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ORIGINAL RESEARCH

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

Masato Okada, MD; Koichi Inoue, MD, PhD; Nobuaki Tanaka, MD; Yasushi Sakata, MD, PhD; Masaharu Akao, MD, PhD; Takeshi Yamashita, MD, PhD; Shinya Suzuki, MD, PhD; Ken Okumura, MD, PhD; J-ELD AF investigators*

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

Atrial fibrillation (AF) is a traditional risk factor for stroke and systemic embolism,[1] and its prevalence increases with age.[2,3] While the efficacy of oral anticoagulants for stroke prevention in patients with AF has been demonstrated,[4] oral anticoagulants are associated with side effects of bleeding. Therefore, their advantages and disadvantages should be carefully weighed before administration.

Owing to the reduction of liver metabolism and/or renal clearance, elderly patients are prone to experience medication-associated complications.[5] As the incidence of bleeding complications increases with age,[6,7]

Correspondence to: Koichi Inoue, MD, PhD, Cardiovascular Division, National Hospital Organization Osaka National Hospital, 2-1-14 Hoenzaka, Chuo-ku, Osaka 540-0006, Japan. E-mail: koichi@inoue.name

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CLINICAL PERSPECTIVE

What Is New?

- Data on outcomes of very elderly patients (aged ≥85 years) receiving appropriate antithrombotic therapy are limited.
- 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.

Nonstandard Abbreviations and Acronyms

EDC	Electronic Data Capture
ISTH	International Society for Thrombosis and Haemostasis
J-ELD AF	Multicenter Prospective Cohort Study to Investigate the Effectiveness and Safety of Apixaban in Japanese Elderly Atrial Fibrillation Patients
PREFER in AF	Prevention of Thromboembolic Events—European Registry in Atrial Fibrillation

physicians are often faced with the challenging problem of whether oral anticoagulants should be administered to elderly patients with AF. Although a subanalysis of randomized controlled trials proved the consistent efficacy of oral anticoagulants in patients aged ≥75 or ≥80 years,[8–12] physicians remain reluctant to use anticoagulants in elderly patients in the real-world setting,[13–15] probably considering their underlying characteristics such as poor adherence,[16] concurrent cognitive disorders,[17] frailty,[18] and multicomorbidities.[19] A meta-analysis of epidemiological studies in Japan revealed that the prevalence rates of frailty in patients aged 70 to 74, 75 to 79, 80 to 84, and ≥85 years were 3.8%, 10.0%, 20.4%, and 35.1%, respectively.[20] These data suggest a rapid deterioration of general conditions of elderly patients after the age of 75 years. Therefore, real-world data on outcomes of very elderly patients aged ≥85 years are required particularly in an aging society.[21]

In the present study, data from the J-ELD AF Registry (Multicenter Prospective Cohort Study to Investigate the Effectiveness and Safety of Apixaban in Japanese Elderly Atrial Fibrillation Patients) were subanalyzed by different age groups (75–79 years versus 80–84 years versus ≥85 years). The J-ELD AF Registry is a large-scale, multicenter prospective observational study of Japanese patients with nonvalvular AF aged ≥75 years who were taking on-label doses of apixaban.[22,23] The baseline characteristics and annual event rates were compared between the age groups, and the impact of age on each event was evaluated in this subanalysis.

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 (eg, 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 m^2)=194×(serum creatinine)$^{-1.094}$×(age)$^{-0.287}$×0.739 (if female). Stroke risk was assessed using the $CHADS_2$ 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.[24] The CHA_2DS_2-VASc score is a refinement of the $CHADS_2$ 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.[25] 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.[26] 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

