# NON-INTERVENTIONAL (NI) STUDY PROTOCOL

## Study information

| | |
|---|---|
| **Title** | Safety and effectiveness of apixaban compared to warfarin in secondary prevention in patients with NVAF with a history of stroke or transient ischemic attack - a nationwide retrospective observational study using claims data in Japan |
| **Protocol number** | B0661176 |
| **Protocol version identifier** | Ver.1.1 |
| **Date** | 24/3/2022 |
| **EU Post Authorization Study (PAS) register number** | Not applicable |
| **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 |
| **Medicinal product** | Eliquis(Apixaban) |
| **Research question and objectives** | Japanese population has shown to have higher rate of incidence of stroke and stroke mortality is also higher[1]. Patients with a history of ischemic stroke are at high risk of recurrence and require more rigorous management to prevent recurrence[2]. The same is true for patients with non-valvular atrial fibrillation (NVAF) and treatment with anticoagulants reduces the risk of recurrent embolic stroke. However,some patients still suffer from recurrent embolic and/or ischemic stroke even if they are on anticoagulants for secondary prevention[3]. In addition to the recurrent stroke, risk of bleeding is also higher in the patients with a history of stroke because they are often chronically treated with antiplatelet agents to prevent recurrence after cerebral infarction and with an anticoagulant after embolic stroke[4 5]. Concomittant use of anticoagulant and anti-platelet agents is sometimes necessary if patients with AF experience cerebral infarction |

| | |
|---|---|
| | and the risk of bleedings largely enhances in these patient[6]. Thus, patients in secondary prevention are at higher risk of both recurrent ischemic stroke and more effective and safter antithrombotic therapy should take this into account.<br>The purposes of this study are 1) to characterize the primary and secondary prevention patients, 2) to calculate incidence rates of stroke/SE or major bleeding in each cohort and 3) to investigate for Japanese secondary prevention patients as RWE on the effectiveness and safety of apixaban compared to warfarin in patients NVAF. |
| **Author** | PPD |

## Contents

## 1. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AF | Atrial fibrillation |
| COPD | Chronic obstructive pulmonary disease |
| DOAC | Direct oral anticoagulant |
| HAS-BLED | Not an abbreviation.<br>Hypertension, Abnormal renal / liver function, Stroke, Bleeding, Labile INRs, Elderly, Drugs / alcohol |
| ICD-10 | International classification of diseases-10 |
| ICH | Intracranial hemorrhage |
| ID | Identifier |
| IEC | Independent ethics committee |
| IPTW | Inverse probability of treatment weighting |
| IRB | Institutional review board |
| MDV | Medical Data Vision Ltd. |
| NSAID | Non-steroidal anti-inflammatory drug |
| NVAF | Non-valvular atrial fibrillation |
| OAC | Oral anticoagulant |
| RWE | Real world evidence |
| SAP | Statistical Analysis Plan |
| SE | Systemic embolism |
| TIA | Transient ischemic attack |

## 2. RESPONSIBLE PARTIES

### Principal Investigator(s) of the Protocol

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

## 3. ABSTRACT

### Title：

Safety and effectiveness of apixaban compared to warfarin in secondary prevention in patients with NVAF with a history of stroke or transient ischemic attack - a nationwide retrospective observational study using claims data in Japan

Protocol Ver1.1 (24-Mar-2022)

PPD

### Rationale and background：

Japanese population has shown to have higher rate of incidence of stroke and stroke mortality is also higher[1]. Patients with a history of ischemic stroke are at high risk of recurrence and require more rigorous management to prevent recurrence[2]. The same is true for patients with non-valvular atrial fibrillation (NVAF) and treatment with anticoagulants reduces the risk of recurrent embolic stroke. However, some patients still suffer from recurrent embolic and/or ischemic stroke even if they are on anticoagulants for secondary prevention[3]. In addition to the recurrent stroke, risk of bleeding is also higher in the patients with a history of stroke because they are often chronically treated with antiplatelet agents to prevent recurrence after cerebral infarction and with an anticoagulant after embolic stroke[4 5]. Concomittant use of anticoagulant and anti-platelet agents is sometimes necessary if patients with AF experience cerebral infarction and the risk of bleedings largely enhances in these patient[6]. Thus, patients in secondary prevention are at higher risk of both recurrent ischemic stroke and more effective and safter antithrombotic therapy should take this into account.

