

Supplementary Information

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Safety and Effectiveness of Apixaban Versus Warfarin in Japanese Patients with Nonvalvular Atrial Fibrillation Stratified by Renal Function: A Retrospective Cohort Study

Takeshi Morimoto¹; Haruhiko Hoshino²; Yukako Matsuo³; Tatsuki Ibuki⁴; Kayoko Miyata³;
Yukihiro Koretsune⁵

¹Department of Clinical Epidemiology, Hyogo Medical University, Hyogo, Japan

²Department of Neurology, Tokyo Saiseikai Central Hospital, Tokyo, Japan

³Medical Department, Bristol Myers Squibb K.K., Tokyo, Japan

⁴Medical Affairs, Pfizer Japan Inc., Tokyo, Japan

⁵Cardiovascular Division, National Hospital Organization Osaka National Hospital, Osaka, Japan

Correspondence

Takeshi Morimoto, MD, PhD, MPH

Department of Clinical Epidemiology, Hyogo Medical University

1-1 Mukogawacho, Nishinomiya, Hyogo 663-8501, Japan

E-mail: morimoto@kuhp.kyoto-u.ac.jp

Online Resource 1: Variables used for the calculation of propensity score and standardized mean difference

Covariate	Variable type	Category	Before matching	After matching
Apixaban, N			7,074	4,523*
Warfarin, N			4,998	4,523*
SMD between the apixaban and warfarin groups				
Sex	Nominal	Male or Female	0.064	0.021
Age (years)	Continuous		0.098	0.042
Bodyweight (kg)	Continuous		0.015	0.008
eGFR (mL/min/1.73 m ²)	Continuous		0.038	0.016
Heart rate (bpm)	Continuous		0.057	0.020
CHA ₂ DS ₂ -VASc score	Continuous		0.029	0.012
Comorbidities				
CHF	Nominal	Yes or No	0.074	0.029
Hypertension	Nominal	Yes or No	0.007	0.000
Diabetes	Nominal	Yes or No	0.016	0.017
Renal disease	Nominal	Yes or No	0.089	0.042
Dyslipidemia	Nominal	Yes or No	0.055	0.031
CAD	Nominal	Yes or No	0.062	0.005
PVD*	Nominal	Yes or No	0.052	0.051
Malignant tumor	Nominal	Yes or No	0.005	0.008
Medical history				
Stroke/TIA	Nominal	Yes or No	0.009	0.010
MI	Nominal	Yes or No	0.030	0.011
SE	Nominal	Yes or No	0.026	0.011
VTE	Nominal	Yes or No	0.007	0.005
Intracranial hemorrhage	Nominal	Yes or No	0.003	0.009
GI bleeding	Nominal	Yes or No	0.031	0.012
Other bleeding [‡]	Nominal	Yes or No	0.018	0.003
Concomitant medication				
ACE inhibitor and ARB	Nominal	Yes or No	0.052	0.005
β-blocker	Nominal	Yes or No	0.026	0.028
Amiodarone	Nominal	Yes or No	0.011	0.005
Statins	Nominal	Yes or No	0.040	0.022
PPI and H ₂ RA	Nominal	Yes or No	0.118	0.062
Aspirin	Nominal	Yes or No	0.115	0.050
P2Y12 inhibitors	Nominal	Yes or No	0.049	0.009

Other antiplatelet drugs	Nominal	Yes or No	0.028	0.011
Other anticoagulants	Nominal	Yes or No	0.107	0.051
NSAIDs	Nominal	Yes or No	0.030	0.018

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*A total of 4,523 patients were included in the study based on the eligibility criteria. The number of patients in this subgroup analysis (n=4,385) are those stratified by renal function. Thus, not every patient included in the study was included in this subgroup analysis

†Includes peripheral artery disease and other peripheral vascular disease

‡Not intracranial or gastrointestinal bleeding

ACE angiotensin-converting enzyme, *ARB* angiotensin II receptor blocker, *bpm* beats per minute, *CAD* coronary artery disease, *CHF* congestive heart failure, *eGFR* estimated glomerular filtration rate, *GI* gastrointestinal, *H₂RA* histamine receptor antagonist, *MI* myocardial infarction, *NSAID* nonsteroidal anti-inflammatory drug, *PPI* proton pump inhibitor, *PVD* peripheral vascular disease, *SE* systemic embolism, *SMD* standardized mean difference, *TIA* transient ischemic attack, *VTE* venous thromboembolism.

