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Effect of 15-mg Edoxaban on Clinical Outcomes in 3 Age Strata in Older Patients With Atrial Fibrillation

A Prespecified Subanalysis of the ELDERCARE–AF Randomized Clinical Trial

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IMPORTANCE Long-term use of oral anticoagulants (OACs) is necessary for stroke prevention in patients with atrial fibrillation (AF). The effectiveness and safety of OACs in extremely older patients (ie, aged 80 years or older) with AF and at high risk of bleeding needs to be elucidated.

OBJECTIVE To examine the effects of very low-dose edoxaban (15 mg) vs placebo across 3 age strata (80-84 years, 85-89 years, and ≥90 years) among patients with AF who were a part of the Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients (ELDERCARE-AF) trial.

DESIGN, SETTING, AND PARTICIPANTS This prespecified subanalysis of a phase 3, randomized, double-blind, placebo-controlled trial was conducted from August 5, 2016, to December 27, 2019. Patients with AF aged 80 years or older who were not considered candidates for standard-dose OACs were included in the study; reasons these patients could not take standard-dose OACs included low creatinine clearance (<30 mL per minute), low body weight (≤45 kg), history of bleeding from critical organs, continuous use of nonsteroidal anti-inflammatory drugs, or concomitant use of antiplatelet drugs. Eligible patients were recruited randomly from 164 hospitals in Japan and were randomly assigned 1:1 to edoxaban or placebo.

INTERVENTIONS Edoxaban (15 mg once daily) or placebo.

MAIN OUTCOMES AND MEASURES The primary efficacy end point was the composite of stroke or systemic embolism. The primary safety end point was International Society on Thrombosis and Hemostasis–defined major bleeding.

RESULTS A total of 984 patients (mean [SD] age: age group 80-84 years, 82.2 [1.4] years; age group 85-89 years, 86.8 [1.4] years; age group ≥90 years, 92.3 [2.1] years; 565 women [57.4%]) were included in this study. In the placebo group, estimated (SE) event rates for stroke or systemic embolism increased with age and were 3.9% (1.2%) per patient-year in the group aged 80 to 84 years (n = 181), 7.3% (1.7%) per patient-year in the group aged 85 to 89 years (n = 184), and 10.1% (2.5%) per patient-year in the group aged 90 years or older (n = 127). A 15-mg dose of edoxaban consistently decreased the event rates for stroke or systemic embolism with no interaction with age (80-84 years, hazard ratio [HR], 0.41; 95% CI, 0.13-1.31; P = .13; 85-89 years, HR, 0.42; 95% CI, 0.17-0.99; P = .05; ≥90 years, HR, 0.23; 95% CI, 0.08-0.68; P = .008; interaction P = .65). Major bleeding and major or clinically relevant nonmajor bleeding events were numerically higher with edoxaban, but the differences did not reach statistical significance, and there was no interaction with age. There was no difference in the event rate for all-cause death between the edoxaban and placebo groups in all age strata.

CONCLUSIONS AND RELEVANCE Results of this subanalysis of the ELDERCARE–AF randomized clinical trial revealed that among Japanese patients aged 80 years or older with AF who were not considered candidates for standard OACs, a once-daily 15-mg dose of edoxaban was superior to placebo in preventing stroke or systemic embolism consistently across all 3 age strata, including those aged 90 years or older, albeit with a higher but nonstatistically significant incidence of bleeding.

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Supplemental content

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The prevalence of atrial fibrillation (AF) increases with age, and AF and age are both independent risk factors for stroke.[1,2] To prevent cardioembolic stroke in patients with AF, clinical guidelines recommend using direct oral anticoagulants (DOACs), even in older patients.[3,4] However, evidence on the use of DOACs in extremely older patients is lacking, and many physicians remain reluctant to prescribe standard doses of DOACs to extremely older patients owing to risk factors for bleeding in this patient group, such as severe kidney impairment, history of bleeding, previous falls, polypharmacy, and frailty.[5-7]

The Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients (ELDERCARE-AF) trial was a randomized clinical trial in which the effect of a once-daily 15-mg dose of edoxaban vs placebo on the primary efficacy end point of stroke or systemic embolism was investigated in older Japanese patients (≥80 years) with AF who were not considered candidates for a standard OAC regimen.[8] Edoxaban was found to be superior to placebo in reducing the incidence of stroke or systemic embolism. In contrast, the incidence of major bleeding was higher with edoxaban vs placebo; however, this difference was not statistically significant. Of major bleeding events, the incidence of gastrointestinal bleeding was higher with edoxaban vs placebo. Although there was no influence of age (≤85 and >85 years) on the effect of edoxaban on stroke or systemic embolism, it remains unclear whether the effects of edoxaban are consistent even in extremely older patients, such as those 90 years or older.