### Research question and objectives：

The pivotal randomized clinical trial, ARISTOTLE study[7], and other RWE[8-11], in which medical and claims data have been retrospectively analyzed, have shown that the risks of incidence of stroke + systemic embolism and major bleeding in patients with NVAF treated with apixaban is equal to or lessor than those in patinets treated with warfarin. As mentioned above, patients with NVAF and with a history of ischemic stroke (that is, in secondary prevention) could be at higher risk of recurrence and bleeding. Although neurologists generally use direct oral anticoagulants

(DOAC) for secondary prevention, a significant portion of the patients in secondary prevention are still treated with warfarin in Japan. The results of randomized trials have been indicated that apixaban is superior to warfarin in reducing the risk of recurrence and/or bleeding with secondary prevention of stroke[12-14]. However, there is no clear evidence in Japanese patients with secondary prevention of stroke[15]. The research question of this study is whether apixaban is associated with lower risk of stroke (ischemic andhemorrhagic) and bleeding compared to warfarin in higher-risk secondary prevention patients as well.

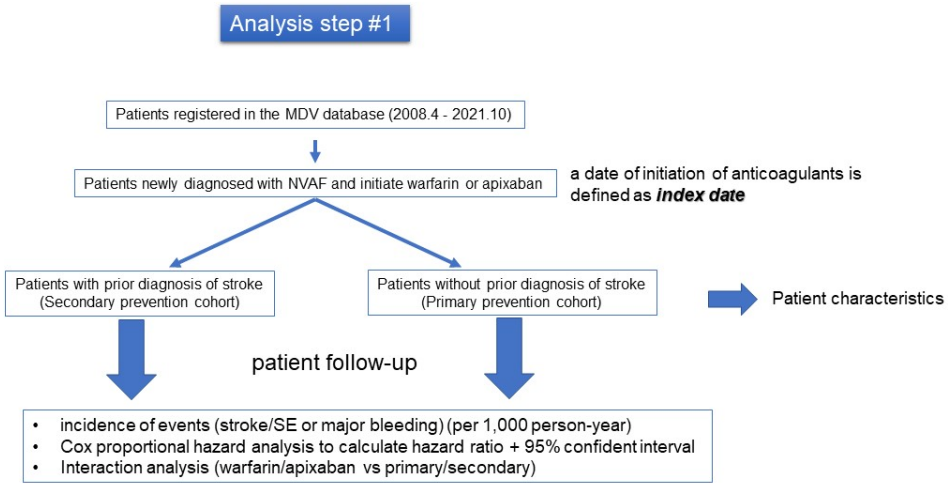
The purposes of this study are 1) to characterize the primary and secondary prevention patients, 2) to calculate incidence rates of stroke/systemic embolism (SE) or major bleeding in each cohort and 3) to investigate for Japanese secondary prevention patients as RWE on the effectiveness and safety of apixaban compared to warfarin in patients NVAF.

## Study design：

It is a non-interventional comparative observational study, in which patients who meet the study criteria are selected and aggregated from the patients registered in the Medical Data Vision (MDV) database.

## Population：

Patients who are newly diagnosed with NVAF and initiate anticoagulation therapy with warfarin or apixaban. Among them, patients with prior diagnosis of stroke (ischemic or hemorrhagic) or transient ischemic attack (TIA) are secondary prevention patients and will be included in the secondary prevention cohort and those who have not diagnosed with stroke will be included in the primary prevention cohort as primary prevention patients. Patient selection and allocation to each cohort is shown in Fig.1 below.



