Outcomes and Safety of Very-Low-Dose Edoxaban in Frail Patients With Atrial Fibrillation in the ELDERCARE-AF Randomized Clinical Trial

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Abstract

IMPORTANCE The prevalence of atrial fibrillation (AF) increases with age and is more common in frail patients. However, data are lacking on outcomes of oral anticoagulants (OACs) in very elderly patients with AF with frailty, who are ineligible for standard anticoagulant treatment.

OBJECTIVE To compare very-low-dose edoxaban (15 mg daily) vs placebo across frailty status, including each of 5 frailty assessment parameters, among patients with AF involved in the ELDERCARE-AF (Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients) trial.

DESIGN, SETTING, AND PARTICIPANTS This is a cohort study using data from ELDERCARE-AF, a multicenter, randomized, double-blind, placebo-controlled phase 3 study of Japanese patients with AF aged 80 years or older who were ineligible for OACs at doses approved for stroke prevention because of their high bleeding risks. Eligible patients were randomly assigned (1:1) to receive edoxaban or placebo. The study duration was from August 5, 2016, to November 5, 2019, with the last patient followed up on December 27, 2019. Data analysis was performed from February 2021 to February 2022.

EXPOSURE Edoxaban (15 mg) once daily or placebo.

MAIN OUTCOMES AND MEASURES The primary efficacy end point was the composite of stroke or systemic embolism, and the primary safety end point was major bleeding.

RESULTS A total of 984 patients were randomly assigned to treatment (492 each to the edoxaban and placebo groups); 944 patients (402 frail patients [42.6%]; 542 nonfrail patients [57.4%]; mean [SD] age, 86.6 [4.3] years; 541 women [57.3%]) were included in this analysis. In the placebo group, the estimated event rates (SE) for stroke or systemic embolism were 7.1% (1.6%) per patient-year in the frail group and 6.1% (1.3%) per patient-year in the nonfrail group. Edoxaban was associated with lower event rates for stroke or systemic embolism with no interaction with frailty status or frailty assessment parameters. Major bleeding and major or clinically relevant nonmajor bleeding events were both numerically higher in the edoxaban group than in the placebo group, and no heterogeneity was observed with frailty status. Although both all-cause death and net clinical composite outcome occurred more frequently in the frail group than in the nonfrail group, there was no association with frailty status between the edoxaban and placebo groups.

CONCLUSIONS AND RELEVANCE Regardless of frailty status, among Japanese patients with AF aged 80 years or older who were ineligible for standard OACs, once-daily 15-mg edoxaban was associated with reduced incidence of stroke or systemic embolism and may be a suitable treatment option for these patients.

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Supplemental content

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Key Points

Question Is very-low-dose edoxaban (15 mg/day) beneficial across frailty status among very elderly Japanese patients with atrial fibrillation considered ineligible for standard dose oral anticoagulants because of their high bleeding risk?

Findings In this cohort study of 944 patients using data from the ELDERCARE-AF trial, very-low-dose edoxaban was associated with lower incidence of stroke or systemic embolism consistently across frailty status, including each assessment parameter, with a numerically higher risk of major or clinically relevant nonmajor bleeding.

Meaning These findings suggest that edoxaban (15 mg) is superior to placebo in preventing stroke or systemic embolism in very elderly patients with atrial fibrillation, regardless of frailty status, and may be a suitable treatment option for these patients.
Introduction

The prevalence of atrial fibrillation (AF), a common arrhythmia, increases with age, and frailty is also a common condition affecting the older population. Frailty is defined as the increased vulnerability resulting from an aging-associated decline in reserve and function across multiple physiological mechanisms, which is associated with an increased risk of a range of adverse outcomes, including weight loss, risk of falls, and renal deterioration. To prevent cardioembolic stroke in patients with AF, the clinical guidelines recommend using direct oral anticoagulants (DOACs) even in elderly and frail patients. However, as use of DOACs can increase the risk of bleeding, assessment and monitoring of the risk factors associated with frailty are recommended. The benefits of DOAC treatment are reported to outweigh the risks associated with frailty; however, evidence for the use of DOACs in very elderly patients with AF with frailty is lacking. Many physicians remain reluctant to prescribe standard doses of DOACs to very elderly patients with frailty because of risk factors for bleeding in this patient group, such as severe renal impairment, history of bleeding, previous falls, low body weight, and polypharmacy.