Online Resource 2: Patient characteristics stratified by baseline renal function (FAS)

Variable	CrCl \geq 15 to <30 mL/min			CrCl \geq 30 to <50 mL/min			CrCl \geq 50 to <80 mL/min			CrCl \geq 80 mL/min		
	Apixaban (n=415)	Warfarin (n=411)	P value	Apixaban (n=1,757)	Warfarin (n=1,177)	P value	Apixaban (n=3,061)	Warfarin (n=2,014)	P value	Apixaban (n=1,841)	Warfarin (n=1,396)	P value
Female sex	286 (68.9)	241 (58.6)	<0.01	959 (54.6)	585 (49.7)	0.01	1,253 (40.9)	784 (38.9)	0.15	463 (25.1)	326 (23.4)	0.24
Age (years)	85.8 \pm 6.7	83.5 \pm 7.7	<0.01	81.1 \pm 6.5	80.5 \pm 6.9	0.01	74.1 \pm 7.6	72.9 \pm 7.9	<0.01	62.5 \pm 9.8	61.7 \pm 9.7	0.04
\geq 75 to <85	128 (30.8)	154 (37.5)		937 (53.3)	636 (54.0)		1,300 (42.5)	782 (38.8)		179 (9.7)	106 (7.6)	
\geq 85	257 (61.9)	205 (49.9)		563 (32.0)	344 (29.2)		230 (7.5)	114 (5.7)		3 (0.2)	6 (0.4)	
Bodyweight (kg)	47.05 \pm 9.87	49.90 \pm 11.27	<0.01	52.67 \pm 9.89	53.26 \pm 10.40	0.12	60.36 \pm 10.19	60.09 \pm 10.18	0.34	72.08 \pm 13.11	71.82 \pm 12.79	0.58
\leq 40.0	111 (26.7)	76 (18.5)		157 (8.9)	103 (8.8)		38 (1.2)	40 (2.0)		2 (0.1)	2 (0.1)	
>40.0 to \leq 50.0	166 (40.0)	154 (37.5)		591 (33.6)	396 (33.6)		467 (15.3)	308 (15.3)		59 (3.2)	40 (2.9)	
>50.0 to \leq 60.0	97 (23.4)	115 (28.0)		628 (35.7)	399 (33.9)		1,041 (34.0)	698 (34.7)		251 (13.6)	170 (12.2)	
BMI (kg/m ²)	21.17 \pm 3.71 ^a	21.67 \pm 3.82 ^a	0.10	22.14 \pm 3.50 ^b	22.32 \pm 3.46 ^b	0.21	23.75 \pm 3.47 ^c	23.64 \pm 3.48 ^c	0.32	26.09 \pm 4.37 ^d	26.11 \pm 4.38 ^d	0.90
SBP (mmHg)	125.8 \pm 24.5 ^e	124.8 \pm 21.3 ^e	0.54	128.5 \pm 21.0 ^f	127.3 \pm 19.7 ^f	0.16	130.7 \pm 20.0 ^g	129.5 \pm 19.7 ^g	0.04	132.0 \pm 19.1 ^h	131.2 \pm 19.3 ^h	0.28
DBP (mmHg)	71.3 \pm 15.7 ^e	70.9 \pm 14.9 ^e	0.73	73.1 \pm 14.7 ⁱ	73.2 \pm 14.2 ⁱ	0.89	76.9 \pm 14.4 ^j	76.5 \pm 13.9 ^j	0.31	81.1 \pm 14.9 ^k	80.1 \pm 13.7 ^k	0.06
CrCl (mL/min)	24.1 \pm 3.9	23.2 \pm 4.1	<0.01	40.7 \pm 5.6	40.4 \pm 5.6	0.15	63.5 \pm 8.5	63.9 \pm 8.6	0.13	102.4 \pm 23.2	102.4 \pm 23.5	0.96
\geq 15 to <30	415 (100.0)	411 (100.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
\geq 30 to <50	0 (0.0)	0 (0.0)		1,757 (100.0)	1,177 (100.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Paroxysmal AF	168 (40.5)	136 (33.1)	0.14	769 (43.8)	437 (37.1)	<0.01	1,346 (44.0)	742 (36.8)	<0.01	766 (41.6)	532 (38.1)	<0.01
CHADS ₂ score	3.0 [2.0–4.0]	3.0 [2.0–3.0]	0.89	2.0 [2.0–3.0]	2.0 [2.0–3.0]	0.70	2.0 [1.0–3.0]	2.0 [1.0–3.0]	0.33	1.0 [1.0–2.0]	1.0 [1.0–2.0]	0.05
CHA ₂ DS ₂ -VASc score	5.0 [4.0–5.0]	5.0 [4.0–5.0]	0.13	4.0 [3.0–5.0]	4.0 [3.0–5.0]	0.61	3.0 [2.0–4.0]	3.0 [2.0–4.0]	0.03	2.0 [1.0–3.0]	2.0 [1.0–3.0]	0.48
HAS-BLED score	3.0 [2.0–4.0]	3.0 [2.0–4.0]	0.02	2.0 [2.0–3.0]	2.0 [2.0–3.0]	0.87	2.0 [2.0–3.0]	2.0 [1.0–3.0]	0.58	1.0 [1.0–2.0]	1.0 [1.0–2.0]	0.89
Comorbidities												
CHF	210 (50.6)	216 (52.6)	0.57	547 (31.1)	410 (34.8)	0.04	699 (22.8)	500 (24.8)	0.09	366 (19.9)	327 (23.4)	0.02
Hypertension	356 (85.8)	364 (88.6)	0.03	1,455 (82.8)	949 (80.6)	0.14	2,305 (75.3)	1,528 (75.9)	0.56	1,296 (70.4)	997 (71.4)	0.54
Diabetes	93 (22.4)	89 (21.7)	0.79	382 (21.7)	257 (21.8)	0.95	642 (21.0)	419 (20.8)	0.91	391 (21.2)	334 (23.9)	0.07
Dyslipidemia	117 (28.2)	120 (29.2)	0.75	583 (33.2)	340 (28.9)	0.01	1,000 (32.7)	609 (30.2)	0.08	560 (30.4)	402 (28.8)	0.31
CAD	91 (21.9)	91 (22.1)	0.94	302 (17.2)	215 (18.3)	0.45	428 (14.0)	340 (16.9)	<0.01	216 (11.7)	200 (14.3)	0.03
PAD ^l	24 (5.8)	27 (6.6)	0.64	93 (5.3)	48 (4.1)	0.13	111 (3.6)	97 (4.8)	0.04	45 (2.4)	74 (5.3)	<0.01
Medical history												
Stroke/TIA	88 (21.2)	78 (19.0)	0.59	288 (16.4)	201 (17.1)	0.58	329 (10.7)	200 (9.9)	0.38	126 (6.8)	93 (6.7)	0.82
Bleeding ^m	7 (1.7)	13 (3.2)	0.14	25 (1.4)	25 (2.1)	0.14	44 (1.4)	26 (1.3)	0.68	21 (1.1)	12 (0.9)	0.42
Concomitant medication												