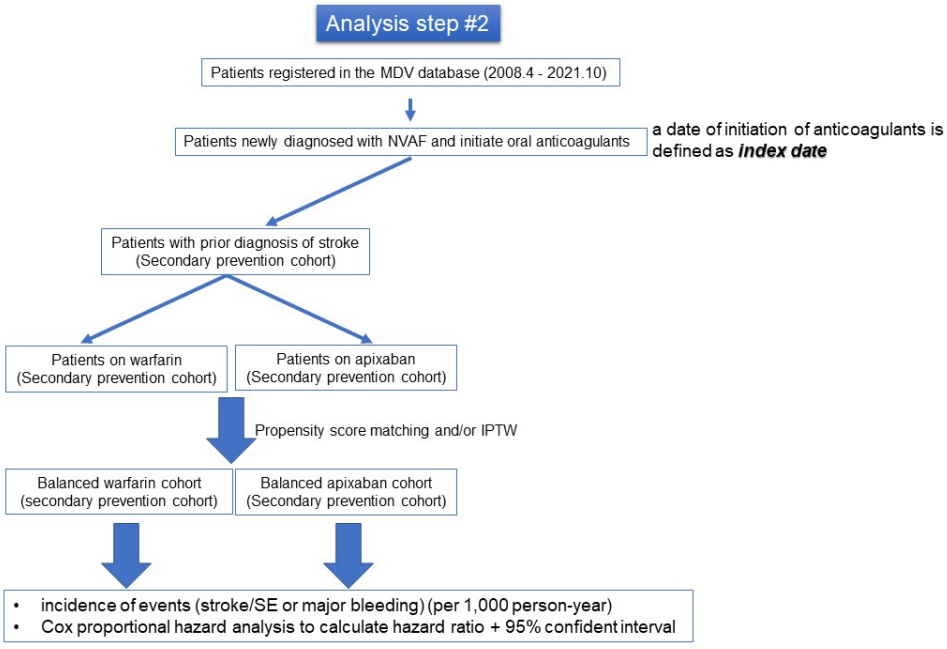




Fig.1a and 1b: patient selection and summary of planned analyses

## Variables：

- Prior diagnosis of stroke (before diagnosis with NVAF)

- Clinical and demographic characteristics of patients eligible for this study.
- Incidence of recurrent stroke (ischemic and hemorrhagic) during the follow-up period
- Incidence of any bleeding including intracranial hemorrhage, gastrointestinal bleeding or intraocular bleeding dufing the follow-up period
- Anticoagulants (warfarin, apixaban or others)
- Concommittent medicines (baseline or on the index date)
- Comorbid diseases (baseline or on the index date)

## Data sources：

Medical Data Vision database

De-identified health claim data from 458 acute-care hospitals across Japan (as of Dec.22, 2021) available from the MDV (Tokyo, Japan, MDV) database. In brief, the MDV database comprises administrative data pertaining to approximately 38 million individuals managed in the inpatient and outpatient settings. Each patient is associated with a specific ID to which all inpatient and outpatient data are linked.

## Study size：

In this study, eligible patients will be aggregated backward.

- The number of estimated patients;
- All registered patients: approximately 38 millions (2008-2021)
- Patients with ischemic stroke: 1.2 millions
- Patients with TIA: 98,887
- Patients with atrial fibrillation: 1.3 millions
- AF patients with a history of ischemic stroke: 226,000
- AF patients on warfarin: 251,000
- AF patients on apixaban: 237,000
- The number of patients who experienced recurrent ischemic stroke on warfarin or apixaban: unknown

**Data analysis：**

The detailed methodology for data analysis will be described in the Statistical Analysis Plan (SAP). Briefly,

As a first step, extracted patients will be divided into two cohorts, primary prevention cohort and secondary prevention cohort based on the previous diagnosis of stroke. Clinical and demigraphic characteristics will be compared with two cohorts at baseline and on the index date (date of the initiation of warfarin and apixaban) and incidence rates of stroke/SE and major bleeding per 1,000 person-years will be calculated during follow-up period. In addition, interaction analysis will be conducted to investigate an interaction between OAC (warfarin/apixaban) and presence or absence of the previous episode of stroke.

- As a second step, only secondary prevention cohort will be used for further analyses as fillows,Crude (before IPTW) patient characteristics will be compared between warfarin and apixaban cohorts using appropriate methods (continuous variables: unpaired t-test or Mann-Whitney U-test, categorical variables: chi-square test)
- A propensity score will be calculated based on multinomial logistic regressions in order to account for confounding effects and to ensure that patient characteristics will be balanced between the warfarin cohort and apixaban cohort. An inverse probability of treatment weighting (IPTW) method using the calculated propensity score will be applied. To avoid sample size inflation and to ensure appropriate estimation of variances, s-IPTW (stabilized IPTW) will be used here.
- Balanced (after IPTW) patient clinical and demographic characteristics will be shown. Covariate balance between apixaban and warfarin cohorts after s-IPTW will be assessed in terms of the standardized differences with a threshold of 0.1.
- Kaplan Meier curves of balanced cohorts for each endpoint will be drawn.
- Incidence rates of endpoints will be calculated and shown per 1000 person-year.
- Hazard ratios with 95% confidence intervals will be calculated using a Cox proportional hazards regression model that incorporate only the index OACs as independent variables.

