Safety and effectiveness of apixaban in very elderly patients with NVAF compared to warfarin using administrative claims data

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Safety and effectiveness of apixaban in very elderly patients with NVAF compared to warfarin using administrative claims data
Protocol number	B0661181
Protocol version identifier	Ver. 2.0
Date	10-AUG-2023
Active substance	B : Blood and blood forming organs B01: Antithrombotic agents B01A : Antithrombotic agents B01AF: Direct factor Xa inhibitors B01AF02: apixaban
Medicinal product	Eliquis (apixaban)
Research question and objectives	Japan is a very elderly society compared to other countries in Europe and the United States, and many patients are newly diagnosed with NVAF even in their 80's or 90's. Most of these very elderly people have many complications and take many medications chronically as a result. In addition, many elderly patients have low body weight, sarcopenia, low ADL, frailty or frail-like characteristics, or high risk of falls. There has been much debate and inconclusive evidence on the value of anticoagulation for these very elderly patients with NVAF. ARISTOTLE study has shown that apixaban is superior or equivalent to warfarin in various populations including higher risk populations. However, there are few evidence, especially on safety and effectiveness of apixaban versus warfarin. Objectives To investigate safety and effectiveness of apixaban compared to warfarin in very elderly patients with NVAF. In addition to the absolute

	age, effects on higher age-related risk factors on relative risk of apixaban to warfarin is also investigated.
Author	PPD Pfizer Japan Inc., Shinjuku Bunka Quint Building 3-22-7 Yoyogi, Shibuya-ku, Tokyo 151-8589, Japan

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	Activity of daily living
AF	Atrial fibrillation
CCI	Charlson comorbidity index
CV/MET	Cardiovascular/Metabolism
DPC	Diagnosis Procedure Combination
ICD	International Statistical Classification of Diseases and Related Health Problems
IPTW	Inverse Probability Treatment Weighting
MDV	Medical Data Vision
NVAF	Non-valvular atrial fibrillation
RWE	Real world evidence

3. RESPONSIBLE PARTIES

Name, degree(s)	Title	Affiliation	Address
PPD	PPD	PPD	PPD
PPD	PPD	PPD	PPD

Name, degree(s)	Job Title	Affiliation	Address
PPD	PPD	PPD	PPD

4. PRINCIPAL INVESTIGATOR(S) OF THE PROTOCOLABSTRACT

- **Title:**
- Safety and effectiveness of apixaban in very elderly patients with NVAF compared to warfarin using administrative claims data

- Version 2.0, 10 AUG, 2023. PPD Pfizer Japan Inc.

4.1. Rationale *and background*:

Japan is a very elderly society compared to other countries in Europe and the United States, and there are many very elderly patients wth NVAF who are treated with any of anticoagulant and there are considerable number of patients who are newly diagnosed with NVAF even in their 80's and 90's. Most of these very elderly people have many complications, including severe ones, and take many medications chronically.In addition, many elderly patients have low body weight, sarcopenia, low ADL, frailty or frail-like characteristics, or high risk of falls. There has been much debate and inconclusive evidence on the value of anticoagulation for these very elderly patients with NVAF.

ARISTOTLE study has shown that apixaban is superior or equivalent to warfarin in various populations including populations at higher risk. However, there are few studies in the real-world settings regarding very elderly patients who are at higher risk.

4.2. Study hypothesis and clinical questions

The ARISTOTLE study and various real-world evidence (RWE) have shown that apixaban is superior or equivalent to warfarin in safety and effectiveness profile. Subgroup analyses of the ARISTOTLE study suggested that superiority over warfarin could be consistent in most populations including high risk populations. Study hypothesis and clinical questions in this study is apixaban is superior to warfarin in both safety and effectiveness even in the very elderly patients with NVAF in the real-world settings.

