ORIGINAL ARTICLE

Low-Dose Edoxaban in Very Elderly Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Implementation of appropriate oral anticoagulant treatment for the prevention of stroke in very elderly patients with atrial fibrillation is challenging because of concerns regarding bleeding.

METHODS

We conducted a phase 3, multicenter, randomized, double-blind, placebo-controlled, event-driven trial to compare a once-daily 15-mg dose of edoxaban with placebo in elderly Japanese patients (≥80 years of age) with nonvalvular atrial fibrillation who were not considered to be appropriate candidates for oral anticoagulant therapy at doses approved for stroke prevention. The primary efficacy end point was the composite of stroke or systemic embolism, and the primary safety end point was major bleeding according to the definition of the International Society on Thrombosis and Haemostasis.

RESULTS

A total of 984 patients were randomly assigned in a 1:1 ratio to receive a daily dose of 15 mg of edoxaban (492 patients) or placebo (492 patients). A total of 681 patients completed the trial, and 303 discontinued (158 withdrew, 135 died, and 10 had other reasons); the numbers of patients who discontinued the trial were similar in the two groups. The annualized rate of stroke or systemic embolism was 2.3% in the edoxaban group and 6.7% in the placebo group (hazard ratio, 0.34; 95% confidence interval [CI], 0.19 to 0.61; P<0.001), and the annualized rate of major bleeding was 3.3% in the edoxaban group and 1.8% in the placebo group (hazard ratio, 1.87; 95% CI, 0.90 to 3.89; P=0.09). There were substantially more events of gastrointestinal bleeding in the edoxaban group than in the placebo group. There was no substantial between-group difference in death from any cause (9.9% in the edoxaban group and 10.2% in the placebo group; hazard ratio, 0.97; 95% CI, 0.69 to 1.36).

CONCLUSIONS

In very elderly Japanese patients with nonvalvular atrial fibrillation who were not appropriate candidates for standard doses of oral anticoagulants, a once-daily 15-mg dose of edoxaban was superior to placebo in preventing stroke or systemic embolism and did not result in a significantly higher incidence of major bleeding than placebo. (Funded by Daiichi Sankyo; ELDERCARE-AF ClinicalTrials.gov number, NCT02801669.)

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*A list of the ELDERCARE-AF committee members and investigators is provided in the Supplementary Appendix, available at NEJM.org.

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The prevalence of atrial fibrillation increases with age, and both atrial fibrillation and age are independent risk factors for stroke.[1,2] Clinical guidelines for the prevention of stroke in patients with atrial fibrillation recommend the use of direct oral anticoagulants, including in elderly patients.[3,4] However, many physicians are reluctant to prescribe direct oral anticoagulants to very elderly patients because of perceived risk factors for bleeding such as renal failure, a history of bleeding, previous falls, polypharmacy, and frailty.[5-7] Considering the aging of the population, evidence to support a beneficial anticoagulation regimen in high-risk, very elderly patients is necessary.

In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) phase 3 trial,[8] both once-daily doses of edoxaban (a high dose of 60 mg [or 30 mg in patients who met the criteria for a dose reduction] and a low dose of 30 mg [or 15 mg in patients who met the criteria for a dose reduction]) were noninferior to warfarin with respect to the prevention of stroke or systemic embolism in patients with nonvalvular atrial fibrillation and were superior to warfarin with respect to the prevention of major bleeding. However, only 17% of the participants were 80 years of age or older.[9] The use of lower-dose edoxaban (30 mg or 15 mg) is considered off-label because of concerns regarding insufficient prevention of stroke, but these doses may still be beneficial in patients with a high risk of bleeding, including in very elderly patients.[8,9] The Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients (ELDERCARE-AF) trial was a placebo-controlled trial comparing a once-daily 15-mg dose of edoxaban with placebo in Japanese patients 80 years of age or older who had nonvalvular atrial fibrillation and in whom standard oral anticoagulants were not recommended.

METHODS

TRIAL DESIGN AND OVERSIGHT

The ELDERCARE-AF trial was a phase 3, multicenter, randomized, double-blind, placebo-controlled, event-driven, superiority trial that was conducted in Japan. All trial personnel are listed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The trial design has been described previously.[10] The trial was funded and sponsored by Daiichi Sankyo and was approved by the institutional review board at each participating site. The trial was conducted in accordance with the standards specified in the Pharmaceutical and Medical Device Act of Japan and with the International Council for Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki.

