# NON-INTERVENTIONAL (NI) STUDY PROTOCOL

## Study information

| | |
|---|---|
| **Title** | Safety and effectiveness of apixaban compared to warfarin in NVAF patients at higher risk of bleeding. |
| **Protocol number** | B0661178 |
| **Protocol version identifier** | Ver.1.0 |
| **Date** | 1 Jun 2022 |
| **EU Post Authorization Study (PAS) register number** | Study not registered |
| **Active substance** | B : Blood and blood forming organs<br>B01: Antithrombotic agents<br>B01A : Antithrombotic agents<br>B01AF: Direct factor Xa inhibitors<br>B01AF02: Apixaban<br><br>B : Blood and blood forming organs<br>B01: Antithrombotic agents<br>B01A : Antithrombotic agents<br>B01AA :Vitamin K Antagonist<br>B01AA03: Warfarin |
| **Medicinal product** | Eliquis (Apixaban)<br>Warfarin |
| **Research question and objectives** | Previous RCTs and RWE have shown that apixaban is associated with lower risk of stroke/SE (effectiveness) and bleeding (safety) when compared to warfarin in patients with NVAF. However, there are limited apixaban data for Japanese elderly patients and some patients are prone to bleed and several risk factors have been already reported. Absolute risk of bleeding is higher in these patients and there is little clear evidence showing superiority of apixaban |

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|---|---|
| | over warfarin in population at higher risk of bleeding.<br>Objectives of the present study are:<br>- To investigate the safety and effectiveness of apixaban compared to warfarin in Japanese NVAF patients with higher bleeding risks<br>- To generate compliment data for ARISTOTLE and support clinicians for their appropriate use |
| **Author** | PPD<br>PPD<br>Pfizer Japan Inc.<br>PPD |

## 1. TABLE OF CONTENTS

## 2. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ACE | Angiotensin-converting enzyme |
| AF | Atrial fibrillation |
| ARB | Angiotensin receptor blocker |
| CER | Cmparative effectiveness research |
| DPC | Diagnosis procedure combination |
| ICD | International Statistical Classification of Diseases and Related Health Problems |
| INR | International normalized ratio |
| IPTW | Inverse probability treatment weighting |
| MDV | Medical Data Vision |
| MI | Myocardial infarction |
| MR | Mineralocorticoid receptor |
| NOAC | Non-vitamin K antagonist oral anticoagulant |
| NSAIDs | Non-steroidal anti-inflammatory drug |
| NVAF | Non-valvular atrial fibrillation |
| OAC | Oral anticoagulant |
| PSM | Propensity score matching |
| RCT | Randomized control trial |
| RWD | Real World Data |
| SAP | Statistical Analysis Plan |
| SE | Systemic embolism |
| TIA | Transient ischemic attack |

## 3. RESPONSIBLE PARTIES

### Principal Investigator(s) of the Protocol

| Name, degree(s) | Job Title | Affiliation | Address |
|---|---|---|---|
| PPD | PPD | Pfizer Japan Inc. | PPD |

## 4. ABSTRACT

**Title:** Safety and effectiveness of apixaban compared to warfarin in NVAF patients at higher risk of bleeding (CER4)

Version 1.0, (26-May-2022).

**Rationale and background:** Atrial fibrillation (AF) is characterized by a rapid, irregular heartbeat which can cause blood to pool in the atria and increase the risk of the formation of blood clots. It has been reported that AF affects 0.6% to 1.6% of the general population and up to 14% in cardiovascular clinics in Japan[1-3]. An anticoagulation therapy is a critical treatment to prevent thromboembolism in non-valvular AF (NVAF) patients. Warfarin, a vitamin K antagonist, is the first oral anticoagulant approved for the treatment for prevention of thromboembolism in Japan in 1962 and it had long been the only oral anticoagulant until the first non-vitamin K antagonist oral anticoagulants (NOACs), dabigatran, was introduced with approval for stroke prevention in NVAF patients in March 2011[4]. Apixaban was approved in December 2012 in Japan and demonstrated superiority compared to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality in patients with atrial fibrillation in Phase 3 clinical trial[5]. Previously we have shown that bleeding risks as well as stroke/ systemic embolism (SE) risks are less in real world clinical practice in Japan compared to warfarin.[6-8] However there are limited apixaban data for Japanese NVAF patients with high bleeding risk(s). This study will evaluate the risk of stroke/SE as well as the risk of bleeding in the real world settings in Japan in patients with NVAF who has higher bleeding risk(s).