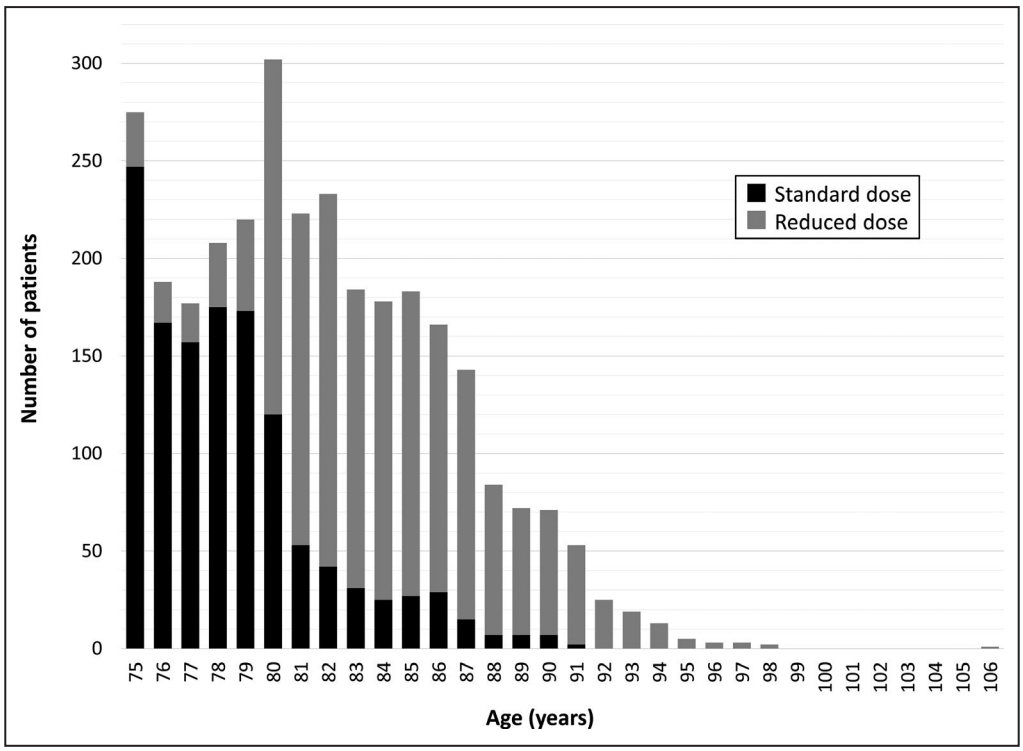


Figure 1. Distribution of age in the J-ELD AF Registry (Multicenter Prospective Cohort Study to Investigate the Effectiveness and Safety of Apixaban in Japanese Elderly Atrial Fibrillation Patients).
The black and gray parts of each bar represent the number of patients with standard and reduced doses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

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	68.6±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 m^2	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 m^2	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
$CHADS_2$ 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*)

Table 1. Continued

	Total (N=3031)	Age 75–79 y (n=1068)	Age 80–84 y (n=1120)	Age ≥85 y (n=843)	*P* Value
CHA_2DS_2-VASc score					
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	87 (2.9)	43 (4.0)	28 (2.5)	16 (1.9)	
3	612 (20.2)	282 (26.4)	217 (19.4)	113 (13.4)	
4	1065 (35.1)	377 (35.3)	404 (36.1)	284 (33.7)	
5	729 (24.1)	223 (20.9)	257 (22.9)	249 (29.5)	
6	357 (11.8)	100 (9.4)	142 (12.7)	115 (13.6)	
7	143 (4.7)	36 (3.4)	56 (5.0)	51 (6.0)	
8	33 (1.1)	6 (0.6)	15 (1.3)	12 (1.4)	
9	5 (0.2)	1 (0.1)	1 (0.1)	3 (0.4)	
HAS-BLED score					
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	1656 (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.

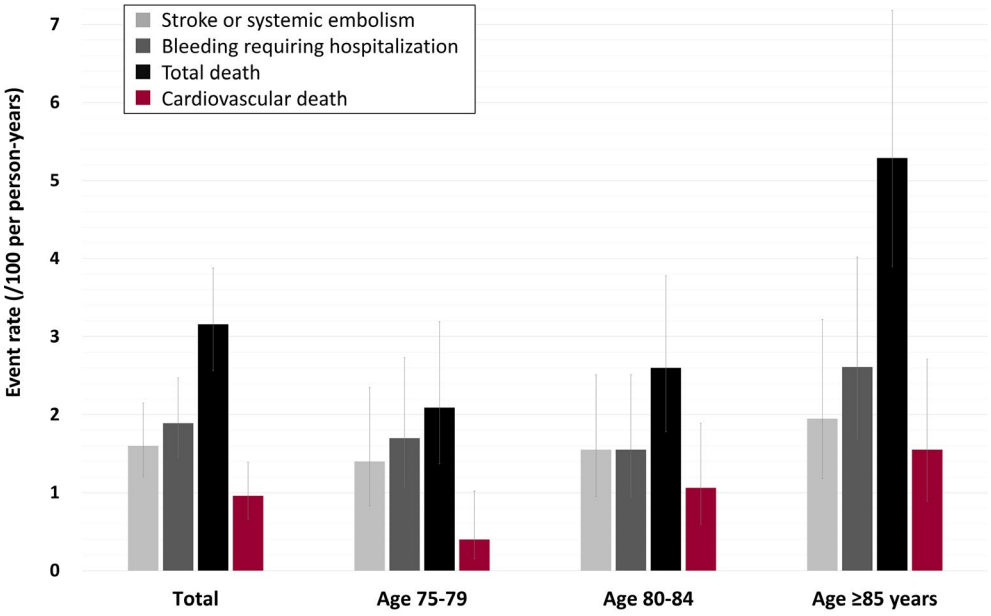
AF indicates atrial fibrillation; BP, blood pressure; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; MI, myocardial infarction; PAD, peripheral artery disease; and TIA, transient ischemic attack.