Edoxaban has been approved for the prevention of ischemic stroke and systemic embolism in patients with AF. The ELDERCARE-AF (Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients) trial compared the efficacy and safety of very-low-dose edoxaban (15 mg) vs placebo in very elderly Japanese patients (aged ≥80 years) with AF who were considered ineligible for standard oral anticoagulant (OAC) therapy because of their high bleeding risk. The results show that edoxaban 15 mg was effective at preventing stroke and systemic embolism (SSE) and did not significantly increase the incidence of major bleeding compared with placebo. In that trial, frailty, which is often a concern when treating very elderly patients, was assessed using the Japanese version of the Fried criteria, which consists of 5 measures of physical condition. Approximately 40% of the enrolled patients had a frailty score 3 or higher and, thus, were classified as frail. On the basis of the results from the ELDERCARE-AF trial, 15 mg edoxaban has been approved for use in elderly patients with AF at high risk of bleeding in Japan, although questions remain regarding the outcomes and safety of edoxaban in frail patients. The present cohort study using data from the ELDERCARE-AF trial was conducted to (1) explore the risk of SSE, major bleeding, and death in very elderly patients with AF across frailty status among the ELDERCARE-AF study population (≥80 years); and (2) to explore the outcomes associated with edoxaban 15 mg vs placebo across frailty status including each frailty assessment parameter.

Methods

Study Design

This cohort study was a subanalysis of the ELDERCARE-AF trial, a phase 3, multicenter, randomized, double-blind, placebo-controlled, event-driven, superiority study. The study duration was from August 5, 2016, to November 5, 2019, and the date of the last patient follow-up was December 27, 2019.

Eligible patients were randomly assigned to treatment with edoxaban 15 mg per day or placebo at a 1:1 ratio. Patients receiving the placebo did not receive anticoagulants during the study. The groups were stratified according to CHADS2 (congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke or transient ischemic attack) score (2 points or ≥3 points; CHADS2 scores range from 0 to 6, with higher scores indicating a greater risk of stroke).

The institutional review board at each participating site approved the study. The study was performed in accordance with the standards specified in the Pharmaceutical and Medical Device Act of Japan, the International Council for Harmonisation guidelines for Good Clinical Practice, and the principles of the Declaration of Helsinki. All patients provided written informed consent.
Patients
The inclusion criteria were as follows: age 80 years or older, history of AF documented by electrocardiogram or monitor recording within 1 year of consent, CHADS2 score of 2 or higher, and ineligibility for a standard OAC regimen (warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) at the recommended therapeutic strength (warfarin) or approved doses for 1 or more of the following 5 hemorrhage risks: low creatinine clearance (15-30 mL/min), history of bleeding from a critical area or organ or gastrointestinal bleeding, body weight 45 kg or less, continuous use of nonsteroidal anti-inflammatory drugs, or current use of an antiplatelet drug. Patients with moderate to severe mitral stenosis and/or mechanical heart valves were excluded.

Efficacy and Safety End Points
The primary efficacy end point was the composite of SSE, and the primary safety end point was International Society on Thrombosis and Hemostasis–defined major bleeding. The net clinical composite outcome was defined as the composite of stroke, systemic embolism, major bleeding, or all-cause death. The secondary efficacy and safety end points have been described previously.10

Frailty
Details of the frailty assessment in this subanalysis are provided in the eAppendix in the Supplement. Patient physical condition was assessed using 5 physical parameters, including weight loss, grip strength, walking speed, exhaustion, and activity level, to yield a frailty score, where 1 point was given for each parameter.11 A score of 0 indicated robust; a score of 1 or 2, prefrail; and a score of 3 or higher, frail.5,10 In this analysis, robust and prefrail were combined and categorized as nonfrail.

Statistical Analysis
The sample size calculations have been described previously.12 The intention-to-treat population, defined as all randomly assigned patients, was used to evaluate efficacy. The safety analysis set, defined as all patients who received at least 1 dose of the study drug, was used to assess safety. This subanalysis was prespecified to evaluate patients in the ELDERCARE-AF trial according to their baseline frailty status. Baseline data were summarized using frequency and percentage for categorical variables, with between-group comparisons made using the χ2 test and mean (SD) for continuous variables, with between-group comparisons made using analysis of variance.

The outcomes were evaluated using the same methods as described previously.12 The effect of frailty on the efficacy and safety end points was evaluated using a Cox proportional-hazards model. Age and sex at baseline were included in the multivariate model as adjustment factors. Two-sided P < .05 was considered statistically significant. SAS statistical software version 9.4 (SAS Institute) was used to perform the statistical analysis. Data analysis was performed from February 2021 to February 2022.