**Research question and objectives:** The research questions are: 1) is there any difference in the risk of major bleeding and of a composite of (ischemic and hemorrhagic) stroke/SE between patients with higher bleeding risk(s) treated with warfarin and those treated with apixaban in OAC naïve NVAF patients who start treatment with OACs.

The primary objective is to compare the risk of major bleeding and composite of (ischemic and hemorrhagic) stroke/SE in warfarin-apixaban cohorts.

**Study design:** This is a retrospective, non-interventional observational study using the database provided by Medical Data Vision Co. Ltd. (MDV Co. Ltd.) (data set from 1 March, 2011 to 31 Jun, 2021) designed to evaluate the difference in safety (major bleeding) and effectiveness (composite of stroke/SE) in the matched cohorts created by using a propensity score matching method or a stabilized IPTW (inverse probability of treatment weighted) method. Comparisons of apixaban versus warfarin will be performed.

**Population:** Data from OAC treatment-naïve Japanese patients with NVAF initiating OAC treatment will be used for the analysis. Further information on patient selection, enrollment and follow-up time periods are included in Subsection 9.2 below.

**Variables:** Index treatment of OACs; outcome measures including major bleeding, stroke/SE and demographic and clinical characteristics of the patients.

**Data sources:** Medical Data Vision database

**Study size:** The required number of eligible patients for each cohort is estimated in Subsection 9.5 below and also in the Statistical Analysis Plan (SAP).

**Data analysis:** Detailed methodology for data analysis will be described in the SAP. Baseline patient demographic information will be compared among the warfarin and apixaban by appropriate tests (e.g., t-test, Mann Whitney-U test, chi-square test) based on the distribution of the measures. Both propensity score matching (PSM) and stabilized IPTW methods will be used to estimate treatment effects of apixaban compared to warfarin. To estimate hazard ratio and 95% confidence intervals of apixaban compared to warfarin using univariable Cox proportional hazards models (OAC treatment as a single variable) will be used.

**Milestones:**
Data extraction from MDV database: Jun. 30 – . Jul 14, 2022;
Analysis: Jul. 15 – Aug. 17, 2022;
Final study report: Oct 20,  2022

## 5. AMENDMENTS AND UPDATES

None

## 6. MILESTONES

| Milestone | Planned date |
|---|---|
| <Completion of feasibility assessment> | 17 Mar 2022 |
| Start of data collection | 30 Jun 2022 |
| End of data collection | 17 Aug 2022 |
| Final study report | 20 Oct 2022 |

## 7. RATIONALE AND BACKGROUND

Atrial fibrillation (AF) is characterized by a rapid, irregular heartbeat which can cause blood to pool in the atria and increase the risk of the formation of blood clots. AF affects 0.6% to 1.6% of the general population and up to 14% in cardiovascular clinics in Japan[1-3]. AF can be categorized into three main categories based on patient characteristics: lone atrial fibrillation – AF in the absence of overt cardiovascular disease or precipitating illness[9] non-valvular AF (NVAF) – presence of AF without concurrent rheumatic mitral valve disease or history of mitral valve repair or prosthetic heart valve; and secondary AF-AF that occurs in the setting of acute myocardial infarction (MI), cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia, or other acute pulmonary disease. Anticoagulation therapy is important to prevent thromboembolism in patients with NVAF. Warfarin, a vitamin K antagonist, is the first oral anticoagulant approved for the treatment and prevention of thromboembolism in Japan in 1962 and it had long been the only oral anticoagulant until the first non-vitamin K antagonist oral anticoagulants (NOACs), dabigatran, was introduced with approval for NVAF treatment in March 2011[4]. Apixaban was approved in December 2012 in Japan and demonsrated superiority compared to walfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality in patients with atrial fibrillation in Phase 3 clinical trial[5].

Although randomized control trials (RCTs) aimed at head-to-head comparison with placebo or a reference drug may provide evidence of safety and efficacy of treatments at the highest level, there are potential limitations derived from a limited number of pre-selected patients and strict patient eligibility criteria with regard to age, comorbidities, and concomitant medications. Accordingly, these studies may not accurately represent what happens when drugs are used in general clinical practice. Especially data for Japanese NVAF patients are limited due to limited number of Japanese patients recruited in the RCT. Also patients with higher risk from a safety perspective, for instance patients with active caner, are generally excluded from RCT and further limited data are exist.

Previously we have shown that bleeding risks as well as stroke/ systemic embolism (SE) risks are less in real world clinical practice in Japan compared to warfarin[6-8], but there are

still little data for Japanese NVAF patients who has higher bleeding risks such as componets of HAS-BLED risk score factors, active cancer, uncontrolled hypertension etc. The objectives of this study is to compare the risk of incidence of stroke and bleeding among NVAF patients with such higher bleeding risk(s) newly prescribed apixaban or warfarin using a nation-wide administrative claims database.

