Clinical Outcomes of Very Elderly Patients With Atrial Fibrillation Receiving On-label Doses of Apixaban: J-ELD AF Registry Subanalysis

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BACKGROUND: Increasing age predisposes patients with atrial fibrillation to both thromboembolic and bleeding events; however, data on outcomes of very elderly patients (aged ≥85 years) receiving appropriate antithrombotic therapy are still limited.

METHODS AND RESULTS: The J-ELD AF (Multicenter Prospective Cohort Study to Investigate the Effectiveness and Safety of Apixaban in Japanese Elderly Atrial Fibrillation Patients) Registry is a multicenter prospective observational study of Japanese patients with nonvalvular atrial fibrillation aged ≥75 years taking on-label doses (standard dose of 5 mg BID or reduced dose of 2.5 mg BID) of apixaban. The entire cohort (3031 patients from 110 institutions) was divided into 3 age groups: 75 to 79 years (n=1068, 35.2%), 80 to 84 years (n=1120, 37.0%), and ≥85 years (n=843, 27.8%). The event incidence rates (/100 person-years) were 1.40, 1.55, and 1.95 for stroke or systemic embolism (log-rank $P=0.65$); 1.70, 1.55, and 2.61 for bleeding requiring hospitalization (log-rank $P=0.33$); 2.09, 2.60, and 5.29 for total deaths (log-rank $P<0.001$); and 0.40, 1.06, and 1.55 for cardiovascular deaths (log-rank $P=0.045$), respectively. After adjusting for confounders using a Cox regression analysis, age ≥85 years was identified as an independent risk of total death (hazard ratio, 1.89; 95% CI, 1.10–3.26 [$P=0.022$]), but not of stroke or systemic embolism, bleeding requiring hospitalization, or cardiovascular death.

CONCLUSIONS: Although mortality increased with age, age ≥85 years was not a significant risk of stroke or systemic embolism, bleeding requiring hospitalization, or cardiovascular death in Japanese patients with nonvalvular atrial fibrillation taking on-label doses of apixaban.

REGISTRATION: URL: https://www.umin.ac.jp/ctr; Unique identifier: UMIN000017895.

Key Words: anticoagulant ■apixaban ■atrial fibrillation ■elderly
physicians are often faced with the challenging problem of whether oral anticoagulants should be administered to elderly patients with AF. Although mortality increased with age, age ≥85 years was not an independent risk factor for stroke or systemic embolism, bleeding requiring hospitalization, or cardiovascular death in patients with atrial fibrillation receiving on-label doses of apixaban.

What Are the Clinical Implications?
- Prescribing on-label doses of apixaban is reasonable for reducing the incidence of thromboembolic events with comparable bleeding events in patients with atrial fibrillation aged ≥85 years.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population

The study design and patients’ baseline clinical characteristics of the J-ELD AF Registry have been reported elsewhere.22,23 The target number of patients in the registry was 3000, and the enrollment period was from September 2015 to August 2016. The observation period for each patient was 1 year. Each investigator involved in the study enrolled patients who fulfilled the inclusion criteria and did not violate the exclusion criteria. The inclusion criteria were Japanese patients with nonvalvular AF aged ≥75 years who had visited the participating facilities after the start of the registry and had been taking or started taking apixaban. Patients with any of the following during the enrollment period were excluded: (1) a history of hypersensitivity to apixaban, (2) active bleeding symptoms, (3) liver disease with coagulation disorders, and (4) creatinine clearance <15 mL/min. In addition, patients who did not meet the apixaban dose reduction criteria but received a reduced dose were excluded.

Apixaban was given at a reduced dose (2.5 mg BID) to those who met 2 or 3 of the following dose reduction criteria: age ≥80 years, body weight ≤60 kg, and serum creatinine level ≥1.5 mg/dL. The standard apixaban dose (5 mg BID) was given to those who did not meet these criteria.

The authors are solely responsible for the design and conduct of this study, all study analyses, drafting and editing of the article, and its final contents.

Ethics and Informed Consent

Before the start of the registry, the investigators in charge received a review from the ethics committee of their main participating facility and acquired approval. Before enrollment, the contents of the study were
explained to the patients using explanatory and consent documents, and written consent was obtained from the patients. If a patient withdrew consent during the observation period, all existing data collected from the patient were discarded. The study plan and its design were registered in the UMIN Clinical Trials Registry (UMIN000017895).

Data Acquisition

Data were collected using the Electronic Data Capture (EDC) system for the observation and inspection items defined in the clinical trial protocol. After obtaining a signature for the informed consent form, baseline characteristics including age, sex, body weight, underlying diseases (e.g., heart failure, hypertension, diabetes mellitus, history of cerebral infarction or transient ischemic attacks, myocardial infarction, peripheral artery disease, history of hospitalization caused by bleeding requiring hospitalization), apixaban dose and its start date, and coadministration of antiplatelet drugs were examined at the time of registration. Estimated glomerular filtration rate was calculated from the data for serum creatinine level, age, and sex using the Modification of Diet in Renal Disease study equation as follows: estimated glomerular filtration rate (mL/min per 1.73 m²) = 194 x (serum creatinine)⁻¹.⁰⁹⁴ x (age)⁻⁰.²⁸⁷ x 0.⁷³⁹ (if female). Stroke risk was assessed using the CHADS² score, which was calculated by assigning 1 point each for congestive heart failure, hypertension, diabetes mellitus, or age ≥75 years, and 2 points for history of cerebral infarction or transient ischemic attack. The CHA²DS₂-VASc score is a refinement of the CHADS₂ score and extends it by including additional common stroke risk factors: age (patients ≥75 years get 2 points and patients 65–74 years get 1 point), vascular disease, and female sex. Bleeding risk was assessed using the HAS-BLED score, calculated by assigning 1 point each for hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (aged ≥65 years), and drugs/alcohol concomitantly. Although these risk scores were not validated in Japanese patients aged ≥75 years, we assessed them to describe the patient background in each age group.

