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Impact of anemia on the clinical outcomes in elderly patients with atrial fibrillation receiving apixaban: J-ELD AF registry subanalysis

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ABSTRACT

Background: The impact of anemia on the safety and efficacy of anticoagulants in elderly patients with atrial fibrillation (AF) has not been elucidated.

Method and Results: The J-ELD AF Registry is a large-scale, multicenter prospective observational study, of the one-year outcomes after administration of on-label doses of apixaban in Japanese patients with non-valvular AF aged ≥ 75 years. The entire cohort (3,015 patients from 110 institutions) was divided into three subgroups according to the WHO classification of anemia: normal (hemoglobin ≥ 13.0 g/dL in men and ≥ 12.0 g/dL in women, n = 1733, 57.5%), mild anemia (11.0 ≤ hemoglobin < 13.0 g/dL in men and 11.0 ≤ hemoglobin < 12.0 g/dL in women, n = 839, 27.8%), and moderate-severe anemia (<11.0 g/dL in both men and women, n = 443, 14.7%). The event rates (/100 person-years) for the normal, mild anemia, and moderate-severe anemia groups were 1.36, 1.81, and 1.99 for strokes or systemic embolisms (log-rank p = 0.556), 1.74, 1.16, and 4.02 for bleeding requiring hospitalization (log-rank p = 0.007), 2.03, 3.72, and 6.44 for total death (log-rank p < 0.001), and 0.86, 1.03, and 1.24 for cardiovascular death (log-rank p = 0.770), respectively. After adjusting for the confounders, moderate-severe anemia was an independent risk of total death (hazard ratio [95% confidence interval]; 2.21 [1.28–3.81], $P = 0.004$), but not for strokes or systemic embolisms and bleeding.

Conclusions: In AF patients aged ≥ 75 years taking an on-label dose of apixaban, moderate-severe anemia was not an independent risk of a stroke or systemic embolism and bleeding requiring hospitalization.

1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia, especially in elderly.[1,2] Because an advanced age is a distinct risk of a stroke in patients with AF, [3,4] anticoagulant therapy is recommended in elderly patients with AF to reduce their high thromboembolic risk.[5].

Anemia is also common in the elderly and is associated with an increased mortality among patients with cardiovascular disease including AF.[6,7] Importantly, AF and anemia often coexist in elderly patients.[8] Approximately one eighth of the AF patients aged 75 to 84 years old and one fourth of those older than 85 have anemia.[9,10] However, because patients who were both elderly and had significant anemia were excluded from the clinical trials, data about the impact of oral anticoagulation on these patients are sparse. Though a low hemoglobin value is a possible risk of bleeding complications with oral anticoagulation, each DOAC does not have a set dose adjustment according to the severity of the anemia.[11–14].

The J-ELD AF Registry is a large-scale, multicenter prospective observational study of Japanese AF patients aged ≥ 75 years taking on-label doses of apixaban.[15] In this study, we divided the study population of the J-ELD AF Registry according to the hemoglobin value and compared the incidence of bleeding and strokes or systemic embolisms among the different hemoglobin levels in elderly AF patients with an on-label dose of apixaban, especially in special reference to moderate-

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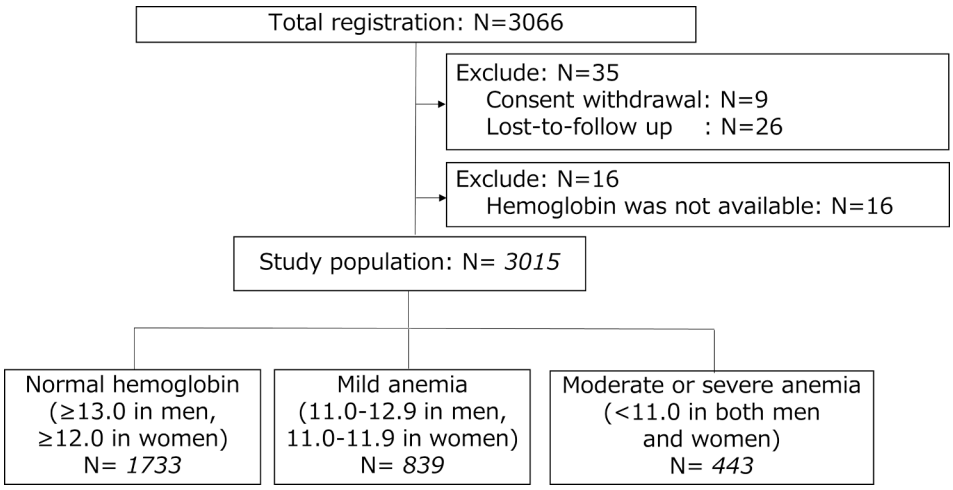


Fig. 1. Study flowchart.

severe anemia.

2. Methods

2.1. Study population

The study design and baseline clinical characteristics of the subjects in the J-ELD AF Registry have been described elsewhere.[15–17] Briefly, the target number of patients in the registry was 3,000, 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, which enrolled Japanese patients with non-valvular AF aged ≥ 75 years who visited the participating facilities after the start of the main study and had been taking or started taking apixaban. Patients with any of the following were excluded: (1) a history of hypersensitivity to apixaban, (2) active bleeding symptoms, (3) liver disease with coagulation disorders, and (4) a creatinine clearance < 15 mL/min, and (5) patients who did not meet the apixaban dose reduction criteria but received a reduced dose and patients who met the apixaban dose reduction criteria but received a standard dose. Apixaban was given in a reduced dose (2.5 mg bid) to those who met 2 or 3 reduced apixaban administration criteria from the following criteria: age ≥ 80 years, body weight ≤ 60 kg, and serum creatinine ≥ 1.5 mg/dL; and apixaban was given in a standard dose (5 mg bid) to those who did not meet the above criteria.