## Milestones：

- Data extraction start: Apr 15, 2022
- End of data extraction: Jun 30, 2022
- Final report approval: Aug 30, 2022

## 4. FINAL REPORT APPROVAL

| Amendment number | Date | Protocol section(s) changed | Summary of amendment(s) | Reason |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Ver 1.1 | 25/Mar/ 2022 | 5. Milestones | Change Data Extraction Date Before: Apr 1, 2022 After: Apr 15, 2022 | To adjust the project schedule |
| | | | | |

## 5. MILESTONES

| Milestone | Planned date |
|---|---|
| <Completion of feasibility assessment> | October 14, 2021 |
| Start of data collection | April 15, 2022 |
| End of data collection | Jun 30, 2022 |
| Final study report | Aug 30, 2022 |

## 6. RATIONALE AND BACKGROUND

Patients with a history of ischemic stroke, including those with cardiogenic cerebral embolism, are at higher risk of recurrence and require more rigorous treatment to prevent recurrence. The same is true for patients with non-valvular atrial fibrillation (NVAF), who are at higher risk of recurrence even if they are taking anticoagulants to prevent cardiogenic cerebral embolism. On the other hand, NVAF patients with previous lacunar infarction are often chronically treated with antiplatelet agents to prevent recurrence, and this could result in an increased risk of bleeding. Thus, patients in secondary prevention are at higher risk of recurrent stroke (both ischemic stroke andhemorrhagic stroke) and bleeding than those in primary prevention, and antithrombotic therapy should take this into account.

## 7. RESEARCH QUESTION AND OBJECTIVES

The pivotal randomized clinical trial, ARISTOTLE study, and other RWE, in which medical and claims data have been retrospectively analyzed, have shown that the risks of incidence of stroke + systemic embolism and major bleeding in patients with NVAF treated with apixaban is equal to or lessor than those in patinets treated with warfarin. As mentioned above, patients with NVAF and with a history of ischemic stroke (that is, in secondary prevention) could be at higher risk of recurrence and bleeding. Although neurologists generally use direct oral anticoagulants (DOAC) for secondary prevention, a significant portion of the patients in secondary prevention are still treated with warfarin in Japan. There is no clear evidence that apixaban is superior to warfarin in reducing the risk of recurrence or bleeding in Japanese patients with secondary prevention of

stroke. The research question of this study is whether apixaban is associated with lower risk of stroke (ischemic stroke and hemorrhagic stroke) and bleeding compared to warfarin in higher-risk secondary prevention patients as well.

### 7.1. Primary objective:

The effectiveness of study in secondary prevention cohort will be conducted to elucidate the following,

1. Incidence rate (per 1,000 person-years) of a composite of recurrent stroke (ischemic stroke and hemorrhage stroke) in NVAF patients treated with warfarin or apixaban.
2. Time course of proportion of a composite of the incidence of recurrent stroke (ischemic stroke and hemorrhage stroke) -free NVAF patients treated with warfarin or apixaban (shown as two Kaplan-Meier curves, for warfarin cohort and apixaban cohort, which will be statistically compared by a Log-rank test).
3. Risk of a composite of recurrent "Ischemic stroke" ("cardiogenic cerebral embolism" + "cerebral infarction") and hemorrhagic stroke and SE in patients treated with apixaban compared to that in patients treated with warfarin (Hazard ratio and 95% confident intervals will be calculated by a COX proportional hazard method) **(primary effectiveness analysis)**.

* TIA is not included in endpoints.