The collected outcome data were the presence or absence of an event during the observation period of each patient, date of occurrence, and situation regarding the apixaban administration during the week the event occurred. Events included stroke, systemic embolism, bleeding requiring hospitalization, total deaths, cardiovascular deaths, acute myocardial infarction, antithrombotic

![Figure 1. Distribution of age in the J-ELD AF Registry (Multicenter Prospective Cohort Study to Investigate the Effectiveness and Safety of Apixaban in Japanese Elderly Atrial Fibrillation Patients). The black and gray parts of each bar represent the number of patients with standard and reduced doses of apixaban, respectively.](image-url)
Table 1. Patient Characteristics

|                          | Total (N=3031) | Age 75–79 y (n=1068) | Age 80–84 y (n=1120) | Age ≥85 y (n=843) | P Value |
|--------------------------|----------------|----------------------|----------------------|-------------------|---------|
| Apixaban dose            |                |                      |                      |                   | <0.001  |
| Standard dose (5 mg BID) | 1284 (42.4)    | 919 (86.0)           | 271 (24.2)           | 94 (11.2)         |         |
| Reduced dose (2.5 mg BID)| 1747 (57.6)    | 149 (14.0)           | 849 (75.8)           | 749 (88.8)        |         |
| Sex                      |                |                      |                      |                   | <0.001  |
| Men                      | 1570 (51.8)    | 657 (61.5)           | 546 (48.8)           | 367 (43.5)        |         |
| Women                    | 1461 (48.2)    | 411 (38.5)           | 574 (51.3)           | 476 (56.5)        |         |
| Age, y                   | 81.7±4.6       | 76.9±1.5             | 81.7±1.4             | 87.7±2.6          | <0.001  |
| Body weight, kg          | 56.3±11.2      | 60.8±11.1            | 55.7±10.6            | 51.5±9.8          | <0.001  |
| Systolic BP, mm Hg       | 127.2±17.4     | 127.3±16.7           | 127.7±17.0           | 126.5±18.6        | 0.315   |
| Diastolic BP, mm Hg      | 70.7±12.3      | 72.0±12.0            | 71.0±12.2            | 68.8±12.6         | <0.001  |
| Pulse rate, beats per min| 74.1±15.0      | 73.9±15.4            | 74.4±14.7            | 74.0±14.8         | 0.750   |
| Serum creatinine, mg/dL  | 1.0±0.3        | 1.0±0.3              | 1.0±0.3              | 1.0±0.3           | <0.001  |
| eGFR, mL/min per 1.73 m² | 52.9±15.4      | 56.6±14.5            | 53.1±15.6            | 48.1±15.1         | <0.001  |
| Creatinine clearance, mL/min | 46.6±16.2 | 55.9±15.5           | 45.9±14.1            | 35.8±12.2         | <0.001  |
| eGFR <45 mL/min per 1.73 m² | 916 (30.2) | 207 (19.4)           | 331 (29.6)           | 378 (44.8)        | <0.001  |
| AF types                 |                |                      |                      |                   | <0.001  |
| Paroxysmal               | 1488 (49.1)    | 546 (51.1)           | 582 (52.0)           | 360 (42.7)        |         |
| Persistent               | 488 (16.1)     | 125 (14.8)           | 172 (15.4)           | 191 (17.9)        |         |
| Permanent                | 1023 (33.8)    | 319 (29.9)           | 354 (31.6)           | 350 (41.5)        |         |
| Unknown                  | 32 (1.1)       | 8 (0.9)              | 12 (1.1)             | 12 (1.1)          |         |
| EHRA score               |                |                      |                      |                   | 0.650   |
| 1                        | 1656 (54.6)    | 590 (55.2)           | 623 (55.6)           | 443 (52.6)        |         |
| 2                        | 1059 (34.9)    | 371 (34.7)           | 384 (34.3)           | 304 (36.1)        |         |
| 3                        | 174 (5.7)      | 55 (5.1)             | 62 (5.5)             | 57 (6.8)          |         |
| 4                        | 27 (0.9)       | 7 (0.7)              | 10 (0.9)             | 10 (1.2)          |         |
| Unknown                  | 115 (3.8)      | 45 (4.2)             | 41 (3.7)             | 29 (3.4)          |         |
| Heart failure            | 1071 (35.3)    | 275 (25.7)           | 383 (34.2)           | 413 (49.0)        | <0.001  |
| Hypertension             | 2720 (89.7)    | 964 (90.3)           | 1004 (89.6)          | 752 (89.2)        | 0.745   |
| Diabetes mellitus        | 702 (23.2)     | 275 (25.7)           | 247 (22.1)           | 180 (21.4)        | 0.042   |
| History of cerebral infarction/TIA | 532 (17.6) | 151 (14.1)           | 217 (19.4)           | 164 (19.5)        | 0.001   |
| History of PAD/MI        | 287 (9.5)      | 101 (9.5)            | 99 (8.8)             | 87 (10.3)         | 0.540   |
| History of bleeding requiring hospitalization | 54 (1.8) | 16 (1.5)             | 22 (2.0)             | 16 (1.9)          | 0.681   |
| Liver dysfunction        | 487 (16.1)     | 211 (19.8)           | 157 (14.0)           | 119 (14.1)        | <0.001  |
| Habitual drinking        | 407 (13.4)     | 192 (18.0)           | 149 (13.3)           | 66 (7.8)          | <0.001  |
| Antiplatelet drugs       | 558 (18.4)     | 196 (18.4)           | 210 (18.8)           | 152 (18.0)        | 0.919   |
| CHADS2 score             |                |                      |                      |                   |         |
| Consecutive value        | 2.8±1.1        | 2.7±1.0              | 2.8±1.1              | 3.0±1.1           | <0.001  |
| Category                 |                |                      |                      |                   | <0.001  |
| 0                        | 0 (0.0)        | 0 (0.0)              | 0 (0.0)              | 0 (0.0)           |         |
| 1                        | 164 (5.4)      | 68 (6.4)             | 65 (5.8)             | 31 (3.7)          |         |
| 2                        | 1187 (39.2)    | 479 (44.9)           | 436 (38.9)           | 272 (32.3)        |         |
| 3                        | 974 (32.1)     | 308 (28.8)           | 349 (31.2)           | 317 (37.6)        |         |
| 4                        | 451 (14.9)     | 149 (14.0)           | 163 (14.6)           | 139 (16.5)        |         |
| 5                        | 206 (6.8)      | 46 (4.3)             | 90 (8.0)             | 70 (8.3)          |         |
| 6                        | 49 (1.6)       | 18 (1.7)             | 17 (1.5)             | 14 (1.7)          |         |