2.2. Data acquisition

Data were collected using the Electronic Data Capture (EDC) system for the observation and inspection items defined in the clinical trial protocol. We collected data on the consent acquisition date, age, sex, body weight, underlying heart diseases, dose of apixaban and its start date, presence or absence of the co-administration of antiplatelet drugs, hemoglobin, serum creatinine level, and estimated glomerular filtration rate (GFR) at the time of registration. The collected outcome data were the presence or absence of an event during the observation period in each patient, date of occurrence, and situation regarding the apixaban administration during the week that the event occurred. Events included (a) a diagnosed stroke with head computed tomography or magnetic resonance imaging with clinical symptoms, (b) systemic embolism confirmed by diagnostic imaging with clinical symptoms, (c) bleeding requiring hospitalization, (d) total death, and (e) cardiovascular death. The patient data were anonymized and imported into the EDC in a non-personally identifiable format. Data were securely managed by an external third party commissioned by the Cardiovascular Institute Academic Research Organization (CVI ARO).

2.3. Evaluation and statistical analysis

The primary efficacy endpoint was a stroke or systemic embolism, and the primary safety endpoint was bleeding requiring hospitalization. The secondary endpoints were total deaths or cardiovascular deaths. Anemia was defined by the standard WHO classification: no anemia (hemoglobin ≥ 13.0 g/dL for men and ≥ 12.0 g/dL for women); mild anemia (hemoglobin 11.0–12.9 g/dL for men and 11.0–11.9 g/dL for women); moderate anemia (hemoglobin 8.0–10.9 g/dL); and severe anemia (hemoglobin < 8.0 g/dL).[18] The target population for the analysis was divided into 3 groups according to the definition of anemia: normal group, mild anemia group, and moderate-severe anemia group.

Data are presented as the number and percentage or mean ± standard deviation. Categorical variables were compared using the chi-squared test or Fisher's exact test. Continuous variables were compared using the Student's *t*-test or Wilcoxon rank-sum test based on their distribution. The event incidence rate and 95% confidence interval (Poisson distribution, 95% CI) were calculated for each anemia group according to the primary and secondary endpoints. The cumulative event incidences were displayed by the Kaplan–Meier method, and the differences among anemia groups were tested by the log rank test. Next, univariate and multivariate models were identified by a Cox regression analysis. In the multivariate model, the anemia groups were forcibly introduced even if they did not show any significant association in the

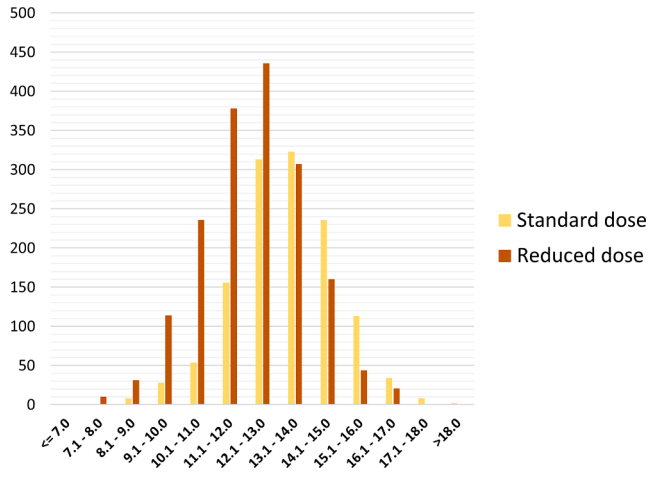
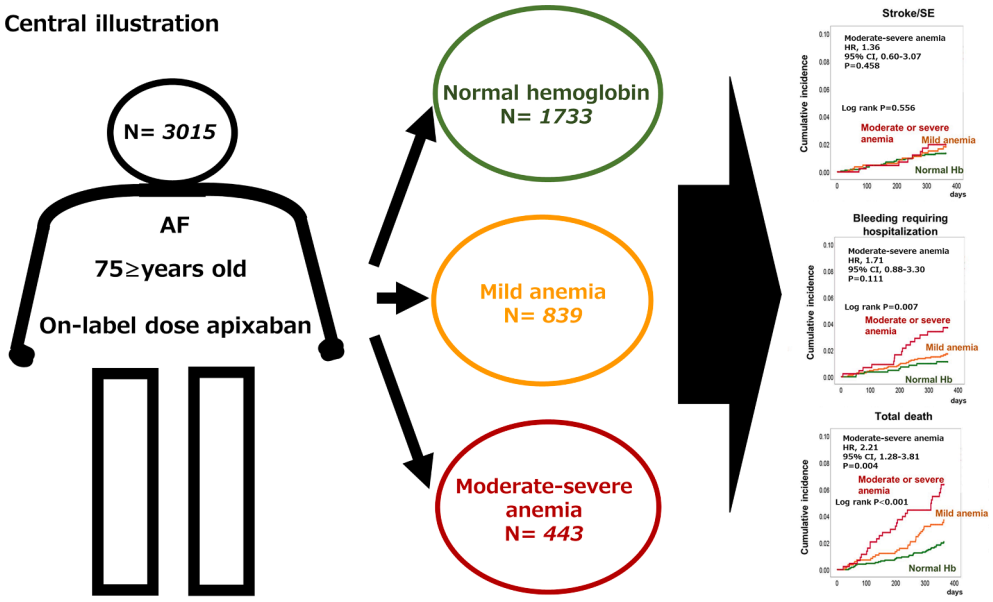


Fig. 2. Distribution of the hemoglobin.

Table 1
Patient characteristics.