Results
Patient Disposition and Characteristics
A total of 984 patients were randomly assigned to treatment (492 each to the edoxaban and placebo groups). One hundred fifty-eight patients (16.1%) withdrew from the study. Frailty status was determined in 474 patients (289 nonfrail patients [61.0%]; 185 frail patients [39.0%]) in the edoxaban group and 470 patients (253 nonfrail patients [53.8%]; 217 frail patients [46.2%]) in the placebo group (Figure 1). The frailty scores of patients were evenly distributed between the edoxaban and placebo groups (eTable 1 in the Supplement). A total of 944 patients (402 frail patients [42.6%]; 542 nonfrail patients [57.4%]; mean [SD] age, 86.6 [4.3] years; 541 [57.3%] women) were included in this subanalysis. Sixty-one of 944 patients (6.5%) were classified as robust and 481 (51.0%) were prefrail. Baseline patient characteristics by frailty status are shown in eTable 2 in the Supplement. Compared with the nonfrail group, the frail group was older, had a higher proportion of
female patients, had a lower body mass index, had worse renal function, had a higher rate of dementia and history of falls, had higher CHADS\textsubscript{2} and CHA\textsubscript{2}DS\textsubscript{2}-VASc (congestive heart failure, hypertension, age $\geq 75$ years, diabetes, stroke, vascular disease, age 65-74 years, sex) scores (CHA\textsubscript{2}DS\textsubscript{2}-VASc scores range from 0 to 9, with higher scores indicating a greater risk of stroke), and had less antiplatelet drug usage. The history of bleeding and HAS-BLED (hypertension, abnormal liver or kidney function, stroke history, bleeding history or predisposition, labile international normalized ratios, elderly, drug or alcohol usage) score (HAS-BLED scores range from 0 to 9, with higher scores indicating a greater risk of bleeding) was similar between the 2 groups. There were no differences in baseline patient characteristics when comparing the nonfrail and frail groups between the edoxaban and placebo groups (Table).

**Association of Edoxaban With Major Outcomes by Frailty Status and Each Frailty Assessment Parameter**

**Stroke or Systemic Embolism**

Forest plots of the association of edoxaban with efficacy and safety end points by frailty status and each frailty assessment parameter are shown in Figure 2 and Figure 3. In the placebo group, the estimated event rates (SE) of SSE were 7.1% (1.6%) per patient-year in the frail group and 6.1% (1.3%) per patient-year in the nonfrail group, and there was no difference between the groups (adjusted hazard ratio [HR], 1.04; 95% CI, 0.56-1.94; adjusted $P = .91$) (eTable 3 in the Supplement). Among the 5 frailty assessment parameters, lower grip strength was associated with increased risk of SSE (38 of 368 frail patients [7.8%] vs 4 of 102 nonfrail patients [2.6%]; unadjusted HR, 2.91; 95% CI, 1.04-8.16; unadjusted $P = .04$) (eTable 3 in the Supplement). In the edoxaban group, SSE occurred at an estimated event rate (SE) of 2.5% (1.0%) of the frail patients and 1.5% (0.6%) of the nonfrail patients (adjusted HR, 1.41; 95% CI, 0.44-4.49; adjusted $P = .56$). Compared with the placebo group, the edoxaban group consistently had fewer SSE events regardless of frailty status including each frailty assessment parameter, and there was no heterogeneity between the groups (Figure 2). The Kaplan-Meier curve for the SSE is shown in panel A of the eFigure in the Supplement.

**Major Bleeding**

In the placebo group, the incidences of major bleeding were 2.3% (6 of 216 patients) in the frail group and 1.5% (5 of 253 patients) in the nonfrail group (adjusted HR, 1.48; 95% CI, 0.47-4.63; adjusted $P = .56$).
# Table. Baseline Patient Characteristics in the Edoxaban and Placebo Groups by Frailty Status