(Continued)
drugs (anticoagulants and antiplatelet drugs) during the observation period, change or no change in dose, and date of change. The patient data were anonymized and imported into the EDC in a nonpersonally identifiable format. Data were securely managed by an external third party commissioned by the Cardiovascular Institute Academic Research Organization (CVI ARO).

### Statistical Analysis

The primary efficacy end point was stroke or systemic embolism, and the primary safety end point was bleeding requiring hospitalization. The secondary end points were total deaths or cardiovascular deaths. Cases with dropout, withdrawal of consent, or missing age data were excluded from all registered cases and subgroup analysis. The target population for the analysis was divided into 3 age groups: 75 to 79, 80 to 84, and ≥85 years. The cutoff age of 85 years was selected in accordance with previous studies.\(^{14,27,28}\) The cutoff age of 80 years was used to balance the number of patients among the 3 age groups.

First, the baseline characteristics were compared between the groups. Second, the event incidences and their 95% CIs were calculated with the person-years method, and the incidence trends among the age groups were examined using a Cochran–Armitage trend test. Moreover, the cumulative event incidence rates were calculated using the Kaplan–Meier method, and the differences between the age groups were tested with the log-rank test. Third, the univariate Cox proportional hazard model was conducted to calculate the hazard ratios (HRs) and 95% CIs for the incidence of clinical events between the age groups. To evaluate whether each clinical event was age-specific, the age groups were forcibly introduced into the multivariable model, and the factors that were significant in the univariate analysis were also forcibly entered for adjustment (model 1). The factors for adjustment were composed of the relevant thromboembolic or bleeding

| Table 1. Continued |
|-------------------|
|                   |
| **CHA2DS2-VASc score** |
|                   |
| **Total (N=3031)** | **Age 75–79 y (n=1068)** | **Age 80–84 y (n=1120)** | **Age ≥85 y (n=843)** | **P Value** |
|                   |
| Consecutive value | 4.4±1.2 | 4.2±1.2 | 4.4±1.2 | 4.7±1.2 | <0.001 |
| Category          |        |        |        |        | <0.001 |
| 0                 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 1                 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 2                 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 3                 | 36 (1.2) | 15 (1.4) | 12 (1.1) | 18 (2.1) |
| 4                 | 104 (3.4) | 45 (4.1) | 35 (3.1) | 44 (5.1) |
| 5                 | 211 (6.9) | 104 (9.8) | 101 (8.8) | 106 (12.5) |
| 6                 | 205 (6.8) | 91 (8.5) | 86 (7.6) | 119 (13.9) |
| 7                 | 160 (5.3) | 68 (6.3) | 59 (5.2) | 92 (10.8) |
| 8                 | 102 (3.4) | 42 (3.9) | 32 (2.8) | 68 (8.1) |
| 9                 | 64 (2.1) | 27 (2.5) | 22 (1.9) | 37 (4.4) |

| HAS-BLED score | **Total (N=3031)** | **Age 75–79 y (n=1068)** | **Age 80–84 y (n=1120)** | **Age ≥85 y (n=843)** | **P Value** |
|----------------|-------------------|--------------------------|--------------------------|----------------------|---------|
| Consecutive value | 2.4±0.8 | 2.4±0.8 | 2.4±0.8 | 2.4±0.7 | 0.102 |
| Category          |        |        |        |        | 0.158 |
| 0                 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 1                 | 198 (6.5) | 72 (6.7) | 74 (6.6) | 52 (6.2) |
| 2                 | 1666 (54.6) | 567 (53.1) | 604 (53.9) | 485 (57.5) |
| 3                 | 901 (29.7) | 331 (31.0) | 321 (28.7) | 249 (29.5) |
| 4                 | 253 (8.3) | 91 (8.5) | 110 (9.8) | 52 (6.2) |
| 5                 | 22 (0.7) | 6 (0.6) | 11 (1.0) | 5 (0.6) |
| 6                 | 1 (0.0) | 1 (0.1) | 0 (0.0) | 0 (0.0) |
| 7                 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 8                 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 9                 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Data are presented as number (percentage) or mean±SD. Chi-square test was used for categorical variables. One-way ANOVA or Kruskal–Wallis test was used for continuous variables.

