Supplementary Materials

Title: Real-world outcomes of rivaroxaban treatment in elderly Japanese patients with nonvalvular atrial fibrillation

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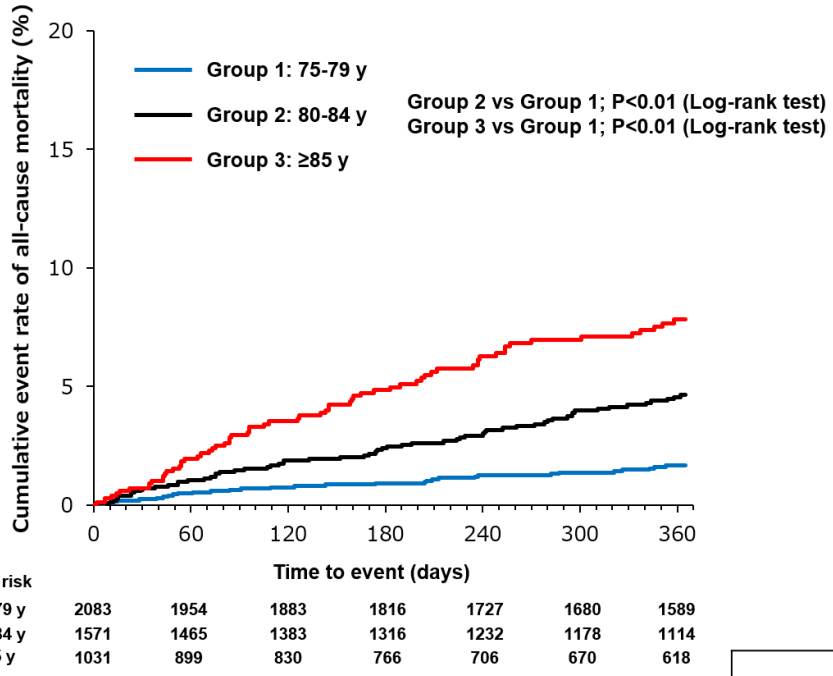
Supplementary Fig.1. Kaplan Meier curves for the cumulative event rates for all-cause mortality in the three elderly patient sub-groups (Group 1-3: ages 75-79, 80-84, and ≥85 years, respectively) with NVAF



No at risk							
75-79 y	2083	1954	1883	1816	1727	1680	1589
80-84 y	1571	1465	1383	1316	1232	1178	1114
≥ 85 y	1031	899	830	766	706	670	618

	HR	95% IC	P value
Group 2 vs Group 1	2.79	1.81-4.28	<0.01
Group 3 vs Group 1	4.88	3.18-7.48	<0.01

	Incidence rate, event per 100 patient-years
Group 1	1.71
Group 2	4.79
Group 3	8.47

Supplementary Table 1. Comparison of hazard ratio between Cox regression and competing risk analysis in elderly NVAF patient sub-groups.

a) Major Bleeding

	Cox regression analysis[1)]		Competing risk analysis[2)]	
Age	HR (95% CI)	P value	HR (95% CI)	P value
75-79	1		1	
80-84	1.45 (0.89-2.37)	0.13	1.44 (0.88-2.35)	0.15
≥ 85	1.60 (0.93-2.76)	0.09	1.56 (0.90-2.69)	0.11

b) Stroke/non-CNS SE/MI

	Cox regression analysis[1)]		Competing risk analysis[2)]	
Age	HR (95% CI)	P value	HR (95% CI)	P value
75-79	1		1	
80-84	1.25 (0.78-1.99)	0.35	1.24 (0.78-1.97)	0.37
≥ 85	1.32 (0.78-2.24)	0.32	1.29 (0.76-2.19)	0.35

1) No competing risk was considered. HR (95% CI) and P value were the same as shown in Fig. 2.

2) Death before developing events was treated as a competing risk. Fine and Gray's proportional subhazards model was used.