Representatives of the sponsor and the academic and clinical authors designed and wrote the protocol (available at NEJM.org) and statistical analysis plan, selected and monitored the participating sites, and analyzed and interpreted the data. An independent safety monitoring committee monitored all safety data and was involved in decisions regarding trial continuation or protocol changes. The manuscript was drafted with medical writing assistance funded by the sponsor. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

TRIAL POPULATION

Eligible patients were 80 years of age or older, had a history of nonvalvular atrial fibrillation documented on an electrocardiogram or on a monitor recording obtained within 1 year before consent was given, and had a $CHADS_2$ score of 2 or higher. The $CHADS_2$ score is an index of stroke risk among patients with atrial fibrillation (scores range from 0 to 6, with higher scores indicating a greater risk of stroke; previous stroke or transient ischemic attack is assigned 2 points, and congestive heart failure, hypertension, diabetes, and an age of 75 years or older are each assigned 1 point toward the total score). Eligible patients were also considered to be inappropriate candidates for oral anticoagulants (i.e., warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) at the recommended therapeutic strength (in the case of warfarin) or at approved doses for one or more of the following reasons: a low creatinine clearance (15 to 30 ml per minute), a history of bleeding from a critical area or organ or gastrointestinal bleeding, low body weight (≤45 kg), continuous use of nonsteroidal antiinflammatory drugs (NSAIDs), or current use of an antiplatelet drug. A full list of inclusion and exclusion criteria is provided in Table S1 in the Supplementary Appendix. Written in-

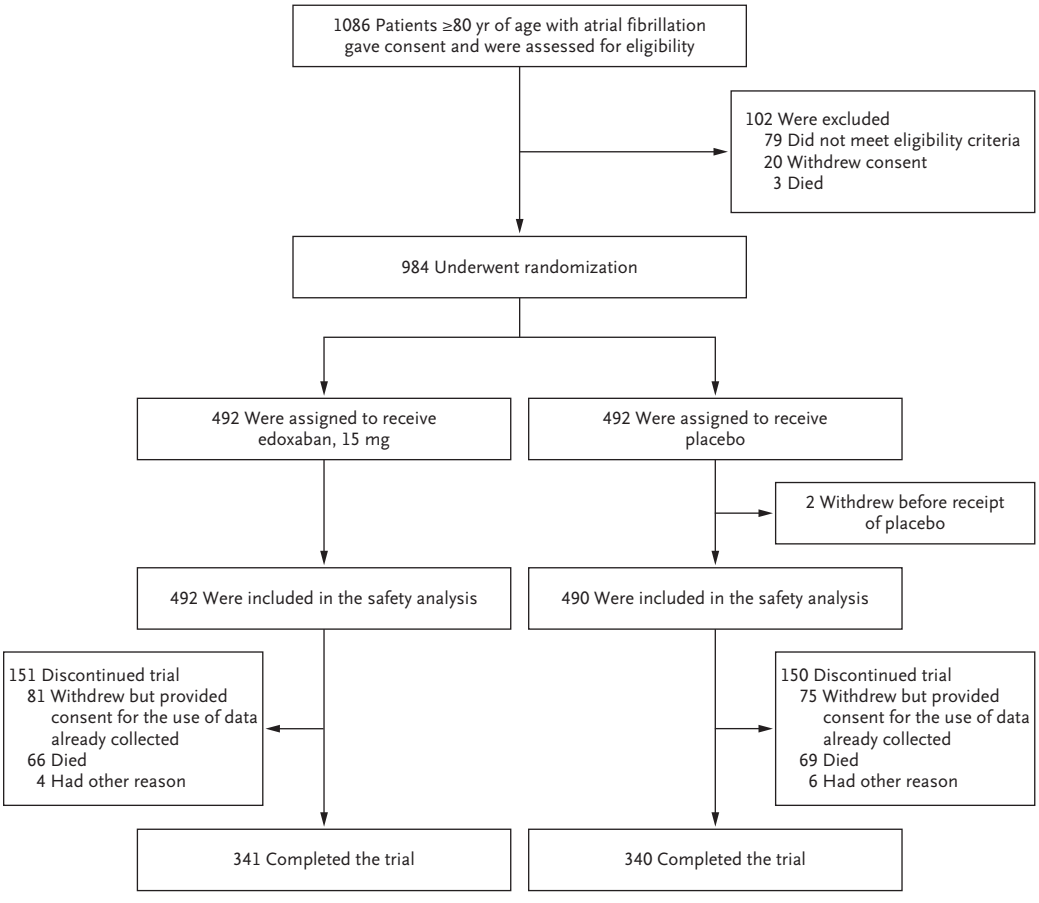

Figure 1. Randomization and Analysis.

Details concerning the 79 patients who did not meet eligibility criteria are provided in Table S2 in the Supplementary Appendix. The 158 patients who withdrew from the trial declined to undergo any assessments after withdrawal of consent, including a final survival assessment. A total of 10 patients were enrolled at a trial site that declared bankruptcy and was at risk of closing; follow-up of patients at this site was discontinued to ensure safety.

formed consent was obtained from all participants (or from legal representatives of patients with cognitive impairment) before enrollment.

