



Aalborg Universitet

AALBORG UNIVERSITY  
DENMARK

**Edoxaban for the management of elderly Japanese patients with atrial fibrillation ineligible for standard oral anticoagulant therapies**

*Rationale and design of the ELDERCARE-AF study*

Okumura, Ken; Lip, Gregory Y H; Akao, Masaharu; Tanizawa, Kimihiko; Fukuzawa, Masayuki; Abe, Kenji; Akishita, Masahiro; Yamashita, Takeshi

*Published in:*  
American Heart Journal

*DOI (link to publication from Publisher):*  
[10.1016/j.ahj.2017.08.017](https://doi.org/10.1016/j.ahj.2017.08.017)

*Creative Commons License*  
CC BY-NC-ND 4.0

*Publication date:*  
2017

*Document Version*  
Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

*Citation for published version (APA):*

Okumura, K., Lip, G. Y. H., Akao, M., Tanizawa, K., Fukuzawa, M., Abe, K., Akishita, M., & Yamashita, T. (2017). Edoxaban for the management of elderly Japanese patients with atrial fibrillation ineligible for standard oral anticoagulant therapies: Rationale and design of the ELDERCARE-AF study. *American Heart Journal*, 194, 99-106. <https://doi.org/10.1016/j.ahj.2017.08.017>

**General rights**

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

**Take down policy**

If you believe that this document breaches copyright please contact us at [vbn@aub.aau.dk](mailto:vbn@aub.aau.dk) providing details, and we will remove access to the work immediately and investigate your claim.



# Edoxaban for the management of elderly Japanese patients with atrial fibrillation ineligible for standard oral anticoagulant therapies: Rationale and design of the ELDERCARE-AF study

Ken Okumura, MD, PhD,<sup>a</sup> Gregory Y. H. Lip<sup>b,c</sup> Masaharu Akao<sup>d</sup> Kimihiko Tanizawa<sup>e</sup> Masayuki Fukuzawa<sup>e</sup> Kenji Abe<sup>f</sup> Masahiro Akishita<sup>g</sup> and Takeshi Yamashita<sup>h</sup> *Kumamoto, Kyoto, Tokyo, Japan; Birmingham, UK; and Aalborg, Denmark*

Edoxaban—a non-vitamin K antagonist oral anticoagulant (NOAC)—60-mg and 30-mg once-daily dose regimens are noninferior versus well-managed warfarin for the prevention of stroke or systemic embolic events (SEE) with less major bleeding in patients with nonvalvular atrial fibrillation (NVAF). There are no published data from phase 3 clinical trials specifically evaluating the use of NOACs in elderly NVAF patients, especially those considered ineligible for available oral anticoagulants. The Edoxaban Low-Dose for Elder CARE AF patients (ELDERCARE-AF) study is a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study that will compare the safety and efficacy of once-daily edoxaban 15 mg versus placebo in Japanese patients with NVAF  $\geq 80$  years of age who are considered ineligible for standard oral anticoagulant therapy. A total of 800 patients (400 in each treatment group) are planned for randomization (1:1) to either edoxaban or placebo using a stratified randomization method with CHADS<sub>2</sub> index score (2 points,  $\geq 3$  points) as a factor. The primary efficacy end point is the time to first onset of stroke or SEE. The net clinical outcome is the composite of stroke, SEE, major bleeding, and all-cause mortality. The primary safety end point is the incidence of major bleeding. The treatment period will continue until 65 patients with the primary efficacy events (ie, stroke or SEE) have been observed (2- to 2.5-year expected mean treatment period). The results of ELDERCARE-AF may provide clarity as to the efficacy and safety of edoxaban for the prevention of stroke or SEE in this high-risk population. (*Am Heart J* 2017;194:99-106.)

Atrial fibrillation (AF) is an independent risk factor for stroke and systemic embolic events (SEE), and AF-associated stroke is more likely to be fatal or disabling compared with non-AF stroke.<sup>1,2</sup> As the prevalence of AF is strongly related to age worldwide, including in Japan, the elderly are at an especially increased risk of stroke or

SEE.<sup>1,3-7</sup> In one community-based study of 41,436 Japanese adults, the incidence of AF was reported to be 3.5% in men and 2.5% in women  $\geq 80$  years of age compared with 0.5% in men and 0.2% in women aged 40 to 59 years.<sup>7</sup>

Oral anticoagulants are first-line treatment for nonvalvular AF patients to reduce the risk of stroke, including in the elderly.<sup>8,9</sup> However, many physicians are reluctant to prescribe oral anticoagulants to elderly patients because of perceived contraindications such as history of bleeding, prior falls, increased polypharmacy, cognitive impairment, and frailty.<sup>10-12</sup> In general, oral anticoagulants are underused for the prevention of stroke in elderly AF patients.<sup>12-21</sup> In the Fushimi AF Registry—a community-based survey of AF patients in Japan—only 41.3% of the extremely elderly ( $\geq 85$  years of age) received oral anticoagulants alone or in combination with antiplatelet therapy despite a significantly higher incidence of stroke or SEE in the extremely elderly patients versus patients  $\leq 84$  years of age.<sup>17,22</sup> Many extremely elderly patients are often left untreated with no antithrombotic therapy.<sup>15-17</sup>

From the <sup>a</sup>Division of Cardiology, Saiseikai Kumamoto Hospital Cardiovascular Center, Kumamoto, Japan, <sup>b</sup>Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom, <sup>c</sup>Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark, <sup>d</sup>Department of Cardiology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan, <sup>e</sup>Clinical Development Department, Daiichi Sankyo Co Ltd, Tokyo, Japan, <sup>f</sup>Clinical Data and Biostatistics Department, Daiichi Sankyo Co Ltd, Tokyo, Japan, <sup>g</sup>Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, and <sup>h</sup>Cardiovascular Institute, Tokyo, Japan.

