Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

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

Original article

Study design of J-ELD AF: A multicenter prospective cohort study to investigate the efficacy and safety of apixaban in Japanese elderly patients

Masaharu Akao (MD, PhD)[a,*], Takeshi Yamashita (MD, PhD, FJCC)[b], Ken Okumura (MD, PhD, FJCC)[c], for the J-ELD AF Investigators

[a] Department of Cardiology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan
[b] Department of Cardiovascular Medicine, The Cardiovascular Institute, Tokyo, Japan
[c] Department of Cardiology and Nephrology, Hirosaki University Graduate School of Medicine, Hirosaki, Japan

ARTICLE INFO

Article history:
Received 4 November 2015
Received in revised form 7 December 2015
Accepted 15 December 2015
Available online xxx

Keywords:
Atrial fibrillation
Stroke
Anticoagulants
Elderly

ABSTRACT

Background: Apixaban, one of the non-vitamin K antagonist oral anticoagulants, was reported to be effective and safe in stroke prevention in patients with atrial fibrillation (AF) based on the global randomized clinical trial, but data are limited on the efficacy and safety of apixaban in Japanese elderly patients.

Methods and results: The J-ELD AF Registry is a large-scale, contemporary observational study, continuously and prospectively registering elderly Japanese patients with AF aged 75 years or older who are currently taking apixaban or the elderly who are to receive apixaban in daily clinical practice, and accumulating the outcomes during one-year follow-up period. In addition to standard baseline characteristics, prothrombin time and anti-Xa activity will be measured to investigate the biomarker characteristics. The primary efficacy endpoints will be stroke and systemic embolism, and the primary safety endpoint will be major bleeding requiring hospitalization. The secondary endpoints in this study will be all-cause death, cardiovascular death, acute myocardial infarction, and the composite of stroke/systemic embolism, cardiovascular death, and acute myocardial infarction. As a primary analysis, the primary/secondary endpoints in the enrolled patients will be totalized for the entire group, and the incidence of events will be described by age, $CHADS_2$ score, HAS-BLED score, and apixaban dose (5 or 2.5 mg bid). The factors that independently predict the incidence of the primary/secondary endpoints will be searched for by Cox regression. The relationship between the biomarkers and the primary/secondary endpoints will also be examined in an explorative manner.

Conclusion: This study will provide important information on the efficacy and safety of apixaban in elderly Japanese patients aged 75 years or older, and those of low-dose administration of apixaban (2.5 mg bid) for which many of the Japanese elderly are indicated.

Introduction

Japan is at the top of the world in the population aging rate, which has not changed in the past 50 years. There are many unsolved medical problems arising in a rapidly growing aging population, and atrial fibrillation (AF) is one of them. AF is common among the elderly, and increases the risks for stroke [1]. The prevalence of AF increases with age, and increasing age is associated with higher risk of stroke, as well as higher severity and worse functional outcome after stroke [2–5]. From the socio-economical standpoints, healthy longevity in which the healthy elderly are active in society should be aimed at, and the prevention of stroke in elderly patients with AF is of paramount importance in Japan.

Oral anticoagulants (OAC) are highly effective in reducing the risk of stroke [6]. For about 50 years, warfarin, a vitamin K antagonist, has been the only available OAC, but it was widely under-used particularly in the elderly because of its inconvenience, instability of effect caused by changes in living environment, etc., and a high frequency of major bleeding [7–11]. Furthermore, it is

* Corresponding author at: Department of Cardiology, National Hospital Organization Kyoto Medical Center, 1-1, Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto 612-8555, Japan. Tel.: +81 75 641 9161; fax: +81 75 643 4325.
E-mail address: akao@kuhp.kyoto-u.ac.jp (M. Akao).

http://dx.doi.org/10.1016/j.jjcc.2015.12.006
0914-5087/

crucial that the prothrombin time international normalized ratios of patients receiving warfarin be maintained within the target therapeutic range to receive the benefit of warfarin therapy [12,13], but this is a major challenge in real-world clinical practice. Recently, non-vitamin K antagonist oral anticoagulants (NOAC) have become available [14–17], and the convenience has been improved [18]. However, some drugs have a frequency of major bleeding in the elderly similar to warfarin, and the situation in which it is difficult to use OAC in the elderly has remained almost unchanged.

Apixaban, one of the NOACs, has a characteristic that it is safer than warfarin for the elderly based on the results from the subanalysis of the large-scale clinical trial (the ARISTOTLE trial) [19,20]. However, elderly patients have not been sufficiently included in this study, and it has a limitation in that it may not represent the elderly seen in clinical practice due to selection bias. For the efficacy and safety of apixaban in the Japanese elderly patients aged 75 years or older, the number of such elderly patients enrolled in the ARISTOTLE trial was small [21]. Furthermore, data are limited on the efficacy and safety of low-dose administration of apixaban (2.5 mg bid) for which many of the Japanese elderly are indicated.