RANDOMIZATION AND TRIAL PROCEDURES

Eligible patients were randomly assigned in a 1:1 ratio to receive 15 mg of edoxaban once daily or placebo. Randomization (in permuted blocks of four) was performed with the use of an interactive response technology system according to a schedule prepared by an independent biostatistician and was stratified according to $CHADS_2$ score (2 points or ≥3 points). Patients, investigators, and the sponsor were unaware of the trial-group assignments. The use of tests that could compromise the masking of the trial-group assignments, such as pharmacodynamics and biomarker data, was prohibited at trial sites. Follow-up assessments were conducted during in-person medical office visits; they occurred every 4 weeks from weeks 4 through 48 and every 8 weeks thereafter until trial completion.

END POINTS

The primary efficacy end point was the composite of stroke or systemic embolism, and the primary safety end point was major bleeding according to the definition of the International Society on Thrombosis and Haemostasis. Secondary efficacy end points included the composite of stroke, systemic embolism, or death from cardiovascular causes; major adverse cardiovas-

Table 1. Demographic and Clinical Characteristics of the Patients.*

Characteristic	All Patients (N=984)	Edoxaban, 15 mg (N=492)	Placebo (N=492)
Age			
Mean — yr	86.6±4.2	86.7±4.2	86.4±4.3
Distribution — no. (%)			
≤85 yr	447 (45.4)	218 (44.3)	229 (46.5)
>85 yr	537 (54.6)	274 (55.7)	263 (53.5)
Male sex — no. (%)	419 (42.6)	212 (43.1)	207 (42.1)
Type of atrial fibrillation — no. (%)			
Nonparoxysmal	521 (52.9)	255 (51.8)	266 (54.1)
Paroxysmal	463 (47.1)	237 (48.2)	226 (45.9)
Weight — kg	50.6±11.0	50.6±10.9	50.6±11.1
Body-mass index†	22.1±3.7	22.1±3.6	22.2±3.8
Creatinine clearance			
Mean — ml/min	36.3±14.4	36.3±14.3	36.2±14.5
Distribution — no. (%)			
≤50 ml/min	823 (83.6)	415 (84.3)	408 (82.9)
>50 ml/min	161 (16.4)	77 (15.7)	84 (17.1)
$CHADS_2$ score‡			
Mean score	3.1±1.1	3.0±1.1	3.1±1.1
Distribution — no. (%)			
2	363 (36.9)	181 (36.8)	182 (37.0)
≥3	621 (63.1)	311 (63.2)	310 (63.0)
Components — no. (%)			
Age ≥75 yr	984 (100.0)	492 (100.0)	492 (100.0)
Previous stroke or transient ischemic attack	236 (24.0)	110 (22.4)	126 (25.6)
Congestive heart failure	533 (54.2)	259 (52.6)	274 (55.7)
Diabetes mellitus	225 (22.9)	115 (23.4)	110 (22.4)
Hypertension	810 (82.3)	412 (83.7)	398 (80.9)
CHA_2DS_2-VASc score§	4.9±1.3	4.9±1.2	5.0±1.3
HAS-BLED score¶	2.3±0.9	2.3±0.9	2.4±0.9
Coronary artery disease	257 (26.1)	130 (26.4)	127 (25.8)
Dementia	160 (16.3)	70 (14.2)	90 (18.3)
History of falling within past yr	340 (34.6)	154 (31.3)	186 (37.8)
Frailty category‖			
Robust or prefrail	542 (55.1)	289 (58.7)	253 (51.4)
Frail	402 (40.9)	185 (37.6)	217 (44.1)
Could not be evaluated	17 (1.7)	7 (1.4)	10 (2.0)
Missing data	23 (2.3)	11 (2.2)	12 (2.4)
History of oral anticoagulant therapy			
Yes	423 (43.0)	207 (42.1)	216 (43.9)
Warfarin	243 (24.7)	115 (23.4)	128 (26.0)

Table 1. (Continued.)

