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Research question and objectives:	<p>The study aims to make safety and effectiveness comparisons between warfarin, dabigatran, and rivaroxaban in real-world clinical settings among Japanese NVAF patients with concomitant CAD.</p> <p><u>Primary objective:</u> To respectively compare the risk of major bleeding between dabigatran and warfarin, and between rivaroxaban and warfarin, among Japanese NVAF patients with concomitant CAD.</p>

	<p><u>Secondary objective:</u> To respectively compare the net clinical benefits of dabigatran vs. warfarin, and rivaroxaban vs. warfarin, among Japanese NVAF patients with concomitant CAD.</p> <p><u>Further objective:</u> If the required sample size can be fulfilled, to compare the safety and net clinical benefits of dabigatran vs rivaroxaban among Japanese NVAF patients with concomitant CAD.</p>
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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 \geq 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 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
MDV	Medical Data Vision
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

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4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa, Xarelto			
Name of active ingredient: Dabigatran, warfarin, rivaroxaban			
Protocol date: May 27 th , 2021	Study number: 1160-0308	Version/Revision: 1.0	Version/Revision date:
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:	<p>Atrial fibrillation (AF) is a common cardiac arrhythmia and is associated with 15-20% of all strokes.^{2,2} Among AF patients, the prevalence of concomitant coronary artery disease (CAD) is estimated to range from 17% to 46.5%,³ which can increase the risks of major bleeding, stroke, and mortality.^{错误!未找到引用源。} Meanwhile, 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.</p> <p>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.⁵ 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 effectiveness 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 patient.^{6,7} 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.⁸ 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 concomitant with CAD.</p>		
Research question and objectives:	The study aims to make safety and effectiveness comparisons between warfarin, dabigatran, and rivaroxaban in real-world clinical settings		

	<p>among Japanese NVAF patients with concomitant CAD.</p> <p><u>Primary objective:</u> To respectively compare the risk of major bleeding between dabigatran and warfarin, and between rivaroxaban and warfarin, among Japanese NVAF patients with concomitant CAD.</p> <p><u>Secondary objective:</u> To respectively compare the net clinical benefits of dabigatran vs. warfarin, and rivaroxaban vs. warfarin, among Japanese NVAF patients with concomitant CAD.</p> <p><u>Further objective:</u> To compare the safety and net clinical benefits of dabigatran vs rivaroxaban among Japanese NVAF patients with concomitant CAD.</p> <p>The null hypothesis is that the two NOACs (dabigatran and rivaroxaban) show equal safety and effectiveness outcomes as warfarin. The alternative hypothesis is that the two NOACs show superiority in the risk of major bleeding and net clinical benefits than warfarin.</p>
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Study design:	<p>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:</p> <p>Group 1: new users of warfarin Group 2: new users of dabigatran Group 3: new users of rivaroxaban</p> <p>Comparative analysis 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 2&3 and Group 1, respectively. Next, a sample size calculation using results from step one will be carried out to assess the feasibility of comparisons between Group 2 and Group3. If feasible, comparisons will be made on the same outcomes as in step one.</p>
Population:	<p>The study period is from April 1st, 2011 to December 31st, 2020. Patients in the Japan Medical Data Vision Co. Ltd. (MDV) database during the study period will be selected based on the following in/exclusion criteria:</p> <p>Inclusion Criteria</p> <ol style="list-style-type: none"> 1. ≥18 years of age 2. Has at least 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 <p>Exclusion Criteria</p> <ol style="list-style-type: none"> 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