	Total (n = 3015)	Normal hemoglobin	Mild anemia	Moderate-severe anemia	P-value
Apixaban dose			–	–	<0.001
Standard dose (5 mg bid), n (%)	1276 (42.3)	885 (51.1)	305 (36.4)	86 (19.4)	
Reduced dose (2.5 mg bid), n (%)	1739 (57.7)	848 (48.9)	534 (63.6)	357 (80.6)	
Gender					<0.001
Male, n (%)	1562 (51.8)	882 (50.9)	522 (62.2)	158 (35.7)	
Female, n (%)	1453 (48.2)	851 (49.1)	317 (37.8)	285 (64.3)	
Hemoglobin, g/dL	12.7 ± 1.7	13.8 ± 1.1	11.9 ± 0.6	10.0 ± 0.8	<0.001
in Male	13.2 ± 1.7	14.3 ± 1.0	12.1 ± 0.6	10.0 ± 0.8	<0.001
in Female	12.2 ± 1.5	13.2 ± 0.9	11.5 ± 0.3	10.0 ± 0.8	<0.001
Age, years	81.7 ± 4.6	80.9 ± 4.5	82.4 ± 4.5	83.6 ± 4.7	<0.001
Body weight, kg	56.3 ± 11.2	57.9 ± 11.0	55.6 ± 11.1	51.5 ± 10.5	<0.001
Systolic BP, mmHg	127.3 ± 17.4	128.2 ± 16.8	126.8 ± 18.1	124.6 ± 17.6	<0.001
Diastolic BP, mmHg	70.7 ± 12.3	72.6 ± 12.2	69.2 ± 12.0	66.0 ± 11.8	0.617
Pulse rate, beats/min	74.1 ± 15.0	75.0 ± 15.3	72.6 ± 14.2	73.5 ± 15.0	<0.001
Serum creatinine, mg/dL	1.0 ± 0.3	0.9 ± 0.3	1.0 ± 0.3	1.1 ± 0.4	<0.001
Creatinine clearance, mL/min	46.6 ± 16.2	50.6 ± 15.7	43.9 ± 14.9	36.3 ± 14.8	<0.001
AF types, n (%)					0.004
Paroxysmal	1479 (49.1)	842 (48.6)	428 (51.0)	209 (47.2)	
Persistent	487 (16.2)	65 (14.7)	105 (12.5)	317 (18.3)	
Permanent	1018 (33.8)	561 (32.4)	295 (35.2)	162 (36.6)	
Unknown	31 (1.0)	7 (1.6)	11 (1.3)	13 (0.8)	
EHRA score, n (%)					0.299
1	1645 (54.6)	956 (55.2)	455 (54.2)	234 (52.8)	
2	1055 (35.0)	615 (35.5)	290 (34.6)	150 (33.9)	
3	174 (5.8)	83 (4.8)	54 (6.4)	37 (8.4)	
4	27 (0.9)	15 (0.9)	8 (1.0)	4 (0.9)	
Unknown	114 (3.8)	64 (3.7)	32 (3.8)	18 (4.1)	
Heart failure, n (%)	1066 (35.4)	528 (30.5)	306 (36.5)	232 (52.4)	<0.001
Hypertension, n (%)	2706 (89.8)	1547 (89.3)	759 (90.5)	400 (90.3)	0.592
Diabetes mellitus, n (%)	698 (23.2)	401 (23.1)	182 (21.7)	115 (26.0)	0.227
History of a cerebral infarction/TIA, n (%)	529 (17.5)	282 (16.3)	162 (19.3)	85 (19.2)	0.102
History of a PAD/MI, n (%)	286 (9.5)	135 (7.8)	109 (13.0)	42 (9.5)	<0.001
History of bleeding requiring hospitalization, n (%)	54 (1.8)	29 (1.7)	13 (1.5)	12 (2.7)	0.281
Liver dysfunction, n (%)	485 (16.1)	326 (18.8)	105 (12.5)	54 (12.2)	<0.001
Habitual drinking, n (%)	404 (13.4)	258 (14.9)	111 (13.2)	35 (7.9)	<0.001
Antiplatelet drugs, n (%)	556 (18.4)	290 (16.7)	179 (21.3)	87 (19.6)	0.015
CHA_2DS_2-VASc score					
Continuous value	4.4 ± 1.2	4.3 ± 1.2	4.4 ± 1.2	4.8 ± 1.2	<0.001
Category, n (%)					<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)	56 (3.2)	23 (2.7)	8 (1.8)	
3	607 (20.1)	377 (21.8)	187 (22.3)	43 (9.7)	
4	1061 (35.2)	626 (36.1)	297 (35.4)	138 (31.2)	
5	726 (24.1)	413 (23.8)	174 (20.7)	139 (31.4)	
6	353 (11.7)	170 (9.8)	104 (12.4)	79 (17.8)	
7	143 (4.7)	71 (4.1)	46 (5.5)	26 (5.9)	
8	33 (1.1)	17 (1.0)	8 (1.0)	8 (1.8)	
9	5 (0.2)	3 (0.2)	0 (0.0)	2 (0.5)	
HAS-BLED score					
Continuous value	2.4 ± 0.8	2.4 ± 0.8	2.5 ± 0.8	2.4 ± 0.7	0.070
Category, n (%)					0.115
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
1	198 (6.6)	113 (6.5)	57 (6.8)	28 (6.3)	
2	1649 (54.7)	979 (56.5)	422 (50.3)	245 (55.3)	
3	898 (29.8)	493 (28.4)	273 (32.5)	130 (29.3)	
4	253 (8.4)	132 (7.6)	81 (9.7)	39 (8.8)	
5	22 (0.7)	16 (0.9)	5 (0.6)	1 (0.2)	
6	1 (0.0)	0 (0.0)	1 (0.1)	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)	

univariate analysis, because this study focused on the impact of anemia on the risk of these events. Factors showing a significant association with each endpoint in the univariate analysis were also entered for an adjustment. The factors for an adjustment were composed of the relevant thromboembolic or bleeding risk scores (i.e., CHA_2DS_2-VASc, and HAS-BLED scores): age (≥85 years), male sex, heart failure, hypertension, diabetes mellitus, history of a cerebral infarction or transient ischemic attack, history of a myocardial infarction or peripheral artery disease, history of bleeding requiring hospitalization, liver dysfunction, habitual drinking, and use of antiplatelet drugs. Among them, the component of age differed from the original definition of each risk score, but we modified them to secure the statistical power for the adjustment (Model 1). In addition, another multivariate model was developed using hemoglobin and age as consecutive values (Model 2). The statistical analyses were performed using SAS® Ver. 9.4 software (SAS Institute Inc., Cary, NC, USA). In all analyses, a $P < 0.05$ was taken to indicate statistical significance.