Supplementary Table 2. Cox regression analysis for major bleeding and stroke/non-CNS SE/MI in patients aged <75 years

	Major Bleeding				Stroke/non-CNS SE/MI			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
Variables	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Female gender								
yes/ no	0.85 (0.47–1.53)	0.579	0.78 (0.40–1.52)	0.461	1.09 (0.60–1.96)	0.785	0.81 (0.41–1.61)	0.547
Body weight, kg								
>50 vs. ≤50	1.71 (0.84–3.50)	0.140	1.93 (0.83–4.54)	0.129	2.83 (1.48–5.42)	0.002*	2.73 (1.23–6.04)	0.014*
CrCl, ml/min								
≥50 vs. <50	1.93 (0.87–4.27)	0.104	1.72 (0.68–4.33)	0.252	3.40 (1.69–6.80)	0.001*	1.73 (0.77–3.89)	0.185
Initial dose								
10 mg vs. 15 mg	0.99 (0.55–1.76)	0.968	0.79 (0.41–1.53)	0.492	2.26 (1.30–3.92)	0.004*	1.77 (0.95–3.32)	0.074
Hypertension								
yes/ no	0.71 (0.41–1.21)	0.208	0.55 (0.31–0.97)	0.038*	1.01 (0.55–1.88)	0.965	0.93 (0.48–1.80)	0.830
Diabetes mellitus								
yes/ no	1.96 (1.15–3.34)	0.014*	1.92 (1.10–3.37)	0.023*	1.85 (1.05–3.26)	0.034*	1.74 (0.95–3.16)	0.071
CHF								
yes/ no	1.63 (0.93–2.88)	0.090	1.42 (0.78–2.58)	0.252	0.94 (0.47–1.87)	0.853	0.85 (0.42–1.75)	0.666
Prior ischemic stroke/TIA								
yes/ no	1.18 (0.61–2.27)	0.628	1.00 (0.50–2.01)	0.990	2.92 (1.66–5.15)	<0.001*	2.27 (1.24–4.13)	0.008*
Vascular disease								
yes/ no	3.12 (1.25–7.81)	0.015*	2.10 (0.77–5.74)	0.146	2.01 (0.63–6.47)	0.239	1.06 (0.31–3.62)	0.922
Hepatic dysfunction								
yes/ no	0.96 (0.35–2.66)	0.944	1.00 (0.36–2.78)	0.997	0.80 (0.25–2.56)	0.701	0.90 (0.28–2.91)	0.858
Oral antiplatelet use								
yes/ no	3.31 (1.50–7.31)	0.003*	2.98 (1.26–7.05)	0.013*	5.08 (2.47-10.4)	<0.001*	4.47 (2.07–9.65)	<0.001*

CHF, congestive heart failure; CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; TIA, transient ischemic attack. *P<0.05

Supplementary Table 3. Predictive factors for major bleeding and stroke/non-CNS SE/MI

	Major Bleeding				Stroke/non-CNS SE/MI			
	< 75 years		≥ 75 years		< 75 years		≥ 75 years	
Variables	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Female gender								
yes/ no								
Body weight, kg								
>50 vs. ≤50					2.52 (1.28–4.97)	0.008		
CrCl, ml/min								
≥50 vs. <50			1.80 (1.15–2.82)	0.010				
Initial dose								
10 mg vs. 15 mg					2.05 (1.15–3.65)	0.015		
Hypertension								
yes/ no	0.55 (0.32–0.97)	0.039	2.14 (1.03–4.46)	0.041				
Diabetes mellitus								
yes/ no	1.95 (1.12–3.39)	0.018						
CHF								
yes/ no								
Prior ischemic stroke/TIA								
yes/ no					2.39 (1.32–4.31)	0.004	1.84 (1.20–2.81)	0.005
Vascular disease								
yes/ no								
Hepatic dysfunction								
yes/ no			2.28 (1.10–4.74)	0.027				
Oral antiplatelet use								
yes/ no	3.45 (1.55–7.67)	0.002	2.51 (1.25–5.04)	0.009	4.61 (2.18-9.74)	<0.001		

Stepwise regression analysis was performed with a 5% significance level. Corresponding HR and P values were shown. CHF, congestive heart failure; CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; TIA, transient ischemic attack.