The present subanalysis of the ELDERCARE-AF trial was conducted to (1) explore the risk of stroke or systemic embolism and major bleeding in the prespecified 3 age strata among older patients with AF in the ELDERCARE-AF trial (≥80 years) and (2) explore the effect of edoxaban 15-mg treatment vs placebo in the 3 age strata.

Key Points

Question Is very low-dose edoxaban (15 mg daily) beneficial among Japanese patients aged 80 to 84 years, 85 to 89 years, and 90 years or older who are not considered candidates for standard-dose oral anticoagulants because of high bleeding risk?

Findings In this prespecified subanalysis of the randomized clinical trial Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients (ELDERCARE-AF) of 984 patients, results showed that very low-dose edoxaban reduced the incidence of stroke or systemic embolism consistently across these 3 age strata, with a numerically higher risk of major or clinically relevant nonmajor bleeding that did not reach statistical significance.

Meaning Very low-dose edoxaban may be considered for reduction of stroke or systemic embolism in older Japanese patients with AF who are at high risk of bleeding.

Methods

Study Design

This was a subanalysis of the ELDERCARE-AF trial. ELDERCARE-AF was a phase 3, multicenter, double-blind, randomized, placebo-controlled, event-driven, superiority study conducted from August 5, 2016, to December 27, 2019.[8,9] Eligible patients were randomized to treatment with edoxaban (15 mg once daily) or placebo in a 1:1 ratio. The ELDERCARE-AF trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The institutional review board at each participating site approved the study. All participants provided written informed consent. The ELDERCARE-AF trial was registered at ClinicalTrials.gov.[10] This study followed Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines. More information on the trial protocol is available in Supplement 1.

Patients

Patients were included in the study if they were aged 80 years or older, had a history of AF documented within 1 year of consent, and had congestive heart failure, hypertension, age (≥75 years), diabetes, previous stroke or transient ischemic attack ($CHADS_2$) score of 2 points or greater. All patients were Japanese. Patients had to be considered ineligible for OACs (warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) at the recommended therapeutic strength (warfarin) or the approved doses for 1 or more of the following reasons: low creatinine clearance (15-30 mL per minute), history of bleeding from a critical area/organ or gastrointestinal bleeding, low body weight (≤45 kg), continuous use of nonsteroidal anti-inflammatory drugs (NSAIDs), and current use of an antiplatelet drug. Patients with moderate-severe mitral stenosis and/or mechanical heart valves were excluded.

Efficacy and Safety End Points

The primary efficacy end point was the composite of stroke or systemic embolism, and the primary safety end point was International Society on Thrombosis and Hemostasis-defined major bleeding. The net clinical outcome was defined as the composite of stroke, systemic embolism, major bleeding, or death from any cause. Secondary efficacy and safety end points have been defined previously.[8]

Statistical Analysis

The target sample size was 800 patients (400 in each group); sample size calculations have been published previously.[8] The primary efficacy analysis was performed in the intent-to-treat population. The safety analysis was performed in the safety analysis set (all patients who received ≥1 dose of the trial drug). This subanalysis was prespecified to evaluate patients in the ELDERCARE-AF trial according to age at baseline. Patients were divided into 3 strata according to age (80-84 years, 85-89 years, and ≥90 years).

Patient demographic and clinical characteristics are described using distributions and summary statistics. Continuous variables are reported as means and SD.

The time to first event of stroke or systemic embolism was analyzed using a Cox proportional hazards model by treatment group; $CHADS_2$ score (2 or ≥3 points) was used as a covariate, with a 2-sided significance level of 5%. Relative risk was estimated using hazard ratios (HRs) with 95% CIs. The

same method was used to analyze the secondary efficacy end points. The cumulative incidence of efficacy events was estimated by treatment group using Kaplan-Meier analysis. Bleeding events are summarized by group and were analyzed for the on-treatment period, which included the treatment period and up to 3 days after the last dose of the study drug or the end of the study. Absolute risk reduction of efficacy and safety end points between treatment groups was estimated.

The effect of age as a categorical and/or continuous variable on the efficacy and safety outcomes was evaluated using a Cox proportional hazards model. The following baseline characteristics were included in the multivariate model as adjustment factors: sex, type of AF, coronary artery disease, dementia, history of falling within the past year, frailty, congestive heart failure, all forms of diabetes, hypertension, previous stroke or transient ischemic attack, history of OAC therapy, history of bleeding, low body weight (≤45 kg), continuous use of NSAIDs, use of an antiplatelet drug, and kidney function based on creatinine clearance. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute).