Variables:	<p><u>Exposure:</u> Initiation of dabigatran, rivaroxaban, or warfarin during the study period (dosage and duration not restricted)</p> <p><u>Primary outcome:</u></p> <ul style="list-style-type: none"> Respective rate of fatal or non-fatal major bleeding (defined as any transfusion and/or any hospitalization with associated bleeding) in all three patient groups <p><u>Secondary outcome:</u></p> <ul style="list-style-type: none"> Respective rate of composite outcomes of stroke/systemic embolism (SE)/myocardial infarction (MI)/all-cause mortality (inpatient)/major bleeding (MI)/gastrointestinal (GI) bleeding/intracranial hemorrhage (ICH) in all three patient groups (the rate indicates the net clinical benefit, calculated as the net rate of all above safety and effectiveness outcomes) <p><u>Further outcomes:</u></p> <ul style="list-style-type: none"> Respective rates of each component outcome of stroke/SE/MI/all-cause mortality (inpatient)/major bleeding/GI bleeding/ICH in all three patient groups <p><u>Covariates (collected at baseline):</u></p> <p><u>Demographic characteristics</u></p> <ul style="list-style-type: none"> Age Gender (male/female/other) <p><u>Ischemic and hematologic characteristics (if available)</u></p> <ul style="list-style-type: none"> CHA2DS2-VASc score HAS-BLED score <p><u>Comorbidities (has at least 1 diagnosis before or on the index date during the look-back period)</u></p> <ul style="list-style-type: none"> Heart failure (yes/no) Peripheral arterial disorder (yes/no) Hypertension (yes/no) Diabetes (yes/no) Prior stroke/transient ischemic attack (TIA)/SE (yes/no) Myocardial infarction (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) Cerebrovascular disease (yes/no)
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	<ul style="list-style-type: none"> • Obesity (yes/no) • Acute Coronary Syndrome (yes/no) <p><u>Baseline co-medication (had used the drug before or on the index date during the look-back period)</u></p> <ul style="list-style-type: none"> • Anti-platelet drugs (include aspirin, clopidogrel, ticagrelor, prasugrel) (yes/no) • The number of anti-platelet drugs per prescription (single antiplatelet, dual antiplatelet, none) • 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) • Single antiplatelet use duration (weeks, if applicable) <p>Dual antiplatelet use duration (weeks, if applicable)</p> <p><u>Baseline medical procedures (underwent the procedure before or on the index date during the look-back period)</u></p> <ul style="list-style-type: none"> • Cardioversion procedures (yes/no) • Ablation procedures (yes/no) • Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting (yes/no)
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Data sources:	<p>The Medical Data Vision Co. Ltd. (MDV; Tokyo, Japan) database is one of the largest databases in Asia, 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.</p>
Study size:	<p>According to a published paper based on the MDV 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.⁹ According to the same article, the major bleeding rate for AF patients is 1.5 per 100 patient-years. In comparison, AF patients concomitant with 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 for about 2-3 times.^{6,7} Therefore, the major bleeding rate is assumed to be 3-4.5 per 100 patient-years among Japanese AF+CAD patients in the MDV database. Further, 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.^{错误;未找到引用源。7} The comparative rates of major bleeding between NOAC- and warfarin- treated patients should follow a similar trend among NVAf patients concomitant with CAD.</p> <p>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.</p> <p>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.</p> <p>Assuming a 20% of sample loss due to propensity score matching, the sample sizes for dabigatran- and rivaroxaban-treated patients need to be greater than 3781 and 6056, which can be satisfied by the database.</p>

<p>Data analysis:</p>	<p>Descriptive analysis will be performed for patient demographic and clinical characteristics.</p> <p>Comparative analysis for primary and secondary outcomes will be conducted between groups. The comparative analysis will follow a two-step approach. The first step will compare the event rates and baseline characteristics of NOAC (Dabigatran, Rivaroxaban) - and warfarin-treated groups. To minimize potential confounding bias, the baseline characteristics of the two NOAC groups will be adjusted against that of the warfarin group using Stabilized Inverse Probability of Treatment Weighting (s-IPTW). Based on estimated HRs from the first step, the second step will determine 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.</p> <p>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.</p>
<p>Milestones:</p>	<p>Protocol finalization: June 2021 Start of data collection: April 2011 End of data collection: Dec. 2020 DMRP completion: June 2021 Final report of study results: Dec. 2021</p>

5. AMENDMENTS AND UPDATES

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

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	Aug 2021
Start of data collection	Sep 2021
End of data collection	Oct 2021
Registration in the EU PAS register	July 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.^{2,2} Among AF patients, the prevalence of concomitant coronary artery disease (CAD) is estimated to range from 17% to 46.5%,³ which can increase the risks of major bleeding, stroke, and mortality.^{错误!未找到引用源。} Meanwhile, 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.⁵ 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 effectiveness 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 patient.^{6,7} 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.⁸ 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 concomitant with CAD.

