Rivaroxaban or Warfarin		

Patients older than 18 year old at drug index date		
Have 1y look-back prior drug index date		
New user of Dabigatran or Rivaroxaban or Warfarin		
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 of Prescription with more than 1 OAC on the index date		
Final cohort	-	
Warfarin	-	
Dabigatran	-	
Rivaroxaban	-	

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

	Overall			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)									
single antiplatelet; n (%)									
dual antiplatelet; n (%)									
none; n (%)									
Antiplatelet use duration									

Single antiplatelet use: 6 months to 1 year; n (%)									
Single antiplatelet use: 1 month to 6 months; n (%)									
Single antiplatelet use: <1 month; n (%)									
Dual antiplatelet use: 6 months to 1 year; n (%)									
Dual antiplatelet use: 1 month to 6 months; n (%)									
Dual antiplatelet use: <1 month; n (%)									
None; n (%)									
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						
Overall						
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)						
PS Matched Hazard Ratio (95% CI)						

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

ANNEX 4. REVIEWERS AND APPROVAL SIGNATURES

The NIS Protocol 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
Global TMM / TMMA / TM Market Access	X	X	
Global Project Statistician	X	X	
Global TM RA	X		
Global PVWG Chair	X		
GPV SC	X	X	X
Global CTIS representative	X		
Local Medical Director	X (if local study)		X
Local Head MAcc / HEOR Director	X (if local study)		X
Global TA Head Epi*	X	X	
Global TA Head Clinical Development / Medical Affairs / Market Access*	X	X	
Global TA Head PV RM*	X		
RWE CoE	X	X	
PSTAT / PSTAT-MA (for NISnd only)	X	X	X
NIS DM	X	X	X
Local Head MA/Clinical Development			X (does not apply to NISed without chart abstraction)

** After review by Global TM for function*

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: 1199.0308

Protocol Version: V1.0

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

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____