Non-Interventional Study Protocol
< B0661176>

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

Statistical Analysis Plan
(SAP)

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Contents

1. AMENDMENTS FROM PREVIOUS VERSION(S)

None

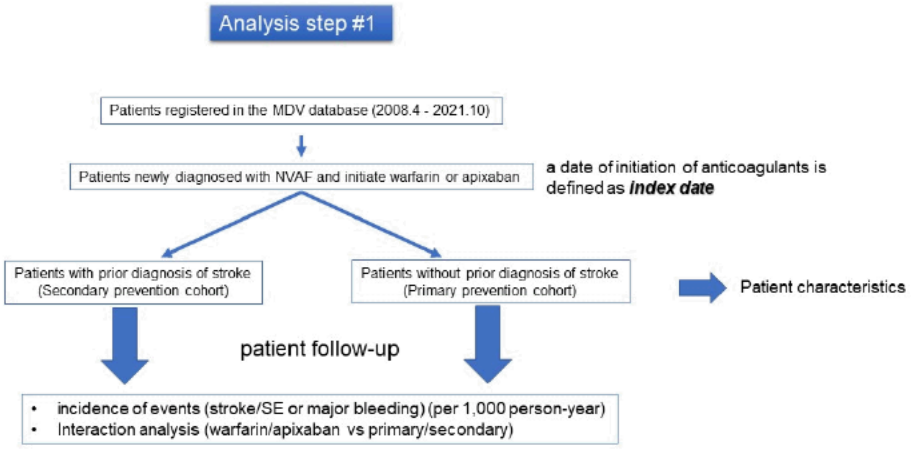
2. INTRODUCTION

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.

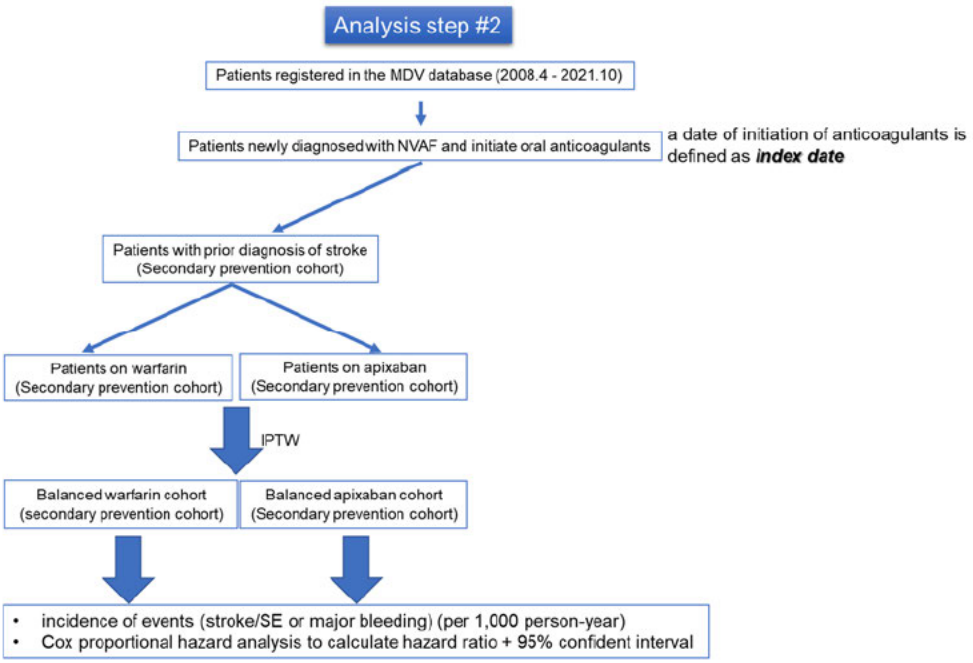
2.1. STUDY DESIGN

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.*

In this study, analyses will be conducted in a 2-step manner. The first step is an epidemiological part and the number of of patients of NVAF patients with a history of stroke (cerebral infarction, cardioembolic stroke, hemorrhagic stroke or TIA) or without a history of stroke in Japan, and clinical and demographic characteristics in each cohort will be investigated. In addition, incidence rate of stroke will be investigated in each cohort and presented as incidence rates per 1,000 person-years. Relative risk of stroke/SE and major bleeding will be estimated by using Logistic regression analysis and p for interaction between OAC (warfarin or apixaban) and a history of stroke (primary or secondary) will be calculated. In this first step, propensity score matching or IPTW will not be performed to balance the patient characteristics between cohorts.



