Study design of GENERAL (general practitioners and embolism prevention in NVAF patients treated with rivaroxaban: Real-life evidence): A multicenter prospective cohort study in primary care physicians to investigate the effectiveness and safety of rivaroxaban in Japanese patients with NVAF

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1. Introduction

In patients with atrial fibrillation (AF), anticoagulant therapy with warfarin can reduce the incidence of stroke by 60% [1]. PT-INR (prothrombin time-international normalized ratio) measurement is essential for assessing the risk of hemorrhage and embolism during anticoagulant therapy with warfarin [2,3]. Although warfarin has excellent stroke preventive effects, considerable time is needed to achieve an effective PT-INR level and many interactions with vitamin K-containing foods and other drugs cause instability in PT-INR. Warfarin may also increase the risk of hemorrhagic events. Considering this, warfarin is a drug that places great burden on patients and medical providers. As the population ages, the number of patients with non-valvular atrial fibrillation increases; more
physicians, including not only specialists but also general practitioners, should be able to treat these patients [4]. Although the prevalence of AF is increasing, cognitive disorders are on the rise with the aging of the population [5]. Therefore, general practitioners treat elderly patients with AF with dementia or frailty [6]. Anticoagulant therapy adjustment with warfarin is not accomplished easily by general practitioners and therefore not commonly used. A foreign study reported the time in therapeutic range (TTR) for warfarin as 65% at anticoagulant therapy-specialized clinics and 51% with general practitioners [7]. This suggests that due to concerns about hemorrhagic event risks and the aforementioned problems, warfarin is not used frequently by general practitioners. It was reported that the incidences of stroke and hemorrhagic events between patients treated with warfarin and those not treated with any anticoagulants were comparable [8]. Recently, several direct oral anticoagulants (DOACs) have become available. Among them, rivaroxaban, a new oral direct factor Xa inhibitor, is administered once a day and exerts an anticoagulant effect soon after administration. As it reacts minimally with food or other drugs, it does not require regular monitoring. A randomized, double-blind, study (the ROCKET AF study) was conducted overseas in 14,264 non-valvular atrial fibrillation (NVAF) patients to compare rivaroxaban with warfarin. The results of the study suggest that rivaroxaban is not inferior to warfarin in terms of stroke preventive effects and the medications are equivalent regarding safety [9]. Additionally, another study J-ROCKET AF was conducted in Japan with 1280 patients with non-valvular atrial fibrillation. The results suggest that rivaroxaban is not inferior to warfarin in terms of safety and is useful for the prevention of ischemic stroke, although the study was not sufficiently powered to evaluate efficacy [10]. The EXPAND study is a nationwide registry study (UMIN clinical Trials Registry: UMIN000009376) conducted in Japan by specialists in universities and hospitals to evaluate rivaroxaban effectiveness in real-life clinical practice. Based on the current evidence, to our knowledge, rivaroxaban effectiveness and safety have never been investigated when used by general practitioners.

2. Material and methods

2.1. Objectives

The GENERAL study has been designed as a multicenter prospective cohort study in primary care physicians to investigate the effectiveness and safety of rivaroxaban in Japanese patients with NVAF (UMIN000019135, NCT02633982).

2.2. Study population

A total of 5000 patients with NVAF treated with rivaroxaban will be investigated. The patient inclusion criteria are as follows: treatment with rivaroxaban and provision of written informed consent for participation in the present study (including those treated with rivaroxaban during the registration period and those who had undergone ablation). The exclusion criteria are as follows: (1) contraindication to rivaroxaban, and (2) judged as inappropriate for this study by the investigators.

The procedure for patient registration is as follows. The informed consent will be obtained from eligible patients by the physician (general practitioner). The physician will be sending a registration form to the Contract Research Organization (CRO) which is contracted by the Japan Cardiovascular Research Foundation. The CRO will register the patient’s information into the Electronic Data Capture (EDC) system. Rivaroxaban will be administered in accordance with the approved dosage/administration in Japan. If the creatinine clearance (CLcr) is 50 mL/min or more, a dose of 15 mg will be administered once a day. If the CLcr lies between 15 mL/min and 49 mL/min, a dose of 10 mg will be administered once a day, regardless of the administration time. The dose can be controlled as necessary by the physician in charge.