RCT# NCT02801669.

Submitted April 7, 2017; accepted August 22, 2017.

Reprint requests: Ken Okumura, MD, PhD, Division of Cardiology, Saiseikai Kumamoto Hospital Cardiovascular Center, Minami-ku, Chikami 5-3-1, Kumamoto, 861-4193, Japan.

E-mail: okumura@hirosaki-u.ac.jp

0002-8703

© 2017 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

<http://dx.doi.org/10.1016/j.ahj.2017.08.017>

Edoxaban is a direct, oral factor Xa inhibitor with linear and predictable pharmacokinetics<sup>23</sup> indicated for the reduction of stroke or SEE in patients with nonvalvular AF and for the treatment of venous thromboembolism.<sup>24</sup> In the Effective aNticoagulation with factor Xa next GENERation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48), edoxaban 60- and 30-mg once-daily dose regimens were noninferior to well-managed warfarin for the prevention of stroke or SEE with superior safety (major bleeding).<sup>25</sup> In this trial, the 60-mg edoxaban dose regimen was associated with a lower rate of stroke or SEE versus the 30-mg edoxaban dose regimen.<sup>25</sup> In a subgroup analysis of this trial, once-daily edoxaban demonstrated consistent efficacy and safety when compared with well-managed warfarin, regardless of age.<sup>26</sup> However, in ENGAGE AF-TIMI 48, only 17% of the patients were  $\geq 80$  years of age, and the study was not specifically designed to assess the efficacy and safety of edoxaban in elderly patients overall or in extremely elderly patients, who are considered ineligible for standard oral anticoagulant therapy.<sup>26</sup> Directly evaluating the efficacy and safety of edoxaban in the elderly patients considered ineligible for standard oral anticoagulant therapy will require a sufficiently powered randomized controlled trial.

The Edoxaban Low-Dose for EldeR CARE AF patients (ELDERCARE-AF) study is a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study that will compare the safety and efficacy of once-daily edoxaban 15 mg versus placebo in Japanese patients with nonvalvular AF  $\geq 80$  years of age who are considered ineligible for standard oral anticoagulant therapy ([ClinicalTrials.gov](http://ClinicalTrials.gov): NCT02801669). In this article, we summarize the rationale and design of the ELDERCARE-AF study.

## Objectives and study design

The primary objective of this study is to evaluate the efficacy and safety of once-daily edoxaban 15 mg in patients with nonvalvular AF who are ineligible for oral anticoagulants at the approved dosage. In addition, this study will evaluate the superiority of the 15-mg dose of edoxaban compared with placebo for the composite primary end point of stroke and SEE. The study will include up to 30 days of screening and eligibility assessment prior to randomization, an event-driven double-blind treatment (edoxaban 15 mg or placebo) lasting an expected mean period of 2 to 2.5 years, an examination within 60 days after the completion of the study, and a final follow-up examination within 30 to 37 days after the examination at the completion of the study (Figure 1). Enrollment commenced in August 2016.

An accurate assessment of the incidence of clinical events (eg, stroke and SEE) will require the observation of a sufficient number of events. Therefore, this study will not have a specified treatment duration and instead will be event driven. Completion of the study will be

determined when the planned number of patients that have experienced the primary efficacy end point event (stroke and SEE) has been observed.

## Ethics and informed consent

This study was funded by Daiichi Sankyo Co Ltd (Tokyo, Japan). Assistance in medical writing and editorial support for this manuscript was provided by AlphaBioCom, LLC (King of Prussia, PA), and funded by Daiichi Sankyo, Inc (Basking Ridge, NJ). All authors materially participated in the design and/or drafting and editing of the paper and approved its final content. This study will be conducted in accordance with the Good Clinical Practice standards for drugs and the ethical principles specified in the Declaration of Helsinki. In addition, the storage of clinical specimens for subsequent genomic or genetic analysis will be conducted in accordance with the Ethical Guidelines for Human Genome/Gene Analysis Research and the Ethical Guidelines for Clinical Research.

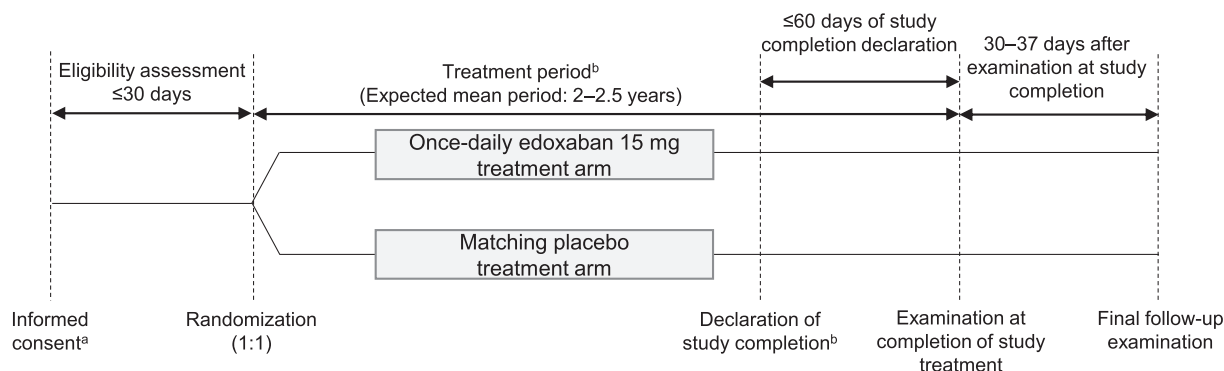
The protocol has been reviewed and approved by an institutional review board prior to the start of the study. During the course of the study, the institutional review board will review the study at least once per year to determine whether it should continue. An independent safety data monitoring committee will monitor safety data as necessary and will consider matters such as whether it is possible to continue the study and whether it is necessary to change the protocol.