The safety of study will be conducted to elucidate the following,

1. Incidence rate of recurrent bleeding, such as major bleeding, intracranial hemorrhage, gastrointestinal tract bleeding or intraocular bleeding in NVAF patients treated with warfarin or apixaban
2. Time course of proportion of each bleeding-free in NVAF patients treated with warfarin or apixaban (shown as two Kaplan-Meier curves, for warfarin cohort and apixaban cohort, which will be statistically compared by a Log-rank test).
3. Risk of each bleeding in NVAF patients treated with apixaban compared to that in patients treated with warfarin (Hazard ratio and 95% confident intervals will be calculated by a COX proportional hazard method) **(primary safety analysis).**

In summary,

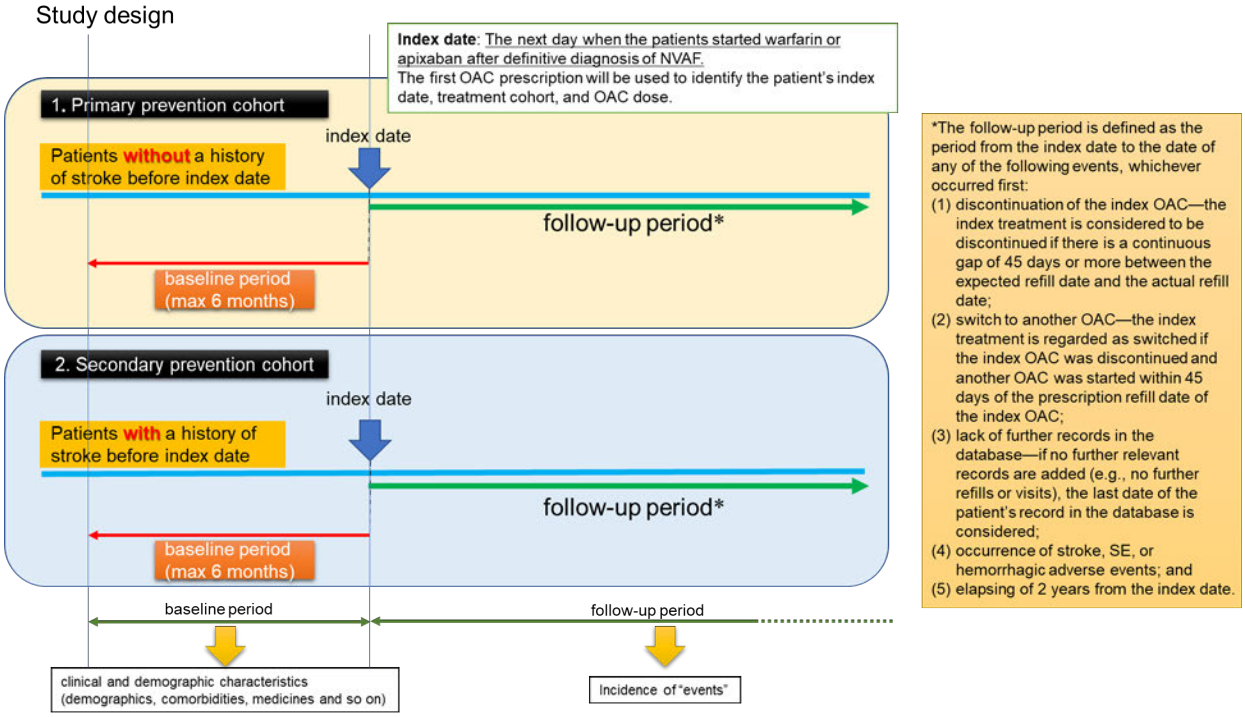
- **Primary effectiveness endpoint** : stroke (ischemic stroke and hemorrhage stroke)/SE

- **Secpondary effectiveness endpoints**:
  - Recurrent cardiogenic embolic stroke
  - Recurrent cerebral infarction
- **Primary safety endpoint** : major bleeding defined as any bleeding requiring hospitalization for treatment
- **Secondary safety endpoints:**
  - Intracranial hemorrhage
  - Gastrointestinal bleeding
  - Intraocular bleeding

# 8. RESEARCH METHODS

## 8.1. Study design

This is a non-interventional, comparative, observational study in which patients registered in the MDV database who met the study criteria are retrospectively aggregated. This is a secondary collection database study, and no primary data collection will be done.