The clinical question of this study is that apixaban has a superior effectiveness and safety profile compared to warfarin, even in very elderly patients who are at particularly high risk, such as those with CCI , frail or frail patients, CCI [redacted]

4.3. Study objectives

The objective of this study is to investigate safety and effectiveness of apixaban compared to warfarin in very elderly patients with NVAF. CCI [redacted]

4.4. *Study design:*

- This is a retrospective non-intervention observational study to evaluate the difference in safety and effectiveness between apixaban and warfarin using a database provided by Medical Data Vision Co. Ltd. (MDV Co. Ltd.). Eligible patients will be extracted from the database and allocated to the pre-defined cohorts based on the actual age, age of NVAF diagnosis and types of anticoagulant therapy.
- Based on the age category and anticoagulants on the index date (a date when patients initiated an anticoagulant for prevention of stroke/SE), eligible patients will be allocated to some cohorts. Patient characteristics will be balanced by an Inverse probability of treatment weighting (IPTW) method, and risk of stroke/SE (primary effectiveness endpoint) and major bleeding (primary safety endpoint) will be compared. Hazard ratios and 95% confident intervals will be calculated by using a COX proportional hazard method.
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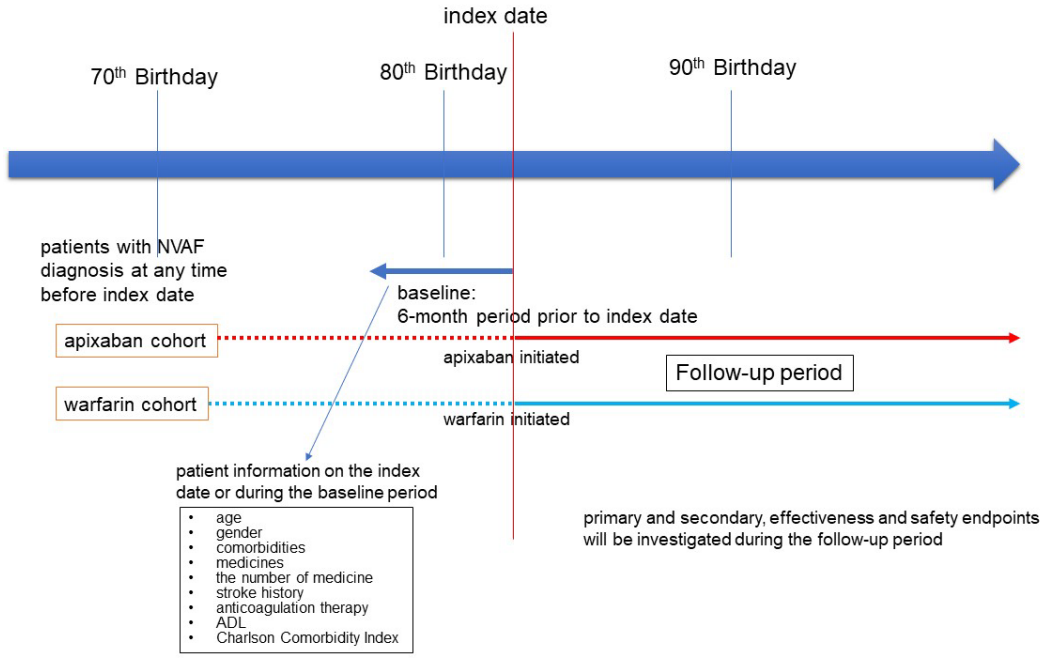
4.5. *Population*

- Patients registered in the MDV database from 26 February, 2013 to 31 December, 2021 will be used. First, atients with a NVAF diagnosis and received apixaban or warfarin as an anticoagulant after the NVAF diagnosis will be identified and then among them only patients who are 80 or older when they initiated these medications.



4.6. *Variables – include exposures, outcomes, and key co-variates*

- Following variables will be collected in this study at the index date (see 9.1 Study design for a definition of index date).