Strict subject confidentiality will be maintained through the use of subject identification codes. Informed consent will be obtained from all participants prior to enrollment. As the prevalence of dementia in this elderly population may be higher than in the general population, if the investigators consider it not feasible to obtain written informed consent from the patient because of dementia, they will obtain written informed consent from the patient's legal representative.

## Patient population and eligibility

Male and female patients  $\geq 80$  years of age with nonvalvular AF will be eligible to enroll if they have a history of AF documented by any electrical tracing within 1 year of informed consent and a score of 2 or higher on the CHADS<sub>2</sub> risk assessment. In addition, to be included, patients must be considered ineligible by their responsible physician for available oral anticoagulants (ie, warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) at *approved doses* for  $\geq 1$  of the following reasons: creatinine clearance (CLCr) calculated by Cockcroft-Gault formula of 15 to 30 mL/min (a common reason for nonanticoagulation among Japanese patients due to risk of bleeding<sup>27,28</sup>); a history of bleeding from critical organs (eg, intracranial, intraocular, or gastrointestinal bleeding); body weight  $\leq 45$  kg; continuous use of nonsteroidal anti-inflammatory medications that are associated with bleeding while on oral anticoagulants;

**Figure 1**



Planned study design for the ELDERCARE-AF study. <sup>a</sup>As the prevalence of dementia in this elderly population may be higher than in the general population, if the investigators consider it not feasible to obtain written informed consent from the patient because of dementia, they will obtain written informed consent from the patient's legal representative. <sup>b</sup>This study is event driven, and study completion will be declared when the planned number of patients with the primary efficacy end point (ie, stroke or systemic embolic events) has been collected; 2 to 2.5 years is the expected mean treatment period.

and currently using an antiplatelet drug for a purpose other than prophylaxis of cardioembolic stroke.

Renal impairment, low body weight, a history of clinically significant bleeding, and concomitant administration of antiplatelet drugs or nonsteroidal anti-inflammatory medications associated with bleeding while on oral anticoagulants may increase the risk of major bleeding during anticoagulant therapy.<sup>28-31</sup> In the Fushimi AF Registry, baseline body weight of AF patients was lower in those untreated versus treated with warfarin.<sup>31</sup> Likewise, in patients  $\geq 85$  years old, those not receiving anticoagulant therapy had lower body weight versus those on anticoagulant therapy.<sup>22</sup> These data from Japanese real-world studies suggest that elderly patients, especially those with lower body weight, are underprescribed oral anticoagulants, including warfarin. On the other hand, unpublished data from ENGAGE AF-TIMI 48 show that major bleeding rates in patients receiving well-managed warfarin were higher in patients  $\leq 45$  kg versus  $>45$  kg (5.74%/y vs 4.82%/y). This was also observed in patients  $\geq 80$  years of age, where major bleeding rates were 9.20%/y versus 6.72%/y in patients  $\leq 45$  kg versus  $>45$  kg, respectively. Therefore, physicians in Japan may consider elderly patients meeting these criteria, including low body weight, as being ineligible for oral anticoagulants because of these potential bleeding risks.

Table I shows the list of exclusion criteria; the exclusion criteria were intended to be consistent with the Japanese treatment guidelines.<sup>28</sup> The Japanese guidelines define nonvalvular AF as AF in patients without prosthetic valve replacement using mechanical valves or bioprosthetic valves, or AF in those patients without rheumatic mitral disease.<sup>28</sup>

This study includes elderly patients with nonvalvular AF who are considered ineligible for available oral anticoag-

ulants by their responsible physician because of concerns about bleeding or who are receiving warfarin at an anticoagulant strength not recommended in the Japanese guidelines (ie, international normalized ratio [INR]  $<1.6$ ).<sup>28</sup> Therefore, patients who were receiving warfarin with an INR  $\geq 1.6$  in 2 of the 3 most recent examinations, including the eligibility assessment examination, were excluded (patients with INR  $\geq 1.6$  at the eligibility assessment examination were also excluded) to strictly and accurately ensure that included patients had an INR  $<1.6$ . Other major exclusion criteria include transient AF secondary to other reversible disorders; treatment with dabigatran, rivaroxaban, apixaban, or edoxaban within 8 weeks prior to randomization; active bleeding on the day of informed consent, unresolved peptic ulcer on the day of informed consent, hemoglobin  $<9$  g/dL or platelet count  $<10 \times 10^4 /\mu\text{L}$  at eligibility assessment, or hereditary hemorrhagic disease; cerebral infarction or transient ischemic attack within 30 days prior to randomization; uncontrolled hypertension; CLCr  $<15$  mL/min; currently on or may start hemodialysis by the final follow-up; treatment with dual antiplatelet therapy at the time of informed consent; hepatic function disorder accompanied by coagulation disorder; history of myocardial infarction within 30 days prior to randomization; and serious heart disease. During the eligibility assessment examination, brain diagnostic imaging will be performed to confirm that there is no active bleeding.