2.3. Data acquisition

Information on participants before the prescription of rivaroxaban and that obtained before the specified observation time will be entered in the EDC system. Even if a participant is transferred to another hospital, information about the participant, and, mainly, information about the onset of endpoint-related and hemorrhagic events should be collected until the

![Image](Fig_1.png)

Fig. 1. Time schedule of GENERAL study. The target number of participants is 5000. After registration, follow-up data will be collected at three times (March 2017, September 2017 and September 2018).
end of the study period. If treatment with rivaroxaban is suspended or discontinued for any reason, observation should be continued as long as possible to collect all needed information. Even if endpoint-related or hemorrhagic events are seen before the end of the study period, observation should be continued until the end of the study period. The event assessment committee could ask the physicians in charge to submit detailed information about the endpoint-related events (Fig. 1).

2.4. Study schedule (figure)

The registration period is between September 2015 and March 2017 (1.5 years).

The study period is between September 2015 and September 2018 [1.5–3 years (2 years on average)].

Table 1
Observational items:

| Observational items                                      |
|----------------------------------------------------------|
| Demographic information                                  |
| Age, sex, weight                                         |
| Blood pressure, pulse rate                               |
| Type of atrial fibrillation (paroxysmal, persistent, temporary, or unknown) |
| Alcohol and smoking habit                                 |
| Complications/previous diseases                          |
| Stroke (ischemic and hemorrhagic/transient ischemic attack |
| Systemic embolism                                        |
| Deep vein thrombosis                                     |
| Pulmonary embolism                                       |
| Peripheral arterial disease                              |
| Coronary heart disease (myocardial infarction, history of PCI/CABG) |
| Congestive heart failure (NYHA class I/II/III/ IV, medication) |
| Hypertension                                             |
| Diabetes                                                 |
| Dyslipidemia                                             |
| Hepatic dysfunction                                      |
| Chronic kidney disease                                   |
| Malignant tumor                                          |
| Major bleeding                                           |
| Dementia                                                 |
| Nursing care level (support need 1/2, care need 1–5)     |
| Laboratory test (laboratory test undergone by investigators optionally) |
| Hematological tests (RBC, Hb, Ht, platelet)               |
| Kidney function tests (BUN, Creatinine)                  |
| Liver function tests (T-Bil, ALT, AST, γ-GTP, Alb)       |
| Coagulation tests (PT, APTT)                             |
| Other (CRP, BNP or NT-pro BNP)                            |
| Status of rivaroxaban intake                             |
| Date of first administration                             |
| Dosage 15 mg od/10 mg od                                  |
| History of anticoagulation therapy before rivaroxaban (warfarin, dabigatran, apixaban, edoxaban, or none) |
| Treatment for atrial fibrillation                         |
| Treatment with antiplatelet drugs                        |
| Other medication                                          |

2.5. Data analysis

2.5.1. Criteria for selection of evaluable patients

Selections of patients to be included in the analyses are all dosed patients, all eligible patients, and all evaluable patients. Due to the exploratory nature of the study, the data obtained from the study will be summarized descriptively. Continuous variables will be expressed as mean ± standard deviation and categorical variables will be expressed as numbers of patients and percentage. Demographic and baseline characteristics of enrolled patients will be summarized by descriptive statistics. These items are shown in Table 1. Concomitant drugs and treatment should be described in patients with complicated diseases as follows:

1) Treatment for AF

- Drug therapy (rhythm/rate control, and drug name).
- Non-drug therapy (data on application such as electrical defibrillation, catheter ablation, and surgery).

If necessary, details of anticoagulant drugs used during non-drug therapy, including heparin and rivaroxaban, will be investigated to assess a causal relationship with adverse events (ischemic stroke, systemic embolism, and clinically significant hemorrhagic events).

2) Treatment with antiplatelet drugs

- Aspirin, clopidogrel, ticlopidine, cilostazol and prasugrel.

3) Treatment with non-steroidal anti-inflammatory drugs (NSAIDs).

4) Treatment for hypertension, diabetes, dyslipidemia, and dementia should be described, as accurately as possible, including the indication or circumstances in which it is used.

2.5.2. Primary and secondary outcome(s) (Table 2)

This is an event-driven study. An individual event assessment committee will investigate endpoint-related events. The primary outcome is a composite of symptomatic stroke and systemic embolism in those where the event is considered the first onset of symptomatic stroke (ischemic/hemorrhagic) and/or systemic embolism.