Results

Patients

In total, 1086 patients were enrolled, and 984 patients were randomly assigned (492 patients in the edoxaban group, 492 patients in the placebo group) and categorized into subgroups by age (354 patients [36.0%] in the group aged 80-84 years, 374 [38.0%] in the group aged 85-89 years, 256 [26.0%] in the group aged ≥90 years). Mean (SD) age for each group was as follows: age group 80 to 84 years, 82.2 (1.4) years; age group 85 to 89 years, 86.8 (1.4) years; age group 90 years or older, 92.3 (2.1) years. A total of 419 men (42.6%) and 565 women (57.4%) were included in the study. **Table 1** shows the baseline patient characteristics by age subgroups.[11,12] The proportion of male patients showed a tendency to decrease with increasing age. Body mass index (calculated as weight in kilograms divided by height in meters squared); creatinine clearance; prevalence of dyslipidemia and diabetes; hypertension, abnormal liver/kidney function, stroke history, bleeding history or predisposition, labile international normalized ratios, elderly (>65 years), drug/alcohol usage (HAS-BLED) score; continuous use of NSAIDs; and use of an antiplatelet drug decreased significantly with age. The prevalence of congestive heart failure, severe kidney impairment, and frail status increased significantly with age.

Effects of Edoxaban on Major Outcomes by Age Subgroups

Baseline patient characteristics in the edoxaban and placebo groups by age subgroups are shown in **Table 2**. There were no differences in the characteristics in each age subgroup between the edoxaban and placebo groups.

Stroke or Systemic Embolism

In the placebo group, stroke or systemic embolism occurred in 10 of 181 patients (estimated [SE] event rate, 3.9% [1.2%] per patient-year) in the group aged 80 to 84 years, 18 of 184 patients (7.3% [1.7%] per patient-year) in the group aged 85 to 89 years, and 16 of 127 patients (10.1% [2.5%] per patient-year) in the group 90 years or older (eTable in Supplement 2). The incidence of stroke or embolism increased with patient age, but there was no statistical difference after adjustment by the baseline characteristics. In the edoxaban group, stroke or systemic embolism occurred in 4 of 173 patients (estimated [SE] event rate, 1.6% [0.8%] per patient-year) in the group aged 80 to 84 years, 7 of 190 patients (2.8% [1.1%] per patient-year) in the group aged 85 to 89 years, and 4 of 129 patients (2.4% [1.2%] per patient-year) in the group 90 years or older. The incidences were all lower in the edoxaban vs placebo group, and there was no interaction with age (80-84 years, HR, 0.41; 95% CI, 0.13-1.31; P = .13; 85-89 years, HR, 0.42; 95% CI, 0.17-0.99; P = .05; ≥90 years, HR, 0.23; 95% CI, 0.08-0.68; P = .008; interaction P = .65) (**Figure 1**).

Major Bleeding

In the placebo group, major bleeding occurred in 1 of 180 patients (0.4% per patient-year) in the group aged 80 to 84 years, 7 of 183 patients (3.0% per patient-year) in the group aged 85 to 89 years, and 3 of 127 patients (2.1% per patient-year) in the group 90 years or older in the safety analysis set (eTable in Supplement 2). In the edoxaban group, major bleeding occurred in 5 of 173 patients (2.2% per patient-year) in the group aged 80 to 84 years, 5 of 190 patients (2.2% per patient-year) in the group aged 85 to 89 years, and 10 of 129 patients (6.5% per patient-year) in the group 90 years or older in the 3 age strata. There was no interaction with age in the incidence of major bleeding (80-84 years, HR, 5.27; 95% CI, 0.61-45.36; P = .13; 85-89 years, HR, 0.74; 95% CI, 0.24-2.33; P = .61; ≥90 years, HR, 3.02; 95% CI, 0.82-11.21; P = .10; interaction P = .15) (**Figure 2**).

Of major bleeding events, the incidences of gastrointestinal bleeding in the placebo and edoxaban groups were 0 of 180 events (0% per patient-year) and 3 of 173 (1.3% per patient-year), respectively, in the group aged 80 to 84 years, and 4 of 183 events (1.7% per patient-year) and 2 of 190 events (0.9% per patient-year), respectively, in the group aged 85 to 89 years, whereas they were 1 of 127 events (0.7% per patient-year) and 9 of 129 events (5.9% per patient-year), respectively, in the group 90 years or older (HR, 8.37; 95% CI, 1.04-67.07; P = .05).

All-Cause Death and Other Bleeding Events

In both placebo and edoxaban groups, the incidence of all-cause death increased with age, and there was no difference between the edoxaban and placebo groups in all age subgroups (80-84 years, HR, 1.28; 95% CI, 0.62-2.67; P = .50; 85-89 years, HR, 0.91; 95% CI, 0.53-1.53; P = .71; ≥90 years, HR, 0.86; 95% CI, 0.49-1.51; P = .60; interaction P = .65) (Figure 1). The incidences of major or clinically relevant nonmajor bleeding (80-84 years, HR, 1.64; 95% CI, 0.90-2.97; P = .10; 85-89 years, HR, 1.63; 95% CI, 0.96-2.77; P = .07; ≥90 years, HR, 1.57; 95% CI, 0.93-2.67; P = .09; interaction P > .99) and clinically relevant nonmajor bleeding (80-84 years, HR, 1.47; 95% CI, 0.79-2.74; P =.23; 85-89 years, HR, 2.00; 95% CI, 1.10-3.64; P = .02; ≥90 years, HR, 1.35; 95% CI, 0.75-2.41; P = .32; interaction P = .64) were both higher in the edoxaban group than in the