## Intervention and randomization

Patients will be randomized 1:1 to receive either edoxaban 15 mg once daily or placebo using a stratified randomization method with the CHADS<sub>2</sub> index score (2 points,  $\geq 3$  points) as a factor. An independent biostatistician will prepare a randomization schedule.

**Table 1.** Exclusion criteria

## Transient AF secondary to other reversible disorders

---

Treatment with dabigatran, rivaroxaban, apixaban, or edoxaban  $\leq 8$  wk prior to randomization

INR controlled at  $\geq 1.6$  in 2 of 3 most recent examinations in patients randomized to warfarin, including eligibility assessment; patients with INR  $\geq 1.6$  at eligibility assessment are excluded

Patients with particularly high bleeding risk meeting any of the following:

- Active bleeding on day of informed consent
- Unresolved peptic ulcer on day of informed consent
- Hereditary hemorrhagic disease

Cerebral infarction or TIA within 30 d prior to randomization

Rheumatic valve disease or history of cardiac valve surgery

Infective endocarditis or atrial myxoma

Left ventricular or atrial thrombus

Hereditary thrombophilia

Scheduled electrical or pharmacologic defibrillation between informed consent and final follow-up

Uncontrolled hypertension (systolic BP persistently  $\geq 160$  mm Hg or diastolic BP persistently  $> 100$  mm Hg)

CLCr (Cockcroft-Gault equation)  $< 15$  mL/min

Started or may start hemodialysis by final follow-up

Treatment with dual antiplatelet therapy at the time of informed consent or expected to start treatment after informed consent

Hepatic function disorder accompanied by coagulation disorder

History of acute myocardial infarction within 30 d prior to randomization or serious heart disease (eg, cardiac failure with New York Heart Association classification  $\geq 3$  or unstable angina pectoris)

Diagnosed malignancy or treated with cancer therapy  $\leq 5$  y prior to informed consent

History of receiving any other study drug within 60 d prior to informed consent

Considered ineligible by the investigators

---

BP, Blood pressure; TIA, transient ischemic attack.

The once-daily edoxaban 15-mg dose was chosen because of its lower risk of bleeding in the ENGAGE AF-TIMI 48 study compared with the 30-mg treatment regimen, particularly in elderly patients.<sup>26,32</sup> In ENGAGE AF-TIMI 48, patients in the edoxaban treatment arms had their dose halved from 60 to 30 mg in the high-dose treatment regimen or from 30 to 15 mg in the low-dose treatment regimen if they had CLCr 30 to 50 mL/min, low body weight ( $\leq 60$  kg), or concomitant use of specific P-glycoprotein inhibitors.<sup>25</sup> The incidence of major bleeding in elderly patients ( $\geq 75$  years old) receiving a dose reduction from edoxaban 30 to 15 mg in the low-dose treatment regimen was approximately half of the incidence in elderly patients who were dose-reduced from 60 to 30 mg in the high-dose treatment regimen (1.6%/y vs 3.4%/y).<sup>26</sup> The risk of stroke or SEE in elderly patients with dose-reduced edoxaban 15 mg was not significantly different to warfarin (hazard ratio [HR] 1.15, 95% CI 0.86-1.54).<sup>26</sup>

## Assessments

Prior to randomization, baseline demographics and clinical characteristics will be recorded, including vital signs, type of AF, risk factors for thromboembolism,

bleeding risk and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly) score, medical history, history of oral anticoagulation treatment, falling risk, and frailty assessment. From initiation of treatment to study completion or discontinuation, study drug compliance (number of tablets administered) will also be noted.

Efficacy events that occur between randomization and final follow-up or discontinuation of study participation, including stroke, SEE, myocardial infarction, transient ischemic attack, hospitalization due to cardiovascular disease, and all-cause mortality, will be recorded. Similarly, all bleeding events that occur between the initiation of treatment and final follow-up or discontinuation will also be surveyed. Information regarding event classification and details, and the situation in which the event occurred, will be entered into the case report. All stroke events will be assessed using the modified Rankin Scale at approximately 1 month following stroke onset. All bleeding events will be classified into major bleeding, clinically relevant nonmajor (CRNM) bleeding, and minor bleeding as defined by the International Society of Thrombosis and Hemostasis. During study drug interruption and after study drug discontinuation, efficacy and bleeding events will be surveyed at least every 8 weeks. All efficacy and safety events will be adjudicated by the independent, blinded Clinical Efficacy Event Committee and Clinical Bleeding Event Committee, respectively.

Between the initiation of treatment and final follow-up or discontinuation of study participation, all adverse events will be surveyed and documented. Adverse events will be coded using the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use Medical Dictionary for Regulatory Activities (MedDRA). The system organ class will be tabulated using MedDRA System Organ Class, and adverse event terms will be tabulated using Preferred Terms. Information that will be recorded includes the details of the adverse event, outcome and resolution, severity, seriousness, and causal relationship to study drug.

Body weight and blood pressure (systolic and diastolic) will be measured at the eligibility assessment and at all visits during the study treatment period, the examination at study completion, and at final follow-up. Blood and urine samples for laboratory samples will be collected and CLCr will be calculated using Cockcroft-Gault formula at eligibility assessment, once every 8 weeks during study treatment, the examination at study completion, and at final follow-up.

At week 8 of the study treatment period, the plasma concentration of edoxaban will be measured. In addition, citrated plasma will be collected and activated partial thromboplastin time and prothrombin time, D-dimer, and prothrombin fragment 1 + 2 will be assessed using standardized laboratory methods.