• ***Items***	• ***definitions***	• ***roles***
• Gender	• Male or female	• Patient characteristics
• CCI [redacted]	• [redacted]	[redacted]
• Timing of NVAF diagnosis	• 80-89 years • ≥ 90 years	• Patient characteristics
• [redacted]	CCI [redacted]	[redacted]
• Medications	• Chronically prescribed medicines • Details are shown in the SAP	• Patient characteristics
• [redacted]	[redacted]	CCI [redacted]
[redacted]	[redacted]	[redacted]
• Stroke history	• Previous diagnosis of cerebral infarction, cardiovascular embolism, hemorrhagic stroke, or TIM	• Patient characteristics

•

4.7. *Data sources*

Medical Data Vision database, commercially available administrative claims database from hospitals introducing DPC (Diagnosis Procedure Combination) system, which comprises administrative data pertaining to approximately 39 million individuals (as of 2021 Dec.) managed in the inpatient and outpatient settings.

4.8. *Study size*

All eligible patients will be used for the analysis. The number of patients to be used for the analysis was estimated in the preliminary feasibility check and we have confirmed that the statistical power may be sufficient to the analysis.

Roughly estimated number of patients are as follows,

- Male with NVAF: ≥ 80: 34,157
- Female with NVAF: ≥ 80: 33,163

The number of patients who are newly diagnosed with NVAF in 80-89 or ≥ 90 are not known.

The dealied results of estimation of power calculation will be described in the Statistical Analysis Plan (SAP)

4.9. *Data analysis*

- The detailed methodology for data analysis is explained in the SAP.

- For each age category, apixaban and warfarin cohorts whose patient characteristics are balanced by propensity score matching or IPTW methods will be created, and incidence rates of stroke/SE or major bleeding in each cohort and hazard ratios+ 95% confident intervals will be calculated.

4.10. *Milestones*

Data extraction from MDV database: Jun 30 – Jun 30, 2022
Analysis: July.01 - Aug.31, 2023
Completion of final study report: Sep.8, 2023
Manuscript submission: Oct.31, 2023

5. AMENDMENTS AND UPDATES

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

1.1	22 JUNE, 2022	4.10 6	Change the date; extraction from MDV database, start and end of data collection	The scheduled Data extraction date has changed.
2.0	10 AUG, 2023	4.5 4.10 6 9.10	Change the patient registration period Change the date of Milestones Change the data analyst	The launch date of apixaban in Japan was considered for concurrent comparison with warfarin. And the scheduled date FSR has changed.

6. MILESTONES

Milestone	Planned date
<Completion of feasibility assessment>	*28 Apr 2022*
Start of data collection	*30 Jun 2022*
End of data collection	*30 Jun 2022*
Final study report	*8 Sep 2023*

7. RATIONALE AND BACKGROUND

Japan is a very elderly society compared to other countries in Europe and the United States, and there are many very elderly patients wth NVAF who are treated with any of anticoagulant and there are considerable number of patients who are newly diagnosed with NVAF even in their 80's and 90's. Most of these very elderly people have many complications, including severe ones, and take many medications chronically.In addition, many elderly patients have low body weight, sarcopenia, low ADL, frailty or frail-like characteristics, or high risk of falls. There has been much debate and inconclusive evidence on the value of anticoagulation for these very elderly patients with NVAF.

ARISTOTLE study has shown that apixaban is superior or equivalent to warfarin in various populations including populations at higher risk. However, there are few studies in the real-world settings regarding very elderly patients who are at higher risk.

8. RESEARCH QUESTION AND OBJECTIVES

The ARISTOTLE study and various real-world evidence (RWE) have shown that apixaban is superior or equivalent to warfarin in safety and effectiveness profile. Subgroup analyses of the ARISTOTLE study suggested that superiority over warfarin could be consistent in most populations including high risk populations. Study hypothesis and clinical questions in this study is apixaban is superior to warfarin in both safety and effectiveness even in the very elderly patients with NVAF in the real-world settings.