8. RESEARCH QUESTION AND OBJECTIVES

The study aims to make safety and effectiveness comparisons between warfarin, dabigatran, and rivaroxaban in real-world clinical settings among Japanese NVAF patients with concomitant CAD.

Primary objective:

To respectively make safety comparisons between dabigatran and warfarin, and between rivaroxaban and warfarin, among Japanese NVAF patients with concomitant CAD.

Specifically, comparative analysis will be made on the risk of major bleeding.

Secondary objective:

To respectively 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, which will be calculated as the net rate of all safety and effectiveness outcomes.

Further objective:

If the required sample size can be fulfilled, to compare the safety and net clinical benefits of dabigatran vs rivaroxaban among Japanese NVAF patients with concomitant CAD.

The null hypothesis is that the two NOACs (dabigatran and rivaroxaban) show equal safety and effectiveness outcomes as warfarin. The alternative hypothesis is that the two NOACs show superiority in the risk of major bleeding and net clinical benefits than warfarin.

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

In the first step, group 2&3 will be respectively matched against Group 1 with an inverse probability of treatment weighting (IPTW) method using calculated propensity score. Comparative analysis will be respectively made between Group 2&3 and Group 1 for primary and secondary outcomes, which respectively are the safety outcome (indicated by the rate of major bleeding events) and net clinical benefit (indicated by the rate of composite outcomes). Between-group comparisons will be made through hazard ratios (HRs). The baseline characteristics will also be compared.

The second step will utilize the estimated results from step one, which are HRs of major bleeding events between Group 2&3 versus Group 1 among NVAF patients concomitant with CAD, to carry out a more accurate sample size calculation. The availability of the required sample size will determine the feasibility of comparative analysis between Group 2 and Group 3. 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 1st, 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 1st, 2012 to December 31st, 2020.
-
- Cohort Entry Date: Date of study entry, which is defined as the drug of interest index date.
-
- 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 1st, 2011.
-
- 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
 - Last data point available
 - Occurrence of outcomes of interest (for primary objective: major bleeding; for secondary objectives: stroke, SE, myocardial infarction (MI), major bleeding, intracranial hemorrhage (ICH), gastrointestinal (GI) bleeding)
 - Death
 - End of study period

The notion of enrollment is not defined in MDV. 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 MDV 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 Medical Data Vision Co. Ltd. (MDV) database during the study period, which is from April 1st, 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 at least 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

9.2.3 Study visits

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

9.2.4 Study discontinuation

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Emergence of any effectiveness/safety information that could significantly affect continuation of the study, or any other administrative reasons.
2. Violation of Good Pharmacoepidemiology Practice (GPP), the study protocol, or the contract by a study site, investigator or research collaborator, disturbing the appropriate conduct of the study

The investigator/the study site/research collaborator will be reimbursed for reasonable expenses incurred in case of study/site termination (except in case of the third reason).

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 MDV Receipt Code. In the MDV 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 MDV database, information related to outcomes include the date of occurrence, the number of events, and the severity.

9.3.2.1 Primary outcomes

Primary outcome:

- Respective rate of fatal or non-fatal major bleeding (defined as any transfusion and/or any hospitalization with associated bleeding) in all three patient groups

9.3.2.2 Secondary outcomes

Secondary outcome:

- Respective rate of composite outcomes of stroke/SE/MI/all-cause mortality (inpatient)/major bleeding/GI bleeding/ICH in all three patient groups (the rate indicates the net clinical benefit, calculated as the net rate of all above safety and effectiveness outcomes)

9.3.2.3 Further outcomes

Further outcomes:

- Respective rates of each component outcome of stroke/SE/MI/all-cause mortality (inpatient)/major bleeding/GI bleeding/ICH in all three patient groups

9.3.3 Covariates

Covariates are recorded with the 10th Revision of the International Classification of Diseases (ICD-10) codes for disease diagnosis and MDV 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)
- Myocardial infarction (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)
- Cerebrovascular disease (yes/no)
- Obesity (yes/no)
- Acute Coronary Syndrome (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)
- 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)
- Single antiplatelet use duration (weeks, if applicable)
- Dual antiplatelet use duration (weeks, if applicable)

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 Medical Data Vision Co. Ltd. (MDV; Tokyo, Japan) database is one of the largest databases in Asia, 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 MDV 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 MDV database.

