Received: 1 October 2021 | Revised: 14 March 2022 | Accepted: 28 March 2022

DOI: 10.1002/joa3.12716

ORIGINAL ARTICLE

Journal of Arrhythmia Open Access WILEY

Impact of different dose reduction criteria for anti-Xa direct oral anticoagulants on bleeding complications: A single center observational study

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Abstract

Background: Each direct oral anticoagulant (DOAC) has different dose reduction criteria. Here, we evaluated the differences in the doses of three anti-Xa DOACs and clinical events based on the dose reduction criteria in patients with atrial fibrillation (AF).

Methods: Consecutive AF patients prescribed with anti-Xa DOACs [rivaroxaban (Riva), apixaban (Apix), and edoxaban (Edox)] between April 2011 and May 2016 were retrospectively evaluated. The incidences of thromboembolic and bleeding events were evaluated by the end of December 2020, focusing on the dose proportion.

Results: A total of 786 patients (72 ± 10 years old, 66.9% male) were enrolled in this study [Riva ($n = 337$), Apix ($n = 239$), and Edox ($n = 210$)]. The proportion of reduced dose prescriptions was significantly greater for Edox (79.2%) than Riva (38.7%) or Apix (31.9%). A Kaplan–Meier analysis showed that the incidence of minor bleeding was significantly higher in the Apix than other groups ($p < .001$), even after propensity score matching. The standard dose of Apix had significantly higher bleeding events than the other DOACs ($p < .001$). Moreover, 23.2% and 51.6% of the patients with a standard dose of Apix were fulfilled with the dose reduction criteria for Riva and Edox and had more minor bleeding events than the unfulfilled ones ($p = .046$).

Conclusions: The patients with a standard dose of Apix had a higher incidence of minor bleeding events than the other dosages. A reduced dose of apixaban was not prone to being chosen because of the dose reduction criteria, which may have been associated with a higher minor bleeding rate in patients with Apix.

KEYWORDS
anti-Xa direct oral anticoagulants, atrial fibrillation, bleeding complications, dose reduction criteria

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1 | INTRODUCTION

Atrial fibrillation (AF) is the most common tachyarrhythmia, and its prevalence is increasing.[1] Anticoagulation therapy for patients with AF has been emphasized to prevent ischemic strokes and systemic thromboembolisms. Recent guidelines[2–4] recommend strict anticoagulation for AF patients based on a thromboembolic risk stratification.[5,6] After the launch of direct oral anticoagulants (DOACs), the total prescription rate of oral anticoagulants (OACs) has been increasing, and the proportion of DOACs among the total OAC prescriptions has been expanded.[7,8] On the other hand, inappropriately reduced prescriptions of DOACs are seen in clinical practice.[9–11] In addition, four currently available DOACs, that is, dabigatran (Dabi), rivaroxaban (Riva), apixaban (Apix), and edoxaban (Edox), have different dose reduction criteria, which may affect the selection of drugs as well as the efficacy or safety outcomes. The dose reduction criteria for Dabi are a recommendation, and the actual prescription is at the discretion of physicians. However, anti-Xa DOACs have strict definitions. Here, we evaluated thromboembolic and bleeding events in three anti-Xa DOACs, focusing on the dose reduction criteria.

2 | METHODS

2.1 | Study population and evaluation parameters

Consecutive AF patients who were prescribed anti-Xa DOACs from April 1, 2011 to May 31, 2016 at Kitasato University Hospital were retrospectively enrolled in this study. Age, sex, body weight (BW), serum creatinine (Cr), and Cr clearance (CCr) were evaluated as baseline characteristics. CCr was estimated by the Cockcroft–Gault equation as follows: CCr = {(140 −age)×(weight in kg)×(0.85 if female)}/(72×serum creatinine).[12] Because patients with severe renal insufficiency (CCr < 15 ml/min) did not have an indication for each DOAC, they were excluded from this study. $CHADS_2$[5] and CHA_2DS_2-VASc[6] scores were used for the risk stratification of stroke and thromboembolic events, and the HAS-BLED score[13] was used as the risk stratification for bleeding events. Their constituent factors were also evaluated. Currently available doses of anti-Xa DOACs in Japan are 15 mg or 10 mg once daily for Riva, 5 mg or 2.5 mg twice daily for Apix, and 60 mg or 30 mg once daily for Edox.