| Characteristics                          | Patients, No. (%) | P values | P values | P values | P values |
|------------------------------------------|-------------------|----------|----------|----------|----------|
|                                          | Edoxaban 15 mg (n = 474) | Placebo (n = 470) | Nonfrail vs frail (edoxaban) | Nonfrail vs frail (placebo) | Nonfrail edoxaban vs placebo | Frail edoxaban vs placebo |
| Age, mean (SD), y                        | 86.1 (4.2)        | 87.5 (4.2) | 85.6 (3.8) | 87.4 (4.6) | <.001    | .15      | .66      |
| Sex                                      |                   |          |          |          |          |
| Female                                   | 149 (51.6)        | 118 (63.8) | 130 (51.4) | 144 (66.4) | .009     | .001     | .97      | .59      |
| Male                                     | 140 (48.4)        | 67 (36.2)  | 123 (48.6) | 73 (33.6)  |          |          |          |          |
| Paroxysmal atrial fibrillation           | 141 (48.8)        | 90 (48.6)  | 119 (47.0) | 97 (44.7)  | .98      | .61      | .68      | .43      |
| Weight, mean (SD), kg                    | 52.2 (10.4)       | 48.3 (11.0) | 53.0 (11.0) | 47.9 (10.6) | <.001    | <.001    | .40      | .73      |
| Body mass index, mean (SD)\(a\)         | 22.2 (3.2)        | 21.9 (4.0)  | 22.7 (3.6)  | 21.7 (3.9)  | .33      | .003     | .09      | .60      |
| Creatinine clearance rate, mL/min        |                   |          |          |          |          |
| Mean (SD)                                | 37.7 (13.5)       | 34.4 (15.5) | 38.9 (15.2) | 32.5 (12.4) | .01      | <.001    | .37      | .18      |
| ≤50                                      | 237 (82.0)        | 162 (87.6) | 197 (77.9)  | 196 (90.3)  | .11      | <.001    | .23      | .38      |
| >50                                      | 52 (18.0)         | 23 (12.4)  | 56 (22.1)   | 21 (9.7)    |          |          |          |          |
| Vascular disease\(b\)                   | 65 (22.5)         | 37 (20.0)  | 65 (25.7)   | 54 (24.9)   | .52      | .84      | .38      | .24      |
| Dementia                                 | 32 (11.1)         | 34 (18.4)  | 26 (10.3)   | 55 (25.3)   | .03      | <.001    | .76      | .09      |
| History of falling within past year      | 75 (26.0)         | 74 (40.0)  | 71 (28.1)   | 107 (49.3)  | .001     | <.001    | .58      | .06      |
| CHADS\(_2\) score\(c\)                  |                   |          |          |          |          |
| Mean (SD)                                | 3.0 (1.1)         | 3.0 (1.0)  | 2.9 (1.1)   | 3.2 (1.2)   | .70      | .006     | .48      | .09      |
| ≥2                                       | 118 (40.8)        | 61 (33.0)  | 109 (43.1)  | 67 (30.9)   | .09      | .006     | .60      | .65      |
| CHA\(_2\)DS\(_2\)-VAsc score\(d\)      |                   |          |          |          |          |
| Mean (SD)                                | 4.8 (1.2)         | 4.9 (1.2)  | 4.7 (1.2)   | 5.2 (1.3)   | .13      | <.001    | .76      | .08      |
| ≤4                                       | 138 (47.8)        | 69 (37.3)  | 118 (46.6)  | 67 (30.9)   | .03      | <.001    | .80      | .18      |
| ≥5                                       | 151 (52.2)        | 116 (62.7) | 135 (53.4)  | 150 (69.1)  |          |          |          |          |
| HAS-BLED score\(e\)                     |                   |          |          |          |          |
| Mean (SD)                                | 2.3 (0.9)         | 2.3 (0.9)  | 2.4 (0.9)   | 2.3 (0.9)   | .68      | .79      | .33      | .31      |
| ≤2                                       | 184 (63.7)        | 117 (63.2) | 159 (62.8)  | 133 (61.3)  | .93      | .73      | .84      | .69      |
| ≥3                                       | 105 (36.3)        | 68 (36.8)  | 94 (37.2)   | 84 (38.7)   |          |          |          |          |
| Hemorrhage risk or ineligible for oral   |                   |          |          |          |          |
| anticoagulants                           |                   |          |          |          |          |
| Severe renal impairment (creatinine      | 101 (34.9)        | 89 (48.1)  | 87 (34.4)   | 113 (52.1)  | .004     | <.001    | .89      | .43      |
| clearance <30 mL/min)                    |                   |          |          |          |          |
| History of bleeding from critical area   | 65 (22.5)         | 45 (24.3)  | 61 (24.1)   | 45 (20.7)   | .64      | .38      | .66      | .39      |
| or organ                                 |                   |          |          |          |          |
| Intracranial                             | 29 (10.0)         | 12 (6.5)   | 22 (8.7)    | 13 (6.0)    | .18      | .27      | .59      | .84      |
| Gastrointestinal                         | 32 (11.1)         | 29 (15.7)  | 36 (14.2)   | 28 (12.9)   | .14      | .68      | .27      | .43      |
| Intracranial                             | 1 (0.3)           | 2 (1.1)    | 1 (0.4)     | 3 (1.4)     | .32      | .25      | .92      | .79      |
| Other                                    | 3 (1.0)           | 3 (1.6)    | 6 (2.4)     | 2 (0.9)     | .58      | .23      | .23      | .53      |
| Low body weight, ≤45 kg                  | 94 (32.5)         | 85 (45.9)  | 69 (27.3)   | 106 (48.8)  | .003     | <.001    | .18      | .56      |
| Continuous use of nonsteroidal anti-      | 86 (29.8)         | 54 (29.2)  | 98 (38.7)   | 64 (29.5)   | .89      | .04      | .03      | .95      |
| inflammatory drugs                       |                   |          |          |          |          |
| Use of an antiplatelet drug              | 155 (53.6)        | 91 (49.2)  | 152 (60.1)  | 105 (48.4)  | .34      | .01      | .13      | .87      |
| Aspirin                                  | 77 (26.6)         | 48 (25.9)  | 93 (36.8)   | 58 (26.7)   | .87      | .02      | .01      | .86      |
| Clopidogrel                              | 46 (15.9)         | 23 (12.4)  | 28 (11.1)   | 31 (14.3)   | .29      | .29      | .10      | .59      |
| Other                                    | 32 (11.1)         | 21 (11.4)  | 31 (12.3)   | 18 (8.3)    | .93      | .16      | .67      | .30      |

(continued)
In the edoxaban group, major bleeding occurred in 3.7% (8 of 185 patients) in the frail group and 2.9% (11 of 289 patients) in the nonfrail group (adjusted HR, 1.04; 95% CI, 0.39-2.77; adjusted \( \text{P} \) = .94). The incidences were all numerically higher in the edoxaban group vs placebo group, and there was no interaction with frailty status or frailty assessment parameters in the association of edoxaban with major bleeding (Figure 3). The Kaplan-Meier curve for major bleeding is shown in panel B of the eFigure in the Supplement.