According to a published paper based on the MDV 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.⁹ According to the same article, the major bleeding rate for AF patients is 1.5 per 100 patient-years. In comparison, AF patients concomitant with 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 for about 2-3 times.^{6, 错误! 未找到引用源。} Therefore, the major bleeding rate is assumed to be 3-4.5 per 100 patient-years among Japanese AF+CAD patients in the MDV database. Further, 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.^{错误! 未找到引用源。} The comparative rates of major bleeding between NOAC- and warfarin- treated patients should follow a similar trend among NVAF patients concomitant with 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.

Assuming a 20% of sample loss due to propensity score matching, the sample sizes for dabigatran- and rivaroxaban-treated patients need to be greater than 3781 and 6056, 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 Instant Health Data (IHD) platform from Panalgo and SAS statistical software (version 9.3 or higher).

Descriptive analysis will be performed for 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.

Rates of each outcome for each treatment group will be reported as the number of events (first per patient) divided by the total number of person-years at risk during follow-up. Risk of each outcome for each treatment group will be reported as the number of events (first per patient) divided by the total number of patients at risk.

Table shells are attached as Annex 3.

9.7.1 Main analysis

Comparative analysis for primary and secondary outcomes will be conducted between groups. The comparative analysis will follow a two-step approach. The first step will compare the event rates and baseline characteristics of NOAC (Dabigatran, Rivaroxaban) - and warfarin-treated groups. Based on estimated HRs from the first step, the second step will determine 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.

During the first step of the comparative analysis, the baseline characteristics of the two NOAC groups will be adjusted against 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 the three patient groups to obtain two matched pairs of 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 model robustness. A covariate (baseline demographics, risk factors, clinical characteristics) will be considered well balanced if the ASD is below 0.1.

The incidence rates of each component outcome of major bleeding, stroke, SE, MI, all-cause mortality (in hospital), GI bleeding, and ICH of the 3 groups after applying s-IPTW will be plotted with Kaplan-Meier curves. Event rates will be compared between groups using hazard ratios. 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. The Cox regression model will incorporate the index OAC as an independent variable and may include covariates that are potentially imbalanced after IPTW adjustments.

9.7.2 Further analysis

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.

A subgroup analysis will be conducted for different dosages of the interested drugs. Specifically, different dose levels of dabigatran (150mg bid, 110mg bid, and 75mg bid) and rivaroxaban (15mg qd, and 10mg qd) will be respectively compared to warfarin. Comparisons between different dose levels of dabigatran and rivaroxaban might be made, depending on whether the sample sizes of the subgroups are sufficient.

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 Panalgo IHD 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 Panalgo IHD.

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 MDV 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.

9.10 OTHER ASPECTS

Not Applicable.

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs) / Independent Ethics Committee (IECs) or by regulatory authorities. 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 the investigator's site.

9.10.2.2 Direct access to source data and documents

The investigator/institution will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. All source documents must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. US Food and Drug Administration (FDA)).

9.10.3 Completion of study

When the study is completed, the investigator should inform the head of the study site of the completion in writing, and the head of the study site should promptly inform the IRB and sponsor of the completion in writing.

9.10.4 Protocol deviations

The investigator or sub-investigator should record all study protocol deviations. The investigator should provide and submit the sponsor and the head of the study site the records of deviations infringing the Japanese GCP or deviations to eliminate an immediate hazard to study subjects and for other medically inevitable reasons.

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). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent quality measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol.

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.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. 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 information is required to collect.

11.2 REPORTING TO HEALTH AUTHORITIES

Based on current guidelines from the International Society for Pharmacoepidemiology [R114318] 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.

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

1. Wolf PA, et al. Arch Intern Med. 1987;147(9):1561-4.
2. Wolf PA, et al. Stroke. 1991;22:983-8.
3. Michniewicz E, et al. Adv Med Sci. 2018;63(1):30-5.
4. KraleV S, et al. PLoS One. 2011;6(9):e24964
5. Hindricks G, et al. Eur Heart J. 2021. 42(5):373-498.
6. Connolly SJ, et al. N Engl J Med. 2009;361(12):1139-51.