Antiplatelet drugs	165 (39.8)	166 (40.4)	0.85	564 (32.1)	392 (33.3)	0.50	681 (22.2)	525 (26.1)	<0.01	289 (15.7)	270 (19.3)	<0.01
ACEi or ARB	202 (48.7)	233 (56.7)	0.02	844 (48.0)	564 (47.9)	0.95	1,249 (40.8)	893 (44.3)	0.01	678 (36.8)	539 (38.6)	0.30
Beta blocker	94 (22.7)	93 (22.6)	0.99	349 (19.9)	225 (19.1)	0.62	541 (17.7)	351 (17.4)	0.82	339 (18.4)	216 (15.5)	0.03
Amiodarone	10 (2.4)	13 (3.2)	0.51	47 (2.7)	23 (2.0)	0.21	21 (0.7)	20 (1.0)	0.23	27 (1.5)	25 (1.8)	0.47
PPI or H ₂ RA	196 (47.2)	174 (42.3)	0.16	631 (35.9)	366 (31.1)	<0.01	877 (28.7)	492 (24.4)	<0.01	436 (23.7)	217 (15.5)	<0.01
NSAIDs	27 (6.5)	26 (6.3)	0.92	120 (6.8)	65 (5.5)	0.15	138 (4.5)	75 (3.7)	0.17	53 (2.9)	42 (3.0)	0.83
Apixaban dose												
5 mg b.i.d.	31 (7.5)	NA		373 (21.2)	NA		1,816 (59.3)	NA		1,531 (83.2)	NA	
2.5 mg b.i.d.	371 (89.4)	NA		1,363 (77.6)	NA		1,205 (39.4)	NA		275 (14.9)	NA	
Other	13 (3.1)	NA		21 (1.2)	NA		40 (1.3)	NA		35 (1.9)	NA	