**Table II.** Study end points

Primary efficacy end point

---

Composite of stroke and SEE
Primary safety end point
Major bleeding
Secondary efficacy end points
Composite of stroke, SEE, and CV mortality
Major adverse CV events
Composite of stroke, SEE, and all-cause mortality
Net clinical outcome: composite of stroke, SEE, major bleeding, and all-cause mortality
All-cause mortality
Other efficacy end points
Hospitalization due to a CV condition (including bleeding)
Modified Rankin Scale approximately 1 m after the onset of stroke
Composite of stroke, SEE, and TIA
Number of occurrences of stroke and SEE
Venous thromboembolism (pulmonary embolism and deep vein thrombosis)
Other safety end points
Composite of major bleeding and CRNM bleeding
CRNM bleeding
Minor bleeding
All bleeding events
Adverse events
Pharmacokinetic/pharmacodynamic end points
Edoxaban plasma concentration
Prothrombin time and activated partial thromboplastin time
D-dimer and prothrombin fragment 1 + 2 levels

---

CV, Cardiovascular.

## End points

Table II shows the list of study end points. The primary efficacy end point is the time to first onset of the composite end point of stroke and SEE from randomization to the final follow-up examination or discontinuation. This primary efficacy end point was chosen because it is the standard efficacy end point that has been used in clinical studies assessing the efficacy of anticoagulants in patients with nonvalvular AF.<sup>33</sup> The net clinical outcome will be the composite of stroke, SEE, major bleeding, and all-cause mortality.

The primary safety end point will be the incidence of major bleeding (Table II). Other safety end points will include the incidence of CRNM bleeding, the composite of major and CRNM bleeding, minor bleeding, and all bleeding. Pharmacokinetic end points will be based on the plasma edoxaban concentration, and pharmacodynamic end points will include activated partial thromboplastin time, prothrombin time, D-dimer, and prothrombin fragment 1 + 2.

## Planned sample size

A total of 800 patients (400 in each treatment group) are planned for randomization, and 65 primary efficacy end points will be collected between randomization and final follow-up.

In the Fushimi AF Registry, the event rate for stroke/SEE in patients  $\geq 85$  years of age was 5.1 per 100 patient-years.<sup>22</sup> In ENGAGE AF-TIMI 48, the event rate in patients receiving a dose reduction from edoxaban 30 to 15 mg was 2.36% per year.<sup>32</sup> From these data, it can be conservatively estimated that edoxaban 15 mg may demonstrate a 50% risk reduction versus the placebo group. Therefore, under the assumption that the annual incidence of stroke or SEE is 5% per year in patients randomized to placebo and that the HR for the risk of stroke or SEE for edoxaban versus placebo is 0.5, 65 events will be required to evaluate superiority of edoxaban at a 2-sided significance level of 5% and 80% power. Approximately 400 patients will need to be enrolled in each group, assuming that the duration of enrollment will be 2 years and 1.5-year follow-up time. As this is an event-driven study, the total number of patients may change as necessary depending on the number of target events collected. At the date of this manuscript submission, there were 113 patients enrolled.

## Statistical analysis

The primary efficacy analysis will be conducted in the intention-to-treat (ITT) population (ie, all randomized patients) based on the randomized treatment assignment even if patients inadvertently receive the incorrect drug or dosage. Sensitivity analyses will be conducted in the modified ITT (mITT) population (all randomized patients who received  $\geq 1$  dose of study drug) and the per-protocol set (ie, patients in the mITT who did not have any major protocol violations). In the primary efficacy analysis using the ITT set, the times to onset of events will be calculated starting from the randomization date to final follow-up examination or the examination at discontinuation and counting all events (whether on or off study drug). For the sensitivity analyses in the mITT and per-protocol sets, the times to onset of events will be calculated starting from the initiation of study treatment to final follow-up examination or the examination at discontinuation and counting all events (whether on or off study drug). The safety analysis set will include all patients who received  $\geq 1$  dose of study drug. The safety analysis will be based on the randomized treatment unless the patient inadvertently receives the wrong study drug during the entire course of the study.

For the primary efficacy analysis, the time to first onset of stroke or SEE will be analyzed using the Cox proportional hazards model by treatment group with CHADS<sub>2</sub> score ( $\leq 2$  or  $\geq 3$ ) as a covariate and tested using a 2-sided significance level of 5%. Based on this model, HR with 95% CI will be used to estimate the relative risk. Any factors found to affect the primary efficacy end point in a blinded review before the data are locked will also be included as covariates. The cumulative incidence of efficacy events will be estimated by treatment group using the Kaplan-Meier method. All key secondary