7. Patel MR, et al. N Engl J Med. 2011;365(10):883-91.
8. Hohnloser SH, et al. Circulation. 2012;125(5):669-76.
9. Kohsaka S, et al. Open Heart. 2020;7(1):e001232

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	<Number>	<dd mmm yyyy>	<Text>
2	<Number>	<dd mmm yyyy>	<Text>
<n>	<Number>	<dd mmm yyyy>	<Text>

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: Study not registered
Study reference number (if applicable): 1160-0308

<u>Section 1: Milestones</u>	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection ¹	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6.0
1.1.2 End of data collection ²	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6.0
1.1.3 Progress report(s)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
1.1.4 Interim report(s)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6.0
1.1.5 Registration in the EU PAS Register®	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
1.1.6 Final report of study results.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6.0

Comments:

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<u>Section 2: Research question</u>	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7.0
2.1.2 The objective(s) of the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.0
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8.0
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	8.0

Comments:

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<u>Section 3: Study design</u>	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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))	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11.0

Comments:

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Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.2
4.2.2 Age and sex	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.2
4.2.3 Country of origin	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.2
4.2.4 Disease/indication	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.2
4.2.5 Duration of follow-up	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.2

Comments:

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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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
5.3 Is exposure categorised according to time windows?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.6 Is (are) (an) appropriate comparator(s) identified?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1

Comments:

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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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
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)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

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

Comments:

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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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.2

Comments:

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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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
9.1.3 Covariates and other characteristics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.2
9.3.3 Covariates and other characteristics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4

Comments:

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Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
10.2 Is study size and/or statistical precision estimated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.5
10.3 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
10.4 Are stratified analyses included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
10.5 Does the plan describe methods for analytic control of confounding?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
10.6 Does the plan describe methods for analytic control of outcome misclassification?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
10.7 Does the plan describe methods for handling missing data?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

<u>Section 10: Analysis plan</u>	Yes	No	N/A	Section Number
10.8 Are relevant sensitivity analyses described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.2

Comments:

<u>Section 11: Data management and quality control</u>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.6
11.2 Are methods of quality assurance described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.10.1
11.3 Is there a system in place for independent review of study results?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

<u>Section 12: Limitations</u>	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9
12.1.2 Information bias?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.5

Comments:

<u>Section 13: Ethical/data protection issues</u>	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
13.3 Have data protection requirements been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12.0
15.2 Are plans described for disseminating study results externally, including publication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12.0

Comments:

Name of the main author of the protocol:

Yijiao Chen

Date: 26/04/2021

Signature: _____

ANNEX 3. TABLE SHELLS

Table 1. Patient Flow Diagram

	Excluded	Total
Total number of patients MDV database 2008-04-01 - 2020-12-32		
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 at least 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

Variable	Unmatched			IPTW-matched			PS-matched		
	Dabigatran	Warfarin	Abs.St d.Dif	Dabigatran	Warfarin	Abs.St d.Dif	Dabigatran	Warfarin	Abs.St d.Dif
Age									
...mean (sd)									
...median [IQR]									
Gender									
...1 - Male; n (%)									
...2 - Female; n (%)									
CHA2DS2-VASc score									
...mean (sd)									
...median									

[IQR]									
Heart failure; n (%)									
Peripheral arterial disorder; n (%)									
Hypertension; n (%)									
Diabetes; n (%)									
Prior stroke/transient ischemic attack (TIA)/S E; n (%)									
Myocardial infarction; n (%)									
Unstable angina; n (%)									
Bleeding history; n (%)									
Renal dysfunction; n (%)									

Hepatic dysfunction; n (%)									
Cancers; n (%)									
Peptic ulcer disease; n (%)									
Cerebrovascular disease; n (%)									
Obesity; n (%)									
Antiplatelet drugs (include aspirin, clopidogrel, ticagrelor, prasugrel); n (%)									
Nonsteroidal anti-inflammatory drugs; n (%)									