Data are presented as mean±SD, n (%), or median [IQR]. The P values are based on Student's *t*-test for continuous variables; chi-square test for categorical variables; and Wilcoxon rank-sum test for CHADS₂, CHA₂DS₂-VASc, and HAS-BLED scores

^aApixaban, n=313; warfarin, n=330

^bApixaban, n=1,388; warfarin, n=931

^cApixaban, n=2,494; warfarin, n=1,663

^dApixaban, n=1,576; warfarin, n=1,198

^eApixaban, n=404; warfarin, n=395

^fApixaban, n=1,700; warfarin, n=1,149

^gApixaban, n=2,949; warfarin, n=1,977

^hApixaban, n=1,779; warfarin, n=1,348

ⁱApixaban, n=1,699; warfarin, n=1,149

^jApixaban, n=2,949; warfarin, n=1,975

^kApixaban, n=1,779; Warfarin, n=1,347

^lPAD and other peripheral vascular diseases

^mIntracranial hemorrhage, gastrointestinal bleeding, and other types of bleeding

ACEi angiotensin-converting enzyme inhibitor, AF atrial fibrillation, ARB angiotensin II receptor blocker, *b.i.d.* twice daily, BMI body mass index, CAD coronary artery disease, CHF congestive heart failure, CrCl creatinine clearance, DBP diastolic blood pressure, FAS full analysis set, H₂RA histamine receptor antagonist, IQR interquartile range, NA not applicable, NSAID nonsteroidal anti-inflammatory drug, PAD peripheral artery disease, PPI proton pump inhibitor, PSM propensity score matching, SBP systolic blood pressure, SD standard deviation, SMD standardized mean difference, TIA transient ischemic attack

Online Resource 3: Patient characteristics stratified by renal function decline (CrCl change <0 mL/min per year) during the study (FAS)