Objectives and study design

Objectives

The J-ELD AF Registry is a large-scale, contemporary observational study, continuously and prospectively registering the Japanese elderly patients with AF aged 75 years or older who are currently taking apixaban or the elderly who are to receive apixaban in our daily clinical practice, and accumulating the outcomes during one-year follow-up period (UMIN Clinical Trials Registry: UMIN000017895). The primary objective of this study is to clarify the efficacy and safety of apixaban in the Japanese elderly in daily clinical practice.

Study population

The Chief Investigators selected the 30 Area Lead Investigators (Appendix A) from all over Japan. Each Area Lead Investigator recruited medical institutions inside his/her area, and subsequently the participating institutions of this study will consist of 50–200 medical facilities with specialists who provide medical care for elderly/very elderly patients with AF. Consecutive patients with non-valvular AF aged 75 years or older who visit the participating institutions after the start of this study and who are receiving apixaban will be enrolled.

Patients with any of the following during the enrollment period will be excluded from the study: (1) a history of hypersensitivity to apixaban, (2) active bleeding symptoms, (3) liver disease complicated with coagulation disorder, (4) a creatinine clearance of $<$15 mL/min, (5) mitral valve stenosis or prosthetic valve, (6) patients in whom apixaban dose reduction criteria (2 or more of the following three criteria: age of 80 years or older, the weight of 60 kg or less, and serum creatinine of 1.5 mg/dL or more) are not indicated, but who receive reduced dose (2.5 mg bid), (7) informed consent not obtained, (8) venous thromboembolism (deep venous thrombosis and pulmonary thromboembolism), (9) patients judged to be inappropriate for the study by the investigators.

The enrollment period of this study is from September 2015 to August 2016, and the observation period is one year for each patient. In case patients withdraw consent for participation or are lost to follow-up, observation will be stopped and the date and the reason will be entered.

The paucity of data on Japanese elderly AF patients taking apixaban makes rational sample size setting difficult. Since this study is not a comparative study with warfarin but an exploratory study, in order to make the efficacy and safety of apixaban in the elderly patients with AF clear as soon as possible, the sample size was set at 3000 patients, considering the feasibility of the study.

Ethics and informed consent

This study will be performed in conformity to the ethical norms based on the Declaration of Helsinki (revised in 2008) and Ethical Guidelines for Medical and Health Research Involving Human Subjects (Public Notice of the Ministry of Education, Culture, Sports, Science and Technology, and the Ministry of Health, Labor and Welfare in Japan, issued in 2014).

The investigators will explain the participation in the study by using reviewed and approved explanation form for patients and informed consent form. Upon obtaining a thorough understanding and consent from patients, informed consent will be obtained from patients in writing. In doing so, the subjects from whom it is difficult to obtain informed consent will not be enrolled in the study. A right to self-determination and a right to choose treatment of patients should not be limited by making patients decide the participation in the study by their free will, by allowing them to withdraw any time after giving consent so that subjects may not suffer any disadvantage, and by giving consideration so that subjects who will not participate in the study or who will withdraw from the study may not suffer any disadvantage. Regarding the handling of existing data in case the study is stopped on the way or patients withdraw their consent, all data of the patient shall be disposed of.

Sufficient consideration should be given to protect secrets of subjects throughout the study implementation period. If there are case report forms, etc. to submit outside the hospital, initials or subject identification codes should be used. In addition, the results obtained from the study are to be published in academic meetings and medical journals. On such occasions, sufficient consideration should be given not to include information which can identify subjects, such as the name of subjects. Furthermore, the data on subjects obtained in the study should not be used for purposes other than the study. When the measurements of the specimens, etc. of subjects are made outside the hospital, they should be anonymized and stored.

Prior to the start of this study, the investigators at the participating institutions will be reviewed by the Institutional Review Board.

Data acquisition

The patient data will be accumulated after anonymizing and masking them, and will be managed by a third-party external agency designated by CVI ARO (The Cardiovascular Institute Academic Research Organization).

The elderly patients with AF meeting the inclusion criteria will be consecutively enrolled, and clinical characteristics at baseline including the co-morbidities and medical treatment will be entered through the web (Table 1). It is well known that the risk of adverse events is so high during the initiation phase after the introduction of NOAC. We will collect data regarding the date of first administration of apixaban for each patient, as indicated in Table 1. Therefore, we will be able to compare the rate of adverse events between newly-initiated patients and those who have already received the drug. At some sites, prothrombin time and anti-Xa activity will be measured to investigate the biomarker characteristics in the elderly (subgroup analysis). For this purpose, blood specimens will be collected before administration and 3–4 h

Please cite this article in press as: Akao M, et al. Study design of J-ELD AF: A multicenter prospective cohort study to investigate the efficacy and safety of apixaban in Japanese elderly patients. J Cardiol (2016), http://dx.doi.org/10.1016/j.jjcc.2015.12.006