Gastri c secreti on inhibit ors; n (%)									
Statin s; n (%)									
Hepari ns; n (%)									
Proto n pump inhibit or; n (%)									
Antihy per tensive drugs; n (%)									
Cardio versio n proce dures; n (%)									
Ablati on proce dures; n (%)									

Table 2b. Baseline Characteristics Comparisons – Rivaroxaban vs. Warfarin

	Unmatched			IPTW-matched			PS-matched		
Variabl e	Rivaro xaban	Warfar in	Abs.St d.Dif	Rivaro xaban	Warfar in	Abs.St d.Dif	Rivaro xaban	Warfar in	Abs.St d.Dif
Age									

...mean (sd)									
...median [IQR]									
Gender									
...1 - Male; n (%)									
...2 - Female; n (%)									
CHA2DS2-VASc score									
...mean (sd)									
...median [IQR]									
Heart failure; n (%)									
Peripheral arterial disorder; n (%)									
Hypertension; n (%)									
Diabetes; n (%)									
Prior stroke/transient									

ischemic attack (TIA)/SE; n (%)									
Myocardial infarction; 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 (%)									
Nonsteroidal anti-inflammatory drugs; n (%)									
Gastric secretion inhibitors; n (%)									
Statins; n (%)									
Heparins; n (%)									
Proton pump inhibitor; n (%)									
Antihy									

pertensive drugs; n (%)									
Cardioversion procedures; n (%)									
Ablation procedures; n (%)									

Table 2c. Dabigatran vs. Rivaroxaban

	Unmatched			IPTW-matched			PS-matched		
Variable	Dabigatran	Rivaroxaban	Abs.St d.Dif	Dabigatran	Rivaroxaban	Abs.St d.Dif	Dabigatran	Rivaroxaban	Abs.St d.Dif
Age									
...mean (sd)									
...median [IQR]									
Gender									
...1 - Male; n (%)									
...2 - Female; n (%)									
CHA2D S2-VASc score									
...mean (sd)									

...medi an [IQR]									
Heart failure; n (%)									
Periph eral arteria l disord er; n (%)									
Hypert ension ; n (%)									
Diabet es; n (%)									
Prior stroke /transi ent ischem ic attack (TIA)/S E; n (%)									
Myoca rdial infarcti on; n (%)									
Unstab le angina ; n (%)									
Bleedi ng history ; n (%)									
Renal dysfun ction;									

n (%)									
Hepatic dysfunction; n (%)									
Cancers; n (%)									
Peptic ulcer disease; n (%)									
Cerebrovascular disease; n (%)									
Obesity; n (%)									
Antiplatelet drugs (include aspirin, clopidogrel, ticagrelor, prasugrel); n (%)									
Nonsteroidal anti-inflammatory drugs;									

n (%)									
Gastri c secreti on inhibit ors; n (%)									
Statin s; n (%)									
Hepari ns; n (%)									
Proto n pump inhibit or; n (%)									
Antihy per tense drugs; n (%)									
Cardio versio n proce dures; n (%)									
Ablati on proce dures; n (%)									

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

	Comparison 1		Comparison 2		Comparison 3*	
	Dabig atran	Warfa rin	Rivaro xaban	Warfa rin	Dabig atran	Rivaroxab an

Number of patients (unmatched)						
Number of patients (IPTW-matched)						
Number of patients (PS-matched)						
Number of events						
Number of person-years						
Rate						
Rate per 1,000 person-years						
Rate Ratio (95% CI)						
Rate Difference per 1,000 person-years (95% CI)						
Risk						
Risk per 1,000 patients						
Risk Ratio (95% CI)						
Risk Difference per 1,000 patients (95% CI)						
Time to first fatal or non-fatal major bleeding episode						
Among unmatched cohort						
...Mean (SD)						
...Median [IQR]						
Among IPTW-matched cohort						
...Mean (SD)						
...Median [IQR]						
Among PS-matched cohort						
...Mean (SD)						
...Median [IQR]						
Hazard ratios						
Unmatched Hazard Ratio (95% CI)						
IPTW-PS Matched 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)

Table 4. Rates and Risks of Composite Outcomes of Stroke/SE/MI/All-cause mortality (inpatient) /Major bleeding/GI bleeding/ICH