Table 1. Baseline Patient Characteristics by Age Subgroups

Characteristic	No. (%)		
	Age 80-84 y (n = 354)	Age 85-89 y (n = 374)	Age ≥90 y (n = 256)
Age, mean (SD), y	82.2 (1.4)	86.8 (1.4)	92.3 (2.1)
Sex			
Male	182 (51.4)	171 (45.7)	66 (25.8)
Female	172 (48.6)	203 (54.3)	190 (74.2)
Paroxysmal atrial fibrillation	179 (50.6)	172 (46.0)	112 (43.8)
Weight, mean (SD), kg	53.9 (11.0)	50.9 (10.6)	45.4 (9.5)
BMI, mean (SD)[a,b]	22.7 (3.7)	22.2 (3.8)	21.2 (3.4)
Creatinine clearance			
Mean (SD), mL/min	42.8 (16.1)	35.5 (12.8)	28.6 (8.9)
Category			
≤50 mL/min	247 (69.8)	325 (86.9)	251 (98.0)
>50 mL/min	107 (30.2)	49 (13.1)	5 (2.0)
Coronary artery disease	93 (26.3)	103 (27.5)	61 (23.8)
Dementia	35 (9.9)	60 (16.0)	65 (25.4)
Dyslipidemia	189 (53.4)	175 (46.8)	86 (33.6)
History of falling within past year	117 (33.1)	132 (35.3)	91 (35.5)
$CHADS_2$ score[c]			
Mean score (SD)	3.1 (1.1)	3.1 (1.1)	3.1 (1.1)
Category			
2	146 (41.2)	129 (34.5)	88 (34.4)
≥3	208 (58.8)	245 (65.5)	168 (65.6)
Components			
Congestive heart failure	158 (44.6)	207 (55.3)	168 (65.6)
Hypertension	302 (85.3)	309 (82.6)	199 (77.7)
Age ≥75 y	354 (100)	374 (100)	256 (100)
Diabetes	98 (27.7)	91 (24.3)	36 (14.1)
Previous stroke or TIA	85 (24.0)	88 (23.5)	63 (24.6)
CHA_2DS_2-VASc score, mean (SD)[d]	4.8 (1.3)	4.9 (1.2)	5.0 (1.2)
HAS-BLED score, mean (SD)[e]	2.4 (0.8)	2.3 (0.9)	2.2 (0.9)
Reasons for oral anticoagulant ineligibility			
Severe kidney impairment (creatinine clearance <30 mL/min)	90 (25.4)	146 (39.0)	167 (65.2)
History of bleeding from critical area or organ	89 (25.1)	85 (22.7)	48 (18.8)
Intracranial	36 (10.2)	28 (7.5)	16 (6.3)
Gastrointestinal	47 (13.3)	50 (13.4)	30 (11.7)
Intraocular	2 (0.6)	5 (1.3)	0 (0.0)
Other[f]	7 (2.0)	4 (1.1)	3 (1.2)
Low body weight (≤45 kg)	96 (27.1)	136 (36.4)	142 (55.5)
Continuous use of NSAIDs	129 (36.4)	122 (32.6)	66 (25.8)
Use of an antiplatelet drug	211 (59.6)	211 (56.4)	107 (41.8)
Aspirin	119 (33.6)	113 (30.2)	59 (23.0)
Clopidogrel	50 (14.1)	55 (14.7)	29 (11.3)
Other[g]	42 (11.9)	45 (12.0)	20 (7.8)
Frailty category[h]			
Robust	39 (11.0)	16 (4.3)	6 (2.3)
Prefrail	185 (52.3)	188 (50.3)	108 (42.2)
Frail	117 (33.1)	153 (40.9)	132 (51.6)
Could not be evaluated	6 (1.7)	7 (1.9)	4 (1.6)
Missing data	7 (2.0)	10 (2.7)	6 (2.3)

(continued)

Table 1. Baseline Patient Characteristics by Age Subgroups (continued)

Characteristic	No. (%)		
	Age 80-84 y (n = 354)	Age 85-89 y (n = 374)	Age ≥90 y (n = 256)
History of oral anticoagulant therapy			
Yes	159 (44.9)	156 (41.7)	108 (42.2)
Warfarin	94 (26.6)	91 (24.3)	58 (22.7)
Direct oral anticoagulants[i]	95 (26.8)	92 (24.6)	64 (25.0)
Unknown	1 (0.3)	0 (0.0)	2 (0.8)

Abbreviations: BMI, body mass index; $CHADS_2$, congestive heart failure, hypertension, age, diabetes, previous stroke or transient ischemic attack (2 points); CHA_2DS_2-VASc, congestive heart failure, hypertension, age (older than 65 year = 1 point, older than 75 years = 2 points), diabetes, previous stroke or transient ischemic attack (2 points), vascular disease, age 65 to 74 years, sex category; HAS-BLED, hypertension, abnormal liver or kidney function, stroke history, bleeding history or predisposition, labile international normalized ratios, elderly, drug/alcohol usage; NSAID, nonsteroidal anti-inflammatory drug; TIA, transient ischemic attack.