Characteristic	All Patients (N=984)	Edoxaban, 15 mg (N=492)	Placebo (N=492)
Direct oral anticoagulants**	251 (25.5)	124 (25.2)	127 (25.8)
Unknown	3 (0.3)	1 (0.2)	2 (0.4)
No	561 (57.0)	285 (57.9)	276 (56.1)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† The body-mass index is the weight in kilograms divided by the square of the height in meters. Data were missing for 1 patient in the edoxaban group and 2 patients in the placebo group.
‡ $CHADS_2$ scores range from 0 to 6, with higher scores indicating a greater risk of stroke. Previous stroke or transient ischemic attack is assigned 2 points, and congestive heart failure, hypertension, diabetes, and an age of 75 years or older are each assigned 1 point toward the total score.
§ CHA_2DS_2-VASc scores range from 0 to 9, with higher scores indicating a greater risk of stroke. Previous stroke or transient ischemic attack and an age of 75 years or older are each assigned 2 points, and congestive heart failure, hypertension, diabetes, an age of 65 to 74 years, female sex, and history of vascular disease are each assigned 1 point toward the total score.
¶ HAS-BLED scores range from 0 to 9, with higher scores indicating a greater risk of bleeding. Abnormal renal or liver function are assigned 1 point each; the use of antiplatelet or nonsteroidal antiinflammatory drugs or alcohol concomitantly are assigned 1 point each (for a total of 1 or 2 points), and hypertension, stroke, history of bleeding or a predisposition to bleeding, labile international normalized ratio, and elderly age (>65 years) are each assigned 1 point toward the total score.
‖ Frailty was assessed with the use of five measures of physical condition; a score of 0 indicated robust, a score of 1 or 2 indicated prefrail, and a score of 3 or higher indicated frail.[13,14] Details of the assessment of frailty are provided in the Supplementary Appendix.
** Direct oral anticoagulants included dabigatran, rivaroxaban, apixaban, and edoxaban.

cular events (the composite of nonfatal myocardial infarction, nonfatal stroke, nonfatal systemic embolism, or death from cardiovascular causes or bleeding); the composite of stroke, systemic embolism, or death from any cause; net clinical benefit (the composite of stroke, systemic embolism, major bleeding, or death from any cause); and death from any cause. Secondary safety end points included the composite of major bleeding or clinically relevant nonmajor bleeding; clinically relevant nonmajor bleeding; minor bleeding; and all bleeding. A complete list of trial end points and definitions is provided in the Supplementary Appendix. Independent clinical efficacy and clinical bleeding event committees, whose members were unaware of the trial-group assignments, adjudicated all primary and secondary efficacy events and bleeding events.

STATISTICAL ANALYSIS

This trial was event-driven, with a target of 65 events of stroke or systemic embolism. On the basis of previous studies, we estimated that the annual incidence of stroke or systemic embolism would be 5% per year in the placebo group and that a 15-mg dose of edoxaban would result in a 50% lower risk than placebo.[8,11] Therefore, 65 events (in approximately 400 patients per group) would be required to give the trial 80% power to show superiority of edoxaban to placebo with respect to the prevention of stroke or systemic embolism, at a two-sided significance level of 5%.

The primary efficacy analysis was conducted in the intention-to-treat population, which included all patients who underwent randomization. The safety population included all patients who received at least one dose of edoxaban or placebo.

Patient characteristics were described with the use of distributions and summary statistics. The time-to-first-event analysis of stroke or systemic embolism used a Cox proportional-hazards model with trial groups and $CHADS_2$ score (≤2 or ≥3) as covariates and was tested with the use of a two-sided significance level of 5%. The proportionality of hazards for the primary end point was confirmed by means of inspection of a log–log survival plot. Relative risk was estimated with the use of hazard ratios with 95% confidence intervals. Secondary efficacy end points were analyzed with the same method. Competing-risk analyses based on the Fine and Gray model were also performed to take into account the competing risk of death or cause-specific death.[12] The cumulative incidences of efficacy events were estimated in each trial group with the use of the Kaplan–Meier method. Events of

Table 2. Primary and Secondary Efficacy and Safety End Points.

End Point	Edoxaban, 15 mg (N=492)	Placebo (N=492)	Hazard Ratio (95% CI)*	P Value
	no. of patients with event (% per patient-yr)			
Primary efficacy end point†				
Stroke or systemic embolism	15 (2.3)	44 (6.7)	0.34 (0.19–0.61)	<0.001
Stroke	12 (1.8)	40 (6.0)	0.30 (0.16–0.57)	
Ischemic	12 (1.8)	39 (5.9)	0.31 (0.16–0.59)	
Hemorrhagic	0	2 (0.3)		
Fatal	1 (0.1)	3 (0.4)	0.34 (0.04–3.30)	
Systemic embolism	3 (0.4)	6 (0.9)	0.50 (0.13–2.01)	
Secondary efficacy end points†				
Stroke, systemic embolism, or death from cardiovascular causes	52 (7.8)	72 (10.9)	0.72 (0.50–1.03)	
Major adverse cardiovascular event‡	51 (7.7)	72 (11.0)	0.70 (0.49–1.01)	
Stroke, systemic embolism, or death from any cause	74 (11.1)	98 (14.8)	0.75 (0.56–1.02)	
Net clinical benefit§	87 (13.5)	103 (15.6)	0.86 (0.65–1.15)	
Death from any cause	66 (9.9)	69 (10.2)	0.97 (0.69–1.36)	
Primary safety end point¶				
Major bleeding	20 (3.3)	11 (1.8)	1.87 (0.90–3.89)	0.09
Intracranial hemorrhage	2 (0.3)	4 (0.6)	0.50 (0.09–2.72)	
Gastrointestinal bleeding	14 (2.3)	5 (0.8)	2.85 (1.03–7.88)	
Secondary safety end points¶				
Major or clinically relevant nonmajor bleeding	97 (17.7)	62 (10.7)	1.65 (1.20–2.27)	
Clinically relevant nonmajor bleeding	81 (14.5)	52 (8.9)	1.62 (1.14–2.30)	
Minor bleeding	190 (45.4)	177 (37.9)	1.18 (0.96–1.45)	
All bleeding	241 (63.0)	202 (45.0)	1.35 (1.12–1.63)	