3. Results

Of the 3,066 cases registered in the J-ELD AF Registry from 110 participating institutions, 51 were excluded (withdrawal with consent, $n = 9$; dropout, $n = 26$; and missing hemoglobin data, $n = 16$), and the remaining 3,015 (average age, 81.7 years; 48.2% women) were adopted as the target population for this subgroup analysis (Fig. 1).

3.1. Patient characteristics

The numbers of patients in the normal hemoglobin, mild anemia, and moderate-severe anemia groups were 1733 (57.5%), 839 (27.8%), and 443 (14.7%), respectively (Fig. 1). As the hemoglobin value decreased, the proportion of patients receiving a reduced dose increased (Fig. 2). The baseline characteristics of each group in the present analysis is shown in Table 1. Half of the patients (51.1%) in the normal group received the standard apixaban dose, while a large proportion of the patients (80.6%) in the moderate-severe anemia group received a reduced apixaban dose.

The average age was 80.9 years in the normal group, 82.4 in the mild anemia group, and 83.6 in the moderate-severe anemia group. The mean age increased significantly as the anemia progressed ($P < 0.001$). While the mild anemia group consisted of predominantly males (62.2%), the moderate-severe anemia group consisted predominantly of females (64.3%).

The moderate-severe anemia group had a lower body weight, lower creatinine clearance, and fewer cases of paroxysmal AF. The moderate-severe anemia group did not have a higher pulse rate (normal hemoglobin vs. mild anemia vs. moderate-severe anemia, 75.0 ± 15.3 vs. 72.6 ± 14.2 vs. 73.5 ± 15.0 bpm, $P < 0.001$). The moderate-severe anemia group had more cases with heart failure, while they had fewer cases with liver dysfunction. There were no significant differences among the three groups regarding hypertension, diabetes mellitus, a history of a cerebral infarction/TIA, and a history of bleeding requiring hospitalization.

The CHA_2DS_2-VASc scores for assessing the risk of a stroke in AF patients, and the HAS-BLED score for assessing the risk of bleeding were 4.3 ± 1.2, and 2.4 ± 0.8 in the normal group, 4.4 ± 1.2, and 2.5 ± 0.8 in the mild anemia group, and 4.8 ± 1.2, and 2.4 ± 0.7 in the moderate-severe anemia group, respectively. The CHA_2DS_2-VASc scores exhibited significant differences among the three groups ($P < 0.001$). However, the differences in the HAS-BLED scores among the three groups did not reach statistical significance.

3.2. Outcomes

Strokes or systemic embolisms: The incidence rates of a stroke or systemic embolism were 1.36, 1.81, and 1.99 per 100 person-years in the normal group, mild anemia group, and moderate-severe anemia

Table 2
Event incidence rates.

	Events	Person-years	Event Rate (/100 person-years)	95% CI Lower	95% CI Upper
Stroke or systemic embolism					
Total	44	2790	1.58	1.17	2.12
Normal hemoglobin	22	1614	1.36	0.9	2.06
Mild anemia	14	775	1.81	1.08	3.03
Moderate-severe anemia	8	402	1.99	1.01	3.93
Bleeding requiring hospitalization					
Total	53	2786	1.9	1.45	2.49
Normal hemoglobin	28	1612	1.74	1.2	2.51
Mild anemia	9	777	1.16	0.61	2.2
Moderate-severe anemia	16	398	4.02	2.47	6.53
Total death					
Total	88	2806	3.14	2.55	3.86
Normal hemoglobin	33	1622	2.03	1.45	2.86
Mild anemia	29	780	3.72	2.59	5.34
Moderate-severe anemia	26	404	6.44	4.39	9.43
Cardiovascular death					
Total	27	2806	0.96	0.66	1.4
Normal hemoglobin	14	1622	0.86	0.51	1.45
Mild anemia	8	780	1.03	0.52	2.02
Moderate-severe anemia	5	404	1.24	0.53	2.9

CI: confidence interval.