[a] Data were missing for 1 patient in each group.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] $CHADS_2$ scores ranged from 0 to 6 points, with higher scores indicating a greater risk of stroke. Previous stroke or TIA was assigned 2 points, and congestive heart failure, hypertension, diabetes, and age 75 years or older were each assigned 1 point toward the total score.

[d] CHA_2DS_2-VASc scores ranged from 0 to 9 points, with higher scores indicating a greater risk of stroke. Previous stroke or TIA and age 75 years or older were each assigned 2 points, and congestive heart failure, hypertension, diabetes, age of 65 to 74 years, female sex, and history of vascular disease were each assigned 1 point toward the total score.

[e] HAS-BLED scores ranged from 0 to 9 points, with higher scores indicating a greater risk of bleeding. Abnormal kidney or liver function were assigned 1 point each; the use of antiplatelets or NSAIDs or alcohol concomitantly were 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 older age (>65 years) were each assigned 1 point toward the total score.

[f] Other category includes bladder, hemoperitoneum, intra-articular of right knee, left retroperitoneal hematoma, lung, pericardiac space, pulmonary alveolar hemorrhage, right iliopsoas, and shoulder joint.

[g] Other includes beraprost, cilostazol, dilazep, dipyridamole, ethyl icosaphentate, limaprost alfadex, prasugrel, sarpogrelate, and ticlopidine.

[h] Frailty was assessed using 5 measures of physical condition; a score of 0 indicated robust, a score of 1 or 2 indicated pre-frail, and a score of 3 or higher indicated frail.[11,12]

[i] Direct oral anticoagulants included dabigatran, rivaroxaban, apixaban, and edoxaban.

placebo group, and there was no interaction with age (Figure 2). Also, there was no interaction with age in the incidences of minor bleeding and all bleeding between the placebo and edoxaban groups. There was no fatal bleeding in the edoxaban group.

Discussion

The present subanalysis of the randomized clinical trial ELDERCARE-AF showed that among older patients with AF aged 80 years or older (1) the incidence of stroke or systemic embolism was higher in the older-age strata; (2) 15-mg edoxaban reduced the incidence of stroke or systemic embolism compared with placebo consistently across the 3 age strata; and (3) the incidences of major or clinically relevant nonmajor bleeding and clinically relevant nonmajor bleeding were numerically higher in the edoxaban group than in the placebo group without an interaction with age.

A previous observational study reported that the overall annual incidence of ischemic stroke among Chinese patients with AF aged 80 years or older was as high as 11.3% per patient-year.[13] A prespecified analysis of the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial on edoxaban vs warfarin for the subgroups aged younger than 65 years, 65 to 74 years, and 75 years or older showed that the annual rates of major efficacy and safety outcomes in the edoxaban and warfarin groups increased with age.[14] Moreover, a post hoc analysis of extremely older patients aged 80 years or older and 85 years or older showed a higher incidence of both stroke and bleeding events with increasing age. A post hoc analysis of the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial on dabigatran vs warfarin for the subgroups aged younger than 75 years, 75 to 79 years, 80 to 84 years, and 85 years or older showed that the event rates for stroke or systemic embolism in the warfarin-treated group increased with advancing age, and those of major bleeding increased with age in both the warfarin- and dabigatran-treated groups.[15] In the present prespecified subanalysis of the ELDERCARE-AF trial for the groups aged 80 to 84 years, 85 to 89 years, and 90 years or older, we found a higher risk of thromboembolism in the older age group in the placebo group treated with no OACs. After adjusting for potential confounders, however, no statistically significant correlation was found between the age and thromboembolic incidence (eTable in Supplement 2). Older age encompasses various risk factors for stroke and bleeding, such as kidney dysfunction, low body weight, multiple comorbidities, polypharmacy, frailty, and others. Although the advancing age may represent a simple indicator for adverse outcomes, not chronological but biological age may matter.[16] The Fushimi AF registry reported that extremely older Japanese patients with AF (n = 479, ≥85 years) had a higher incidence of stroke but similar major bleeding risks than the younger population with AF.[17] Interestingly, the incidence of stroke or systemic embolism was higher in extremely older patients taking OACs, most of which was warfarin, than those not taking OACs. This paradoxical finding may be explained by lower levels of warfarin control and unidentified risk factors. Using the National Health Insurance Research Database, a Taiwan nationwide cohort study reported that among patients with AF who were 90 years of age or older, warfarin was associated with a lower risk of