Variable	Quartile 1			Quartile 2			Quartile 3			Quartile 4		
	Apixaban (n=968)	Warfarin (n=659)	P value	Apixaban (n=968)	Warfarin (n=659)	P value	Apixaban (n=968)	Warfarin (n=659)	P value	Apixaban (n=967)	Warfarin (n=658)	P value
Female sex	431 (44.5)	255 (38.7)	0.02	404 (41.7)	263 (39.9)	0.46	446 (46.1)	291 (44.2)	0.45	424 (43.8)	279 (42.4)	0.56
Age (years)	75.3±9.2	74.3±10.2	0.04	75.7±9.3	73.9±10.1	<0.01	74.2±10.6	73.0±10.4	0.02	73.0±12.2	72.3±12.5	0.26
≥75 to <85	418 (43.2)	254 (38.5)		414 (42.8)	251 (38.1)		366 (37.8)	239 (36.3)		315 (32.6)	202 (30.7)	
≥85	144 (14.9)	98 (14.9)		168 (17.4)	90 (13.7)		153 (15.8)	84 (12.7)		171 (17.7)	113 (17.2)	
Bodyweight (kg)	59.34±12.86	59.01±12.63	0.62	59.58±12.30	59.76±12.39	0.78	60.49±13.28	61.36±13.49	0.20	61.65±14.90	60.80±14.35	0.26
≤40.0	44 (4.5)	37 (5.6)		36 (3.7)	28 (4.2)		46 (4.8)	33 (5.0)		53 (5.5)	37 (5.6)	
>40.0 to ≤50.0	202 (20.9)	135 (20.5)		190 (19.6)	133 (20.2)		176 (18.2)	107 (16.2)		168 (17.4)	126 (19.1)	
>50.0 to ≤60.0	292 (30.2)	198 (30.0)		300 (31.0)	187 (28.4)		279 (28.8)	180 (27.3)		249 (25.7)	167 (25.4)	
BMI (kg/m ²)	23.52±3.69 ^a	23.38±3.70 ^a	0.49	23.76±4.03 ^b	23.58±3.61 ^b	0.42	23.96±4.19 ^c	24.46±4.20 ^c	0.03	24.22±4.58 ^d	24.10±4.59 ^d	0.64
SBP (mmHg)	129.4±18.6 ^e	128.9±18.9 ^e	0.59	130.5±19.9 ^f	129.8±19.3 ^f	0.52	131.5±20.7 ^g	130.5±19.6 ^g	0.33	133.0±23.0 ^h	129.3±20.6 ^h	<0.01
DBP (mmHg)	74.8±13.3 ^e	75.7±13.3 ^e	0.18	75.7±14.2 ^f	76.3±13.6 ^f	0.35	77.6±15.1 ^g	76.7±14.1 ^g	0.20	79.3±17.2 ⁱ	77.1±15.2 ⁱ	0.01
CrCl (mL/min)	59.1±22.5	59.3±25.9	0.84	62.3±24.2	62.4±26.9	0.95	68.7±27.4	68.9±27.9	0.90	74.7±35.4	73.8±36.2	0.64
≥15 to <30	66 (6.8)	75 (11.4)		49 (5.1)	55 (8.3)		38 (3.9)	33 (5.0)		60 (6.2)	44 (6.7)	
≥30 to <50	284 (29.3)	177 (26.9)		265 (27.4)	172 (26.1)		219 (22.6)	147 (22.3)		187 (19.3)	130 (19.8)	
Paroxysmal AF	441 (45.6)	250 (37.9)	<0.01	434 (44.8)	215 (32.6)	<0.01	386 (39.9)	241 (36.6)	<0.01	353 (36.5)	233 (35.4)	0.06
CHADS ₂ score	2.0 [1.0–3.0]	2.0 [1.0–3.0]	0.65	2.0 [1.0–3.0]	2.0 [1.0–3.0]	0.08	2.0 [1.0–3.0]	2.0 [1.0–3.0]	0.01	2.0 [1.0–3.0]	2.0 [1.0–3.0]	0.81
CHA ₂ DS ₂ -VASc score	3.0 [2.0–4.0]	3.0 [2.0–4.0]	0.17	4.0 [3.0–5.0]	3.0 [2.0–4.0]	<0.01	3.0 [2.0–4.0]	4.0 [2.0–5.0]	0.10	4.0 [2.0–5.0]	3.0 [2.0–5.0]	0.79
HAS-BLED score	2.0 [2.0–3.0]	2.0 [1.0–3.0]	0.41	2.0 [2.0–3.0]	2.0 [1.0–3.0]	0.01	2.0 [2.0–3.0]	2.0 [2.0–3.0]	0.15	2.0 [1.0–3.0]	2.0 [1.0–3.0]	0.77
Comorbidities												
CHF	216 (22.3)	173 (26.3)	0.06	252 (26.0)	195 (29.6)	0.12	292 (30.2)	254 (38.5)	<0.01	345 (35.7)	241 (36.6)	0.70
Hypertension	737 (76.1)	502 (76.2)	0.86	778 (80.4)	518 (78.6)	0.39	782 (80.8)	541 (82.1)	0.44	771 (79.7)	508 (77.2)	0.21
Diabetes	215 (22.2)	144 (21.9)	0.90	228 (23.6)	165 (25.0)	0.49	205 (21.2)	164 (24.9)	0.08	233 (24.1)	147 (22.3)	0.41
Dyslipidemia	324 (33.5)	211 (32.0)	0.58	341 (35.2)	201 (30.5)	0.05	319 (33.0)	208 (31.6)	0.58	280 (29.0)	152 (23.1)	<0.01
CAD	152 (15.7)	114 (17.3)	0.37	166 (17.1)	126 (19.1)	0.31	146 (15.1)	130 (19.7)	0.01	127 (13.1)	103 (15.7)	0.15
PAD ^j	51 (5.3)	33 (5.0)	0.83	46 (4.8)	34 (5.2)	0.71	33 (3.4)	42 (6.4)	<0.01	35 (3.6)	24 (3.6)	0.98
Medical history												
Stroke/TIA	132 (13.6)	83 (12.6)	0.52	131 (13.5)	68 (10.3)	0.05	115 (11.9)	96 (14.6)	0.09	104 (10.8)	77 (11.7)	0.49
Bleeding ^k	15 (1.5)	13 (2.0)	0.53	15 (1.5)	12 (1.8)	0.68	11 (1.1)	12 (1.8)	0.24	16 (1.7)	13 (2.0)	0.61