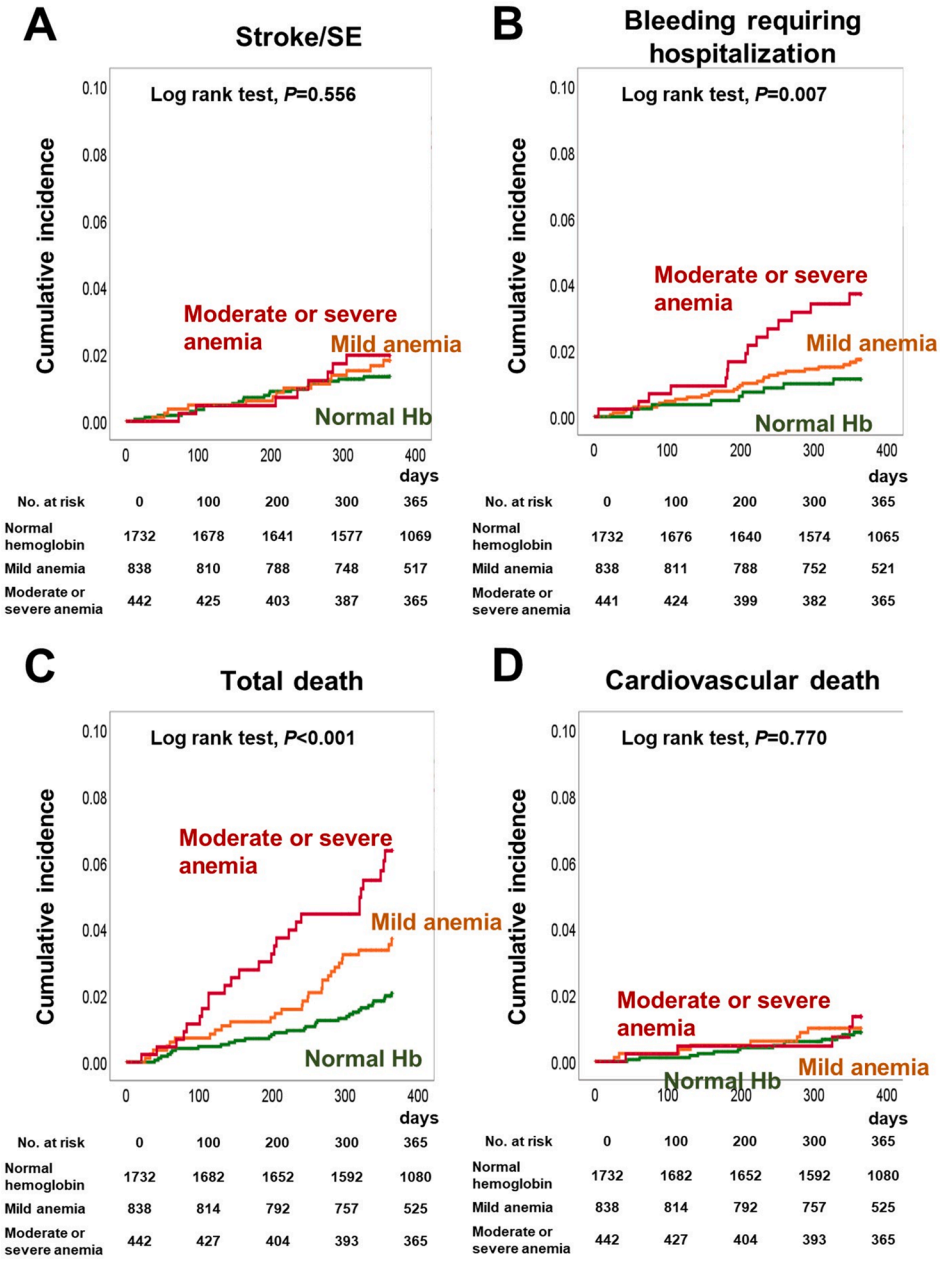


Fig. 3. Cumulative incidence rates (Kaplan-Meier Method). (A) Stroke or systemic embolism (SE). (B) Bleeding requiring hospitalization. (C) Total death. (D) Cardiovascular death.

group, respectively (Table 2). There were no significant differences among the 3 groups (log rank test, $P = 0.556$; Fig. 3A). Among the stroke and systemic embolism events in the normal and mild anemia groups, they predominantly consisted of ischemic strokes, while in the moderate-severe anemia group they predominantly consisted of hemorrhagic strokes. The HRs (95% CI) and *P*-values of each anemia group with reference to the normal group in the multivariate analysis for strokes or systemic embolisms were 1.31 (0.67–2.55, $P = 0.436$) and 1.36 (0.60–3.07, $P = 0.458$) for the mild anemia group and moderate-severe anemia group, respectively (Table 4).

Bleeding requiring hospitalization: The incidence rates of bleeding requiring hospitalization were 1.74, 1.16, and 4.02 per 100 person-years in the normal group, mild anemia group, and moderate-severe anemia group, respectively (Table 2). There were significant differences among the 3 groups (log rank test, $P = 0.007$; Fig. 3B). Among the bleeding events requiring hospitalization, all three groups included predominantly bleeding in the gastrointestinal tract (46.4–66.6%) and intracranial hemorrhages in 22.2–31.3% (Table 3). The HRs (95% CI) and *P*-values of each anemia group with reference to the normal group in the multivariate analysis for bleeding requiring hospitalization were 0.59 (0.28–1.26, $P = 0.170$) and 1.71 (0.88–3.30, $P = 0.111$) for the mild anemia group and moderate-severe anemia group, respectively (Table 4).

Total death: The incidence rates of the total death were 2.03, 3.72, and 6.44 per 100 person-years in the normal group, mild anemia group, and moderate-severe anemia group, respectively (Table 2). There was a significant difference among the 3 groups (log rank test, $P < 0.001$; Fig. 3C). Of the total deaths, the proportion of non-cardiovascular deaths was higher in the moderate-severe anemia group (80.8%) than normal group (57.6%). The HRs (95% CI) and *P*-values of each anemia group with reference to the normal group in the multivariate analysis for the total deaths were 1.39 (0.83–2.31, $P = 0.210$) and 2.21 (1.28–3.81, $P = 0.004$) for the mild anemia group and moderate-severe anemia group, respectively (Table 4).

Table 3
Event incidence number and description.

	Total	Normal hemoglobin	Mild anemia	Moderate-severe anemia
Stroke or systemic embolism, n (%)	44 (100.0)	22 (100.0)	14 (100.0)	8 (100.0)
Ischemic stroke	32 (72.7)	15 (68.2)	13 (92.9)	4 (50.0)
Hemorrhagic stroke	14 (31.8)	8 (36.4)	1 (7.1)	5 (62.5)
Systemic embolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bleeding requiring hospitalization, n (%)	53 (100.0)	28 (100.0)	9 (100.0)	16 (100.0)
Intracranial hemorrhage	15 (28.3)	8 (28.6)	2 (22.2)	5 (31.3)
Upper gastrointestinal bleeding	9 (17.0)	4 (14.3)	2 (22.2)	3 (18.8)
Lower gastrointestinal bleeding	12 (22.6)	6 (21.4)	2 (22.2)	4 (25.0)
Gastrointestinal bleeding, site unknown	7 (13.2)	3 (10.7)	2 (22.2)	2 (12.5)
Others	10 (18.9)	7 (25.0)	1 (11.1)	2 (12.5)
Total death, n (%)	88 (100.0)	33 (100.0)	29 (100.0)	26 (100.0)
Non-cardiovascular death	61 (69.3)	19 (57.6)	21 (72.4)	21 (80.8)
Cardiovascular death	27 (30.7)	14 (42.4)	8 (27.6)	5 (19.2)
Ischemic stroke	2 (2.3)	1 (3.0)	0 (0.0)	1 (3.8)
Hemorrhagic stroke	1 (1.1)	1 (3.0)	0 (0.0)	0 (0.0)
Bleeding requiring hospitalization	1 (1.1)	1 (3.0)	0 (0.0)	0 (0.0)
Heart failure	20 (22.7)	9 (27.3)	8 (27.6)	3 (11.5)
Myocardial infarction	1 (1.1)	1 (3.0)	0 (0.0)	0 (0.0)
Ventricular arrhythmia	1 (1.1)	1 (3.0)	0 (0.0)	0 (0.0)
Sudden death	2 (0.1)	1 (0.1)	0 (0.0)	1 (0.2)