Regarding the efficacy and safety outcomes, the incidence of strokes, STEs, and major and minor bleeding events was evaluated among the three groups until the end of 2020. To avoid events with inappropriate dose prescriptions, the patients with inappropriate under or overdose prescriptions were excluded. The definitions of major bleeding were a decrease in the hemoglobin level of >2.0 g/dl, transfusion of >2 units of blood, or symptomatic bleeding in a critical area or organ, which were the same as the definitions used in the phase III studies of each DOAC.[14–18] The definition of minor bleeding was not clinically relevant, but significant bleeding events, such as nose bleeding needing intervention, macro-hematuria, blackish feces/melena, or hemoptysis, which were not matched with the definition of major bleeding. We also calculated the adjusted hazard ratio (HR) for the outcomes between each DOAC with the factors that exhibited a statistical significance in the univariate analyses.

2.2 | Statistical analyses

Continuous variables were compared by an ANOVA and post hoc Tukey–Kramer analysis or Kruskal–Wallis analysis with a Steel–Dwass post hoc analysis when applicable. Data are presented as the mean value +/− standard deviation or median with the interquartile range. Categorical variables were compared by using the chi-square test if appropriate and are reported as percentages. Ordinal variables were compared by a Wilcoxon analysis and are shown as median values with data ranges. The survival distribution in each group was calculated using the Kaplan–Meier method. The log-rank test was used to compare the stroke/STE and major and minor bleeding events among the three groups during the observation period. A two-sided p-value <.05 was considered statistically significant. If the analyses included multiple comparisons, a p-value <.01 was considered statistically significant using a Bonferroni correction. A Cox proportional hazard model was used to compare the outcomes among the three groups, followed by a multivariate analysis to adjust for any significantly different factors. Further, propensity score matching as a sensitivity analysis was performed using 1:1 nearest neighbor matching algorithm with the factors used for the adjustment in the multivariate analysis. Optimal caliper was set as 0.05. All analyses were performed with JMP 13.1 software (SAS).

This study was approved by the ethical committee of clinical studies in Kitasato University Hospital (IRB # B20-105).

3 | RESULTS

3.1 | Study population and baseline patient characteristics

There were 1485 consecutive patients prescribed DOACs assigned to this study. To focus on the relationship between the dose reduction criteria and clinical events, patients prescribed Dabi were excluded (n = 500). A total of 65 patients were also excluded because of a lack of data (n = 39), contraindications to DOACs (n = 2), and indications for catheter ablation despite a $CHADS_2$ score of 0 (n = 24). A total of 920 patients were finally enrolled, and 134 patients with an inappropriate-under (n = 118) or -overdose (n = 16) prescription were excluded from the evaluation of the outcomes; therefore, 786 patients were ultimately enrolled in this study (Figure 1).

Table 1 shows the patient characteristics among the groups. The Apix and Edox groups had a significantly higher age (<0.001), lower BW (p < .001), higher serum Cr (p = .003), and lower CCr (p < .001) than the Riva group. Regarding the factors constituting the $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores, the proportion of patients

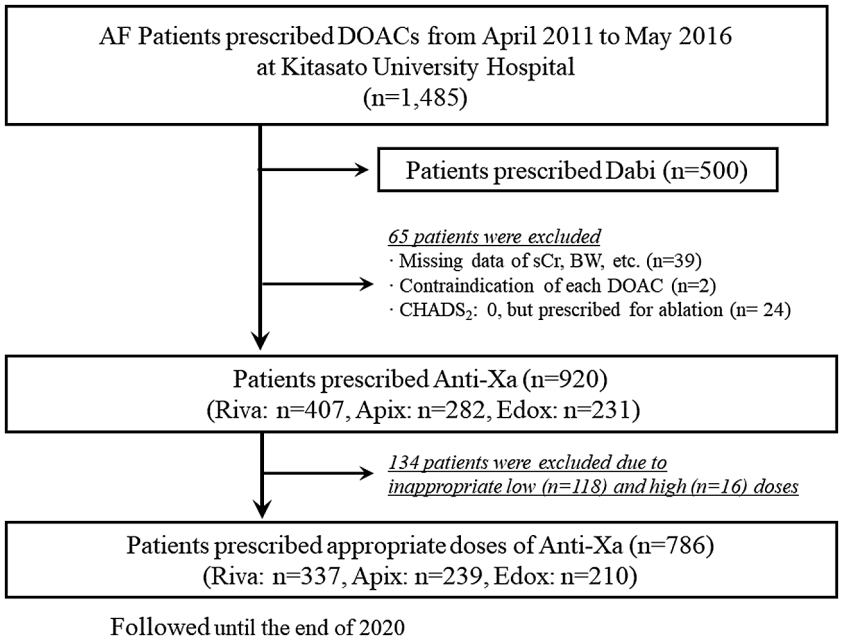

FIGURE 1 The study flow chart. A total of 786 patients prescribed an anti-Xa direct oral anticoagulant were finally enrolled and followed until the end of 2020. See the text for the details.

