Journal of Arrhythmia 33 (2017) 297–301

Contents lists available at ScienceDirect

Journal of Arrhythmia

journal homepage: www.elsevier.com/locate/joa

Original Article

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

Kengo Kusano, MD, PhD[a,*], Masaharu Akao, MD, PhD[b], Hikari Tsuji, MD[c], Kunihiko Matsui, MD, MPH[d], Shinya Hiramitsu, MD[e], Yutaka Hatori, MD[f], Hironori Odakura, MD[g]

[a] Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Japan
[b] Department of Cardiology, National Hospital Organization Kyoto Medical Center, Japan
[c] Tsuji Clinic, Japan
[d] Kumamoto University Hospital, Japan
[e] Hiramitsu Heart Clinic, Japan
[f] Hatori Clinic, Japan
[g] Dobashi Naika Clinic, Japan

ARTICLE INFO

Article history:
Received 21 September 2016
Received in revised form
12 November 2016
Accepted 9 December 2016
Available online 9 March 2017

Keywords:
Anticoagulants
DOAC
Non-valvular atrial fibrillation
Stroke
General practitioner

ABSTRACT

Background: Rivaroxaban, a direct oral anticoagulant (DOAC), has become available for stroke prevention in patients with non-valular atrial fibrillation (NVAF). However, little is known about its effectiveness and safety when prescribed by general practitioners in real-life settings.
Methods: GENERAL is a multicenter, prospective, non-interventional observational study of patients receiving rivaroxaban for NVAF in daily clinical practice prescribed specifically by general practitioners. The target number of participating medical institutions is 500–700 clinics with fewer than 20 beds and the target number of participants is 5000. The baseline clinical data, including antidementia medication and frailty, and follow-up data including concomitant treatment and outcomes until September 2018 (maximum three years) will be collected. The primary efficacy endpoints will be stroke and/or systemic embolism and the secondary endpoints will be major bleeding meeting the ISTH guidelines, non-major and clinically relevant bleeding, onset of symptomatic stroke (ischemic/hemorrhagic), systemic embolism, deep vein thrombosis/pulmonary thromboembolism, myocardial infarction and/or cardiovascular death, and systemic embolism. Based on the provided information, the event assessment committee will investigate the endpoint-related events. The annual incidence and predictive factors for primary/secondary endpoint will be investigated based on underlying disease, age, renal function, and $CHADS_2$, CHA_2DS_2-VASC, and HAS-BLED scores using Cox regression. We will also compare the incidence of the primary/secondary endpoint between the present study, EXPAND study, and FUSHIMI AF registry study.
Results: The results of this study are currently under investigation.
Conclusion: This study will provide important information regarding the effectiveness and safety of rivaroxaban treatment in Japanese patients with NVAF among general practitioners.

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

* Correspondence to: Department of Cardiovascular Medicine National Cerebral and Cardiovascular Center, 5-7-1, Fujishiro-dai, Suita, Osaka 565-8565, Japan. Fax: +816-6872-7486.
E-mail address: kusanokengo@hotmail.com (K. Kusano).

http://dx.doi.org/10.1016/j.joa.2016.12.001
1880-4276/

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. The FUSHIMI AF registry, a regional registry study with duration of one year has been conducted with 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

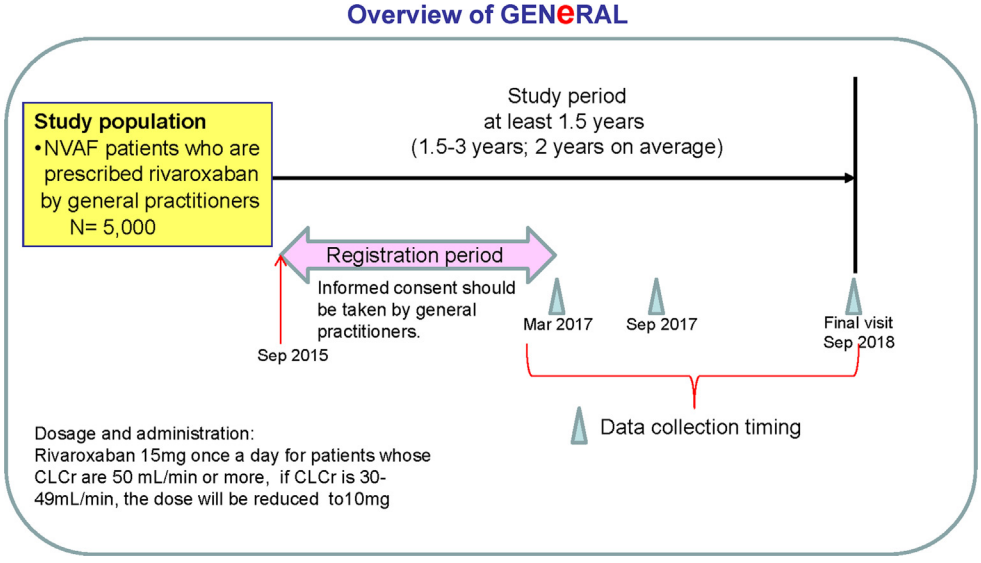

Fig. 1. Time schedule of GENERAL study. The target number of participants is 5000. After registration, follow-up data will be collected at three times (March 2017, September 2017 and September 2018).

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, permanent, 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)
Congested 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

PCI: Peripheral Component Interconnect.
CABG: Coronary Artery Bypass Grafting.
NYHA: New York Heart Association.
RBC: Red Blood Cell.
Hb: Haemoglobin.
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.

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

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.

embolism as follows: (1) symptomatic stroke (ischemic/hemorrhagic)/transient ischemic attack (the onset date will be essential, if these events occur within two weeks of rivaroxaban prescription) 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 analyzed. 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/hemorrhagic), systemic embolism, myocardial infarction and/or cardiovascular death, (4) symptomatic ischemic stroke, (5) symptomatic hemorrhagic stroke, and (6) systemic embolism.

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

The incidence (events per 100 patient-years) and its 95% confidence interval of the following events during rivaroxaban therapy 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 endpoints. 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, $CHADS_2$ [11], CHA_2DS_2-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 $CHADS_2$ score.
- Incidence of the primary endpoint according to CHA_2DS_2-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 version. Interim analysis of the analytical items above will be performed 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 incidence 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 considered 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 practitioners. 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 rivaroxaban, 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 Cardiovascular 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 Company Limited, Mitsubishi Tanabe Pharma, and Merck Corporation. Kunihiko 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

< frailty >

* 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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