### 8.1.1. Definition 1

#### 8.1.1.1. Index date

The next day of the day when patients diagnosed NVAF initiate warfarin or apixaban

#### 8.1.1.2. stroke

#### 8.1.1.3. Defined using pre-designated ICD-10 codes (see Statistical Analysis Plan). Ischemic and hemorrhagic stroke will be included,stroke

Stroke is defined using predefined ICD-10 codes and if hospitalization for the treatment of the stroke is necessary, it will be regarded as stroke incident during the followup period. (applicable only to the outpatients when recurrent stroke occurs)

#### 8.1.1.4. Major bleeding

Major bleeding is defined any bleeding that needs hospitalization for the treatment of bleeding. Any bleeding is defined using pre-designated ICD-10 codes (see Statistical Analysis Plan).

#### 8.1.1.5. Other clinical critical bleeding

Intracranial hemorrhage, gastrointestinal tract bleeding or intraocular bleeging

#### 8.1.1.6. Baseline period

Period of 180 days before the index date.

#### 8.1.1.7. Follow up period:

The end of observation is the period until the first observation of the earlier of the following items.

1. discontinuation of the index OAC (warfarin or apixaban, OAC prescribed on the index date); the index treatment is considered to be discontinued if there is a continuous gap of 45 days or more between the expected refill date and the actual refill date.
2. switch to another OAC; the index treatment is regarded as switched if the index OAC was discontinued and another OAC was started within 45 days of the prescription refill date of the index OAC.
3. lack of further records in the database; if no further relevant records are added (e.g., no further refills or visits), the last date of the patient's record in the database is considered.
4. occurrence of stroke or major bleeding (endpoints).
5. elapsing of 2 years from the index date.

## 8.2. Setting

### 8.2.1. Inclusion criteria

Patients must meet all the following selection criteria

1. Patients registered in the MDV database 2008 though 2021.
2. Patients newly with non-valvular atrial fibrillation
3. Patients who newly receive warfarin or apixaban after diagnosis of NVAF
4. Age 20 years or older on the index date
5. Patients who have a history of stroke or TIA are inclusion criteria only for secondary prevention cohort, otherwise patients will be concluded in the primary prevention cohort.

### 8.2.2. Exclusion criteria

Patients who meet the following exclusion criteria will be excluded from this study

1 Patients with a diagnosis of valvular AF (standard disease code: 8846941), postoperative AF (8847772), AF associated with mechanical valve malfunction (T82.0), mechanical complication of heart valve prosthesis (T82.0), or rheumatic AF (I05-I09) during the baseline period.

2 Patients with a diagnosis of VTE during the baseline period

3 Patients who are prescribed any anticoagulants before index date.

4 Patients who are prescribed anticoagulants other than warfarin and apixaban on the index date

5 Patients who are continuously hospitalized due to the first incidence of stroke or other serious diseases.

## 8.3. Variables

- Clinical and demographic characteristics of patients eligible for this study.
- Incidence of recurrent stroke (types of stroke)
- Incidence of bleeding (any bleeding, major bleeding, intracranial stroke, gastrointestinal stroke or intraocular bleeding)
- Medicines (types of anticoagulant, anti-platelet drugs and others)
- Comorbid diseases

Table1: Variables

| Variable | Role | Operational definition |
|---|---|---|
| **Previous stroke or TIA** | | |
| Privious incidence of stroke | Patient characteristic: | |
| Previous incidence of TIA | Patient characteristic: | Defined elsewhere using ICD-10 codes |