* The widths of the confidence intervals for secondary end points were not adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.
† Efficacy end points were assessed in the intention-to-treat population, which included all patients who underwent randomization.
‡ Major adverse cardiovascular events included nonfatal myocardial infarction, nonfatal stroke, nonfatal systemic embolism, or death from cardiovascular causes or bleeding.
§ Net clinical benefit was the composite of stroke, systemic embolism, major bleeding, or death from any cause.
¶ The safety population included all patients who received at least one dose of edoxaban or placebo (492 patients in the edoxaban group and 490 in the placebo group). Data shown are events that occurred during the treatment period plus up to 3 days after the last dose of edoxaban or placebo or the end of the trial.

bleeding were summarized according to trial group and were assessed during the treatment period plus up to 3 days after the last dose of edoxaban or placebo or the end of the trial.

No adjustment for multiple testing was performed; therefore, P values are not reported for secondary end points. The widths of the confidence intervals were not adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

RESULTS

RANDOMIZATION, PATIENT CHARACTERISTICS, AND FOLLOW-UP

Between August 5, 2016, and November 5, 2019, a total of 1086 patients were enrolled at 164 institutions; 984 underwent randomization (492 were assigned to receive edoxaban, and 492 were assigned to receive placebo). Of the 102 patients who were excluded, 20 withdrew consent, 3 died,

and 79 did not meet eligibility criteria (Fig. 1 and Table S2).

Patients were very elderly (mean age, 86.6±4.2 years), had low body weight (mean, 50.6±11.0 kg), and had reduced renal function (mean creatinine clearance, 36.3±14.4 ml per minute) (Table 1). A total of 40.9% of the patients were categorized as frail; the assessment of frailty is described in the Supplementary Appendix.[13,14] Overall, 423 patients (43.0%) had previously received oral anticoagulants. Table S3 provides the reasons that a standard regimen of oral anticoagulants was not recommended in patients.

The date of the last patient follow-up was December 27, 2019. The median duration of participation in the trial was 466.0 days (interquartile range, 293.5 to 708.0). Two patients in the placebo group withdrew from the trial before receiving the first dose and were not included in the safety population; 301 additional patients did not complete the trial (156 withdrew consent before completion of the trial, 135 died during the trial period, and 10 discontinued participation for other reasons).

The most common reasons for withdrawal were adverse events unrelated to bleeding and loss of motivation or lack of capability to continue participation in the trial (Table S4). Further details regarding the patients who withdrew from the trial are provided in Tables S5 and S6 and in Figures S1 through S3.