In the second step, only the secondary prevention patients who are newly diagnosed with NVAF and initiate warfarin or apixaban for prevention of cardioembolic stroke. To balance the patient characteristics between warfarin and apixaban cohorts, an IPTW methods will be applied. Using the bananced warfarin cohort and apixaban cohort, incidence of events (stroke/SE or major bleeding) (per 1,000-year) will be calculated. Additionally, Cox proportional hazard analysis will be conducted to calculate hazard ratio + 95% confident interval.



2.1.1. Study population

NVAF patients in secondary prevention of ischemic stroke who are treated with warfarin or apixaban, registered in the MDV database (2008-2021).

In the preliminary survey the number of patients will be estimated as follows (this was a rough estimation)

- *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*
- *NVAF patients with a history of ischemic stroke: 226,000*
- *NVAF patients on warfarin: 251,000*
- *NVAF patients on apixaban: 237,000*
- *The number of patients who experienced recurrent ischemic stroke on warfarin or apixaban: unknown*

2.1.2. Data source

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 identifier (ID) to which all inpatient and outpatient data are linked.

2.1.3. Treatment/cohort labels

Step-1

1. Primary prevention patients who are newly diagnosed with NVAF and initiated warfarin or apixaban (*primary prevention cohort*)
2. Secondary prevention patients who are newly diagnosed with NVAF and initiated warfarin or apixaban (*secondary prevention cohort*)

Step-2

1. Balanced Warfarin cohort of secondary prevention (*warfarin cohort*)
2. Balanced apixaban cohort of secondary prevention (*apixaban cohort)*

Patients will be assigned to each cohort based on the first prescription of oral anticoagulants after the diagnosis of NVAF (warfarin or apixaban). If the first oral anticoagulant prescribed was other than warfarin or apixaban or no oral anticoagulant was used, the patients will be excluded. Patient clinical and demographic characteristics wlll be balanced by using an IPTW method.

2.2. STUDY 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 and hemorrhagic) 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/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.

3. HYPOTHESES AND DECISION RULES

3.1. STATISTICAL HYPOTHESES

Not applicable

3.2. STATISTICAL DECISION RULES

When the effect of factors in an analysis is statistically evaluated, the alpha level of 0.05 will be referred.

4. ANALYSIS SETS/POPULATIONS

4.1. FULL ANALYSIS SET

4.1.1. Inclusion criteria

Patients must meet all the following selection criteria

1. *Patients registered in the MDV database 2008 through 2021.*
2. *Patients newly diagnosed with non-valvular atrial fibrillation*
3. *Patients who started anticoagulation treatment with either 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 (cerebral infarction, cardioembolic stroke, or hemorrhagic stroke) or TIA before the index date are inclusion criteria only for secondary prevention cohort, otherwise patients will be included in the primary prevention cohort.*

* A history of stroke is checked as far back as possible from the INDEX DATE to see if there is a history of stroke. That is, the period is from the date each patient first appeared in the MDV database to the day before the index date.

4.1.2. 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 anticoagulant during the baseline period.*
4. *Patients who are prescribed anticoagulants other than warfarin and apixaban on the index date*
5. *Patients who were hospitalized for more than 6 months (including index date) regardless of reason for hospitalization.*

   ***: maximally 6 months prior to the index date. If sufficient patient information is available for the analysis, patients who cannot have a 6-month baseline period will be included in the analysis.*

4.2. SAFETY ANALYSIS SET

Bleeding other than safety-related reactions will not be investgated here. Bleeding events will be evaluated using the same analysis set as effectiveness.