AF indicates atrial fibrillation; BP, blood pressure; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; MI, myocardial infarction; PAD, peripheral artery disease; and TIA, transient ischemic attack.
risk scores (ie, CHADS\textsubscript{2}, CHA\textsubscript{2}-DS\textsubscript{2}-VASc, and HAS-BLED scores) as follows: age, male sex, heart failure, hypertension, diabetes mellitus, history of cerebral infarction or transient ischemic attack, history of myocardial infarction or peripheral artery disease, history of bleeding requiring hospitalization, liver dysfunction, renal dysfunction (estimated glomerular filtration rate <45 mL/min per 1.73 m\textsuperscript{2}), habitual drinking, and use of antiplatelet drugs. In addition, another multivariable model was developed using ages as consecutive values (model 2). The proportional hazards assumption was confirmed using Schoenfeld residuals or visual inspections of the Kaplan–Meier survival curves. The discrimination performance of the different models was tested using Harrell concordance statistics (C statistics). Statistical analysis was performed using SAS version 9.4 software (SAS Institute Inc). In all analyses, \( P \) values <0.05 were considered to indicate statistical significance.

### RESULTS

Of the 3066 cases registered in the J-ELD AF Registry from 110 participating institutions, 35 were excluded (lost to follow-up during the whole period, \( n=26 \); withdrawal of consent, \( n=9 \)), and the remaining 3031 cases (mean age, 82±5 years; 48% women) were adopted as the target population for this subgroup analysis.

### Patient Characteristics

The distribution of age in the present analysis is shown in Figure 1. The numbers of patients aged 75 to 79 years, 80 to 84 years, and ≥85 years were 1068 (35.2%), 1120 (37.0%), and 843 (27.8%), respectively, and their baseline characteristics are presented in Table 1. Most patients (86.0%) in the age group 75 to 79 years received the standard apixaban dose, and most patients (88.8%) in the age group ≥85 years received the reduced apixaban dose.
Figure 3. Kaplan–Meier curves for the outcomes according to age category. Cumulative incidence rates of (A) stroke or systemic embolism, (B) bleeding requiring hospitalization, (C) total death, and (D) cardiovascular death are compared between the 3 age groups using the log-rank test.
Patients aged ≥85 years included more women and had lower body weights, diastolic blood pressures, serum creatinine levels, and estimated glomerular filtration rates. They had more cases of permanent AF and heart failure, and history of cerebral infarction/transient ischemic attack as comorbidities. Conversely, they had fewer cases of diabetes mellitus, liver dysfunction, and habitual drinking. No significant differences in systolic blood pressure, pulse rate, European Heart Rhythm Association score distribution, hypertension prevalence, history of peripheral artery disease, myocardial infarction, history of bleeding, or number of patients taking antiplatelet drugs were found among the age groups.

The CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores for assessing the risk of stroke in patients with AF and the HAS-BLED scores for assessing the risk of bleeding were 2.7±1.0, 4.2±1.2, and 2.4±0.8 for the age group 75 to 79 years; 2.8±1.1, 4.4±1.2, and 2.4±0.8 for the age group 80 to 84 years; and 3.0±1.1, 4.7±1.2, and 2.4±0.7 for the age group ≥85 years, respectively. The CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores showed significant differences between the age groups (P<0.001).

### Clinical Outcomes

The incidence rates of the clinical outcomes in the entire study population and different age groups are described in Figure 2. In all of the age groups, the incidence rates of stroke or systemic embolism and bleeding requiring hospitalization were equivalent. In patients aged ≥85 years, the incidence rate of total death was notably higher than that of the other events, but most deaths were of noncardiovascular causes. The impact of age on each clinical outcome is described in the following.

#### Stroke or Systemic Embolism

The incidence rates of stroke or systemic embolism were 1.40, 1.55, and 1.95 per 100 person-years in patients aged 75 to 79, 80 to 84, and ≥85 years (Figure 2). No significant differences were found among the 3 groups (log-rank test, P=0.647; Figure 3A). Among the events of stroke or systemic embolism, about two thirds were ischemic stroke and the remaining one third were hemorrhagic stroke. These ratios were almost similar between the 3 age groups (Table 2). Multivariable Cox regression analysis revealed that neither age 80 to 84 years