## 8. RESEARCH QUESTION AND OBJECTIVES

The research questions are:

1. Are there any differences in the risk of major bleeding between apixaban and warfarin for patients with higher bleeding risk(s) in the general practice settings in Japan?
2. Are there any differences in the risk of stroke/systemic embolism between apixaban and warfarin for patients with higher bleeding risk(s) in the general practice settings in Japan?

**The primary objective** of the study is to compare effectiveness (a composit risk of stroke/SE) and safety (major bleeding events) of warfarin and apixaban among NVAF patients with at least one bleeding risk (that is, patients at higher risk of bleeding)

**The secondary objectives** are:

1. to compare the risk of major gastrointestinal or intracranial bleeding between warfarin-initiators and apixaban-initiators in patients with at least one bleeding risk.
2. to compare the risk of ischemic stroke, hemorrhagic stroke or SE between warfarin-initiators and apixaban-initiators in patients with at least one bleeding risk.

Objectives of other exploratory analysis are to explore the risk of major bleeding and stroke/SE in the specific populations at higher bleeding risk(s).

In this study, predetermined high bleeding risk subgroups are 1) patients with hypertension diagnosis, 2) patients with liver dysfunction, 3) patients with renal dysfunction diagnosis, 4) patients with a history of beleeding, 5) patiens with hemorrphagic stroke, 6) patients with alcohol abuse, 7) patients with concomitamt used of antiplatelet drugs, 8) patients with chronic (continuously for longer than 90 days) comcomitant use of NSAID, 9) highly elderly (> 80 years old) , 10) patients with refractory hypertension, 11) patients with a history of peptic ulcer diagnosis, 12) patients with active cancer, 13) patients with diabetes mellitus, 14) patients whose body weight is <40kg, 15) patients with polypharmacy.

In the previous feasibility analysis, we found that the numbers of patients with hemorrhagic stroke, alcohol abuse, chronic concomitant used of NSAIDs (for continuously > 90 days), and refractory hypertension were less than 2,000. Due to the insufficient statistical power, we will not include these subgroups for the future analysis.

Subgroups to be analyzed for exploratory analysis will be described in a SAP.

# 9. RESEARCH METHODS

## 9.1. Study design

This is a retrospective observational study using data from the MDV database (data set from 1 March, 2011 to 31 Jun, 2021). Among patients registered in the database patients are selected based on the inclusion and exclusion criteria (see blow)..

Study measures include: (1) for safety evaluation: major bleeding ; (2) for effectiveness evaluation: a composite of ischemic stroke, hemorrhagic stroke or SE.

The primary purpose of this study is to investigate the safety and effectiveness of apixaban compared to warfarin in NVAF patients who are prone to bleeding, with at least one known risk factor for bleeding. In this study, predetermined high bleeding risk subgroups are 1) patients with hypertension diagnosis, 2) patients with liver dysfunction, 3) patients with renal dysfunction diagnosis, 4) patients with a history of beleeding, 5) patiens with hemorrphagic stroke, 6) patients with alcohol abuse, 7) patients with concomitamt used of antiplatelet drugs, 8) patients with chronic (continuously for longer than 90 days) comcomitant use of NSAID, 9) highly elderly (> 80 years old) , 10) patients with refractory hypertension, 11) patients with a history of peptic ulcer diagnosis, 12) patients with active cancer, 13) patients with diabetes mellitus, 14) patients whose body weight is <40kg, 15) patients with polypharmacy.

The follow-up period is variable, and will begin on the next day of the index date and continue until the earliest of the following scenarios – occurrence of target outcome event (details available in Subsection 9.2); discontinuation of apixaban or warfarin; switching from apixaban or warfarin; withdrawal from the database.

## 9.2. Setting

This study uses data from the MDV database, which includes the data used for both inpatient and outpatient insurance claims by hospitals according to the Diagnosis Procedure Combination (DPC) procedure.

The study population will consist of adults with NVAF who are newly prescribed apixaban or warfarin. Follow-up time period starts from the next day of the index date, and ends depending on following outcomes which observed first.

1. Major bleeding when the target outcome for the analysis is major bleeding.

2. Composite of (ischemic or hemorrhagic) stroke and SE when the target outcome for the analysis is the composite endpoint.