Supplementary Table 4. Baseline patient characteristics

Characteristic	75- 79 years (N=2,083)	80- 84 years (N=1,571)	≥85 years (N=1,031)
Age, years	76.9 ± 1.4	81.8 ± 1.4	87.7 ± 2.8
Female sex	894 (42.92)	749 (47.68)	583 (56.55)
Body weight, kg	59.62 ± 11.76	56.32 ± 11.23	51.74 ± 11.07
Body weight, kg [n (%)]			
≤50	428 (20.55)	481 (30.62)	483 (46.85)
>50	1,519 (72.92)	971 (61.81)	462 (44.81)
Unknown	136 (6.53)	119 (7.57)	86 (8.34)
BMI, kg/m^2	23.86 ± 3.91	23.22 ± 4.20	22.10 ± 3.93
CrCl, ml/min	60.6 ± 18.7	51.5 ± 16.6	42.1 ± 14.1
CrCl, ml/min [n (%)]			
<50	529 (25.40)	714 (45.45)	718 (69.64)
≥50	1,403 (67.35)	724 (46.09)	221 (21.44)
Unknown	151 (7.25)	133 (8.47)	92 (8.92)
$CHADS_2$ score, mean ± SD	2.7 ± 1.1	2.9 ± 1.2	3.0 ± 1.2
Score, n (%)			
0	0 (0.00)	0 (0.00)	0 (0.00)
1	221 (10.61)	151 (9.61)	75 (7.27)
2	840 (40.33)	511 (32.53)	336 (32.59)
3	511 (24.53)	411 (26.16)	277 (26.87)
4	353 (16.95)	315 (20.05)	207 (20.08)
5	125 (6.00)	150 (9.55)	112 (10.86)
6	33 (1.58)	33 (2.10)	24 (2.33)
25^{th} percentile	2	2	2
Median	2	3	3
75^{th} percentile	3	4	4
CHA_2DS_2-VASc score	4.2 ± 1.2	4.4 ± 1.3	4.6 ± 1.3
Score			
0	0 (0.00)	0 (0.00)	0 (0.00)
1	0 (0.00)	0 (0.00)	0 (0.00)
2	118 (5.66)	79 (5.03)	31 (3.01)
3	531 (25.49)	307 (19.54)	170 (16.49)
4	679 (32.60)	465 (29.60)	323 (31.33)
5	438 (21.03)	390 (24.82)	249 (24.15)
6	235 (11.28)	226 (14.39)	159 (15.42)

7	70 (3.36)	89 (5.67)	80 (7.76)
8	10 (0.48)	15 (0.95)	19 (1.84)
9	2 (0.10)	0 (0.00)	0 (0.00)
25th percentile	3	4	4
Median	4	4	4
75th percentile	5	5	6
Modified HAS-BLED score*	1.8 ± 0.8	1.9 ± 0.9	2.0 ± 0.9
Score			
0	0 (0.00)	0 (0.00)	0 (0.00)
1	934 (44.84)	557 (35.46)	322 (31.23)
2	784 (37.64)	643 (40.93)	433 (42.00)
3	290 (13.92)	305 (19.41)	223 (21.63)
4	66 (3.17)	58 (3.69)	49 (4.75)
5	9 (0.43)	8 (0.51)	3 (0.29)
6	0 (0.00)	0 (0.00)	1 (0.10)
7	0 (0.00)	0 (0.00)	0 (0.00)
8	0 (0.00)	0 0.000	0 (0.00)
25th percentile	1	1	1
Median	2	2	2
75th percentile	2	2	3
Baseline comorbidities			
Hypertension	1,641 (78.78)	1,243 (79.12)	799 (77.50)
Diabetes mellitus	463 (22.23)	319 (20.31)	175 (16.97)
Prior ischemic stroke/TIA	482 (23.14)	480 (30.55)	343 (33.27)
Congestive heart failure	476 (22.85)	491 (31.25)	405 (39.28)
Hepatic dysfunction	99 (4.75)	83 (5.28)	46 (4.46)
Type of AF			
Paroxysmal	736 (35.33)	487 (31.00)	270 (26.19)
Persistent	710 (34.09)	581 (36.98)	411 (39.86)
Permanent	509 (24.44)	387 (24.63)	255 (24.73)
Other	7 (0.34)	3 (0.19)	2 (0.19)
Unknown	121 (5.81)	113 (7.19)	93 (9.02)

Data are presented as n (%) or mean ± standard deviation.

*Maximum score is 8 because of the exclusion of the factor "labile INR" from the HAS-BLED score.

AF, atrial fibrillation; BMI, body mass index; CrCl, creatinine clearance; INR, international normalized ratio; TIA, transient ischemic attack