| Table 2. | Detailed Event Incidence Number and Rate By Age Category |
|----------|---------------------------------------------------------|
|          | Total (N=3031) | Age 75–79 y (n=1068) | Age 80–84 y (n=1120) | Age ≥85 y (n=843) |
| Stroke or systemic embolism | 45 (14.8)* | 14 (13.1)* | 16 (14.3)* | 15 (17.8)* |
| Ischemic stroke | 33 (10.9) | 10 (9.4) | 12 (10.7) | 11 (13.0) |
| Hemorrhagic stroke | 14 (4.6) | 4 (3.7) | 5 (4.5) | 5 (5.9) |
| Systemic embolism | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Bleeding requiring hospitalization | 53 (17.5)* | 17 (15.9)* | 16 (14.3)* | 20 (23.7)* |
| Intracranial hemorrhage | 15 (4.9) | 4 (3.7) | 5 (4.5) | 6 (7.1) |
| Upper gastrointestinal bleeding | 9 (3.0) | 3 (2.8) | 4 (3.6) | 2 (2.3) |
| Lower gastrointestinal bleeding | 12 (4.0) | 4 (3.7) | 3 (2.7) | 5 (5.9) |
| Gastrointestinal bleeding, site unknown | 7 (2.3) | 2 (1.9) | 2 (1.8) | 3 (3.6) |
| Others | 10 (3.3) | 4 (3.7) | 2 (1.8) | 4 (4.7) |
| Cardiovascular and noncardiovascular deaths | | | | |
| Total death | 89 (29.4)* | 21 (19.7)* | 27 (24.1)* | 41 (48.6)* |
| Noncardiovascular death | 62 (20.5) | 17 (15.9) | 16 (14.2) | 29 (34.4) |
| Cardiovascular death | 27 (8.9)* | 4 (3.7)* | 11 (9.8)* | 12 (14.2)* |
| Ischemic stroke | 2 (0.7) | 1 (0.9) | 1 (0.9) | 0 (0.0) |
| Hemorrhagic stroke | 1 (0.3) | 0 (0.0) | 1 (0.9) | 0 (0.0) |
| Bleeding requiring hospitalization | 1 (0.3) | 0 (0.0) | 1 (0.9) | 0 (0.0) |
| Heart failure | 20 (6.6) | 2 (1.9) | 6 (5.4) | 12 (14.2) |
| Myocardial infarction | 1 (0.3) | 0 (0.0) | 1 (0.9) | 0 (0.0) |
| Ventricular arrhythmia | 1 (0.3) | 1 (0.9) | 0 (0.0) | 0 (0.0) |
| Sudden death | 2 (0.7) | 0 (0.0) | 2 (1.8) | 0 (0.0) |

Data are presented as number (permillage).

*The end points of the J-ELD AF registry.
(HR, 1.05; 95% CI, 0.51–2.15) nor age ≥85 years (HR, 1.32; 95% CI, 0.63–2.73) was an independent risk factor for stroke or systemic embolism as compared with the age 75 to 79 years (Table 3: model 1). The results were consistent when age was included as a numerical variable (HR, 1.04; 95% CI, 0.97–1.10 [Table 3: model 2]). Harrell C statistical values for multivariable models 1 and 2 were 0.629 (95% CI, 0.543–0.717) and 0.642 (95% CI, 0.552–0.731), respectively.

### Table 3. Risk Factors for Stroke or Systemic Embolism

|                        | Univariate Model |          | Multivariable Model 1 |          | Multivariable Model 2 |          |
|------------------------|------------------|----------|-----------------------|----------|-----------------------|----------|
|                        | HR (95% CI)      | P Value  | HR (95% CI)           | P Value  | HR (95% CI)           | P Value  |
| Age 75–79 y            | 1.00 (reference) | 0.786    | 1.00 (reference)      | ...      | ...                   | ...      |
| Age 80–84 y            | 1.10 (0.54–2.26) | 0.368    | 1.05 (0.51–2.15)      | 0.898    | ...                   | ...      |
| Age ≥85 y              | 1.40 (0.67–2.89) | 0.372    | 1.32 (0.63–2.73)      | 0.461    | ...                   | ...      |
| Age (consecutive value)| 1.04 (0.98–1.11) | 0.198    | ...                   | ...      | 1.04 (0.97–1.10)      | 0.254    |
| Female sex             | 0.85 (0.47–1.54) | 0.591    | ...                   | ...      | ...                   | ...      |
| Heart failure          | 0.53 (0.26–1.06) | 0.073    | ...                   | ...      | ...                   | ...      |
| Hypertension           | 1.63 (0.51–5.27) | 0.412    | ...                   | ...      | ...                   | ...      |
| Diabetes mellitus      | 1.07 (0.54–2.10) | 0.855    | ...                   | ...      | ...                   | ...      |
| History of cerebral infarction/TIA | 2.33 (1.26–4.34) | 0.007    | 2.29 (1.23–4.27)      | 0.009    | 2.27 (1.22–4.22)      | 0.010    |
| History of PAD/MI      | 0.95 (0.34–2.67) | 0.930    | ...                   | ...      | ...                   | ...      |
| History of bleeding requiring hospitalization | 4.11 (1.27–13.27) | 0.018    | 4.02 (1.24–12.96)     | 0.020    | 4.03 (1.25–13.00)     | 0.020    |
| Liver dysfunction      | 1.16 (0.54–2.49) | 0.706    | ...                   | ...      | ...                   | ...      |
| eGFR <45 mL/min per 1.73 m² | 0.85 (0.44–1.64) | 0.623    | ...                   | ...      | ...                   | ...      |
| Habitual drinking      | 1.87 (0.92–3.77) | 0.082    | ...                   | ...      | ...                   | ...      |
| Antiplatelet drugs     | 1.14 (0.55–2.36) | 0.727    | ...                   | ...      | ...                   | ...      |

Hazard ratios (HRs) and 95% CIs were calculated for each variable using Cox proportional hazards model. In the multivariable analysis, age was forcibly entered as categorical and consecutive variables in models 1 and 2, respectively. In model 1, the age group 75 to 79 y was adopted as a reference. Variables that were significant in the univariate analysis were also entered in the multivariable models for adjustment.

eGFR indicates estimated glomerular filtration rate; MI, myocardial infarction; PAD, peripheral artery disease; and TIA, transient ischemic attack.