3. Discontinuation of apixaban or warfarin: The index treatment will be considered to be "discontinued" if apixaban or warfarin is not prescribed within 45 days after prescription refill date (calculated from the last refill date plus days of supply) of apixaban or

warfarin, even though the patient has >1 medical encounter records after more than 45 days following the prescription refill date. The supposed prescription refill date is regarded as the last day of the follow-up for discontinued patients.

4. Switching from apixaban or warfarin: The index treatment is regarded as "switched" if OAC is prescribed within 45 days after prescription refill date of apixaban or warfarin when the patient has 1> medical encounter records after more than 45 days following the prescription refill date. The switched day is regarded as the last day of the follow-up for the switched patients.

5. Withdrawal from the database: The patients are regarded as “withdrawal” from the database if apixaban or warfarin is not prescribed within 45 days after prescription refill date of the apixaban or warfarin and there is no data of the patient on the database after prescription refill date. The last medical encounter is regard as the last day of the follow-up for patients withdrawn from the database.

6. An elapse of 2 years from the index date without any of the event above.

### 9.2.1. Inclusion criteria

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

1. Diagnosed with AF anytime in the baseline period or on the index date, also have definitive diagnosis of AF anytime in the baseline period, on the index date, or post-index period.

2. Prescribed apixaban or wararin on or after the day of AF diagnosis. The first observed prescription will be used to identify the patient’s index date and treatment cohort

3. No use of the any OACs during the baseline period (the 180 days before the index date)

4. Age of 18 years or older on the index date.

### 9.2.2. Exclusion criteria

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

1. Having a diagnosis of valvular atrial fibrillation, post-operative atrial fibrillation, rheumatic atrial fibrillation or mechanical-valvular atrial fibrillation during the baseline and post-index period

2. Having a procedure of prosthetic heart valve during the baseline period

3. Having a cardiac surgery procedure record during the baseline period

4. Having a diagnosis of venous thromboembolism during the baseline period

5. Having a hemodialysis during the baseline period

6. Female patients with pregnancy during the baseline and follow-up period

7. Patients prescribed apixaban other than approved daily dose (<5 mg or >10 mg)

8. Patients prescribed OACs during baseline period

## 9.3. Variables

Demographic and clinical characteristics are collected during the baseline period, at the index date or during follow-up period. Detail definition available in SAP.

| Variable | Role | Data source(s) |
|---|---|---|
| Sex Category | Baseline characteristic | Index date |
| Age | Baseline characteristic | Index date |
| Age (> 80y, >90 y) | Sub-group identifier | Index date |
| $CHADS_2$ | Baseline characteristic | Baseline period |
| $CHA_2DS_2$-VASc | Baseline characteristic | Baseline period |
| Heart failure diagnosis | Baseline characteristic | Baseline period |
| Coronary heart disease diagnosis | Baseline characteristic | Baseline period |
| Peripheral arterial disorder diagnosis | Baseline characteristic | Baseline period |
| Myocardial infarction diagnosis | Baseline characteristic | Baseline period |
| Hyperthyroidism or thyrotoxicosis | Baseline characteristic | Baseline period |
| Stroke, TIA or SE diagnosis | Baseline characteristic | Baseline period |
| Renal dysfunction diagnosis | Baseline characteristic<br>Sub-group identifier | Baseline period |
| Liver dysfunction diagnosis | Baseline characteristic<br>Sub-group identifier | Baseline period |
| Bleeding diagnosis | Baseline characteristic | Baseline period |
| Hypertension diagnosis | Baseline characteristic<br>Sub-group identifier | Baseline period |
| Refractory hypertension diagnosis | Sub-group identifier | Baseline period |
| Diabetes mellitus diagnosis | Baseline characteristic<br>Sub-group identifier | Baseline period |
| Cancer diagnosis | Baseline characteristic<br>Sub-group identifier | Baseline period |
| Treated with antiplatelet drug | Baseline characteristic | Baseline period |
| Treated with antiplatelet drug (>28 d) | Sub-group identifier | Baseline period |
| Treated with NSAIDs | Baseline characteristic | Baseline period |
| Treated with NSAIDs (>90 d) | Sub-group identifier | Baseline period |
| Treated with gastric secretion inhibitor | Baseline characteristic | Baseline period |
| Treated with statin-based drug | Baseline characteristic | Baseline period |
| Treated with anti-hypertensives | Baseline characteristic | Baseline period |
| Treated with anti-arrhythmics | Baseline characteristic | Baseline period |
| Treated with beta-blockers | Baseline characteristic | Baseline period |
| Treated with heparins | Baseline characteristic | Baseline period |
| Cardioversion | Baseline characteristic | Baseline period |
| Alcohol abuse | Sub-group identifier | Baseline period |
| Bleeding diagnosis | Sub-group identifier | Baseline period |