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



	Total	Age 75-79	Age 80-84	Age ≥85
Stroke or systemic embolism				
Number of events/ person-years	45 / 2805	14 / 1001	16 / 1035	15 / 769
Incidence rate (95% CI)	1.60 (1.20-2.15)	1.40 (0.83-2.35)	1.55 (0.95-2.51)	1.95 (1.18-3.22)
Bleeding requiring hospitalization				
Number of events/ person-years	53 / 2801	17 / 999	16 / 1034	20 / 768
Incidence rate (95% CI)	1.89 (1.45-2.47)	1.70 (1.06-2.73)	1.55 (0.95-2.51)	2.61 (1.69-4.02)
Total death				
Number of events/ person-years	89 / 2821	21 / 1006	27 / 1040	41 / 775
Incidence rate (95% CI)	3.16 (2.56-3.88)	2.09 (1.37-3.19)	2.60 (1.78-3.78)	5.29 (3.90-7.18)
Cardiovascular death				
Number of events/ person-years	27 / 2821	4 / 1006	11 / 1040	12 / 775
Incidence rate (95% CI)	0.96 (0.66-1.39)	0.40 (0.15-1.02)	1.06 (0.59-1.89)	1.55 (0.89-2.71)

Figure 2. Event incidence rates by age category.
Event incidence rates (95% CIs) per 100 person-years are described in all patients and different age groups.

risk scores (ie, $CHADS_2$, CHA_2DS_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^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.