Table 2. Baseline Patient Characteristics in Edoxaban and Placebo Groups by Age Subgroups

Characteristic	No. (%)					
	Edoxaban 15 mg			Placebo		
	Age 80-84 y (n = 173)	Age 85-89 y (n = 190)	Age ≥90 y (n = 129)	Age 80-84 y (n = 181)	Age 85-89 y (n = 184)	Age ≥90 y (n = 127)
Age, mean (SD), y	82.3 (1.5)	86.8 (1.4)	92.3 (2.2)	82.1 (1.4)	86.7 (1.4)	92.3 (2.1)
Sex						
Male	93 (53.8)	82 (43.2)	37 (28.7)	89 (49.2)	89 (48.4)	29 (22.8)
Female	80 (46.2)	108 (56.8)	92 (71.3)	92 (50.8)	95 (51.6)	98 (77.2)
Paroxysmal atrial fibrillation	91 (52.6)	92 (48.4)	54 (41.9)	88 (48.6)	80 (43.5)	58 (45.7)
Weight, mean (SD), kg	53.6 (10.5)	51.0 (11.0)	46.0 (9.5)	54.3 (11.5)	50.9 (10.2)	44.8 (9.4)
Creatinine clearance, mean (SD), mL/min	42.6 (16.7)	35.6 (12.4)	29.1 (8.6)	43.0 (15.6)	35.3 (13.2)	28.0 (9.2)
Coronary artery disease	47 (27.2)	53 (27.9)	30 (23.3)	46 (25.4)	50 (27.2)	31 (24.4)
Dementia	14 (8.1)	33 (17.4)	23 (17.8)	21 (11.6)	27 (14.7)	42 (33.1)
History of falling within past year	57 (32.9)	54 (28.4)	43 (33.3)	60 (33.1)	78 (42.4)	48 (37.8)
$CHADS_2$ score, mean (SD)[a]	3.0 (1.1)	3.1 (1.1)	3.1 (1.0)	3.1 (1.2)	3.1 (1.1)	3.1 (1.2)
CHA_2DS_2-VASc score, mean (SD)[b]	4.7 (1.3)	4.9 (1.3)	5.0 (1.1)	4.9 (1.4)	4.9 (1.2)	5.1 (1.3)
HAS-BLED score, mean (SD)[c]	2.4 (0.8)	2.3 (0.9)	2.1 (0.9)	2.4 (0.9)	2.4 (0.9)	2.3 (1.0)
Reasons for oral anticoagulant ineligibility						
Creatinine clearance, <30 mL/min	45 (26.0)	72 (37.9)	81 (62.8)	45 (24.9)	74 (40.2)	86 (67.7)
History of bleeding from critical area	43 (24.9)	39 (20.5)	28 (21.7)	46 (25.4)	46 (25.0)	20 (15.7)
Low body weight, ≤45 kg	52 (30.1)	71 (37.4)	65 (50.4)	44 (24.3)	65 (35.3)	77 (60.6)
Continuous use of NSAIDs	58 (33.5)	62 (32.6)	29 (22.5)	71 (39.2)	60 (32.6)	37 (29.1)
Use of an antiplatelet drug	100 (57.8)	114 (60.0)	46 (35.7)	111 (61.3)	97 (52.7)	61 (48.0)
Frailty category[d]						
Robust	21 (12.1)	7 (3.7)	4 (3.1)	18 (9.9)	9 (4.9)	2 (1.6)
Prefrail	97 (56.1)	98 (51.6)	62 (48.1)	88 (48.6)	90 (48.9)	46 (36.2)
Frail	50 (28.9)	75 (39.5)	60 (46.5)	67 (37.0)	78 (42.4)	72 (56.7)
Could not be evaluated	1 (0.6)	4 (2.1)	2 (1.6)	5 (2.8)	3 (1.6)	2 (1.6)
Missing data	4 (2.3)	6 (3.2)	1 (0.8)	3 (1.7)	4 (2.2)	5 (3.9)
History of oral anticoagulant therapy	80 (46.2)	72 (37.9)	55 (42.6)	79 (43.6)	84 (45.7)	53 (41.7)

Abbreviations: $CHADS_2$, congestive heart failure, hypertension, age, diabetes, previous stroke or transient ischemic attack (2 points); CHA_2DS_2-VASc, congestive heart failure, hypertension, age (older than 65 year = 1 point, older than 75 years = 2 points), diabetes, previous stroke or transient ischemic attack (2 points), vascular disease, age 65 to 74 years, sex category; HAS-BLED, hypertension, abnormal liver or kidney function, stroke history, bleeding history or predisposition, labile international normalized ratios, elderly, drug/alcohol usage; NSAID, nonsteroidal anti-inflammatory drug.