	Comparison 1		Comparison 2		Comparison 3*	
	Dabiga tran	Warfari n	Rivaroxa ban	Warfari n	Dabig atran	Rivaro xaban
Number of patients (unmatched)						
Number of patients (IPTW- matched)						
Number of patients (PS-matched)						
Number of events						
Number of person-years						
Rate						
Rate per 1,000 person-years						
Rate Ratio (95% CI)						
Rate Difference per 1,000 person- years (95% CI)						
Risk						
Risk per 1,000 patients						
Risk Ratio (95% CI)						
Risk Difference per 1,000 patients (95% CI)						
Time to first composite outcomes of stroke/SE/MI/all- cause mortality (inpatient) /major bleeding/GI bleeding/ICH						
Among unmatched cohort						
...Mean (SD)						
...Median [IQR]						
Among IPTW-matched cohort						
...Mean (SD)						
...Median [IQR]						
Among PS-matched cohort						
...Mean (SD)						
...Median [IQR]						
Hazard ratios						
Unmatched Hazard Ratio (95% CI)						
IPTW-PS Matched 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)

Table 5. Rates and Risks of Stroke

	Comparison 1		Comparison 2		Comparison 3*	
	Dabigatran	Warfarin	Rivaroxaban	Warfarin	Dabigatran	Rivaroxaban
Number of patients (unmatched)						
Number of patients (IPTW-matched)						
Number of patients (PS-matched)						
Number of events						
Number of person-years						
Rate						
Rate per 1,000 person-years						
Rate Ratio (95% CI)						
Rate Difference per 1,000 person-years (95% CI)						
Risk						
Risk per 1,000 patients						
Risk Ratio (95% CI)						
Risk Difference per 1,000 patients (95% CI)						
Time to first stroke event						
Among unmatched cohort						
...Mean (SD)						
...Median [IQR]						

Among IPTW-matched cohort						
...Mean (SD)						
...Median [IQR]						
Among PS-matched cohort						
...Mean (SD)						
...Median [IQR]						
Hazard ratios						
Unmatched Hazard Ratio (95% CI)						
IPTW-PS Matched 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)

Table 6. Rates and Risks of SE

	Comparison 1		Comparison 2		Comparison 3*	
	Dabigatran	Warfarin	Rivaroxaban	Warfarin	Dabigatran	Rivaroxaban
Number of patients (unmatched)						
Number of patients (IPTW-matched)						
Number of patients (PS-matched)						
Number of events						
Number of person-years						
Rate						
Rate per 1,000 person-years						
Rate Ratio (95% CI)						
Rate Difference per 1,000 person-years (95% CI)						
Risk						

Risk per 1,000 patients						
Risk Ratio (95% CI)						
Risk Difference per 1,000 patients (95% CI)						
Time to first SE event						
Among unmatched cohort						
...Mean (SD)						
...Median [IQR]						
Among IPTW-matched cohort						
...Mean (SD)						
...Median [IQR]						
Among PS-matched cohort						
...Mean (SD)						
...Median [IQR]						
Hazard ratios						
Unmatched Hazard Ratio (95% CI)						
IPTW-PS Matched 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)

Table 7. Rates and Risks of MI

	Comparison 1		Comparison 2		Comparison 3*	
	Dabigatran	Warfarin	Dabigatran	Warfarin	Dabigatran	Rivaroxaban
Number of patients (unmatched)						
Number of patients (IPTW-matched)						
Number of patients (PS-matched)						
Number of events						

Number of person-years						
Rate						
Rate per 1,000 person-years						
Rate Ratio (95% CI)						
Rate Difference per 1,000 person-years (95% CI)						
Risk						
Risk per 1,000 patients						
Risk Ratio (95% CI)						
Risk Difference per 1,000 patients (95% CI)						
Time to first MI event						
Among unmatched cohort						
...Mean (SD)						
...Median [IQR]						
Among IPTW-matched cohort						
...Mean (SD)						
...Median [IQR]						
Among PS-matched cohort						
...Mean (SD)						
...Median [IQR]						
Hazard ratios						
Unmatched Hazard Ratio (95% CI)						
IPTW-PS Matched 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)