Table 2
Endpoints:

| Primary endpoint                                      |
|-------------------------------------------------------|
| Composite of stroke (ischemic/hemorrhagic)/transient ischemic attack and systemic embolism |

| Secondary endpoint                                  |
|-----------------------------------------------------|
| Major bleeding (ISTH criteria)                      |
| Non-major and clinically relevant bleeding          |
| Composite of symptomatic stroke (ischemic/ hemorrhagic), systemic embolism, myocardial infarction and/or cardiovascular death |
| Symptomatic ischemic stroke                         |
| Symptomatic hemorrhagic stroke                      |
| Systemic embolism                                   |
| Acute myocardial infarction/ unstable angina, CABG/PCI, or cardiovascular death |
| Transient ischemic attack                           |
| All-cause death                                     |

Adherence of medication: the annual prescription rate is calculated by dividing the annual number of tablets prescribed by 365 days. (The physician reports the annual number of tablets in Case Report Form.)

The rivaroxaban prescription status will be reported by the physician in each data collection timing.

ISTH: International Society on Thrombosis and Hemostasis.

CABG: Coronary Artery bypass grafting.

PCI: Peripheral Component Interconnect.

PCI: Peripheral Component Interconnect.

CABG: Coronary Artery Bypass Grafting.

NYHA: New York Heart Association.

RBC: Red Blood Cell.

Hb: Hemoglobin.

Ht: Hematocrit.

BUN: Blood Urea Nitrogen.

T-Bil: Total Bilirubin.

ALT: Alanine Transaminase.

AST: Aspartate Aminotransferase.

γ-GTP: γ glutamic Pyruvic Transaminase.

Alb: Albumin.

PT: Prothrombin Time.

APTT: Activated Partial Thromboplastin Time.

CRP: C-Reactive Protein.

BNP: Brain Natriuretic Peptide.

NT-pro BNP: N-terminal pro b-type Natriuretic Peptide.

AST: Aspartate Aminotransferase.

ALT: Alanine Transaminase.

T-Bil: Total Bilirubin.

BUN: Blood Urea Nitrogen.

Ht: Hematocrit.

Hb: Haemoglobin.

RBC: Red Blood Cell.

NYHA: New York Heart Association.

CABG: Coronary Artery bypass grafting.

PCI: Peripheral Component Interconnect.
embolism as follows: (1) symptomatic stroke (ischemic/hemor-
rhagic)/transient ischemic attack (the onset date will be essential,
if these events occur within two weeks of rivaroxaban prescrip-
tion) and (2) systemic embolism. The annual incidence of the
primary endpoint (onset of stroke and/or systemic embolism)
and risk factors analysis for the primary endpoint will be ana-
lyzed. The secondary outcomes are as follows: (1) major bleeding
meeting ISTH guidelines, (2) non-major and clinically relevant
bleeding, (3) the onset of symptomatic stroke (ischemic/hemor-
rhagic), systemic embolism, myocardial infarction and/or cardio-
vascular death, (4) symptomatic ischemic stroke, (5) sympto-
matic hemorrhagic stroke, and (6) systemic embolism.

The annual incidence of major bleeding and non-major clinici-
cally relevant bleeding, and predictive factors for the primary
endpoint will be analyzed.

The incidence (events per 100 patient-years) and its 95% con-
fidence interval of the following events during rivaroxaban ther-
apy will be summarized. Multivariable Cox proportional hazard
models and multivariable logistic regression models will be used,
and hazard ratios, odds ratios, and corresponding 95% confidence
intervals are presented to assess factors associated with the end-
points. The Kaplan–Meier method will be used to estimate the
cumulative incidences of the events.

2.5.3. Subgroup analysis

A subgroup analysis of the events with respect to the possible
prognostic factors, e.g., underlying disease, age, renal function,
CHA2DS2-VASc [11], CHA2DS2-VASc [12], and HAS-BLED [13] scores at
baseline, will be conducted. When appropriate, a COX model will
be also utilized to explore the prognostic factors as follows:

- Incidence of the primary endpoint according to CHADS2 score.
- Incidence of the primary endpoint according to CHA2DS2-
  VASc score.
- Incidence of the primary endpoint according to the presence or
  absence of complications/previous diseases.
- Incidence of the primary endpoint according to the presence or
  absence of dementia.
- Incidence of the primary endpoint according to frailty.
- Incidence of the primary endpoint according to adherence of
  medication.
- Incidence of major bleeding according to HAS-BLED score.
- Incidence of non-major clinically relevant bleeding according to
  HAS-BLED score.
- Predictive risk factors for the primary or secondary endpoints.
- Comparisons of incidences of the primary endpoint and major
  bleeding meeting the ISTH guidelines between the present
  study, EXPAND study, and FUSHIMI AF registry study.
- Laboratory data.