| | | |
|---|---|---|
| Types of previous stroke | Patient characteristic: | cardioembolic stroke or cerebral infarction |
| Hospitalization status | Patient characteristic: | Inpatients or outpatients |
| Hospitalization days | Patient characteristic: | 0 or days in hospital |
| **NVAF diagnosis and treatment** | | |
| Year | Patient characteristic | Year first diagnosed with NVAF |
| Anticoagulant | Patient characteristic | Warfarin or apixaban |
| **Patients** | | |
| age | Patient characteristics on index date | Years |
| Age category | Patient characteristics on index date | |
| age ≦65 | | |
| age 65 < , ≦75 | | |
| age 75 < | | |
| Gender categry | Patient characteristics on index date | Male or female |
| Body weight | Baseline characteristic | Kg (if available) |
| Height | Baseline characteristic | cm (if available) |
| BMI | Baseline characteristic | Calculated from body weight and height using a formula of (weight [kg] / (height [m])$^2$ |
| **Comorbidity profile** | | |
| Chronic obstructive pulmonary disease (COPD) | Baseline characteristic | Defined elsewhere using ICD-10 codes |
| Congestive heart disease | Baseline characteristic | Defined elsewhere using ICD-10 codes |
| Ischemic heart/coronary artery disease | Baseline characteristic | Defined elsewhere using ICD-10 codes |
| Diabetes | Baseline characteristic | Defined elsewhere using ICD-10 codes |
| Hyperlipidemia | Baseline characteristic | Defined elsewhere using ICD-10 codes |
| Hypertension | Baseline characteristic | Defined elsewhere using ICD-10 codes |
| Liver disease | Baseline characteristic | Defined elsewhere using ICD-10 codes |
| Renal disease | Baseline characteristic | Defined elsewhere using ICD-10 codes |
| Peripheral vascular disease | Baseline characteristic | Defined elsewhere using ICD-10 codes |
| Pregnancy | Exclusion criteria | Presence of “pregnancy”-related ICD-10 codes. |
| Cancer | Baseline characteristic | Defined elsewhere using ICD-10 codes |

| | | |
|---|---|---|
| VTE | Baseline characteristic (exclusion criteria) | Defined elsewhere using ICD-10 codes |
| **Medicines** | | |
| Anti-hypertensive drugs | Baseline characteristic | Defined elsewhere using drug codes |
| Anti-platelet drugs | Baseline characteristic | Defined elsewhere using drug codes |
| NSAIDs (chronic use*) | Baseline characteristic | Defined elsewhere using drug codes |
| Statins | Baseline characteristic | Defined elsewhere using drug codes |
| **Outcomes** | | |
| **Ischemic stroke (1)+(2)** | Outcome | Defined elsewhere using ICD-10 codes |
| (1) Cardiogenic cerebral embolism | Outcome | Defined elsewhere using ICD-10 codes |
| (2) Cerebral infarction | Outcome | Defined elsewhere using ICD-10 codes |
| Hemorrhagic stroke | Outcome | Defined elsewhere using ICD-10 codes |
| Systemic embolism | Outcome | Defined elsewhere using ICD-10 codes |
| Bleeding | Outcome | |
| Major bleeding (Any bleeding requiring hospitalization) | Outcome | Refer to SAP |
| Intracranial hemorrhage | Outcome | Defined elsewhere using ICD-10 codes |
| Gastrointestinal tract bleeding | Outcome | Defined elsewhere using ICD-10 codes |
| Intraocular bleeging | Outcome | Defined elsewhere using ICD-10 codes |

*NSAIDs chronic use

Patients who have been prescribed NSAIDs at least for 90 days during the baseline period. For non-oral drugs, the difference between each prescription day is counted as the number of prescription days.

## 8.4. Data sources

Medical Data Vision database

This study will use an anonymized Medical Data Vision Co. Ltd. (Tokyo, Japan, MDV) database from 450 acute care hospitals nationwide in Japan (as of June 2021) (23% of acute care hospitals with a combined diagnostic procedure (DPC) system). The MDV database consists of

administrative claims data on approximately 37 million individuals maintained in inpatient and outpatient settings. Each patient is associated with a specific ID to which all inpatient and outpatient data is linked.

## 8.5. Study size

In this study, eligible patients will be aggregated backward.

- The number of estimated patients;
- All registered patients: approximately 38 millions (2008-2021)
- Patients with ischemic stroke: 1.2 millions
- Patients with atrial fibrillation: 1.3 millions
- AF patients with a history of ischemic stroke: 226,000
- AF patients on warfarin: 251,000
- AF patients on apixaban: 237,000
- The number of patients who experienced recurrent ischemic stroke on warfarin or apixaban: unknown

## 8.6. Data management

The data will be provided by MDV. All the data is already structured in the database, so there is no need for new database development or manual review. The provided data can be used as-is for analysis. Therefore, there is no need for data management.

All analyses will be conducted using SAS software (Version 9.0 or higher, SAS Institute, Cary, NC, USA), and findings are presented in charts and tables created in Microsoft Excel.