**Bleeding Requiring Hospitalization**

The incidence rates of bleeding requiring hospitalization were 1.70, 1.55, and 2.61 per 100 person-years in the age groups 75 to 79, 80 to 84, and ≥85 years, respectively (Figure 2), with no significant differences among the 3 age groups (log-rank test, P=0.325; Figure 3B). Among the bleeding events requiring hospitalization, bleeding in the gastrointestinal tract accounted for about half of the events in all of the age groups (Table 2). The multivariable Cox regression analysis revealed that neither age 80 to 84 years (HR, 0.83; 95% CI, 0.42–1.65) nor age ≥85 years (HR, 1.25; 95% CI, 0.64–2.44) was an independent risk factor for bleeding requiring hospitalization as compared with age 75 to 79 years (Table 4: model 1). The results were consistent when age was included as a numerical variable (HR, 1.03; 95% CI, 0.97–1.10 [Table 4: model 2]). Harrell C statistical values for multivariable models 1 and 2 were 0.663 (95% CI, 0.588–0.737) and 0.662 (95% CI, 0.586–0.737), respectively.

**Total Death**

The incidence rates of total death were 2.09, 2.60, and 5.29 per 100 person-years in the age groups 75 to 79, 80 to 84, and ≥85 years, respectively (Figure 2), with significant differences among the 3 groups (log-rank test, P<0.001; Figure 3C). Of the total deaths, ≈70% were noncardiovascular deaths (Table 2). Although age 80 to 84 years (HR, 1.09; 95% CI, 0.61–1.93) was not a risk factor for total death, age ≥85 years (HR, 1.89; 95% CI, 1.10–3.26) was found to be an independent risk factor as compared with age 75 to 79 years in the multivariable Cox regression analysis (Table 5: model 1). Similarly, age was an independent predictor of total death when it was evaluated as a numerical variable (HR, 1.04; 95% CI, 0.97–1.10 [Table 5: model 2]). Harrell C statistical values for multivariable models 1 and 2 were 0.688 (95% CI, 0.634–0.742) and 0.691 (95% CI, 0.637–0.745), respectively.
Cardiovascular Death

The incidence rates of cardiovascular death were 0.40, 1.06, and 1.55 per 100 person-years in the age groups 75 to 79, 80 to 84, and ≥85 years, respectively (Figure 2), with a significant difference among the 3 groups (log-rank test, \( P = 0.045 \); Figure 3D). Among the cases of cardiovascular death, those caused by heart failure was the most common. The number of deaths caused by ischemic stroke, hemorrhage stroke, and bleeding was 2 (0.7%), 1 (0.3%), and 1 (0.3%), respectively (Table 2).

The multivariable Cox regression analysis revealed that neither age 80 to 84 years (HR, 2.17; 95% CI, 0.69–6.86) nor age ≥85 years (HR, 2.54; 95% CI, 0.80–8.04) was an independent risk factor for cardiovascular death as compared with age 75 to 79 years (Table 6: model 1). Conversely, age was an independent predictor of cardiovascular death when it was evaluated as a numerical variable (HR, 1.09; 95% CI, 1.01–1.17 [Table 6: model 2]). Harrell C statistical values for multivariable models 1 and 2 were 0.764 (95% CI, 0.676–0.851) and 0.776 (95% CI, 0.687–0.865), respectively.

### DISCUSSION

In this study, on-label doses of apixaban were administered to Japanese elderly patients with AF aged ≥75 years, and 1-year outcomes were analyzed for the 3 age groups. Although the incidence rates of stroke or systemic embolism, bleeding requiring hospitalization, and cardiovascular deaths were numerically higher in patients aged ≥85 years than in those aged 75 to 79 and 80 to 84 years, age ≥85 years was not an independent risk factor for those events in the multivariable Cox regression analysis.

Management with oral anticoagulants in the very elderly (aged ≥85 years) is challenging because of the need to carefully balance the risk of thromboembolism with that of hemorrhage. To date, clinical trials have not specifically targeted very elderly patients, and most study participants are not representative of patients aged ≥85 years. In this subanalysis of the J-ELD AF Registry, the event rates of stroke or systemic embolism and bleeding requiring hospitalization in 843 patients aged ≥85 years were 1.95 and 2.61 per 100 person-years, respectively. Although the incidence rates should differ according to the patient characteristics of each cohort, the incidence rate of stroke or systemic embolism in the J-ELD AF Registry was lower than that in the other registries that examined patients aged ≥85 years. A population-based study that used data from electronic records of general practices in Darlington, England, showed that the incidence of