**Table III.** Underuse of oral anticoagulants in elderly patients with nonvalvular AF

Study	Country/ region	Date	Age, y	Stroke risk	Antithrombotic therapy		
					OAC or OAC + AP	AP alone	None
Medical record review of AF patients <sup>14</sup>	Israel	1990-1998	>80	N/A	37.2%*	N/A	N/A
Record-linkage analysis of administrative database <sup>15</sup>	Italy	2002	≥85	N/A	3.9%	25.1%	71.0%
REPOSI medical record database <sup>13</sup>	Italy	January-December, 2008	>80	CHADS <sub>2</sub> ≥ 2: 84.1%	29.2%	42.5%	28.3%
Cross-sectional study of AF patients aged ≥75 y with clear anticoagulation indication <sup>20</sup>	Belgium	2008-2010	Median: 85.0	Mean annual stroke risk (CHADS <sub>2</sub> ): 6.9%/y	50.3%	30.1%	19.5%
Cohort study of nursing home residents with AF <sup>12</sup>	France	March 2012	Mean: 87.1	Mean CHA <sub>2</sub> DS <sub>2</sub> -VASc: 5.1	49.9%	45.5%	4.6%
PREFER in AF Registry <sup>19</sup>	Europe <sup>†</sup>	2012-2013	>80 (mean: 83.7)	Mean CHADS <sub>2</sub> : 2.7 Mean CHA <sub>2</sub> DS <sub>2</sub> -VASc: 4.6	81.6% <sup>‡</sup>	12.4% <sup>‡</sup>	6.0% <sup>‡</sup>
J-RHYTHM Registry <sup>18</sup>	Japan	January-July, 2009	≥70	Mean CHADS <sub>2</sub> : 1.7 <sup>§</sup>	89.2%	6.9%	3.9%
Fushimi AF Registry <sup>16,17,22</sup>	Japan	Enrollment: 2011-2012 Follow-up: 2013	>85	Mean CHADS <sub>2</sub> : 2.09 <sup>  </sup> Mean CHA <sub>2</sub> DS <sub>2</sub> -VASc: 3.43 <sup>  </sup>	~40% <sup>‡</sup>	~20% <sup>‡</sup>	~40% <sup>‡</sup>
Medical record review of AF patients ≥65 y <sup>21</sup>	China	2012-2013	Mean: 75.3	Median CHA <sub>2</sub> DS <sub>2</sub> -VASc: 4	29.1%	39.5%	31.4%

AP, Antiplatelet; N/A, not available; OAC, oral anticoagulant.

\* Percentage of patients at discharge prescribed warfarin.

† Austria, France, Germany, Italy, Spain, Switzerland, and the United Kingdom.

‡ Values are for 1-year follow-up; the published manuscript that presents this data shows it in a stacked bar chart and does not provide the precise values.

§ Mean CHADS<sub>2</sub> for the entire study population (mean age 69.7).

|| Mean CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc for the entire study population at baseline (mean age 74.2).

efficacy end points will be analyzed using the same method as the primary analysis. All other efficacy end points will be summarized descriptively.

Bleeding events will be summarized by treatment group and analyzed in the same fashion as the primary efficacy end point. Adverse events, including treatment emergent adverse events, will be tabulated by event and severity.

## Discussion

ELDERCARE-AF is the first phase 3, randomized, double-blind, placebo-controlled study designed to directly assess the efficacy and safety of edoxaban for the prevention of stroke or SEE in an elderly population. This study will evaluate once-daily edoxaban 15 mg versus placebo in Japanese patients ≥80 years of age with nonvalvular AF who are considered ineligible for standard oral anticoagulant therapy due to factors including impaired renal function, a history of bleeding, low body weight, and use antiplatelet drugs for a purpose other than stroke prophylaxis. In the Japanese real-world clinical practice, extremely elderly patients are significantly more likely to present with many of these factors and comorbidities versus younger patients.<sup>22</sup> As this is an event-driven study, the treatment period will continue until the prespecified number of primary end point events (ie, stroke or SEE) has been observed (expected mean treatment period of 2-2.5 years).

Current data pertaining to the efficacy and safety of non-vitamin K antagonist oral anticoagulants (NOACs), also referred to as *direct oral anticoagulants*, in elderly patients are mainly derived from subgroup analyses of the phase 3 clinical trials. Consistent with the overall study results, in a subgroup analysis of ENGAGE AF-TIMI 48, the risk of stroke or SEE in patients ≥75 years of age was similar with edoxaban and warfarin (HR 0.83, 95% CI 0.66-1.04), and the risk of major bleeding was lower with edoxaban (HR 0.83, 95% CI 0.70-0.99).<sup>26</sup> Because of the higher bleeding risk in the elderly as compared with the younger patients, the primary net clinical outcome (ie, stroke/SEE/major bleeding/death) of edoxaban over warfarin was improved in older patients. Similar results have been reported for apixaban, rivaroxaban, and dabigatran.<sup>34-38</sup>

Elderly patients are at an increased risk of bleeding on oral anticoagulants. In one cohort study, the incidence of major hemorrhage in patients newly started on warfarin was significantly higher in patients ≥80 years of age relative to younger patients (incidence rate ratio 2.75, 95% CI 1.27-5.95).<sup>39</sup> In addition, elderly patients have a high number of comorbidities and contraindications, including falls, cognitive disorder, and polypharmacy, that may make physicians reluctant to treat elderly patients with anticoagulants.<sup>10-12</sup> Reflecting this, the use of oral anticoagulants in elderly patients with nonvalvular AF is often suboptimal worldwide, including in Japan, and

many elderly patients are left untreated with no antithrombotic therapy (Table III). Furthermore, warfarin tends to be underused in patients at high risk of stroke and overused in those at low risk of stroke.<sup>17</sup> However, according to a recent registry database analysis, the introduction of NOACs has coincided with a significant increase in the appropriate use of anticoagulants in elderly patients with nonvalvular AF and a CHADS<sub>2</sub> score  $\geq 1$  (eg, in one registry: post-NOAC approval: 28.5% vs pre-NOAC approval: 22.5%;  $P < .0001$ ).<sup>40</sup>

In clinical practice, for clinicians to balance the risk of stroke with the chance of bleeding, they need assess the relevant data. There are currently no published clinical data from large, double-blind, placebo-controlled, phase 3 clinical trials specifically evaluating the use of NOACs in elderly patients with nonvalvular AF, especially in those patients considered ineligible for available oral anticoagulants. The results of ELDERCARE-AF may provide clarity as to the efficacy and safety of edoxaban for the prevention of stroke or SEE in this high-risk population.