Net Clinical Composite Outcome and All-Cause Death

In the placebo group, both net clinical composite outcome and all-cause death occurred more frequently in the frail group than in the nonfrail group (net clinical composite outcome, 55 of 217 frail patients [25.3%] vs 41 of 253 nonfrail patients [16.2%]; adjusted HR, 1.61; 95% CI, 1.06-2.45; adjusted \( \text{P} \) = .02; all-cause death, 43 of 217 frail patients [19.9%] vs 21 of 253 nonfrail patients [8.3%]; adjusted \( \text{HR} \), 2.44; 95% CI, 1.42-4.18; adjusted \( \text{P} \) = .001) (eTable 3 in the Supplement). Among the 5 parameters, lower grip strength was associated with significantly increased risks of both net clinical composite outcome (91 of 368 frail patients [18.8%] vs 5 of 102 nonfrail patients [4.9%]; adjusted \( \text{HR} \), 2.44; 95% CI, 1.42-4.18; adjusted \( \text{P} \) = .001) and all-cause death (63 of 368 frail patients [16.9%] vs 1 of 102 nonfrail patients [0.7%]; adjusted \( \text{HR} \), 16.26; 95% CI, 2.28-121.00; adjusted \( \text{P} \) = .006) (eTable 3 in the Supplement). There was no significant interaction in the association of edoxaban with these outcomes (Figure 2).

Other Bleeding Events

Major or clinically relevant nonmajor (CRNM) bleeding occurred more frequently in the frail group than in the nonfrail group (36 of 216 frail patients [16.9%] vs 21 of 253 nonfrail patients [8.3%]; adjusted \( \text{HR} \), 2.00; 95% CI, 1.13-3.53; adjusted \( \text{P} \) = .02) (eTable 3 in the Supplement). Among the 5
Figure 2. Association of Edoxaban on Efficacy Outcomes by Frailty Status and Each Frailty Assessment Parameter