[a] $CHADS_2$ scores ranged from 0 to 6 points, with higher scores indicating a greater risk of stroke. Previous stroke or transient ischemic attack was assigned 2 points, and congestive heart failure, hypertension, diabetes, and age 75 years or older were each assigned 1 point toward the total score.

[b] CHA_2DS_2-VASc scores ranged from 0 to 9 points, with higher scores indicating a greater risk of stroke. Previous stroke or transient ischemic attack and age 75 years or older were each assigned 2 points, and congestive heart failure, hypertension, diabetes, age of 65 to 74 years, female sex, and history of vascular disease were each assigned 1 point toward the total score.

[c] HAS-BLED scores ranged from 0 to 9 points, with higher scores indicating a greater risk of bleeding. Abnormal kidney or liver function were assigned 1 point each; the use of antiplatelets or NSAIDs or alcohol concomitantly were 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 older age (>65 years) were each assigned 1 point toward the total score.

[d] Frailty was assessed using 5 measures of physical condition; a score of 0 indicated robust, a score of 1 or 2 indicated pre-frail, and a score of 3 or higher indicated frail.[11,12]

ischemic stroke and positive net clinical benefit.[18] It was estimated that OACs may still be effective for thromboprophylaxis in extremely older patients.

One of the main features of the present ELDERCARE-AF trial is its study design: a double-blind, randomized, placebo-controlled trial. Because of the absence of a standard of care for older patients with AF who are not considered candidates for a standard OAC regimen owing to their high bleeding risk, placebo was selected as a comparator with 15-mg edoxaban. The results showed that 15-mg edoxaban significantly reduced the incidence of stroke or systemic embolism compared with placebo,[8] and furthermore, the efficacy was consistent across the prespecified 3 age strata including patients aged 90 years or older. The subanalysis or post hoc analysis of the previous DOAC trials showed the consistent efficacies of the drugs to warfarin regardless of age.[14-16,19] It is worth noting that the baseline patient characteristics in these trials were different from those in the ELDERCARE-AF trial in which only

Figure 1. Effects of Edoxaban on Major Outcomes by Age Subgroups, Efficacy End Points

Subgroup by age, y	No. of patients with event/total No. of patients (event rate, %/y) Edoxaban 15 mg	Placebo	Absolute risk reduction % (95% CI)	Hazard ratio (95% CI)	Interaction *P* value
Stroke or systemic embolism					
80-84	4/173 (1.6)	10/181 (3.9)	3.2 (-1.4 to 7.8)	0.41 (0.13 to 1.31)	
85-89	7/190 (2.8)	18/184 (7.3)	6.1 (0.5 to 11.7)	0.42 (0.17 to 0.99)	.65
≥90	4/129 (2.4)	16/127 (10.1)	9.5 (2.2 to 16.8)	0.23 (0.08 to 0.68)	
Net clinical outcome					
80-84	25/173 (10.5)	21/181 (8.2)	-2.8 (-10.4 to 4.7)	1.26 (0.71 to 2.25)	
85-89	30/190 (12.2)	47/184 (19.2)	9.8 (1.1 to 18.4)	0.66 (0.42 to 1.05)	.23
≥90	32/129 (19.6)	35/127 (22.1)	2.8 (-8.8 to 14.3)	0.88 (0.54 to 1.42)	
All-cause death					
80-84	16/173 (6.4)	13/181 (5.0)	-2.1 (-8.4 to 4.2)	1.28 (0.62 to 2.67)	
85-89	26/190 (10.3)	30/184 (11.8)	2.6 (-5.2 to 10.4)	0.91 (0.53 to 1.53)	.65
≥90	24/129 (14.2)	26/127 (16.2)	1.9 (-8.6 to 12.4)	0.86 (0.49 to 1.51)	

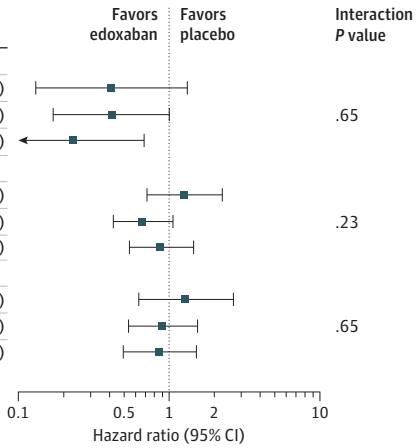
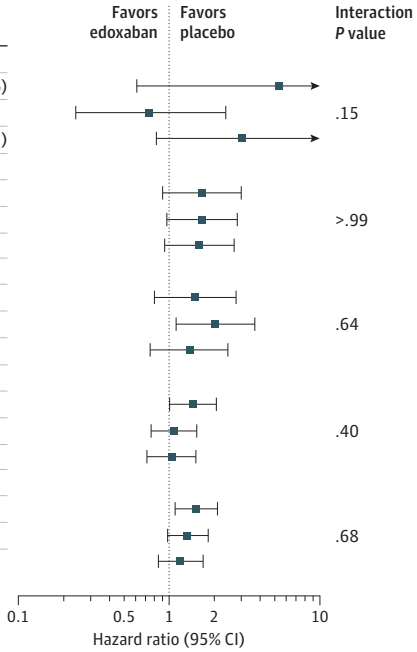