## Conflicts of interest

Dr Okumura received lecture fees from Boehringer Ingelheim, Daiichi-Sankyo, Bayer, Johnson and Johnson, and Medtronic.

Dr Lip is a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo and has been a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. No personal fees were received.

Dr Akao received lecture fees from Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, Bayer Healthcare, and Daiichi-Sankyo.

Kimihiko Tanizawa, Masayuki Fukuzawa, and Kenji Abe are employees of Daiichi Sankyo.

Dr Akishita received lecture fees from Astellas Pharma, Boehringer Ingelheim, Daiichi-Sankyo, Eisai, Eli Lilly Japan, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, MSD, Pfizer, Sumitomo Dainippon Pharma, Takeda Pharmaceutical, and Ono Pharmaceutical. He also received research funding from Astellas Pharma, AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, Chugai Pharmaceutical, Daiichi-Sankyo, Kowa Pharmaceutical, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, MSD, Ono Pharmaceutical, Otsuka Pharmaceutical, Pfizer, Taisho Toyama Pharmaceutical, Takeda Pharmaceutical, and Tsumura.

Dr Yamashita received research funding from Bristol-Myers Squibb, Bayer Healthcare, Daiichi-Sankyo, and Mitsubishi-Tanabe Pharmaceutical and remuneration from Daiichi-Sankyo, Bayer Healthcare, Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, Eisai, Toa Eiyo, Takeda, and Ono Pharmaceutical.

The Fushimi AF Registry is supported by research funding from Boehringer Ingelheim, Bayer Healthcare, Pfizer, Bristol-Myers Squibb, Astellas Pharma, AstraZeneca,

Daiichi-Sankyo, Novartis Pharma, MSD, Sanofi-Aventis, and Takeda Pharmaceutical. This research is partially supported by the Practical Research Project for Life-Style related Diseases including Cardiovascular Diseases and Diabetes Mellitus from Japan Agency for Medical Research and Development (15656344, 16768811).

## Funding

The study is funded by Daiichi Sankyo Co Ltd (Tokyo, Japan).

## Acknowledgements

Medical writing and editorial support was provided by Stefan Kolata, PhD, of AlphaBioCom, LLC (King of Prussia, PA) and funded by Daiichi Sankyo, Inc (Basking Ridge, PA).

## References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983-8.
2. Lin HJ, Wolf PA, Kelly-Hayes M, et al. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke* 1996;27:1760-4.
3. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;285:2370-5.
4. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation* 2006;114:119-25, <http://dx.doi.org/10.1161/CIRCULATIONAHA.105.595140>.
5. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* 2014;129:837-47, <http://dx.doi.org/10.1161/CIRCULATIONAHA.113.005119>.
6. Ohsawa M, Okayama A, Sakata K, et al. Rapid increase in estimated number of persons with atrial fibrillation in Japan: an analysis from national surveys on cardiovascular diseases in 1980, 1990 and 2000. *J Epidemiol* 2005;15:194-6.
7. Iguchi Y, Kimura K, Aoki J, et al. Prevalence of atrial fibrillation in community-dwelling Japanese aged 40 years or older in Japan: analysis of 41,436 non-employee residents in Kurashiki-city. *Circ J* 2008;72:909-13.
8. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation* 2014;130:e199-67, <http://dx.doi.org/10.1161/CIR.0000000000000041>.
9. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration With EACTS. *Rev Esp Cardiol (Engl Ed)* 2017;70:50, <http://dx.doi.org/10.1016/j.rec.2016.11.033>.
10. Perera V, Bajorek BV, Matthews S, et al. The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation. *Age Ageing* 2009;38:156-62, <http://dx.doi.org/10.1093/ageing/afn293>.
11. Hylek EM, D'Antonio J, Evans-Molina C, et al. Translating the results of randomized trials into clinical practice: the challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation.