| Variable                        | Patients with event, No./total patients, No. (% per patient-y) | HR (95% CI)a | Favors edoxaban | Favors placebo | P value | Interaction P value |
|---------------------------------|-----------------------------------------------------------------|--------------|----------------|----------------|---------|-------------------|
| **Stroke or systemic embolism** |                                                                   |              |                |                |         |                   |
| Frail                           |                                                                  |              |                |                |         |                   |
| Yes                             | 6/185 (2.5)                                                      | 0.35 (0.14-0.87) |                |                | .02     | .55               |
| No                              | 6/289 (1.5)                                                     | 0.24 (0.10-0.59) |                |                | .002    |                   |
| Weight loss                     |                                                                  |              |                |                |         |                   |
| Yes                             | 1/66 (1.1)                                                      | 0.22 (0.03-1.87) |                |                | .16     |                   |
| No                              | 11/408 (2.0)                                                    | 0.29 (0.15-0.56) |                |                | <.001   |                   |
| Low grip strength               |                                                                  |              |                |                |         |                   |
| Yes                             | 11/375 (2.2)                                                    | 0.28 (0.14-0.54) |                |                | <.001   |                   |
| No                              | 1/99 (0.7)                                                      | 0.29 (0.03-2.61) |                |                | .27     |                   |
| Slow walking speed              |                                                                  |              |                |                |         |                   |
| Yes                             | 9/343 (2.0)                                                     | 0.25 (0.12-0.52) |                |                | <.001   |                   |
| No                              | 3/131 (1.6)                                                     | 0.46 (0.12-1.77) |                |                | .26     |                   |
| Exhaustion                      |                                                                  |              |                |                |         |                   |
| Yes                             | 1/82 (0.9)                                                      | 0.14 (0.02-1.09) |                |                | .06     | .47               |
| No                              | 11/392 (2.0)                                                    | 0.31 (0.16-0.62) |                |                | <.001   |                   |
| Low activity                    |                                                                  |              |                |                |         |                   |
| Yes                             | 5/185 (2.1)                                                     | 0.35 (0.13-0.95) |                |                | .04     | .63               |
| No                              | 7/289 (1.7)                                                     | 0.25 (0.11-0.56) |                |                | .001    |                   |
| **Net clinical composite outcome** |                                                              |              |                |                |         |                   |
| Frail                           |                                                                  |              |                |                |         |                   |
| Yes                             | 35/185 (14.9)                                                   | 0.77 (0.50-1.17) |                |                | .22     |                   |
| No                              | 45/289 (11.4)                                                   | 0.99 (0.65-1.51) |                |                | .95     |                   |
| Weight loss                     |                                                                  |              |                |                |         |                   |
| Yes                             | 15/66 (16.4)                                                    | 1.25 (0.60-2.59) |                |                | .55     |                   |
| No                              | 65/408 (12.1)                                                   | 0.79 (0.57-1.09) |                |                | .15     |                   |
| Low grip strength               |                                                                  |              |                |                |         |                   |
| Yes                             | 71/375 (14.5)                                                   | 0.77 (0.57-1.05) |                |                | .10     |                   |
| No                              | 9/99 (6.4)                                                      | 2.08 (0.69-6.23) |                |                | .19     |                   |
| Slow walking speed              |                                                                  |              |                |                |         |                   |
| Yes                             | 63/343 (14.1)                                                   | 0.83 (0.59-1.16) |                |                | .27     |                   |
| No                              | 17/131 (9.3)                                                    | 0.97 (0.50-1.86) |                |                | .92     |                   |
| Exhaustion                      |                                                                  |              |                |                |         |                   |
| Yes                             | 15/82 (14.2)                                                    | 0.94 (0.48-1.82) |                |                | .85     | .75               |
| No                              | 65/392 (12.4)                                                   | 0.83 (0.60-1.16) |                |                | .27     |                   |
| Low activity                    |                                                                  |              |                |                |         |                   |
| Yes                             | 27/185 (11.9)                                                   | 0.72 (0.44-1.16) |                |                | .18     |                   |
| No                              | 53/289 (12.3)                                                   | 0.92 (0.63-1.35) |                |                | .67     |                   |
| **All-cause death**             |                                                                  |              |                |                |         |                   |
| Frail                           |                                                                  |              |                |                | .06     |                   |
| Yes                             | 26/185 (10.7)                                                   | 0.72 (0.45-1.18) |                |                | .19     |                   |
| No                              | 34/289 (8.3)                                                    | 1.46 (0.85-2.51) |                |                | .18     |                   |
| Weight loss                     |                                                                  |              |                |                | .16     |                   |
| Yes                             | 13/66 (13.6)                                                    | 1.67 (0.71-1.90) |                |                | .24     |                   |
| No                              | 47/408 (8.5)                                                    | 0.85 (0.57-1.25) |                |                | .41     |                   |
| Low grip strength               |                                                                  |              |                |                | .06     |                   |
| Yes                             | 54/375 (10.6)                                                   | 0.84 (0.59-1.21) |                |                | .36     |                   |
| No                              | 6/99 (4.2)                                                      | 6.87 (0.82-57.27) |                |                | .07     |                   |
| Slow walking speed              |                                                                  |              |                |                | .63     |                   |
| Yes                             | 50/343 (10.9)                                                   | 0.99 (0.67-1.47) |                |                | .97     |                   |
| No                              | 10/131 (5.3)                                                    | 0.82 (0.36-1.88) |                |                | .64     |                   |
| Exhaustion                      |                                                                  |              |                |                | .16     |                   |
| Yes                             | 11/82 (10.2)                                                    | 0.91 (0.42-1.95) |                |                | .80     |                   |
| No                              | 49/392 (9.1)                                                    | 0.98 (0.66-1.46) |                |                | .91     |                   |
| Low activity                    |                                                                  |              |                |                | .12     |                   |
| Yes                             | 20/185 (8.5)                                                    | 0.67 (0.38-1.17) |                |                | .16     |                   |
| No                              | 40/289 (9.6)                                                    | 1.21 (0.76-1.93) |                |                | .43     |                   |

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a Hazard ratios (HRs) and 95% CIs are indicated relative to the placebo group.

b Efficacy endpoints were assessed in the intention-to-treat population, which included all patients randomly assigned to treatment.

c Net clinical composite outcome was the composite of stroke, systemic embolism, major bleeding, or all-cause death.
parameters, exhaustion was related to significantly increased risk of major or CRNM bleeding (19 of 106 frail patients [16.3%] vs 38 of 363 nonfrail patients [8.4%]; adjusted HR, 1.97; 95% CI, 1.12-3.47; adjusted P = .02) (eTable 3 in the Supplement). The incidences were all higher in the edoxaban group than in the placebo group, and there was no interaction with frailty status or frailty assessment parameters in the association of edoxaban on major or CRNM bleeding (Figure 3).

Discussion

The present cohort study found that among very elderly patients with AF who were ineligible for standard anticoagulation treatment, (1) the risks of SSE and major bleeding were not significantly different between nonfrail and frail patients, and the incidence of death was higher in frail than in nonfrail patients; (2) lower grip strength was associated with an increased risk of SSE and significantly