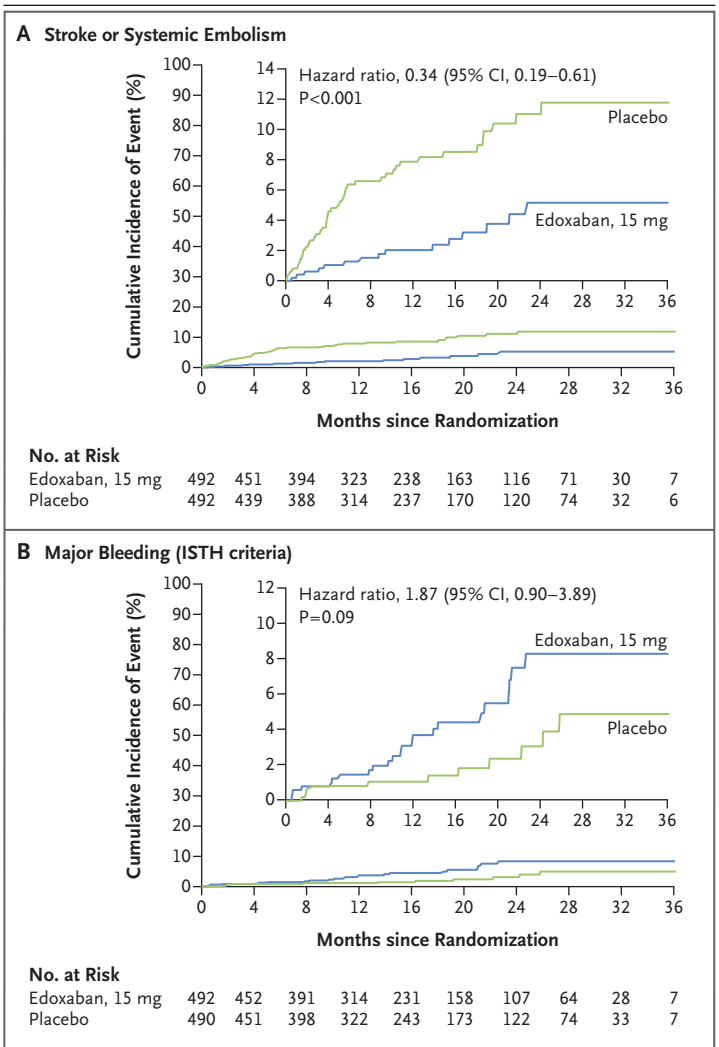

Figure 2. Primary Efficacy and Safety End Points.

Panel A shows the estimate of the cumulative incidence of the primary efficacy end point (stroke or systemic embolism), and Panel B shows the estimate of the cumulative incidence of the primary safety end point (major bleeding according to the criteria of the International Society on Thrombosis and Haemostasis [ISTH]). The inset in each panel shows the same data on an enlarged y axis.

EFFICACY END POINTS

A total of 66 events of stroke or systemic embolism (the primary efficacy end point) were reported; 7 events were not adjudicated as primary efficacy end-point events by the clinical efficacy event committee. Therefore, 59 events were included in the analysis. In the intention-to-treat population, 15 patients (2.3% per patient-year) in the edoxaban group and 44 patients (6.7% per patient-year) in the placebo group had stroke or systemic embolism (hazard ratio, 0.34; 95% confidence interval [CI], 0.19 to 0.61; P<0.001 for superiority) (Table 2 and Fig. 2A). To take into account the possibility that discontinuation of follow-up could have influenced the results, we also analyzed the primary end point with the use of an inverse probability of censoring weighted analysis (described in the Supplementary Appendix).[15] In this analysis, the results were similar to those of the primary analysis (hazard ratio, 0.38; 95% CI, 0.21 to 0.71). The effect of edoxaban on the primary end point was generally consistent across selected subgroups, although the data suggest potential heterogeneity of treatment effect according to NSAID use (Fig. 3).

There were 66 deaths from any cause in the edoxaban group and 69 in the placebo group (9.9% per patient-year and 10.2% per patient-year, respectively; hazard ratio, 0.97; 95% CI, 0.69 to 1.36) (Table 2). The causes of death are listed in Table S8.

The annualized rate of the secondary efficacy end point (the composite of stroke, systemic

embolism, or death from cardiovascular causes) was 7.8% in the edoxaban group and 10.9% in the placebo group (hazard ratio, 0.72; 95% CI, 0.50 to 1.03). The annualized rate of major adverse cardiovascular events was 7.7% in the edoxaban group and 11.0% in the placebo group (hazard ratio, 0.70; 95% CI, 0.49 to 1.01). The annualized rate of the composite secondary efficacy end point of stroke, systemic embolism, or death from any cause was 11.1% in the edoxaban group and 14.8% in the placebo group (hazard ratio, 0.75; 95% CI, 0.56 to 1.02). And the annualized rate of the net clinical benefit outcome (stroke, systemic embolism, major bleeding, or death from any cause) was 13.5% in the edoxaban group and 15.6% in the placebo group (hazard ratio, 0.86; 95% CI, 0.65 to 1.15).

SAFETY END POINTS

In the safety population, there were 20 events of major bleeding (3.3% per patient-year) in the edoxaban group and 11 (1.8% per patient-year) in the placebo group (hazard ratio, 1.87; 95% CI, 0.90 to 3.89; P=0.09) (Table 2 and Fig. 2B). The effect of edoxaban on major bleeding was generally consistent across selected subgroups (Fig. S4). Of the events of major bleeding, 6 were intracranial hemorrhages (2 events in the edoxaban group [0.3% per patient-year] and 4 events, 1 of which was fatal, in the placebo group [0.6% per patient-year]). There were substantially more events of gastrointestinal bleeding in the edoxaban group (14 events [2.3% per patient-year]) than in the placebo group (5 events [0.8% per patient-year]) (hazard ratio, 2.85; 95% CI, 1.03 to 7.88). There were two events of fatal bleeding in the placebo group and none in the edoxaban group. Table S7 provides the hazard ratios with death as a competing risk, and Table S9 lists the sites of major bleeding. The rates of many of the secondary safety end points — including clinically relevant nonmajor bleeding, all bleeding, and the composite of major bleeding or clinically relevant nonmajor bleeding — were higher in the edoxaban group than in the placebo group (Table 2).