The clinical question of this study is that apixaban has a superior effectiveness and safety profile compared to warfarin, even in very elderly patients who are at particularly high risk, such as those with CCI , frail or frail patients, CCI [redacted]

The objective of this study is to investigate safety and effectiveness of apixaban compared to warfarin in very elderly patients with NVAF. In addition to the absolute age, effects on higher age-related risk factors on relative risk of apixaban to warfarin is also investigated through subgroup analyses.

9. RESEARCH METHODS

9.1. Study design

This is a retrospective non-intervention observational study to evaluate the difference in safety and effectiveness between apixaban and warfarin using a database provided by Medical Data Vision Co. Ltd. (MDV Co. Ltd.). Eligible patients will be extracted from the database and allocated to the pre-defined cohorts based on the actual age, age of NVAF diagnosis and types of anticoagulant therapy.

Based on the age category and anticoagulants on the index date (a date when patients initiated an anticoagulant for prevention of stroke/SE), eligible patients will be allocated to some cohorts. Patient characteristics will be balanced by an Inverse probability of treatment weighting (IPTW) method, and risk of stroke/SE (primary effectiveness endpoint) and major bleeding (primary safety endpoint) will be compared. Hazard ratios and 95% confident intervals will be calculated by using a COX proportional hazard method.

The following definitions will be used here

- **Index date**: the date when warfarin or apixaban was initiated

- **Baseline period**: the 180 days before the index date
- **Cohorts**:
  - Apixaban cohorts: patients who started an anticoagulant therapy with apixaban
  - Warfarin cohorts: patients who started an anticoagulant therapy with warfarin
- **Observational period:**

Follow-up 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. Any bleeding when the target outcome for the analysis is any bleeding.
4. Discontinuation of the index OAC: The index treatment will be "discontinued" if the index OAC is not prescribed within 45 days after prescription refill date (calculated from the last refill date plus days of supply) of the index OAC, 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.
5. Switching from the index OAC: The index treatment is regarded as "switched" if non-index OAC is prescribed within 45 days after prescription refill date of the index OAC 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.
6. Withdrawal from the database: The patients are regarded as “withdrawal” from the database if the index OAC is not prescribed within 45 days after prescription refill date of the index OAC 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.

9.2. Endpoints

- Primary effectiveness endpoint: stroke/SE (a composite of ischemic stroke, hemorrhagic stroke and SE)
- Primary safety endpoing: Major bleeding (any bleeding requiring hospitalization for treatment)

- Seconary effectiveness endpoint:
  - Cardiogenic embolic stroke
  - Ischemic stroke
- Secondary safety endpoint:
  - Intracranial hemorrhage
  - Gastrointestinal bleeding
  - Intraocular bleeding

9.3. 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. That is, medical information will be collected in the real-world settings.

9.3.1. Inclusion criteria

Patients must meet all 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 warfarin 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.
5. Index date is at age 80 or older

9.3.2. 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 cardiac surgery procedure record during the baseline period

3. Having a joint replacement procedure record during the baseline period
4. Having a procedure of prosthetic heart valve during the baseline period
5. Having a diagnosis of venous thromboembolism during the baseline period
6. Female patients with pregnancy during the follow-up period
7. Patients prescribed “off-label” doses of OACs (per Japanese package insert of each OAC) or patients treated with OAC but in “off-label” or “contraindicated” manners.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

CCI

9.5. Variables

Items	definitions	roles
Gender	Male or female	Patient characteristics
CCI		
	CCI	

[redacted]	CCI [redacted]	[redacted]
Medications		
The number of chronically prescribed medicine		Patient characteristics
Treated with antiplatelet drug in baseline	Defined using prespecified drug-specific codes: Yes or No	Patient characteristics
Treated with NSAIDs in baseline	Defined using prespecified drug-specific codes: Yes or No	Patient characteristics
Treated with gastric secretion inhibitor in baseline	Defined using prespecified drug-specific codes: Yes or No	Patient characteristics
Treated with statin-based drug in baseline	Defined using prespecified drug-specific codes: Yes or No	Patient characteristics
Treated with anti-hypertensives in baseline	Defined using prespecified drug-specific codes: Yes or No	Patient characteristics
Treated with anti-arrhythmics in baseline	Defined using prespecified drug-specific codes: Yes or No	Patient characteristics
Treated with beta-blockers in baseline	Defined using prespecified drug-specific codes: Yes or No	Patient characteristics
Procedures		
Cardioversion	Defined using prespecified medical procedure codes: Yes or No	Patient characteristics
Cardiac ablation	Defined using prespecified medical	Patient characteristics