4.3. OTHER ANALYSIS SET

Not applicable. All eligible patients will be used for the analysis except the pre-degignated sub-analysis.

4.4. SUBGROUPS

- None

5. ENDPOINTS AND COVARIATES

5.1. EFFICACY/EFFECTIVENESS ENDPOINT(S)

5.1.1. Primary effectiveness endpoint and primary analyses

The following outcomes will be assessed as effectiveness endpoints. Primary endpoint is incidence of a composite of recurrent stroke (ischemic and hemorrhagic stroke)/SE in NVAF patients treated with warfarin or apixaban. The definition of "recurrent" is as follows, "once patients discharge from the hospital and become outpatients and then rehospitalized due to stroke (major reason for the hospitalization is stroke described in the DPC admission information)

1. Incidence rate (per 1,000 person-years) of a composite of recurrent stroke (ischemic and hemorrhagic stroke)/SE during the follow-up period in NVAF patients treated with warfarin or apixaban
2. Time course of proportion of the incidence of a composite of recurrent stroke (ischemic and hemorrhagic stroke)/SE-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 stroke (ischemic and hemorrhagic stroke)/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

5.1.2. Secondary effectiveness endpoint and secondary analyses

Secondary effectiveness endpoints are the incidence of "cardiogenic cerebral embolism" or "cerebral infarction" or "hemorrhagic stroke" during the follow-up period. in NVAF patients treated with warfarin or apixaban.

1. Incidence rate (per 1,000 person-years) of recurrent "**cardiogenic cerebral embolism**" during the follow-up period in NVAF patients treated with warfarin or apixaban.
2. Time course of proportion of the incidence of recurrent "**cardiogenic cerebral embolism**" -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 recurrent "**cardiogenic cerebral embolism**" 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.

4. Incidence rate (per 1,000 person-years) of recurrent **"cerebral infarction"** during the follow-up period in NVAF patients treated with warfarin or apixaban.
5. Time course of proportion of the incidence of recurrent **"cerebral infarction"**-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).
6. Risk of recurrent **"cerebral infarction"** 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.

5.2. SAFETY ENDPOINTS

5.2.1. Primary safety endpoint and primary analyses

The following outcomes will be assessed as safety endpoints. The primary safety endpoint is **major bleeding**, which is defined as any bleeding requiring hospitalization for treatment (the primary reason for the hospitalization is to treat the bleeding). Because "hospitalization" is a requirement, only outpatients will be included in the analysis and patients who are already hospitalized at the time of bleeding (bleeding during hospitalization) will be excluded from the analysis.

1. Incidence rate (per 1,000 person-year) of **major bleeding** during the follow-up period in NVAF patients treated with warfarin or apixaban.
2. Time course of proportion of **major 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 **major 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.

5.2.2. Secondary safety endpoint and secondary analyses

Secondary safety endpoints are intracranial hemorrhage, gastrointestinal bleeding or intraocular bleeding during the follow-up period. Because hospitalization is not used for the definitions of these secondary endpoints, It does not matter whether the patient is hospitalized or visiting a hospital as outpatients when these endpoints occur.

1. Incidence rate (per 1,000 person-year) of **intracranial hemorrhage** during the follow-up period in NVAF patients treated with warfarin or apixaban.
2. Time course of proportion of **intracranial hemorrhage**-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 **intracranial hemorrhage** 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.
4. Incidence rate (per 1,000 person-year) of **gastrointestinal bleeding** during the follow-up period in NVAF patients treated with warfarin or apixaban.
5. Time course of proportion of **gastrointestinal 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).
6. Risk of **gastrointestinal 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.
7. Incidence rate (per 1,000 person-year) of **intraocular bleeding** during the follow-up period in NVAF patients treated with warfarin or apixaban.
8. Time course of proportion of **intraocular 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).
9. Risk of **intraocular 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.