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**Table 4. Risk Factors for Bleeding Requiring Hospitalization**

|                     | Univariate Model |                           |                           |                           |
|---------------------|-----------------|---------------------------|---------------------------|---------------------------|
|                     | HR (95% CI)     | \( P \text{ Value} \)    | HR (95% CI)              | \( P \text{ Value} \)    |
| Age 75–79 y         | 1.00 (reference)| ...                       | 1.00 (reference)          | ...                       |
| Age 80–84 y         | 0.91 (0.46–1.80)| 0.787                     | 0.83 (0.42–1.65)          | 0.589                     |
| Age ≥85 y           | 1.46 (0.76–2.80)| 0.260                     | 1.25 (0.64–2.44)          | 0.512                     |
| Age (consecutive value) | 1.05 (0.99–1.11) | 0.124 | ... | ... |
| Female sex          | 0.99 (0.57–1.69)| 0.965                     | ...                       | ...                       |
| Heart failure       | 1.06 (0.61–1.87)| 0.827                     | ...                       | ...                       |
| Hypertension        | 0.89 (0.38–2.08)| 0.785                     | ...                       | ...                       |
| Diabetes mellitus   | 0.89 (0.45–1.72)| 0.719                     | ...                       | ...                       |
| History of cerebral infarction/TIA | 0.97 (0.47–1.98) | 0.926 | ... | ... |
| History of PAD/MI   | 2.06 (1.00–4.22)| 0.049                     | 1.41 (0.63–3.12)          | 0.403                     |
| History of bleeding requiring hospitalization | 3.51 (1.09–11.25) | 0.035 | 3.85 (1.19–12.43) | 0.024 |
| Liver dysfunction   | 1.44 (0.74–2.80)| 0.283                     | ...                       | ...                       |
| eGFR <45 mL/min per 1.73 m² | 2.00 (1.16–3.45) | 0.012 | 1.84 (1.05–3.22) | 0.033 |
| Habitual drinking   | 1.00 (0.45–2.23)| 0.991                     | ...                       | ...                       |
| Antiplatelet drugs  | 2.02 (1.23–3.65)| 0.019                     | 1.80 (0.93–3.46)          | 0.080                     |

The hazard ratios (HRs) and 95% CIs were calculated for each variable using a Cox proportional hazards model. In the multivariable analysis, age was forcibly entered as categorical and consecutive variables in models 1 and 2, respectively. In model 1, the age group 75 to 79 y was adopted as a reference. Variables that were significant in the univariate analysis were also entered in the multivariable models for adjustment.

eGFR indicates estimated glomerular filtration rate; MI, myocardial infarction; PAD, peripheral artery disease; and TIA, transient ischemic attack.
stroke during 1-year follow-up was 5.2% in 561 patients aged ≥85 years. In PREFER in AF (Prevention of Thromboembolic Events—European Registry in Atrial Fibrillation), a prospective registry of patients with AF from 7 European countries, the incidence of stroke or systemic embolism was 4.8 per 100 person-years in 505 patients aged ≥85 years. Similar results were obtained in the subanalysis of Fushimi AF Registry, which performed follow-up in 479 Japanese patients with AF aged ≥85 years (5.1 per 100 person-years).

On the other hand, the incidence rate of bleeding in the J-ELD AF Registry was lower than that in the PREFER in AF (4.0 per 100 person-years) and comparable with that in the Fushimi AF Registry (2.0 per 100 person-years). In the PREFER in AF, bleeding events were defined in accordance with the International Society for Thrombosis and Haemostasis (ISTH) criteria. Therefore, it may be inappropriate to directly compare the event rates. However, considering that most of the ISTH major bleeding events are assumed to result in hospitalization, the bleeding event rate was thought to be lower in the patients in the J-ELD AF Registry than in the PREFER in AF.

Several conceivable reasons can explain these results. First, the high prescription rate of oral anticoagulants (100% in the J-ELD AF Registry) would have contributed to the low incidence rate of stroke or systemic embolism. The above-mentioned registries permitted the use of aspirin/placebo in enrolled patients, and the prescription rates of oral anticoagulants in the very elderly patients were limited (78% in the PREFER in AF and 40% in the Fushimi AF Registry). In addition, warfarin was the primary oral anticoagulant used in the prior registries (92% in the PREFER in AF and 93% in the Fushimi AF Registry). A more prevalent use of direct oral anticoagulants would have decreased the incidence rates of stroke or systemic embolism and bleeding events. Second, the short-term (1-year) follow-up period of the prospective observational study might have prevented negative outcomes from occurring. The results could not be extrapolated to a long-term clinical course of >1 year. Finally, patient selection by the investigators would have also affected the results of the present study. Research physicians might not have enrolled very high-risk patients who were not suitable to receive long-term on-label doses of apixaban. However, the J-ELD AF Registry included >800 patients aged ≥85 years who were taking on-label doses of apixaban. This feature enabled us to evaluate the appropriateness of on-label doses of apixaban in very elderly patients.