Figure 2. Effects of Edoxaban on Major Outcomes by Age Subgroups, Safety End Points

Subgroup by age, y	No. of patients with event/total No. of patients (event rate, %/y) Edoxaban 15 mg	Placebo	Absolute risk increase % (95% CI)	Hazard ratio (95% CI)	Interaction *P* value
Major bleeding					
80-84	5/173 (2.2)	1/180 (0.4)	2.3 (-1.0 to 5.6)	5.27 (0.61 to 45.36)	
85-89	5/190 (2.2)	7/183 (3.0)	-1.2 (-5.3 to 2.9)	0.74 (0.24 to 2.33)	.15
≥90	10/129 (6.5)	3/127 (2.1)	5.4 (-0.7 to 11.5)	3.02 (0.82 to 11.21)	
Major or clinically relevant nonmajor bleeding					
80-84	27/173 (13.0)	18/180 (7.8)	5.6 (-1.9 to 13.1)	1.64 (0.90 to 2.97)	
85-89	34/190 (16.8)	22/183 (10.2)	5.9 (-1.9 to 13.6)	1.63 (0.96 to 2.77)	>.99
≥90	36/129 (26.0)	22/127 (16.2)	10.6 (-0.4 to 21.5)	1.57 (0.93 to 2.67)	
Clinically relevant nonmajor bleeding					
80-84	23/173 (11.0)	17/180 (7.4)	3.9 (-3.3 to 11.0)	1.47 (0.79 to 2.74)	
85-89	31/190 (15.0)	16/183 (7.4)	7.6 (0.4 to 14.8)	2.00 (1.10 to 3.64)	.64
≥90	27/129 (19.2)	19/127 (14.0)	6.0 (-4.2 to 16.1)	1.35 (0.75 to 2.41)	
Minor bleeding					
80-84	67/173 (42.4)	55/180 (29.1)	8.2 (-2.3 to 18.6)	1.43 (1.00 to 2.03)	
85-89	67/190 (42.0)	68/183 (39.1)	-1.9 (-12.2 to 8.4)	1.07 (0.76 to 1.50)	.40
≥90	56/129 (55.5)	54/127 (51.9)	0.9 (-12.0 to 13.8)	1.03 (0.71 to 1.50)	
All bleeding					
80-84	81/173 (55.4)	65/180 (35.7)	10.7 (-0.1 to 21.5)	1.49 (1.08 to 2.06)	
85-89	86/190 (60.5)	75/183 (44.8)	4.3 (-6.3 to 14.9)	1.31 (0.97 to 1.79)	.68
≥90	74/129 (78.7)	62/127 (62.6)	8.5 (-4.4 to 21.5)	1.18 (0.84 to 1.66)	



the older patients with high risks of bleeding, such as severe kidney impairment, were enrolled. Thus, 15-mg edoxaban may be an effective treatment option even in extremely older patients who have additive bleeding risk factors. It should be reemphasized, however, that this trial involved only older Japanese patients with AF with a relatively low body weight and high risk of bleeding. Therefore, the results may not be applied to other ethnic populations.

Conversely, the patients treated with 15-mg edoxaban had a higher tendency toward major bleeding than those who received placebo without an interaction with age. It is noted that of the 13 major bleeding events occurring in the group aged 90 years or older, 10 were gastrointestinal bleeding, with 9 in the edoxaban group. Although there was no fatal bleeding in the edoxaban group, a careful attention to bleeding risk, especially to gastrointestinal bleeding, needs to be given when treating the extremely older patients with 15-mg edoxaban.

Limitations

This study had some limitations. A large proportion of patients discontinued the ELDERCARE-AF trial because of their high-risk status. However, no patients were lost to follow-up, and only 6 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 was conducted to evaluate whether patient discontinuation influenced the results; however, similar results to those of the primary analysis were obtained. The trial sample size was not powered for any subgroup analyses, and the event rates in the subgroups were low. Furthermore, this trial was conducted in older Japanese individuals with low body mass and a high risk for bleeding, limiting extrapolation of current findings to other elderly populations.

Conclusions

In this subanalysis of the ELDERCARE-AF randomized clinical trial, results showed that among Japanese patients 80 years or older with AF who were not considered candidates for standard OACs, a once-daily 15-mg edoxaban dose was superior to placebo in preventing stroke or systemic embolism consistently in all 3 age strata, including the nonagenarians, with a relatively higher incidence of major bleeding than placebo.

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