To assess the safety of rivaroxaban, we will examine laboratory
tests optionally (Table 1).

2.5.4. Statistical analysis and sample size feasibility

Statistical analysis will be performed using SAS software ver-
sion. Interim analysis of the analytical items above will be per-
formed as necessary. We primarily considered feasibility to
determine the sample size of the study. No formal sample size
estimation was made. Five thousand patients will be enrolled
during the 1.5-year recruitment period and will be followed for at
least 1.5 years (and a maximum of 3 years). Assuming linear
recruitment and a 5% drop-out rate (among total patient-years),
approximately 10,687.5 patient-years is expected to be enrolled.

According to the ROCKET AF & J-ROCKET AF study, the inci-
dence rate for rivaroxaban is expected to be 1.7–2.1 events per 100
patient-years. If the true incidence rate is 2.1 events per 100
patient-year, the expected number of events will be about 224
events (among 10,687.5 patient-years), and the 95% CI would be
1.83–2.37 (as calculated with Poisson model). Because we con-
sidered the historical event rate for warfarin that was about
3.0 events per 100 patient-years using the FUSHIMI AF registry, we
assumed that the accuracy would be adequate.

3. Results

The results of this study are currently under investigation.

4. Discussion

The GENERAL study will be the first prospective investigation
to assess effectiveness/safety of rivaroxaban among general prac-
titioners. With aging, the number of patients with dementia and/or
frailty is increasing. The present study would also include these
patients. The results would provide further evidence of the utility
of rivaroxaban in real-life clinical settings.

There are some limitations of this study. First, four kinds of
DOACs are available now, but only rivaroxaban is used in this
prospective study; therefore, the results of this study are not valid
for other DOACs. To investigate the effectiveness or safety of riv-
axaban, the lack of a direct comparator group (such as VKA-
treated patients) could be considered a limitation.

Second, there is no limitation of registration in the first
administration date of rivaroxaban; the result might therefore
reflect only the relatively safe patients’ data. Thus, another study
focusing on these issues would be needed.

Finally, all suspected outcome events are centrally adjusted
based on information collected from general practitioners, and
thus it is possible that some events will remain unreported.

5. Conclusions

This GENERAL study will provide important information
regarding the effectiveness and safety of rivaroxaban in Japanese
patients with NVAF among general practitioners.

Role of the funding source

The GENERAL study is a project planned by the Japan Cardio-
vascular Research Foundation and is financially supported by
Bayer Yakuhin, Ltd., which had no role in the study design or in
conducting of the study, the collection of the data, its analysis or
its interpretation, or in the preparation of the manuscript. The
Corresponding author had full access to all the data and takes full
responsibility for the integrity of the data in this study, as well as
for the decision to submit this manuscript for publication.

Conflict of interest

Masaharu Akao received honoraria for educational lectures from
Bayer, Boeringer Ingelheim, Pfizer, Brystol-Myers Squibb,
Daiichi-Sankyo, and Pfizer. Shinya Hiramitsu received honoraria
for educational lectures from Bayer, Takeda Pharmaceutical Com-
pany Limited, Mitsubishi Tanabe Pharma, and Merck Corporation.
Kunihiro Matsui received honoraria for educational lectures from
AstraZeneca.
Appendix A

The following persons participate in this trial: The End Points Committee: Urabe T (Chiba); Okada Y, Ueno T (Fukuoka); Tsujino A (Nagasaki); Morino Y (Iwate); Tada H (Fukui); Statistical Analysis: Matsui K (Kumamoto).

Appendix B

The background report by the physician must report the degree of dementia and frailty as follows:

- degree of dementia
  - the patient receiving anti-dementia drugs
  - Certification of needed long-term care

1. Unknown
2. Needed Support Condition 1/2
3. Needed Care Condition 1/2/3/4/5

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