5.3. OTHER ENDPOINTS

Not applicable

5.4. COVARIATES

Variable	Role	Operational definition
Previous stroke		
Previous 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
Treatment 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 bleeging requiring hospitalization)	Outcome	Refer to excel sheet in section 10.3
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 a 90-day during the baseline period. For non-oral drugs, the difference between each prescription day is counted as the number of prescription days.

6. HANDLING OF MISSING VALUES

Patients with all required data will be excluded from the analysis.

7. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1. STATISTICAL METHODS

7.1.1. Patient characteristics

Patients characteristic will be compared between two grouls before and after IPTW. Means, medians, and standard deviations will be provided for continuous variables when performing descriptive analysis of continuous data. Numbers and percentages will be provided for dichotomous and polychotomous variables when performing descriptive analysis of categorical data. Bivariate comparisons of baseline characteristics and outcomes measures will be provided. Appropriate tests (unpaired t-test or Mann-Whitney U-test, categorical variables: chi-square test) will be used based on the distribution of the measure. The balance of these covariates between cohorts will be assess using the standardized difference (cutoff: 0.1)

7.1.2. Patient characteristic balancing

In this study, matched cohorts (warfarin cohort versus apixaban cohort) will be created. A propensity score will be calculated based on multivariable 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) is 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. We will present the data for each variables and standardized differences in the same table side by side to ensure that two cohorts are balanced after IPTW.

* Covariates used for the calculation of propensity score

- Gender: male or female
- Age: absolute years
- BMI: categories BMI (kg/m2) (<18,18 to <22, 22 to <25, 25+, missing)
- CHADS2 score: absolute score, categories (0, 1, 2, 3, 4, 5, 6)

- CHA2DS2-VASc: absolute score, categories (0, 1, 2, 3, 4, 5, 6, 7, 8, 9)
- Treatment status of the most recent stroke before the index date (outpatient treatment, inpatient treatment, missing)
- mRS (modified Rankin Scale) at time of admission due to most recent stroke (0,1,2,3,4,5, missing)
- JCS (Japan coma scale) at time of admission due to most recent stroke (I, II, III, missing)
- ADL (Activities of daily living) at time of admission due to most recent stroke (0-19, 20-39, 40-59, 60-79, 80-100, missing)
- Duration of hospitalization due to most recent stroke
- Destination after discharge from hospitalization due to most recent stroke (1 or 5 or other (2,3,4,6,7,8,9))
- Use of tPA or urokinase for treatment of most recent ischemic stroke (thrombolytic therapy)
- Type of most recent stroke stroke (TIA, ischemic stroke, cerebral bleeding, cardiogenic thromboembolism, unknown/others)
- *Note: in patients with a medical history of incidence multiple stroke events, only information regarding most recent stroke (i.e., stroke event closest to the index date) will be used.*
- Comorbidities
  - Hypertension
  - Heart failure in baseline
  - Coronary heart disease in baseline
  - Peripheral arterial disorder in baseline
  - History of myocardial infarction
  - Hyperthyroidism or thyrotoxicosis in baseline
  - Diabetes in baseline
  - Liver diseases in baseline
  - Diabetes mellitus diagnosis in baseline
  - Cancer diagnosis in baseline
  - Dementia in baseline
  - Renal diseases in baseline
  - Gastrointestinal ulcer in baseline

- History of bleeding

- Medicines
  - Treated with antiplatelet drug in baseline
  - Treated with NSAIDs in baseline
  - Treated with anti-hypertensives in baseline
  - Treated with anti-arrhythmics in baseline
  - Treated with beta-blockers in baseline
  - Treated with heparins in baseline
- Others
  - Cardioversion
  - Cardiac ablation

7.2. STATISTICAL ANALYSES

- SAS software version 9.4 (SAS Institute Inc. NC, USA)) will be used for the analysis.
- For primary effectiveness analysis and primary safety analysis (see 5.1 and 5.2), statistical tests will be performed at p=0.05 (two-sided) with no adjustment for multiplicity. P values less than 0.05 will be regarded as statistically significant.
- We will conduct multiple secondary analysis as shown below and these repetitive statistical analyses may cause the "Multiple Testing Problem". Here these multiple analyses will be concluded only as an explorartry purpose and we do not intend to conclude anything from the results obtained from sub-endpoint analyses here. No multiple testing adjustment will be taken.