### 8.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

Not applicable

### 8.6.2. Record retention

Not applicable

## 8.7. Data analysis

The detailed methodology for data analysis will be described in the Statistical Analysis Plan (SAP).

As a first step, extracted patients will be divided into two cohorts, primary prevention cohort and secondary prevention cohort based on the previous diagnosis of stroke. Clinical and demographic characteristics will be compared with two cohorts at baseline and on the index date (date of the initiation of warfarin and apixaban) and incidence rates of stroke/SE and major bleeding per 1,000 person-years will be calculated during follow-up period. In addition, interaction analysis will be conducted to investigate an interaction between OAC (warfarin/apixaban) and presence or absence of the previous episode of stroke.

- As a second step, only secondary prevention cohort will be used for further analyses as follows, Crude (before IPTW) patient characteristics are compared between warfarin and apixaban cohorts using appropriate methods (continuous variables: unpaired t-test or Mann-Whitney U-test, categorical variables: chi-square test)
- A propensity score is calculated based on multinomial logistic regressions in order to account for confounding effects and to ensure that patient characteristics are balanced between the warfarin cohort and apixaban cohort. An inverse probability of treatment weighting (IPTW) method using the calculated propensity score will be applied. To avoid sample size inflation and to ensure appropriate estimation of variances, s-IPTW (stabilized IPTW) is used here.
- Balanced (after IPTW) patient clinical and demographic characteristics are shown. Covariate balance between apixaban and warfarin cohorts after s-IPTW is assessed in terms of the standardized differences with a threshold of 0.1
- Kaplan Meier curves of balanced cohorts for each endpoint are drawn.
- Incidence rates of endpoints are calculated and shown per 1000 person-years.
- Hazard ratios with 95% confidence intervals will be calculated using a Cox proportional hazards regression model that incorporate only the index OACs as independent variables.

## 8.8. 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 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. For quality assurance of analysis, the vendor

which deals with the analysis 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.

Statistical analysis will be also outsourced to a specialist (a vender specialized to the statistics). Validity of analysis programs and the obtained results will be confirmed by the vender according to the internal standard of procedures.

## 8.9. Limitations of the research methods

Our study, like most retrospective analyses using claims data, has several intrinsic limitations and certain expected biases.

1. The data we will use is obtained from a claims database containing information provided by hospitals applying the flat-fee payment system, which are mostly large hospitals responsible for acute care. Therefore, a significant proportion of the patients included in the present analysis will be likely in poorer health than the average population requiring hospitalization, possibly having more comorbidities and higher risk of stroke and bleeding.

2. The claims data we will use here do not include vital signs or laboratory data such as blood pressure, international normalized ratio values, and renal function parameters, which is also why we could not calculate a HAS-BLED score. These variables will not be considered in the calculation of the propensity score, and there is no guarantee that such characteristics are fully balanced after s-IPTW. Therefore, although we will compute a propensity score based on multiple variables that may affect the risk of stroke and bleeding, the influence of unexamined confounding factors will not be fully excluded.

3. We will not provide an estimation of follow-up loss, as we will have no subsequent data on patients who visited a different hospital or clinic after being registered with one of the hospitals contributing to the MDV database. This could result in an underestimation of the incidence of stroke or major bleeding events.

## 8.10. Other aspects

Not applicable

# 9. PROTECTION OF HUMAN SUBJECTS

## 9.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information. According to the ethical guidelines for epidemiological studies in Japan, informed consent is not always required for studies by unlinkable anonymized data.

## 9.2. 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.

## 9.3. Patient withdrawal

Not applicable.

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

Since the MDV database is comprised of unlinkable anonymized data, IRB/IEC approval is not required according to the Pfizer's SOP/Policy and local regulations in Japan.

## 9.5. 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 practices described in CT24-WI-GL02-RF04 and references to any additional relevant guidance.

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

Although this study will examine the safety and effectiveness of specific Pfizer's product (apixaban), due to the nature of the database, individuals cannot be identified. Therefore, the management and the reporting of adverse events/adverse reactions is not required for this study.

# 11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

All final data will be shared with co-author. It is also anticipated that results from this study will generate a manuscript for submission to an local or international peer-reviewed journal. 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

participants aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

## 12. REFERENCES

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## 13. LIST OF TABLES

## 14. 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