Cardiovascular death: The incidence rates of cardiovascular deaths were 0.86, 1.03, and 1.24 per 100 person-years in the normal group, mild anemia group, and moderate-severe anemia group, respectively (Table 2). There was no significant difference among the 3 groups (log rank test, $P = 0.770$; Fig. 3D). Of the cardiovascular deaths, heart failure was the most common cause in all three groups (Table 3). The HRs (95% CI) and *P*-values of each anemia group with reference to the normal group in the multivariate analysis for cardiovascular deaths were 0.94 (0.39–2.27, $P = 0.894$) and 0.76 (0.26–2.21, $P = 0.618$) for the mild anemia group and moderate-severe anemia group, respectively (Table 4). We confirmed that the results were consistent when age and hemoglobin were included as numerical variables in the multivariate analysis (Table 4: Model 2).

4. Discussion

The main findings of the current sub-analysis of the J-ELD AF Registry were as follows: (1) the patients in the moderate-severe anemia group had higher CHA_2DS_2-VASc scores than those in the no and mild anemia groups, however, the moderate-severe anemia group did not have a higher HAS-BLED score than those in the normal and mild anemia groups. (2) Although the incident rates of strokes or systemic embolisms and cardiovascular death were comparable among each hemoglobin value group, the patients in the moderate-severe anemia group had a higher incidence of events than the mild anemia and normal groups in terms of bleeding requiring hospitalization and total deaths. (3) After an adjustment for the potential confounders, moderate-severe anemia was a distinct risk factor for total death, but not for either bleeding requiring hospitalization or strokes or systemic embolisms.

The J-ELD AF Registry was a large prospective observational study to assess the efficacy and safety of apixaban in more than 3000 Japanese patients with AF aged $\geq$ 75 years enrolled from 110 facilities treated with apixaban according to the package insert dose (standard dose of 5 mg bid or reduced dose of 2.5 mg bid). In the primary analysis, the incidence rates of strokes or systemic embolisms and bleeding events requiring hospitalization were identical between the standard-dose group and reduced-dose group, while those for the total death and cardiovascular death were significantly higher in the reduced-dose group.[15].

In this subgroup analysis of the J-ELD AF registry, we focused on anemia in the elderly patients. Patients with a low hemoglobin value possibly had a risk for bleeding complications with oral anticoagulation, and therefore were excluded from the clinical trials. There have been few reports about the impact of anemia on the incidence of strokes or systemic embolisms and bleeding events in AF patients under an on-label dose of a DOAC including apixaban.[19].

While the prevalence of anemia was 11.9% in the RE-LY trial and 12.6% in the ARISTOTLE trial, [20] the prevalence of anemia was 42.6% in this current real-world registry of elderly AF patients, including 14.7% in the moderate-severe anemia group. These results indicated that anemia was an underestimated problem in the clinical trials and is a more important matter in clinical practice with elderly AF patients. Notably, in the present study, 63.6% of the mild anemia patients and 80.6% of the moderate-severe anemia patients took an on-label reduced apixaban dose among the elderly AF patients, because patients with anemia tended to have a more advanced age, lower body mass, and lower creatinine clearance. Despite the dose criteria for apixaban not including the hemoglobin value or anemia, it seems like the current dose reduction criteria for apixaban mostly correspond to the diagnosis of anemia in elderly AF patients.

Regarding the efficacy of an on-label dose of apixaban in elderly AF patients, anemia was not associated with an increased risk of thromboembolic events in the present study and ARISTOTLE trial, however, it was associated with the risk of thromboembolic events in some other studies.[21] The incident rate of strokes or systemic embolisms in the no anemia patients in the present study (1.36%) was similar to that in the ARISTOTLE (1.41%) and RE-LY (1.3%) trials, and furthermore, that in the patients with mild-severe anemia (1.87%) was comparable to that in the ARISTOTLE (1.57%) and RE-LY (2.2%) trials.[19,20] Although this study population consisted of elderly patients, those event rates were consistent with those in the previous studies including both young and elderly patients.

Regarding the safety of an on-label dose of apixaban in elderly AF patients, moderate-severe anemia was significantly associated with a higher incidence of bleeding requiring hospitalization (Fig. 2B). However, it was not a significant risk after an adjustment by the confounding factors, while a history of a bleeding hospitalization, which would be a possible cause of anemia, was a distinct risk factor of bleeding (Table 4). The results of these two analyses indicated that the patient characteristics, including comorbidities, associated with anemia were risks of bleeding; moderate-severe anemia would be a marker of a bleeding risk, not the risk itself. [22] Of note, the majority of patients with anemia in the present study were already taking an on-label reduced-dose of apixaban as described above. Therefore, our data suggested that there was an unmet need of how to reduce the risk of bleeding in the moderate-severe anemia group; at least, careful monitoring and management of treatable bleeding risks, including discontinuation of antiplatelet agents and an investigation and/or intervention for bleeding sources would be mandatory.