7.2.1. Sensitivity analysis

E-values (evidence for causality) will be calculated for the primary effectiveness and safety analysis from calculated hazard ratios and 95% confident intervals to estimate the extent of unmeasured confounding. In this study, the E-value is defined as the minimum strength of association on the calculated hazard ratio and the limit of the confidence interval closest to the null in the primary effectiveness and safety analysis.

7.2.2. Power calculation

The randomized clinical trial, ARISTOTLE study, has revealed that hazard ratios of apixaban to warfarin in patients with a previous history of stroke/TIA are almost similar to those without a history of stroke/TIA (p for interaction : 0.71). The hazard ratio for Stroke/SE in the previous Japanese comparison of Apixaban and warfarin using the MDV database that will be used in this study was 0.65. Based on these two results, we can estimate that the hazard ratio in the current secondary prevention patients is also about 0.65. All statistical tests will be performed at p=0.05 (two-sided) with no adjustment for multiplicity.

The following sample size calculation will be based on the significance level of 0.05 (two-sided) and power of 80%.Desired Power	Hazard Ratio	Event Rate (Control)	Required Sample Size per Group
0.8	0.6	1.2 %/year	3,166
		1.6 %/year	2,378
		2.1 %/year	1,815
		2.6 %/year	1,469
	0.7	1.2 %/year	6,083
		1.6 %/year	4,570
		2.1 %/year	3,488
		2.6 %/year	2,823
	0.8	1.2 %/year	14,683
		1.6 %/year	11,031
		2.1 %/year	8,422
		2.6 %/year	6,817

In the preliminary study, we have found that more than 15,000 secondary prevention patients with NVAF who take apixaban or warfarin. So, probably the power may be higher than 0.8 in this study.

7.2.3. Summary of Analyses

All analysis other than patient characteristics will be conducted as a two-sided p-value less than 0.05.

Patient charactertistics will be compared using standardized differenece as a cut-off value of 0.1.

Outcome/items to be examined	Analysis Cohort	Supports Protocol Objective Number	Subgroup	Statistical Method	Covariates/Strata	Missing Data

Patients characteristics	Cohorts in Step 1 and Step 2		None	unpaired t-test or Mann-Whitney U-test, categorical variables: chi-square test		No imputation
The incidence rates of stroke/SE and major bleeding per 1,000 person-years	Cohorts in Step 1 and Step 2		None	1000 person-years	Refer to section 5.4	No imputation
Interaction analysis	Cohorts in Step 1 and Step 2		None	Cox proportional hazards regression model	Warfarin/apixaban, primary/secondary	No imputation
Incidence rate of a composite of recurrent stroke (ischemic and hemorrhgic)/SE (primary effectiveness analysis)	Balanced cohorts	Effectiveness 1	None	1000 person-years	Refer to section 5.4	No imputation
Incidence of cardiogenic cerebral embolism (secondary effectiveness endpoint)	Balanced cohorts	Effectiveness 1	None	1000 person-years	Refer to section 5.4	No imputation
Incidence of cerebral infarction (secondary effectiveness endpoint)	Balanced cohorts	Effectiveness 1	None	1000 person-years	Refer to section 5.4	No imputation
Incidence rate of major bleeding (primary safety endpoint)	Balanced cohorts	Safety 1	None	1000 person-years	Refer to section 5.4	No imputation
Incidence rate of intracranial hemorrhage (secondary safety endpoint)	Balanced cohorts	Safety 1	None	1000 person-years	Refer to section 5.4	No imputation
Incidence rate of gastrointestinal bleeding (secondary safety endpoint)	Balanced cohorts	Safety 1	None	1000 person-years	Refer to section 5.4	No imputation
Incidence of rate of intraocular bleeding (secondary safety endpoint)	Balanced cohorts	Safety 1	None	1000 person-years	Refer to section 5.4	No imputation
Time course of proportion of a composite of the incidence of recurrent stroke (ischemic and hemorrhgic)/SE -free NVAF patients treated with warfarin or apixaban	Balanced cohorts	Effectivess 2	None	Kaplan Meier curves	Refer to section 5.4	No imputation