	procedure codes: Yes or No	

9.6. Data sources

The analysis will be based on administrative claims data provided 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 45%). The database provides claims data from 450 hospitals (as of Sep.2021) using the DPC system for medical service claims (21% of general hospitals but 55% of general beds in Japan is under the DPC system) including approximately 38 million patient data.

9.7. Study size

All eligible patients will be used for the analysis. The number of patients to be used for the analysis was estimated in the preliminary feasibility check and we have confirmed that the statistical power may be sufficient to the analysis.

Roughly estimated number of patients are as follows,

- Male with NVAF: ≥ 80: 34,157
- Female with NVAF: ≥ 80: 33,163

The number of patients who are newly diagnosed with NVAF in 80-89 or ≥ 90 are not known.

The dealied results of estimation of power calculation will be described in the Statistical Analysis Plan (SAP)

9.8. Data management

Data will be securely provided by MDV Co. Ltd. All data have been structured and no development of new database and human review are not required. Provided data will be able to be used directly for the analysis.

9.9. Data analysis

Baseline patient demographic information will be compared among cohorts to be compared by appropriate tests (e.g., t-test, Mann Whitney-U test, chi-square test) based on the distribution of the measures.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (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.

9.10. Quality control

This study is a retrospective analysis using quality controlled structured 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.

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.

9.11. Limitations of the research methods

- The data we will use are 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 are likely in poorer health than the average population requiring hospitalization, possibly having more comorbidities and higher risk of stroke/SE and bleeding.
- CCI [redacted].

9.12. Other aspects

There is slight duplicated analyses between and the current study and previously approved on-going study (named CER4 which will be investigated safety and effectiveness of apixaban compared to warfarin in bleeding-prone patients with NVAF)

- CER-4 is a study focused on the risk of bleeding in the bleeding-prone (with at least one risk factor for bleeding) population taking anticoagulants. On the other hand, the current study is to investigate the risk of developing Stroke / SE and bleeding in the very elderly people receiving anticoagulant therapy. Like this, study populations to be examined are at least in part similar but basically different.

- Different, important unmet medical needs in Japan underlie these two studies. Anticoagulant therapy for patients at higher risk of bleeding and for very elderly patients are still critical unmet medical needs in Japan and these topics have been often discussed at the scientific meetings such as Japanese Circulation Society.

- A part of analysis, safety and effectiveness in very elderly patients, is suplicatedly conducted in the two study because higher age is often considered as a risk of bleeding. CCI [redacted] In contrast, in the current very elderly patients study, patients' age is the main factor, and the effectiveness and safety of apixaban in the super-elderly will be investigated as the primary analysis. CCI [redacted]

- Therefore, two studies are quite different in the purposes, underlying unmet medical needs to be met, populations to be investigated.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study without human review of unstructured data 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. Patient withdrawal

Not applicable

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

According to the Japanese regulations, this type of database study does not always need approval of IRB or IEC. This study is an actual survey and epidemiological study and will not submit protocol synopsis to IRB of Research Institute of Healthcare Data Science for protocol review and approval.

10.5. 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.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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 investigator 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.

If not, a part or all results of the study will be published in one of the peer-reviewed medical scientific journals. No design paper, progress reports and interim reports will be published elsewhere.

13. REFERENCES

14. LIST OF TABLES

15. LIST OF FIGURES

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16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

17. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

18. ANNEX 3. ADDITIONAL INFORMATION

Not applicable