| Variable                          | Edoxaban 15 mg | Placebo | HR (95% CI)*  |
|-----------------------------------|---------------|---------|---------------|
| Major bleeding                     |               |         |               |
| Frail                             |               |         |               |
| Yes                               | 8/185 (3.7)   | 6/216 (2.8) | 1.67 (0.58-4.75) |
| No                                | 11/289 (3.9)  | 5/253 (1.5)  | 2.02 (0.70-5.78)  |
| Weight loss                        |               |         |               |
| Yes                               | 3/66 (4.5)    | 0/72 (0.0)   | NA             |
| No                                | 16/408 (3.7)  | 11/397 (2.2) | 1.46 (0.68-3.14) |
| Low grip strength                  |               |         |               |
| Yes                               | 17/375 (4.5)  | 10/367 (2.7) | 1.70 (0.78-3.72)  |
| No                                | 2/99 (1.5)    | 1/102 (0.9)  | 2.01 (0.25-16.53) |
| Slow walking speed                 |               |         |               |
| Yes                               | 14/345 (4.1)  | 9/340 (2.6)  | 1.58 (0.68-3.64)  |
| No                                | 5/131 (3.8)   | 2/129 (1.5)  | 2.61 (0.55-12.52) |
| Exhaustion                         |               |         |               |
| Yes                               | 2/82 (2.5)    | 2/106 (1.9)  | 1.25 (0.19-8.20)  |
| No                                | 17/392 (4.3)  | 9/363 (2.5)  | 1.82 (0.82-4.05)  |
| Low activity                       |               |         |               |
| Yes                               | 7/185 (3.8)   | 4/188 (2.1)  | 2.00 (0.61-6.53)  |
| No                                | 12/289 (3.2)  | 7/281 (2.5)  | 1.60 (0.62-4.12)  |
| Major or clinically relevant nonmajor bleeding | | | |
| Frail                             |               |         |               |
| Yes                               | 42/185 (23.4) | 36/216 (16.9) | 1.43 (0.91-2.23)  |
| No                                | 53/289 (18.6) | 21/253 (8.3)  | 2.44 (1.47-4.03)  |
| Weight loss                        |               |         |               |
| Yes                               | 13/66 (19.7)  | 9/72 (12.5)   | 1.64 (0.70-3.85)  |
| No                                | 82/408 (20.2) | 48/397 (12.2)| 1.78 (1.24-2.54)  |
| Low grip strength                  |               |         |               |
| Yes                               | 79/375 (21.4) | 48/367 (13.1) | 1.72 (1.20-2.46)  |
| No                                | 16/99 (16.1)  | 9/102 (8.9)   | 1.99 (0.89-4.44)  |
| Slow walking speed                 |               |         |               |
| Yes                               | 74/345 (21.4) | 47/340 (13.9)| 1.67 (1.16-2.41)  |
| No                                | 21/131 (16.1) | 10/129 (8.5)  | 2.16 (1.03-4.52)  |
| Exhaustion                         |               |         |               |
| Yes                               | 21/82 (26.7)  | 19/106 (18.3)| 1.50 (0.81-2.78)  |
| No                                | 74/392 (18.8) | 38/363 (10.5)| 1.95 (1.32-2.88)  |
| Low activity                       |               |         |               |
| Yes                               | 35/185 (18.8) | 26/188 (13.8)| 1.54 (0.93-2.57)  |
| No                                | 60/289 (20.8) | 31/281 (10.7)| 1.97 (1.27-3.04)  |

NA indicates not applicable.

a Hazard ratios (HRs) and 95% CIs are indicated relative to the placebo group.
b The safety population included all patients who received at least 1 dose of edoxaban or placebo. 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.
increased risks of net clinical composite outcome and all-cause death, and exhaustion was associated with a significantly increased risk of major or CRNM bleeding; (3) regardless of frailty status, edoxaban 15 mg was associated with significantly reduced incidence of SSE compared with placebo and did not result in a significantly higher incidence of major bleeding than placebo; and (4) similar trends for the association of edoxaban 15 mg were shown for each frailty assessment parameter. The distribution of the frailty scores in this study is striking. A previous meta-analysis that examined the prevalence of frailty based on Fried criteria among elderly Japanese individuals showed the pooled prevalences of frailty were 20.4% for those aged 80 to 84 years and 35.1% for those aged 85 years and older. Our results show that of the 944 patients aged 80 years and older in this study, 42.6% (402 patients) were frail, 51.0% (481 patients) were prefrail, and 6.5% (61 patients) were robust, according to very similar frailty criteria. The reason the prevalence of frailty was higher (and the proportion of robust patients was lower) in this study can be attributed to the enrollment of patients with AF with high bleeding risks, such as low creatinine clearance (15-30 mL/min) or low body weight (<45 kg), in addition to age 80 years and older.

Frailty status is associated with an increased risk of poor health outcomes in elderly individuals, such as falls, fractures, hospitalization, care home institutionalization, disability, dementia, and mortality. A post hoc analysis from the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction (ENGAGE AF-TIMI) 48 trial showed that the annual rates of major efficacy and safety outcomes in both warfarin and edoxaban groups increased with frailty category. After adjusting for baseline differences, frailty remained re factor independently associated with risk of adverse outcomes. In the present prespecified subanalysis of a prospective, randomized study, we confirmed an association between frailty category and risk of death in the placebo group, even after adjusting for potential confounders such as age and sex. There was, however, no clear interaction between frailty and risk of both thromboembolism and major bleeding, supporting the clinical guidelines recommending the use of DOACs in older patients.