Table 5. Risk Factors for Total Death

|                  | Univariate Model |                  |                  |                  | Multivariable Model 1 |                  |                  | Multivariable Model 2 |                  |
|------------------|------------------|------------------|------------------|------------------|-----------------------|------------------|------------------|-----------------------|------------------|
|                  | HR (95% CI)      | P Value          | HR (95% CI)      | P Value          | HR (95% CI)          | P Value          |
| Age 75–79 y      | 1.00 (reference) | …                | 1.00 (reference) | …                | …                    | …                |
| Age 80–84 y      | 1.25 (0.70–2.20) | 0.449            | 1.09 (0.61–1.93) | 0.775            | …                    | …                |
| Age ≥85 y        | 2.54 (1.50–4.29) | <0.001           | 1.89 (1.10–3.26) | 0.022            | …                    | …                |
| Age (consecutive value) | 1.09 (1.05–1.14) | <0.001           | …                | …                | 1.07 (1.02–1.11) | 0.003            |
| Female sex       | 0.66 (0.43–1.01) | 0.055            |                  |                  |                       |                  |
| Heart failure    | 2.85 (1.86–4.35) | <0.001           | 2.31 (1.49–3.59) | <0.001           | 2.27 (1.46–3.53) | <0.001           |
| Hypertension     | 1.18 (0.57–2.43) | 0.663            |                  |                  |                       |                  |
| Diabetes mellitus| 1.15 (0.71–1.85) | 0.569            |                  |                  |                       |                  |
| History of cerebral infarction/TIA | 0.65 (0.35–1.22) | 0.182            |                  |                  |                       |                  |
| History of PAD/MI| 1.97 (1.13–3.43) | 0.017            | 1.40 (0.75–2.59) | 0.288            | 1.39 (0.75–2.59) | 0.294            |
| History of bleeding requiring hospitalization | 1.95 (0.62–6.17) | 0.255            |                  |                  |                       |                  |
| Liver dysfunction| 1.27 (0.75–2.15) | 0.382            |                  |                  |                       |                  |
| eGFR <45 mL/min per 1.73 m² | 2.08 (1.37–3.15) | <0.001           | 1.49 (0.97–2.29) | 0.072            | 1.45 (0.94–2.24) | 0.090            |
| Habitual drinking | 0.64 (0.31–1.32) | 0.229            |                  |                  |                       |                  |
| Antiplatelet drugs | 1.76 (1.11–2.80) | 0.016            | 1.56 (0.93–2.60) | 0.091            | 1.56 (0.93–2.61) | 0.092            |

The hazard ratios (HRs) and 95% CIs were calculated for each variable using a Cox proportional hazards model. In the multivariable analysis, age was forcibly entered as categorical and consecutive variables in models 1 and 2, respectively. In model 1, the age group 75 to 79 years was adopted as a reference. Variables that were significant in the univariate analysis were also entered in the multivariable models for adjustment.

eGFR indicates estimated glomerular filtration rate; MI, myocardial infarction; PAD, peripheral artery disease; and TIA, transient ischemic attack.
Although previous studies demonstrated that the incidence rates of stroke and bleeding increases with age,\(^6,7\) age ≥85 years was not an independent risk factor for stroke or systemic embolism and major bleeding events in the J-ELD AF Registry. The limited number of events during the short-term follow-up may have affected the results, but the prescription of on-label doses of apixaban may help reduce the incidence of stroke with a reasonable bleeding event rate in very elderly patients. Furthermore, although age ≥85 years was a risk factor for total death in the J-ELD AF Registry, none of the patients died of stroke or systemic embolism and bleeding requiring hospitalization in this age group. It may be a coincidence that none of the patients developed AF- or anticoagulant-related death in this population. However, we can probably conclude that death from a non–AF-related cause is predominant in very elderly patients who are taking on-label doses of apixaban. To sum up, the results of the J-ELD AF Registry indicated that stroke and major bleeding were well balanced under the on-label administration of apixaban in patients aged ≥85 years who were at high risk of cardiovascular and noncardiovascular deaths.

With the progress of an aging society, further evidence of antithrombotic therapy in the very elderly patients is required. Considering the benefit of oral anticoagulants over antiplatelet therapy in real-world studies\(^\text{29}\) and the consistent benefit of direct oral anticoagulants over warfarin in the elderly cohorts of randomized controlled trials,\(^8-12\) the use of direct oral anticoagulants should be the first choice of antithrombotic therapy even in very elderly patients. A recently published meta-analysis of randomized controlled trials revealed that apixaban appears to provide the best combination of efficacy and safety in patients aged >75 years.\(^12\) In the present study, we confirmed that the efficacy and safety of appropriate doses of apixaban were maintained in patients aged ≥85 years. Because large-scale randomized controlled trials targeting very elderly patients are not feasible, real-world data would help dispel these uncertainties in patients aged ≥85 years.

### Study Limitations

The present study has several limitations. First, this J-ELD AF Registry was a single-arm prospective observational study; therefore, no control arm was included with which the effect of apixaban was compared. Second, patient selection bias was possible. The data in this registry were derived from institutions that specialized in cardiology and in the management for cardiac arrhythmias. Thus, patients with relatively...
well-managed AF might have been included in this study. The patients’ health conditions and medical environment might have affected the incidence rates of events. Third, the outcome events were reported by each participating center, and a central adjudication was not performed. However, by simplifying the definitions of stroke and bleeding events, we believe that the variation in the local diagnosis between participating centers was modest. Fourth, the status of treatment adherence, discontinuation, or change to other anticoagulants, which would affect patient outcomes, was not recorded in the present study. Fifth, the risk factors other than age that were identified in the multivariable models were appealing. They may have been elderly-specific, but this is not conclusive because data on younger controls (<75 years) were not available in the J-ELD AF Registry. Last, this study did not include patients taking off-label underdoses of apixaban, which is common in real-world clinical practice. The benefit of using off-label underdoses of apixaban, which is lower than the recommended dose, is unknown. However, it is possible to use lower doses of apixaban in patients with AF receiving on-label doses of apixaban.

CONCLUSIONS
This subgroup analysis stratified by age was based on the data of >3000 Japanese elderly patients with AF aged ≥75 years. Although age ≥85 years was a significant risk factor for total death, it was not an independent risk factor for stroke or systemic embolism, bleeding requiring hospitalization, or cardiovascular death in patients with AF receiving on-label doses of apixaban.

ARTICLE INFORMATION
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 Supplementary Material
Data S1

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Okada et al  Outcomes of Very Elderly Patients Using Apixaban

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List of 110 participating institutions in the J-ELD AF Registry

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