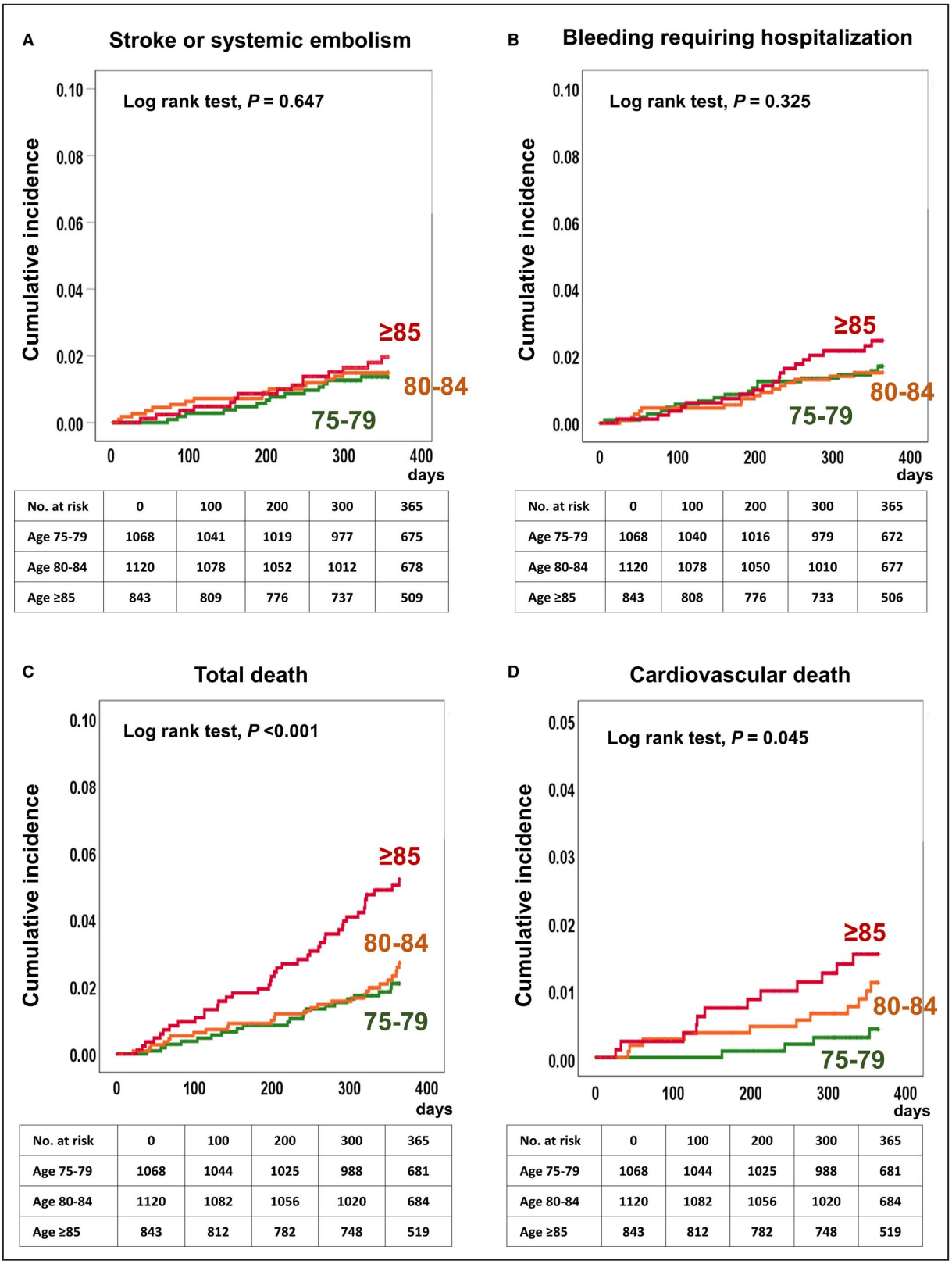


Figure 3. Kaplan–Meier curves for the outcomes according to age category.
Cumulative incidence rates of (**A**) stroke or systemic embolism, (**B**) bleeding requiring hospitalization, (**C**) total death, and (**D**) cardiovascular death are compared between the 3 age groups using the log-rank test.

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.

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 $CHADS_2$ and CHA_2DS_2-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 $CHADS_2$ and CHA_2DS_2-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 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 m^2	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.

(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.

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.

Table 4. Risk Factors for Bleeding Requiring Hospitalization

	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	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	…	…	1.03 (0.97–1.10)	0.275
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	1.41 (0.64–3.14)	0.397
History of bleeding requiring hospitalization	3.51 (1.09–11.25)	0.035	3.85 (1.19–12.43)	0.024	3.77 (1.17–12.13)	0.026
Liver dysfunction	1.44 (0.74–2.80)	0.283				
eGFR <45 mL/min per 1.73 m^2	2.00 (1.16–3.45)	0.012	1.84 (1.05–3.22)	0.033	1.78 (1.02–3.12)	0.043
Habitual drinking	1.00 (0.45–2.23)	0.991				
Antiplatelet drugs	2.02 (1.12–3.65)	0.019	1.80 (0.93–3.46)	0.080	1.78 (0.93–3.44)	0.084

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.

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

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 m^2	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.

stroke during 1-year follow-up was 5.2% in 561 patients aged ≥85 years.[14] 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.[27] 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).[28]

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 6. Risk Factors for Cardiovascular 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	2.67 (0.85–8.38)	0.093	2.17 (0.69–6.86)	0.188	…	…
Age ≥85 y	3.89 (1.26–12.07)	0.019	2.54 (0.80–8.04)	0.114	…	…
Age (consecutive value)	1.13 (1.05–1.21)	0.002	…	…	1.09 (1.01–1.17)	0.031
Female sex	0.45 (0.20–1.02)	0.057				
Heart failure	5.27 (2.23–12.46)	<0.001	4.03 (1.66–9.78)	0.002	3.87 (1.59–9.42)	0.003
Hypertension	1.45 (0.34–6.14)	0.610				
Diabetes mellitus	1.94 (0.89–4.24)	0.096				
History of cerebral infarction/TIA	0.58 (0.17–1.91)	0.368				
History of PAD/MI	2.77 (1.12–6.86)	0.028	2.27 (0.91–5.67)	0.080	2.31 (0.93–5.77)	0.072
History of bleeding requiring hospitalization	4.48 (1.06–18.90)	0.041	4.12 (0.97–17.51)	0.055	4.36 (1.03–18.49)	0.046
Liver dysfunction	1.54 (0.62–3.80)	0.354				
eGFR <45 mL/min per 1.73 m^2	2.50 (1.18–5.32)	0.017	1.58 (0.72–3.44)	0.253	1.53 (0.70–3.35)	0.282
Habitual drinking	0.81 (0.24–2.69)	0.733				
Antiplatelet drugs	1.9 (0.83–4.33)	0.129				

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 for 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[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 underdosing direct oral anticoagulants is controversial, but this is not within the scope of the present study.