Additionally, we noted a significant association with lower grip strength and risk of net clinical composite outcomes and all-cause death and an association with SSE, although lower grip strength is not included as a risk factor in the clinical guidelines. However, our results may have been affected by patient bias, in that most of the patients in the nonfrail group in this study were prefrail patients. Therefore, this is not a comparison between robust and frail patients. Although lacking in statistical power because of a small number of robust patients, neither SSE nor major bleeding occurred in the robust patients of the placebo group, indicating an association between the risks of adverse outcomes and the degree of frailty.

Although the incidence of SSE or major bleeding was not significantly different between frail and nonfrail patients in the present subanalysis, each frailty parameter seemed to contribute differently to these outcomes. In particular, slow walking speed has been reported to be associated with the incidence of disability, dependency, mortality, and care home institutionalization among elderly individuals. In this subanalysis, surprisingly, grip strength showed an association with adverse events. In elderly patients with lower grip strength, there was nearly a 3-fold increase in risk of SSE and major bleeding and a more than 16-fold significant increase in risk of death. In addition, in those with exhaustion, there was nearly a 2-fold significant increase in major or CRNM bleeding. In the elderly high-risk patients with AF, most of whom were categorized as prefrail or frail, an objective physical assessment of grip strength or exhaustion in addition to the well-known walking speed may more accurately estimate the risks of clinical outcomes than the overall frailty assessment.

The rate of appropriate oral anticoagulation decreases with age, which appears to be related to the fear of frailty status in elderly individuals with AF. In Canada, frail elderly patients with AF are less likely to receive anticoagulation therapy than nonfrail elderly patients. The results of a recent subanalysis of the All Nippon AF in the Elderly Registry reported that the prescription rate of OACs in elderly Japanese patients with AF was as high as 92% overall and more than 90% in patients younger than 90 years, whereas inappropriate low doses of DOACs that did not fulfill dose reduction criteria were prescribed for 20% to 30% of patients. As supported by our results, and the results of
the ENGAGE AF-TIMI 48 trial low-dose regimen, full doses of edoxaban should be given to elderly patients with AF who can receive standard-dose anticoagulants. Although the clinical guidelines caution that low-dose use of DOACs may result in reduced efficacy, our results showed a significant reduction in SSE events in patients treated with low-dose edoxaban (15 mg). Therefore, low-dose edoxaban should be considered in elderly patients with high risk of bleeding.

One of the main features of the ELDERCARE-AF trial is its study design: a randomized, double-blind, placebo-controlled trial. Because of the absence of a standard of care for elderly patients with AF considered inappropriate for standard OAC regimen due to their high bleeding risk, a placebo was selected as a comparator to edoxaban 15 mg. Thus, the present subanalysis provided important information showing that when elderly, high-risk, frail patients remain untreated with any OACs, they have a substantially higher risk of SSE (7.1%). In these high-risk patients, edoxaban 15 mg significantly reduced the incidence of SSE compared with placebo (2.5%). There was no significant interaction between frail and nonfrail status; therefore, the 15-mg dose of edoxaban used in the present study showed consistent association of edoxaban with reduced SSE independently of frailty status. Furthermore, of the 5 frailty parameters, elderly patients with AF with low grip strength and/or exhaustion are at higher risk for adverse events and may receive the most benefit from treatment with edoxaban 15 mg.

Limitations
The present study has several limitations. A considerable number of patients withdrew from the ELDERCARE-AF trial (158 patients [16.1%]) but provided consent for the use of data already collected, which may have affected the results of this study. The results may have differed with the use of other frailty evaluation criteria. Only Japanese patients were included in this subanalysis, and it is unknown whether our results are generalizable to other ethnic populations. The study sample size was not powered for any subgroup analyses, and the event rates in the subgroups were low.

Conclusions
Regardless of frailty status, among very elderly Japanese patients with AF who were considered ineligible for standard anticoagulant treatment because of their high bleeding risks, very-low-dose edoxaban (15 mg) was associated with reduced incidence of SSE and a higher incidence of major or CRNM bleeding than placebo. Edoxaban may be a suitable treatment option for these patients.

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Author Contributions: Drs Akashi and Yamashita had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Administrative, technical, or material support: Okumura, Akishita, Yamashita.

Supervision: Akishita, Yamashita.

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SUPPLEMENT.
eAppendix. Frailty Assessment
eReference
eFigure. Kaplan-Meier Curves for Effect of Edoxaban on Outcomes by Frailty Status for Stroke/Systemic Embolism (A) and Major Bleeding (B)
eTable 1. Frailty Scores by Number of Patients
eTable 2. Baseline Patient Characteristics by Frailty Status
eTable 3. Efficacy and Safety Endpoints in the Placebo Group by Frailty Status and Each Frailty Assessment Parameter