Concomitant medication												
Antiplatelet drugs	252 (26.0)	205 (31.1)	0.03	279 (28.8)	199 (30.2)	0.55	235 (24.3)	198 (30.0)	0.01	253 (26.2)	169 (25.7)	0.83
ACEi or ARB	422 (43.6)	299 (45.4)	0.48	426 (44.0)	318 (48.3)	0.09	430 (44.4)	311 (47.2)	0.27	406 (42.0)	292 (44.4)	0.34
Beta blocker	162 (16.7)	109 (16.5)	0.92	187 (19.3)	124 (18.8)	0.80	190 (19.6)	130 (19.7)	0.96	200 (20.7)	125 (19.0)	0.40
Amiodarone	7 (0.7)	12 (1.8)	0.04	12 (1.2)	12 (1.8)	0.34	28 (2.9)	11 (1.7)	0.11	17 (1.8)	14 (2.1)	0.59
PPI or/and H ₂ RA	285 (29.4)	168 (25.5)	0.08	319 (33.0)	178 (27.0)	0.01	304 (31.4)	186 (28.2)	0.17	351 (36.3)	190 (28.9)	<0.01
NSAIDs	45 (4.6)	18 (2.7)	0.05	43 (4.4)	25 (3.8)	0.52	54 (5.6)	33 (5.0)	0.62	63 (6.5)	42 (6.4)	0.92
Apixaban dose												
5 mg b.i.d.	462 (47.7)	NA		479 (49.5)	NA		487 (50.3)	NA		529 (54.7)	NA	
2.5 mg b.i.d.	491 (50.7)	NA		478 (49.4)	NA		470 (48.6)	NA		418 (43.2)	NA	
Other	15 (1.5)	NA		11 (1.1)	NA		11 (1.1)	NA		20 (2.1)	NA	

Data are presented as mean±SD, n (%), or median [IQR]. The P values are based on Student's *t*-test for continuous variables; chi-square test for categorical variables; and Wilcoxon rank-sum test for CHADS₂, CHA₂DS₂-VASc, and HAS-BLED scores

^aApixaban, n=763; warfarin, n=521

^bApixaban, n=786; warfarin, n=518

^cApixaban, n=784; warfarin, n=541

^dApixaban, n=844; warfarin, n=577

^eApixaban, n=947; warfarin, n=650

^fApixaban, n=933; warfarin, n=646

^gApixaban, n=944; warfarin, n=643

^hApixaban, n=926; warfarin, n=639

ⁱApixaban, n=926; warfarin, n=637

^jPAD and other peripheral vascular diseases

^kIntracranial hemorrhage, gastrointestinal bleeding, and other types of bleeding

ACEi angiotensin-converting enzyme inhibitor, *AF* atrial fibrillation, *ARB* angiotensin II receptor blocker, *b.i.d.* twice daily, *BMI* body mass index, *CAD* coronary artery disease, *CHF* congestive heart failure, *CrCl* creatinine clearance, *DBP* diastolic blood pressure, *FAS* full analysis set, *IQR* interquartile range, *H₂RA* histamine receptor antagonist, *NA* not applicable, *NSAID* nonsteroidal anti-inflammatory drug, *PAD* peripheral artery disease, *PPI* proton pump inhibitor, *PSM* propensity score matching, *SBP* systolic blood pressure, *SD* standard deviation, *SMD* standardized mean difference, *TIA* transient ischemic attack

Online Resource 4: Impact of the magnitude of renal function decline during the study on the incidence rates of major bleeding and stroke/SE (FAS)

Event	Group	HR (95% CI)^a
Major bleeding	Apixaban (n=3,871)	1.65 (1.35–2.02)
	Warfarin (n=2,635)	1.53 (1.23–1.91)
Stroke/SE	Apixaban (n=3,871)	1.34 (1.08–1.65)
	Warfarin (n=2,635)	1.58 (1.28–1.95)

^aBased on a Cox proportional hazards regression model that included the CrCl quartile (1, 2, 3, and 4) as a continuous variable

CI confidence interval, *CrCl* creatinine clearance, *FAS* full analysis set, *HR* hazard ratio, *SE* systemic embolism.