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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Affiliations

Cardiovascular Center, Sakurabashi-Watanabe Hospital, Osaka, Japan (M.O., K.I., N.T.); Cardiovascular Division, National Hospital Organization Osaka National Hospital, Osaka, Japan (K.I.); Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka, Japan (Y.S.); Department of Cardiology, National Hospital Organization Kyoto Medical Center, Kyoto, Japan (M.A.); Department of Cardiovascular Medicine, The Cardiovascular Institute, Tokyo, Japan (T.Y., S.S.); and Division of Cardiology, Saiseikai Kumamoto Hospital, Kumamoto, Japan (K.O.).

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Supplementary Material

Data S1

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SUPPLEMENTAL MATERIAL

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

Caress Sapporo Hokko Memorial Clinic (Ichiro SAKUMA), Tosei General Hospital (Masayoshi AJIOKA), National Cerebral and Cardiovascular Center (Kengo KUSANO), Tokyo Dental College Ichikawa General Hospital (Takahiro OHKI), Kyoto University Graduate School of Medicine (Takeshi KIMURA), Kyoto Medical Center (Masaharu AKAO), Yamamashi Kousei Hospital (Tetsuya ASAKAWA), Tachikawa General Hospital (Masaaki OKABE), Uwajima City Hospital (Akiyoshi OGIMOTO), Toho University Faculty of Medicine (Takanori IKEDA), Nara Medical University Hospital (Taku NISHIDA), Kameda Medical Center (Akira MIZUKAMI), Tabuchi Cardiovascular Internal Medicine Clinic (Toshifumi TABUCHI), The Cardiovascular Institute (Takeshi YAMASHITA), Honjo Daiichi Hospital (Yasushi SUZUKI), Kitasato University (Junya AKO), Keio University Hospital (Seiji TAKATSUKI), Kitaishikai Hospital (Takumi SUMIMOTO), Tokyo Women`s Medical University (Nobuhisa HAGIWARA), Osaka General Medical Center (Takahisa YAMADA), Chikamori Hospital, Chikamori Health Care Group (Masahiko FUKATANI), Kanto Central Hospital (Nobuhiko ITO), Fukuda Memorial Hospital (Kohsuke NAKAJIMA), Japanese Red Cross Society Yamaguchi Hospital (Hiroyuki MICHISHIGE), National Hospital Organization Osaka National Hospital (Yukihiro KORETSUNE), Nakamura Memorial Hospital (Kenji KAMIYAMA), Ogori Daiichi General Hospital (Naoki SUGI), Yamato Municipal Hospital (Takaaki KUBO), Sendai City Hospital (Tetsuo YAGI), Hekinan Municipal Hospital (Atsushi SUGIURA), National Hospital Organization Tokyo Medical Center (Yukihiko MOMIYAMA), Oita Red Cross Hospital (Tetsu IWAO), Yao Municipal Hospital (Tetsuya WATANABE), Yuri Kumiai General Hospital (Tohru NAKANISHI), Fukushima Medical University Hospital (Yasuchika TAKEISHI), Okamisawa Clinic (Kunihiko KAMEDA), Dokkyo Medical University (Teruo INOUE), Saiseikai Kawaguchi General Hospital (Toshikazu FUNAZAKI), Nara Prefectural Seiwa Medical Center (Naofumi DOI), Osaka Police Hospital (Yoshiharu HIGUCHI), Tokyo Metropolitan Geriatric Hospital (Yusuke Tsuboko), Kitakami Saiseikai Hospital (Yoshihiro SATO), Machii Cardiovascular Internal Medicine Clinic (Kazuo MACHII), Tokyo Metropolitan Health and Medical Treatment Corporation Ebara Hospital (Yasunaga HIYOSHI), Ube-kohsan Central