DISCUSSION

In this trial, a once-daily 15-mg dose of edoxaban was superior to placebo with respect to the primary efficacy end point of stroke or systemic embolism in very elderly Japanese patients with nonvalvular atrial fibrillation who were considered to be inappropriate candidates for a standard oral anticoagulant regimen. The incidence of major bleeding was higher with edoxaban than with placebo, although this difference was not significant. There were substantially more events of gastrointestinal bleeding, as well as bleeding defined as secondary safety end points, with edoxaban. Edoxaban did not result in higher incidences of death from any cause or death from cardiovascular causes than placebo; the most common causes of death were congestive heart failure or cardiogenic shock and infection — not stroke or systemic embolism — in this very elderly population with clinically significant coexisting conditions.

Clinical guidelines recommend the use of direct oral anticoagulants for the prevention of stroke in patients with nonvalvular atrial fibrillation, including in elderly patients.[3,4] The mean or median age of the patients enrolled in previous landmark clinical trials of direct oral anticoagulants was 70 to 73 years, which is 5 to 10 years younger than the average age in the general population with atrial fibrillation.[8,16-18] Therefore, the findings in these major trials cannot be easily generalized to older patients, especially those who are 80 years of age or older.[19] In this trial, in addition to the eligibility requirement of an age of 80 years or older, patients had to meet at least one of the criteria for being an inappropriate candidate for standard oral anticoagulants; these are additional risk factors for bleeding in very elderly patients, who are already at high risk for both stroke and bleeding.[20-23]

We used a 15-mg dose of edoxaban in this trial on the basis of data from the ENGAGE AF-TIMI 48 trial, which compared two doses of edoxaban (60 mg and 30 mg) with warfarin. If patients in either edoxaban group met criteria for dose reductions, the 60-mg dose was reduced to 30 mg, and the 30-mg dose was reduced to 15 mg. Among patients who received the 15-mg reduced dose, the risk of major bleeding was lower than that among patients who received warfarin (1.5% vs. 4.9%), and the incidence of stroke or systemic embolism did not differ significantly between these groups (2.4% among patients who received 15 mg of edoxaban and 2.2% among patients who received warfarin).[24] Because there is no established standard of care for very elderly patients at high risk for both stroke

Subgroup	Edoxaban, 15 mg	Placebo	Hazard Ratio (95% CI)
	no. of patients with event/total no. of patients (% per patient-yr)		
All patients	15/492 (2.3)	44/492 (6.7)	0.34 (0.19–0.61)
Age			
≤85 yr	5/218 (1.7)	17/229 (5.4)	0.31 (0.11–0.83)
>85 yr	10/274 (2.8)	27/263 (7.8)	0.36 (0.17–0.73)
Sex			
Male	4/212 (1.4)	17/207 (6.0)	0.24 (0.08–0.72)
Female	11/280 (2.8)	27/285 (7.1)	0.39 (0.19–0.79)
Type of atrial fibrillation			
Nonparoxysmal	8/255 (2.3)	32/266 (8.8)	0.26 (0.12–0.56)
Paroxysmal	7/237 (2.3)	12/226 (4.0)	0.55 (0.22–1.39)
Previous stroke or transient ischemic attack			
Yes	5/110 (3.2)	13/126 (7.9)	0.42 (0.15–1.18)
No	10/382 (2.0)	31/366 (6.2)	0.31 (0.15–0.64)
$CHADS_2$ score			
2	2/181 (0.8)	10/182 (3.9)	0.20 (0.04–0.91)
≥3	13/311 (3.2)	34/310 (8.3)	0.38 (0.20–0.72)
HAS-BLED score			
≤2	10/311 (2.5)	25/305 (6.1)	0.40 (0.19–0.83)
≥3	5/181 (1.9)	19/187 (7.6)	0.27 (0.10–0.71)
Reasons that oral anticoagulants were not recommended			
Severe renal impairment			
Yes	9/198 (3.5)	26/205 (9.7)	0.33 (0.16–0.71)
No	6/294 (1.5)	18/287 (4.6)	0.34 (0.13–0.85)
History of bleeding			
Yes	1/110 (0.6)	8/112 (5.3)	0.12 (0.02–0.99)
No	14/382 (2.8)	36/380 (7.1)	0.40 (0.21–0.74)
Low body weight, ≤45 kg			
Yes	8/188 (3.3)	21/186 (9.0)	0.36 (0.16–0.80)
No	7/304 (1.6)	23/306 (5.4)	0.31 (0.13–0.73)
Continuous use of NSAIDs			
Yes	6/149 (3.0)	6/168 (2.4)	1.24 (0.40–3.85)
No	9/343 (1.9)	38/324 (9.2)	0.21 (0.10–0.44)
Use of an antiplatelet drug			
Yes	9/260 (2.5)	18/269 (4.8)	0.54 (0.24–1.21)
No	6/232 (1.9)	26/223 (9.1)	0.21 (0.08–0.50)
Frailty category			
Robust or prefrail	6/289 (1.5)	22/253 (6.1)	0.24 (0.10–0.59)
Frail	6/185 (2.5)	20/217 (7.1)	0.35 (0.14–0.87)

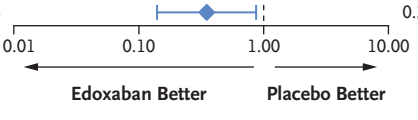

Figure 3. Primary Efficacy End Point in Selected Subgroups.