Time course of proportion recurrent cardiogenic cerebral embolism-free NVAF patients treated with warfarin or apixaban	Balanced cohorts	Effectivess 2	None	Kaplan Meier curves	Refer to section 5.4	No imputation
Time course of proportion of recurrent cerebral infarction"-free NVAF patients treated with warfarin or apixaban	Balanced cohorts	Effectivess 2	None	Kaplan Meier curves	Refer to section 5.4	No imputation
Time course of proportion of major-free NVAF patients treated with warfarin or apixaban	Balanced cohorts	Safety 2	None	Kaplan Meier curves	Refer to section 5.4	No imputation
Time course of proportion of intracranial hemorrhage-free NVAF patients treated with warfarin or apixaban	Balanced cohorts	Safety 2	None	Kaplan Meier curves	Refer to section 5.4	No imputation
Time course of proportion of gastrointestinal bleeding-free NVAF patients treated with warfarin or apixaban	Balanced cohorts	Safety 2	None	Kaplan Meier curves	Refer to section 5.4	No imputation
Time course of proportion of intraocular bleeding-free NVAF patients treated with warfarin or apixaban	Balanced cohorts	Safety 2	None	Kaplan Meier curves	Refer to section 5.4	No imputation
Risk of a composite of recurrent stroke (ischemic and hemorrhgic)/SE during the follow-up period in NVAF patients treated with warfarin or apixaban	Balanced cohorts	Effectivess 3	None	Cox proportional hazards regression model	Refer to section 5.4	No imputation
Risk of recurrent cardioembolic strole during the follow-up period in NVAF patients treated with warfarin or apixaban	Balanced cohorts	Effectivess 3	None	Cox proportional hazards regression model	Refer to section 5.4	No imputation
Risk of recurrent cerebral infarction during the follow-up period in NVAF patients treated with warfarin or apixaban	Balanced cohorts	Effectivess 3	None	Cox proportional hazards regression model	Refer to section 5.4	No imputation
Risk of major bleeding in patients treated with apixaban compared to that in patients treated with warfarin	Balanced cohorts	Safety 3	None	Cox proportional hazards regression model	Refer to section 5.4	No imputation

Risk of intracranial hemorrhage in patients treated with apixaban compared to that in patients treated with warfarin	Balanced cohorts	Safety 3	None	Cox proportional hazards regression model	Refer to section 5.4	No imputation
Risk of gastrointestinal tract bleeding in patients treated with apixaban compared to that in patients treated with warfarin	Balanced cohorts	Safety 3	None	Cox proportional hazards regression model	Refer to section 5.4	No imputation
Risk of intraocular bleeding in patients treated with apixaban compared to that in patients treated with warfarin	Balanced cohorts	Safety 3	None	Cox proportional hazards regression model	Refer to section 5.4	No imputation

8. LIST OF TABLES AND TABLE SHELLS

9. REFERENCES

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APPENDICES

9.1. APPENDIX 1: DATA DERIVATION DETAILS

Not applicable

9.2. APPENDIX 2: ADDITIONAL STATISTICAL METHODOLOGY DETAILS

Not applicable

9.3. APPENDIX 3: DIAGNOSIS AND PROCEDURE CODES USED IN THE STUDY

The list of ICD-10 codes is shown in following excel sheet.

ICD-10 codes.xlsx