Table 8. Rates and Risks of All-cause Mortality (Inpatient)

	Comparison 1		Comparison 2		Comparison 3*	
	Dabigatran	Warfarin	Dabigatran	Warfarin	Dabigatran	Rivaroxaban
Number of patients (unmatched)						
Number of patients (IPTW-matched)						
Number of patients (PS-matched)						
Number of events						
Number of person-years						
Rate						
Rate per 1,000 person-years						
Rate Ratio (95% CI)						
Rate Difference per 1,000 person-years (95% CI)						
Risk						
Risk per 1,000 patients						
Risk Ratio (95% CI)						
Risk Difference per 1,000 patients (95% CI)						
Time to first 'all-cause mortality (inpatient)' event						
Among unmatched cohort						
...Mean (SD)						
...Median [IQR]						
Among IPTW-matched cohort						
...Mean (SD)						
...Median [IQR]						
Among PS-matched cohort						
...Mean (SD)						
...Median [IQR]						
Hazard ratios						

Unmatched Hazard Ratio (95% CI)						
IPTW-PS Matched 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)

Table 9. Rates and Risks of Major Bleeding

	Comparison 1		Comparison 2		Comparison 3*	
	Dabigatran	Warfarin	Dabigatran	Warfarin	Dabigatran	Rivaroxaban
Number of patients (unmatched)						
Number of patients (IPTW-matched)						
Number of patients (PS-matched)						
Number of events						
Number of person-years						
Rate						
Rate per 1,000 person-years						
Rate Ratio (95% CI)						
Rate Difference per 1,000 person-years (95% CI)						
Risk						
Risk per 1,000 patients						
Risk Ratio (95% CI)						
Risk Difference per 1,000 patients (95% CI)						
Primary Estimates						
Unmatched Hazard Ratio (95% CI)						

IPTW-PS Matched 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)

Table 10. Rates and Risks of GI Bleeding

	Comparison 1		Comparison 2		Comparison 3*	
	Dabigatran	Warfarin	Dabigatran	Warfarin	Dabigatran	Rivaroxaban
Number of patients (unmatched)						
Number of patients (IPTW-matched)						
Number of patients (PS-matched)						
Number of events						
Number of person-years						
Rate						
Rate per 1,000 person-years						
Rate Ratio (95% CI)						
Rate Difference per 1,000 person-years (95% CI)						
Risk						
Risk per 1,000 patients						
Risk Ratio (95% CI)						
Risk Difference per 1,000 patients (95% CI)						
Time to first GI bleeding event						
Among unmatched cohort						
...Mean (SD)						
...Median [IQR]						
Among IPTW-matched						

cohort						
...Mean (SD)						
...Median [IQR]						
Among PS-matched cohort						
...Mean (SD)						
...Median [IQR]						
Hazard ratios						
Unmatched Hazard Ratio (95% CI)						
IPTW-PS Matched 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)

Table 11. Rates and Risks of ICH

	Comparison 1		Comparison 2		Comparison 3*	
	Dabigatran	Warfarin	Rivaroxaban	Warfarin	Dabigatran	Rivaroxaban
Number of patients (unmatched)						
Number of patients (IPTW-matched)						
Number of patients (PS-matched)						
Number of events						
Number of person-years						
Rate						
Rate per 1,000 person-years						
Rate Ratio (95% CI)						
Rate Difference per 1,000 person-years (95% CI)						
Risk						
Risk per 1,000 patients						

Risk Ratio (95% CI)						
Risk Difference per 1,000 patients (95% CI)						
<i>Time to first ICH bleeding event</i>						
Among unmatched cohort						
...Mean (SD)						
...Median [IQR]						
Among IPTW-matched cohort						
...Mean (SD)						
...Median [IQR]						
Among PS-matched cohort						
...Mean (SD)						
...Median [IQR]						
<i>Hazard ratios</i>						
Unmatched Hazard Ratio (95% CI)						
IPTW-PS Matched 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 / TMMMA / 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: NIS Lead Name/Date: <Cherry Shi /28May2021> Signature: _____

Position: NIS Lead Name/Date: < Xiaohe Bian/28May2021> Signature: _____

Position: _____ Name/Date: _____ Signature: _____