| Variable | Role | Data source(s) |
|---|---|---|
| Peptic ulcer diagnosis | Sub-group identifier | Baseline period |
| Hemorrhagic stroke diagnosis | Sub-group identifier | Baseline period |
| Low body weight (<40 kg) | Sub-group identifier | Baseline period |
| Polypharmacy | Sub-group identifier | Baseline period |
| PT-INR (Prothrombin time-international normalized ratio) | potential confounder | Baseline period |
| Physician specialty | potential confounder | Index date |
| Hospital size (<500 beds or not) | potential confounder | Index date |
| Hospitalization status on index date | potential confounder | Index date |
| Major bleeding | Outcome | Follow-up period |
| Any bleeding | Outcome | Follow-up period |
| Stroke/SE | Outcome | Follow-up period |

## 9.4. Data sources

The analysis will be based on administrative data from MDV Co. Ltd., a longitudinal database based on health insurance claims and medical records obtained from the hospitals in which the DPC payment system for utilization of both inpatient and outpatient hospital claims (percentage of inpatients is about 20%). The database provides claims data from 449 hospitals (as of Aug 2021) using the DPC system for medical service claims (26% of general hospitals in Japan is under the DPC system) including approximately 36.7 million patient data.

## 9.5. Study size

All eligible patients are extracted from the database and used for the analysis. In the previous study (CER3; conducted based on the data from March 1st, 2011 to July 31st, 2018 for apixaban, dabigatran, edoxaban, rivaroxaban and warfarin), 15,902 patients on warfarin, 22,336 patients on apixaban were eligible for the analysis. The required number of patients for the planned analysis and the estimated number of eligible patients for each cohort is shown in a SAP.

## 9.6. Data management

Data will be securely provided by MDV Co. Ltd (data set from 1 March, 2011 to 31 Jun, 2021). All analyses will be conducted using SAS software (Version 9.0 or higher, SAS Institute, Cary, NC, USA) with study results presented in Microsoft Excel tables.

## 9.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

### 9.8. Quality control

This study is a retrospective analytical study using quality controlled data in a pre-existing database, and primary data collection will not be conducted. As for the data provided, quality of the data is guaranteed by MDV Co. Ltd., which has professional teams specialized in the maintenance and improvement of data quality. All of these processes are consistently managed in-house. All of operations for data management in MDV Co. Ltd. are conducted in accordance with standard operational procedures of MDV Co. Ltd..

Data analysis will be conducted by Macromill Carenet, Inc. (Tokyo, Japan). The final results will be quality checked internally by Macromill Carenet according to their internal procedures. For quality assurance of analysis, they will conduct code review of all modules of program, descriptive statistics review of all variables and patients row data examination of all output results in a test phase.

### 9.9. Limitations of the research methods

1) Identification of NVAF, bleeding, stroke, TIA and SE events, and high bleeding risk factors will be based on insurance claims data, and there is no medical record review to adjudicate these diagnosis, which may subject the study of misclassification bias. 2) There is no information about the therapeutic range of warfarin therapy or INR monitoring results, which are important factors related to the safety and efficacy of warfarin treatment. In Japan, it has been pointed out that coagulation status is often sub-optimally controlled by warfarin in NVAF patients. 3) This is an observational study and patients with different treatments may be incomparable. These differences may impact the comparison between treatment groups. In this study, a PSM method or IPTW with stabilized weights will be used to make well matched cohorts. Although the cohorts are matched, some differences in patient background which are neither available from the database nor included in matching score might still affect the results.

### 9.10. Other aspects

Not applicable

## 10. PROTECTION OF HUMAN SUBJECTS

### 10.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information.

### 10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

### 10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

Regarding MDV database, IRB/IEC approval is not required since MDV database comprised of unlinkable anonymized data.

### 10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practice described in Ethical Guidelines for Medical and Health Research Involving Human Subjects.

## 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

## 12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

All final data will be shared with BMSKK/BMS. It is also anticipated that results from this study will generate at least one study abstract for submission to a medical conference and one

manuscript for submission to an international peer-reviewed journal. The appropriate conferences and journal will be decided upon by the alliance medical team. Abstract, presentation materials (poster or slide deck) or a manuscript will be reviewed and approved both by Pfizer and BMS

## 13. REFERENCES

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10.

## 14. LIST OF TABLES

None

## 15. LIST OF FIGURES

None

## ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

## ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

## ANNEX 3. ADDITIONAL INFORMATION

Not applicable