The strong association between moderate-severe anemia at baseline and subsequent mortality in this study suggested that anemia represented a nonspecific condition and concomitant chronic diseases such as cancer or renal dysfunction. [23,24] In contrast to the total deaths, the risk of a cardiovascular death was comparable among the anemia groups, and moderate-severe anemia was not a risk of cardiovascular death, however, moderate-severe anemia patients had a more frequent

Table 4
Cox hazard ratio for a stroke or systemic embolism, bleeding requiring hospitalization, total death, and cardiovascular death, Stroke or systemic embolism, Total death. Cardiovascular death, Bleeding requiring hospitalization.

	Univariate model		Multivariate model 1		Multivariate model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Stroke or systemic embolism			–	–		
Normal hemoglobin	Reference		Reference		–	–
Mild anemia	1.33 (0.68–2.59)	0.41	1.31 (0.67–2.55)	0.436	–	–
Moderate-severe anemia	1.46 (0.65–3.29)	0.355	1.36 (0.60–3.07)	0.458	–	–
Hemoglobin (consecutive value)	0.95 (0.80–1.14)	0.587	–	–	0.96 (0.81–1.15)	0.661
Age ≥ 85	1.37 (0.74–2.56)	0.319			–	–
Age (consecutive value)	1.04 (0.98–1.11)	0.196	–	–		
Heart failure	0.54 (0.27–1.10)	0.088				
Hypertension	1.59 (0.49–5.14)	0.437				
Diabetes mellitus	1.10 (0.56–2.17)	0.787				
History of a cerebral infarction/ TIA	2.18 (1.15–4.10)	0.016	2.13 (1.13–4.02)	0.020	2.15 (1.14–4.06)	0.018
Female sex	0.81 (0.45–1.47)	0.485				
History of a PAD/MI	0.98 (0.35–2.73)	0.966				
History of bleeding requiring hospitalization	4.20 (1.30–13.55)	0.016	4.05 (1.25–13.16)	0.020	4.07 (1.26–13.17)	0.019
Liver dysfunction	1.19 (0.55–2.56)	0.656				
Habitual drinking	1.93 (0.95–3.90)	0.068				
eGFR < 45 mL/min/m2	0.87 (0.45–1.68)	0.675				
Antiplatelet drugs	1.17 (0.56–2.43)	0.674				

	Univariate model		Multivariate model 1		Multivariate model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Bleeding requiring hospitalization			–	–		
Normal hemoglobin	Reference		Reference		–	–
Mild anemia	0.67 (0.31–1.41)	0.290	0.59 (0.28–1.26)	0.170	–	–
Moderate-severe anemia	2.18 (1.16–4.08)	0.015	1.71 (0.88–3.30)	0.111	–	–
Hemoglobin (consecutive value)	0.85 (0.73–1.00)	0.055	–	–	0.90 (0.76–1.06)	0.210
Age ≥85	1.53 (0.87–2.68)	0.142			–	–
Age (consecutive value)	1.05 (0.99–1.11)	0.124	–	–		
Heart failure	1.06 (0.61–1.87)	0.828				
Hypertension	0.89 (0.38–2.08)	0.782				
Diabetes mellitus	0.89 (0.46–1.72)	0.722				
History of a cerebral infarction/ TIA	0.97 (0.47–1.98)	0.923				
Female sex	0.99 (0.57–1.70)	0.964				
History of a PAD/MI	2.05 (1.00–4.22)	0.049	1.51 (0.67–3.39)	0.316	1.41 (0.63–3.14)	0.402
History of bleeding requiring hospitalization	3.49 (1.09–11.19)	0.036	3.41 (1.06–11.00)	0.040	3.57 (1.11–11.51)	0.033
Liver dysfunction	1.44 (0.74–2.80)	0.284				
Habitual drinking	1.01 (0.45–2.23)	0.985				
eGFR <45 mL/min/m2	1.99 (1.15–3.43)	0.013	1.72 (0.97–3.04)	0.065	1.73 (0.98–3.04)	0.059
Antiplatelet drugs	2.02 (1.12–3.64)	0.019	1.72 (0.89–3.33)	0.107	1.74 (0.90–3.36)	0.097

	Univariate model		Multivariate model 1		Multivariate model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Total death			–	–		
Normal hemoglobin	Reference		Reference		–	–
Mild anemia	1.83 (1.11–3.01)	0.018	1.39 (0.83–2.31)	0.210	–	–
Moderate-severe anemia	3.17 (1.90–5.30)	<0.001	2.21 (1.28–3.81)	0.004	–	–
Hemoglobin (consecutive value)	0.78 (0.69–0.88)	<0.001	–	–	0.84 (0.73–0.95)	0.007
Age ≥85	2.30 (1.51–3.50)	<0.001	1.76 (1.14–2.74)	0.011	–	–
Age (consecutive value)	1.09 (1.05–1.14)	<0.001	–	–	1.06 (1.01–1.11)	0.010
Heart failure	2.79 (1.82–4.28)	<0.001	2.16 (1.38–3.37)	<0.001	2.10 (1.34–3.28)	0.001
Hypertension	1.16 (0.56–2.40)	0.690				
Diabetes mellitus	1.17 (0.73–1.88)	0.524				
History of a cerebral infarction/ TIA	0.66 (0.35–1.24)	0.195				
Female sex	0.64 (0.42–0.98)	0.042	0.54 (0.34–0.84)	0.007	0.49 (0.31–0.77)	0.002
History of a PAD/MI	1.99 (1.14–3.48)	0.015	1.35 (0.72–2.51)	0.348	1.32 (0.71–2.47)	0.383
History of bleeding requiring hospitalization	1.97 (0.62–6.22)	0.250				
Liver dysfunction	1.28 (0.76–2.18)	0.357				
Habitual drinking	0.65 (0.31–1.35)	0.246				
eGFR <45 mL/min/m2	2.11 (1.39–3.21)	<0.001	1.45 (0.93–2.26)	0.101	1.43 (0.92–2.22)	0.116
Antiplatelet drugs	1.69 (1.06–2.70)	0.028	1.37 (0.81–2.33)	0.237	1.35 (0.79–2.30)	0.267