- Stroke 2006;37:1075-80, <http://dx.doi.org/10.1161/01.STR.0000209239.71702.ce>.
12. Bahri O, Roca F, Lechani T, et al. Underuse of oral anticoagulation for individuals with atrial fibrillation in a nursing home setting in France: comparisons of resident characteristics and physician attitude. *J Am Geriatr Soc* 2015;63:71-6, <http://dx.doi.org/10.1111/jgs.13200>.
  13. Marucci M, Iorio A, Nobili A, et al. Factors affecting adherence to guidelines for antithrombotic therapy in elderly patients with atrial fibrillation admitted to internal medicine wards. *Eur J Intern Med* 2010;21:516-23, <http://dx.doi.org/10.1016/j.ejim.2010.07.014>.
  14. Cohen N, Almozni-Sarafian D, Alon I, et al. Warfarin for stroke prevention still underused in atrial fibrillation: patterns of omission. *Stroke* 2000;31:1217-22.
  15. Monte S, Macchia A, Pellegrini F, et al. Antithrombotic treatment is strongly underused despite reducing overall mortality among high-risk elderly patients hospitalized with atrial fibrillation. *Eur Heart J* 2006;27:2217-23, <http://dx.doi.org/10.1093/eurheartj/ehl208>.
  16. Akao M, Chun YH, Wada H, et al. Current status of clinical background of patients with atrial fibrillation in a community-based survey: the Fushimi AF Registry. *J Cardiol* 2013;61:260-6, <http://dx.doi.org/10.1016/j.jcc.2012.12.002>.
  17. Akao M, Chun YH, Esato M, et al. Inappropriate use of oral anticoagulants for patients with atrial fibrillation. *Circ J* 2014;78:2166-72.
  18. Atarashi H, Inoue H, Okumura K, et al. Present status of anticoagulation treatment in Japanese patients with atrial fibrillation: a report from the J-RHYTHM Registry. *Circ J* 2011;75:1328-33.
  19. Hanon O, Vidal JS, Le Heuzey JY, et al. Oral anticoagulant use in octogenarian European patients with atrial fibrillation: a subanalysis of PREFER in AF. *Int J Cardiol* 2017;232:98-104, <http://dx.doi.org/10.1016/j.ijcard.2017.01.046>.
  20. Maes F, Dalleur O, Henrard S, et al. Risk scores and geriatric profile: can they really help us in anticoagulation decision making among older patients suffering from atrial fibrillation? *Clin Interv Aging* 2014;9:1091-9, <http://dx.doi.org/10.2147/CIA.S62597>.
  21. Xiang W, Zhang J, Liu M, et al. Antithrombotic therapy in elderly patients with non-valvular atrial fibrillation: a pilot study. *Clin Interv Aging* 2015;10:515-9, <http://dx.doi.org/10.2147/CIA.S67974>.
  22. Yamashita Y, Hamatani Y, Esato M, et al. Clinical characteristics and outcomes in extreme elderly (age  $\geq$  85 years) Japanese patients with atrial fibrillation: the Fushimi AF Registry. *Chest* 2016;149:401-12, <http://dx.doi.org/10.1378/chest.15-1095>.
  23. Parasrampur DA, Truitt KE. Pharmacokinetics and pharmacodynamics of edoxaban, a non-vitamin K antagonist oral anticoagulant that inhibits clotting factor Xa. *Clin Pharmacokinet* 2016;55:641-55, <http://dx.doi.org/10.1007/s40262-015-0342-7>.
  24. SAVAYSA™ (edoxaban) tablets for oral use. Full prescribing information. Parsippany, NJ, USA: Daiichi Sankyo Inc. 2015.
  25. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093-104, <http://dx.doi.org/10.1056/NEJMoa1310907>.
  26. Kato ET, Giugliano RP, Ruff CT, et al. Efficacy and Safety of edoxaban in elderly patients with atrial fibrillation in the ENGAGE AF-TIMI 48 Trial. *J Am Heart Assoc* 2016;5, <http://dx.doi.org/10.1161/JAHA.116.003432>.
  27. Suzuki M, Matsue Y, Nakamura R, et al. Improvement of HAS-BLED bleeding score predictive capability by changing the definition of renal dysfunction in Japanese atrial fibrillation patients on anticoagulation therapy. *J Cardiol* 2014;64:482-7, <http://dx.doi.org/10.1016/j.jcc.2014.03.006>.
  28. JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). *Circ J* 2014;78:1997-2021.
  29. Palareti G, Cosmi B. Bleeding with anticoagulation therapy—who is at risk, and how best to identify such patients. *Thromb Haemost* 2009;102:268-78, <http://dx.doi.org/10.1160/TH08-11-0730>.
  30. Hughes M, Lip GY. Risk factors for anticoagulation-related bleeding complications in patients with atrial fibrillation: a systematic review. *QJM* 2007;100:599-607, <http://dx.doi.org/10.1093/qjmed/hcm076>.
  31. Abe M, Ogawa H, Ishii M, et al. Relation of stroke and major bleeding to creatinine clearance in patients with atrial fibrillation (from the Fushimi AF Registry). *Am J Cardiol* 2017;119:1229-37, <http://dx.doi.org/10.1016/j.amjcard.2017.01.005>.
  32. Ruff CT, Giugliano RP, Braunwald E, et al. Association between edoxaban dose, concentration, anti-factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. *Lancet* 2015;385:2288-95, [http://dx.doi.org/10.1016/S0140-6736\(14\)61943-7](http://dx.doi.org/10.1016/S0140-6736(14)61943-7).
  33. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955-62, [http://dx.doi.org/10.1016/S0140-6736\(13\)62343-0](http://dx.doi.org/10.1016/S0140-6736(13)62343-0).
  34. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011;123:2363-72, <http://dx.doi.org/10.1161/CIRCULATIONAHA.110.004747>.
  35. Halperin JL, Hankey GJ, Wojdyla DM, et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). *Circulation* 2014;130:138-46, <http://dx.doi.org/10.1161/CIRCULATIONAHA.113.005008>.
  36. Halvorsen S, Atar D, Yang H, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. *Eur Heart J* 2014;35:1864-72, <http://dx.doi.org/10.1093/eurheartj/ehu046>.
  37. Ng KH, Shestakovska O, Connolly SJ, et al. Efficacy and safety of apixaban compared with aspirin in the elderly: a subgroup analysis from the AVERROES trial. *Age Ageing* 2016;45:77-83, <http://dx.doi.org/10.1093/ageing/afv156>.
  38. Sardar P, Chatterjee S, Chaudhari S, et al. New oral anticoagulants in elderly adults: evidence from a meta-analysis of randomized trials. *J Am Geriatr Soc* 2014;62:857-64, <http://dx.doi.org/10.1111/jgs.12799>.
  39. Hylek EM, Evans-Molina C, Shea C, et al. Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. *Circulation* 2007;115:2689-96, <http://dx.doi.org/10.1161/CIRCULATIONAHA.106.653048>.
  40. Zheng Q, Aneke-Nash C, Halperin JL, et al. Novel oral anticoagulant availability increases appropriate use of anticoagulants for non-valvular atrial fibrillation in the elderly aged  $\geq$  75 years old in clinical practice. *Circulation* 2016;134:A18905.