Hospital (Masahiko HARADA), Kitano Hospital, Tazuke Kofukai Medical Research Institute (Moriaki INOKO), Hirakata Kohsai Hospital (Hiroyuki TAKENAKA), Kobe City Medical Center General Hospital (Yutaka FURUKAWA), Kokura Memorial Hospital (Kenji ANDO), Tenri Hospital (Yoshihisa NAKAGAWA), Hyogo Prefectural Amagasaki General Medical Center (Kazuyasu YOSHITANI), Shimabara Hospital (Mamoru TAKAHASHI), Mitsubishi Kyoto Hospital (Shinji MIKI), Koto Memorial Hospital (Tomoyuki MURAKAMI), Sakurabashi Watanabe Hospital (Koichi INOUE), Japan Community Health Care Organization Hoshigaoka Medical Center (Yuzuru TAKANO), Nippon Medical School (Wataru SHIMIZU), Daido Hospital (Tomoharu ARAKAWA), Tokushima University Graduate School (Masataka SATA), Mashiko Hospital (Shogo SHIMIZU), Hirosaki Stroke and Rehabilitation Center (Joji HAGII), Kashiwaba Neurosurgical Hospital (Tetsuyuki YOSHIMOTO), Sendai Cardiovascular Center (Shinya Fujii), Faculty of Medicine, Oita University (Naohiko TAKAHASHI), Tsuji Clinic (Hikari TSUJI), Yamato Kashihara Hospital (Tamio NAKAJIMA), Omori Internal Medicine and Cardiology Clinic (Masayuki WATANABE), Fujita Health University School of Medicine (Eiichi WATANABE), Oita Medical Center (Masaya ARIKAWA), Ota Clinic (Akira OTA), Ozaki Cardiology Clinic (Masaharu OZAKI), NHO Kumamoto Saishusou Hospital (Ikuo MISUMI), Kansai Rosai Hospital (Masaaki UEMATSU), Hatayama Clinic (Toru HATAYAMA), SATO Internal Medicine Pediatrics clinic (Atsushi SATO), Narita Medical Clinic (Hidetoshi NARITA), Toyamori Internal Medicine pediatrics clinic (Hiroshi TOYAMORI), St.Mary's Heart Clinic (Kazuhiro YOSHIDA), Furukawa Medical Clinic (Kayoko FURUKAWA), Iwate Medical University (Takashi KOMATSU), Yamaguchi University Graduate School of Medicine (Akihiko SHIMIZU), Shizuoka City Shizuoka Hospital (Tomoya ONODERA), Igarashi Clinic, Cardiology and Internal Medicine (Morio IGARASHI), Fujino Circulation Clinic (Takao FUJINO), Japan Community Health Care Organization Osaka Hospital (Shinji HASEGAWA), Suzuki Internal Medicine Clinic (Tomomi SUZUKI), Odawara municipal hospital (Masaru YUGE), Inoue Cardiology and Internal Medicine Clinic (Takeshi INOUE), Okidate Heart Clinic (Takeshi KUDO), Saien Heart Medical Clinic (Toshihiko KOEDA), Japanese Red Cross Society Fukushima Hospital (Takayuki OHWADA), Sumi Cardiovascular Clinic (Hirokuni SUMI), Takei Clinic (Jinko YAMABE), Iwate Prefectural Kamaishi Hospital (Mahito OZAWA), Medical Corporation Association Koukeikai Sugiura Clinic (Toshiyuki SUGIURA), Hirosaki

University Graduate School of Medicine (Ken OKUMURA and Hirofumi TOMITA), Kondo Internal Medicine Clinic (Kazuhiko KONDO), Chiba Surgical Hospital (Yasuhide MORIKAWA), Tokyo Women's Medical University, Yachiyo Medical Center (Shoji HARUTA), ISHIDA Medical Clinic (Shuji ISHIDA), Kindai University Nara Hospital (Manabu SHIROTANI), Nara Prefecture General Medical Center (Fumitaka INOUE), Kumamoto City Hospital (Koji SATO), National Hospital Organization Kumamoto Medical Center (Kazuteru FUJIMOTO), Tohoku Medical and Pharmaceutical University Hospital (Yoshiaki KATAHIRA), Awa Regional Medical Center (Akira MIZUKAMI), Horii Clinic (Norihiko MATSUMURA), JCHO Kumamoto General Hospital (Shinji TAYAMA), Japanese Red Cross Kumamoto Hospital (Ryusuke TSUNODA), Shiga General Hospital Cardiology division (Shigeru IKEGUCHI)