	Univariate model		Multivariate model 1		Multivariate model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Cardiovascular death			–	–		
Normal hemoglobin	Reference		Reference		–	–
Mild anemia	1.19 (0.50–2.83)	0.697	0.94 (0.39–2.27)	0.894	–	–
Moderate-severe anemia	1.44 (0.52–3.99)	0.486	0.76 (0.26–2.21)	0.618	–	–
Hemoglobin (consecutive value)	1.02 (0.81–1.28)	0.881	–	–	1.24 (0.99–1.56)	0.062

(*continued on next page*)

Table 4 (*continued*)

	Univariate model		Multivariate model 1		Multivariate model 2	
Age ≥85	2.11 (0.99–4.50)	0.054			–	–
Age (consecutive value)	1.13 (1.05–1.21)	0.002	–	–	1.10 (1.02–1.19)	0.012
Heart failure	5.27 (2.23–12.46)	<0.001	4.58 (1.89–11.10)	<0.001	4.22 (1.73–10.28)	0.002
Hypertension	1.45 (0.34–6.13)	0.611				
Diabetes mellitus	1.94 (0.89–4.24)	0.095				
History of a cerebral infarction/ TIA	0.58 (0.17–1.91)	0.366				
Female sex	0.45 (0.20–1.02)	0.057				
History of a PAD/MI	2.77 (1.12–6.85)	0.028	2.22 (0.88–5.59)	0.089	2.44 (0.98–6.08)	0.056
History of bleeding requiring hospitalization	4.45 (1.05–18.80)	0.042	4.25 (0.99–18.32)	0.052	5.10 (1.19–21.80)	0.028
Liver dysfunction	1.53 (0.62–3.80)	0.355				
Habitual drinking	0.81 (0.25–2.70)	0.737				
eGFR <45 mL/min/m2	2.48 (1.17–5.28)	0.018	1.79 (0.81–3.95)	0.148	1.76 (0.80–3.89)	0.163
Antiplatelet drugs	1.89 (0.83–4.33)	0.130				

history of heart failure, peripheral artery disease, and myocardial infarctions, all of which were distinct risks of cardiovascular death. This may be because in elderly AF patients with moderate-severe anemia, non-cardiac death related to non-cardiac conditions and comorbidities has a great impact on the prognosis and can be a competing risk that precludes the occurrence of a future cardiovascular event related to a frequent history of cardiovascular diseases.

In summary, because moderate-severe anemia was not an independent risk for bleeding requiring hospitalization and a stroke or systemic embolism, an on-label dose of apixaban seems to be a reasonable option for elderly AF patients with anemia after identifying the sources of bleeding and discontinuation of antiplatelet agents. However, the prognosis in this population was worse than that in others, because a non-cardiac condition and comorbidities in patients with moderate-severe anemia seemed to have a larger impact on the total death than anemia itself.

4.1. Limitations

There were several limitations to this present study. First, this registry was a prospective, observational, and single-arm study. This study had no control arm with which the effect of apixaban was compared. Second, there may have been a selection bias for the patients. The research physicians might not have enrolled patients at extremely high risk who were not suitable for long-term on-label dosing of apixaban because we did not enroll consecutive patients with AF. Third, this study consisted of patients with relatively well-managed AF, since they could be fully followed up by a medical institution with cardiovascular specialists on staff. Thus, the patients' health conditions and medical environment may have affected the event incidence rates. Fourth, the observational period was limited to 1 year, and therefore, the results could not be extrapolated to a long-term clinical course of more than 1 year. Fifth, some patients were lost to follow-up. Further, fewer patients in the moderate or severe anemia group were lost to follow-up and that would lead to finding more events in moderate or severe anemia group as compared to the other two groups. Sixth, the outcome events were reported by each participating center, and a central adjudication was not performed. However, by simplifying the definition of the stroke and bleeding events, we believe the variation in the local diagnosis between the participating centers was modest. Seventh, the status of the adherence, discontinuation, or a change to other anticoagulants, which would affect the patient outcomes, was not recorded in the present study. Eighth, this study did not include patients receiving an off-label under-dose, which is common in elderly patients with anemia. The benefit or harm of an under-dose DOAC is an important matter of debate, but this was not the scope of the study because this study included patients with an on-label dose of apixaban only, when considering the feasibility of the study. Ninth, we did not have any data on the concomitant antiarrhythmic drugs and treatment strategies such as rhythm control or rate control. Finally, our study subjects were Asian, which might have impacted the outcomes.

5. Conclusion

In AF patients aged ≥ 75 years taking an on-label dose of apixaban, moderate-severe anemia was not an independent risk of a stroke or systemic embolism or bleeding requiring hospitalization.

Disclosures.

Dr. Inoue received lecture fees from Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, Bayer Healthcare, Daiichi-Sankyo, Medtronic, and Johnson and Johnson. Dr. Sakata received lecture fees from Daiichi-Sankyo, Bayer, Boehringer Ingelheim, and Bristol-Myers Squibb. Dr. Akao received lecture fees from Pfizer, Bristol-Myers Squibb, Boehringer Ingelheim, Bayer Healthcare, and Daiichi-Sankyo. Dr. Yamashita received lecture fees from Bristol-Myers Squibb, Daiichi-Sankyo, Bayer, Pfizer, Ono Pharmaceutical, and Toa Eiyo and research funding from Bayer and Daiichi Sankyo. Dr. Suzuki received research funding from Daiichi-Sankyo and Mitsubishi-Tanabe. Dr. Okumura received lecture fees from Daiichi-Sankyo, Boehringer Ingelheim, Bristol-Myers Squibb, Medtronic, and Johnson and Johnson. The other authors declare no conflicts of interest.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.100994.

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