The primary efficacy end point was the composite of stroke or systemic embolism. $CHADS_2$ scores range from 0 to 6, with higher scores indicating a greater risk of stroke; previous stroke or transient ischemic attack is assigned 2 points, and congestive heart failure, hypertension, diabetes, and an age of 75 years or older are each assigned 1 point toward the total score. HAS-BLED scores range from 0 to 9, with higher scores indicating a greater risk of bleeding; abnormal renal or liver function are assigned 1 point each; the use of antiplatelet or nonsteroidal antiinflammatory drugs or alcohol concomitantly are assigned 1 point each (for a total of 1 or 2 points), and hypertension, stroke, history of bleeding or a predisposition to bleeding, labile international normalized ratio, and elderly age (>65 years) are each assigned 1 point toward the total score. Severe renal impairment was defined as a creatinine clearance of less than 30 ml per minute. History of bleeding was defined as bleeding from a critical area or organ or gastrointestinal bleeding. Among patients who were using nonsteroidal antiinflammatory drugs (NSAIDs), 133 of 149 of those in the edoxaban group and 157 of 168 of those in the placebo group used low-dose aspirin; after exclusion of these patients, the number of events was 0 in the edoxaban group and 1 in the placebo group. Frailty was assessed with the use of five measures of physical condition; a score of 0 indicated robust, a score of 1 or 2 indicated prefrail, and a score of 3 or higher indicated frail.[13,14] The widths of the confidence intervals were not adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.

and bleeding, we used a placebo as the control. We did not use an antiplatelet drug as a comparator because in previous studies, aspirin was ineffective for the prevention of stroke in patients with atrial fibrillation and was not recommended in patients at high risk for stroke.[25-27]

The annualized rate of stroke or systemic embolism with the 15-mg dose of edoxaban in the current trial (2.3%) was similar to that of the 60-mg and 30-mg dose regimens of edoxaban (2.5% and 2.8%, respectively) and with that of warfarin (2.9%) in the ENGAGE AF-TIMI 48 trial among patients who were 80 years of age or older, even though that trial included patients with lower risk than that of patients in the current trial (Table S10).[9] The annualized rates of major bleeding (3.3%) and intracranial hemorrhage (0.3%) among patients in the current trial who received 15 mg of edoxaban were similar to those among patients 80 years of age or older in the ENGAGE AF-TIMI 48 trial who received a 30-mg regimen of edoxaban (annualized rate of major bleeding, 2.6%; annualized rate of intracranial hemorrhage, 0.5%) and lower than the rates among patients 80 years of age or older in the warfarin group (6.2% and 1.6%, respectively).[9] In a previous study, elderly Japanese patients with atrial fibrillation (mean age, 81 years) with low creatinine clearance (15 to 30 ml per minute) who received a once-daily 15-mg dose of edoxaban had plasma concentrations of edoxaban that were similar to those in patients with a creatinine clearance of 50 ml per minute or higher who received 30-mg or 60-mg doses.[28] These results may partly explain the similarity of the efficacy and safety results between patients who received 15 mg of edoxaban in this trial and those who received 60-mg and 30-mg doses in the ENGAGE AF-TIMI 48 trial.

Some limitations of this trial should be noted. Because of their high-risk backgrounds, a substantial number of patients discontinued the trial. However, no patients were lost to follow-up, and only six withdrew consent because of bleeding-related concerns. Most patients who withdrew did so because of adverse events unrelated to bleeding or because they were no longer capable of participation. A separate analysis that took into account the potential that discontinuation of follow-up influenced the results showed similar results to those of the primary analysis. This trial involved Japanese patients with atrial fibrillation, and therefore the results may not be applicable to other populations; East Asian patients with atrial fibrillation who were treated with the lower-dose regimen of edoxaban (30 mg in patients who did not have their dose reduced and 15 mg in patients who had their dose reduced) in the ENGAGE AF-TIMI 48 trial had higher rates of stroke or systemic embolism and higher rates of overt bleeding of any kind (major bleeding, clinically relevant nonmajor bleeding, or minor bleeding) than patients who were not East Asian.[29]

In very elderly Japanese patients with nonvalvular atrial fibrillation who were not appropriate candidates for a standard oral anticoagulation regimen, a once-daily 15-mg dose of edoxaban was superior to placebo in preventing stroke or systemic embolism and did not result in a significantly higher incidence of major bleeding than placebo.

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APPENDIX

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