TABLE 1 Baseline characteristics

	All	Riva	Apix	Edox	
	n = 786	*n* = 337	*n* = 239	*n* = 210	*p* value
Age, y.o.	72 ± 10	71 ± 10	74 ± 9	73 ± 11	<.001
Female: *n* (%)	260 (33.1)	104 (30.9)	75 (31.4)	81 (38.6)	.145
BW, kg	58.5 [50.2-67.0]	60.0 [51.6-67.4]	59.3 [50.8-68.0]	55.3 [47.4-64.9]	<.001
Cr, mg/dL	0.89 [0.75-1.08]	0.86 [0.73-1.03]	0.93 [0.77-1.08]	0.94 [0.76-1.19]	.003
CCr, ml/min	58.2 [42.8-74.1]	65.0 [47.3-79.1]	57.2 [44.9-71.0]	46.6 [35.8-67.5]	<.001
HF: *n* (%)	300 (38.2)	115 (34.1)	94 (38.1)	94 (44.8)	.046
HT: *n* (%)	491 (62.5)	215 (63.8)	160 (67.0)	116 (55.2)	.032
Age≧75 y.o.: *n* (%)	369 (47.0)	133 (39.5)	123 (51.5)	113 (53.8)	.001
Age 65–74 y.o.: *n* (%)	271 (34.5)	124 (36.8)	80 (33.5)	67 (31.9)	.467
DM: *n* (%)	186 (23.7)	87 (25.8)	57 (23.9)	42 (20.0)	.297
Stroke/TIA: *n* (%)	142 (18.1)	49 (14.5)	61 (25.5)	32 (15.2)	.002
Vascular disase: *n* (%)	163 (20.7)	73 (21.7)	51 (21.3)	39 (18.6)	.646
Liver/kidney disease: *n* (%)	26 (3.3)	10 (3.0)	7 (2.9)	9 (4.2)	.626
Bleeding tendency: *n* (%)	29 (3.7)	9 (2.7)	8 (3.4)	12 (5.7)	.175
Antiplatelets co-prescpription: *n* (%)	115 (14.6)	61 (18.1)	32 (13.4)	22 (10.5)	.040
AF type					.056
Paroxysmal	344	127	116	101	
Persistent	90	45	23	22	
Long-standing persistent	352	165	100	87	
Underwent CA: n (%)	44 (5.6)	15 (4.5)	18 (7.5)	11 (5.2)	.275
$CHADS_2$ score	2 [1-3]	2 [1-3]	2 [1-3]	2 [1-3]	.091
$CHADS_2$-VA_2Sc score	3 [2-4]	3 [2-4]	4 [2-5]	3 [2-4]	.002
HAS-BLED score	2 [1-2]	2 [1-2]	2 [1-3]	2 [1-2]	.064

Abbreviations: BW, body weight; CA, catheter ablation; Cr, serum creatinine; CCr, creatinine clearance; DM, diabetes mellitus; HF, heart failure; HT, hypertension; TIA, transient ischemic attack.

≥75 years old was higher in the Apix and Edox groups than the Riva group ($p = .003$). The proportion with heart failure was higher ($p = .046$) and with hypertension was lower ($p = .032$) in the Edox group than in other groups. The proportion of patients with a prior stroke or transient ischemic attack (TIA), that is, for secondary prevention, was higher in the Apix group than Riva and Edox groups. That of antiplatelets co-prescriptions was higher in the Riva group ($p = .040$). As a result, the Apix group had the highest CHA_2DS_2-VASc scores, whereas the $CHADS_2$ and HAS-BLED scores did not significantly differ among the three groups.

3.2 | Incidence of bleeding complications

The Kaplan–Meier analysis for the incidence of a stroke/STE and major and minor bleeding events during 561 [113–1473] days of the observational period among the groups are shown in Figure 2. Although the incidences of stroke/STE (Figure 2 left) and major bleeding events (Figure 2 middle) did not significantly differ among the three groups ($p = .093$ and $p = .075$, respectively), the Apix group had a significantly higher incidence of minor bleeding events than the Riva and Edox groups (Figure 2 right, log-rank <0.001). Figure 3 shows the minor bleeding events for the different doses. In the standard dose subgroup analysis (Figure 3 left), the Apix group had a further higher incidence of minor bleeding than the others (log-rank <0.001), whereas the reduced dose in the Apix group was comparable to that in the Riva group (Figure 3 right).

We also evaluated the patient characteristics with or without minor bleeding events for each DOAC (Table 2). There were no statistical differences in the proportion of the dose selections in the Apix group (standard dose: 75.0% vs. 80.0% for with vs. without minor bleeding events). Further, the age, BW, and CCr also did not differ between the sub-groups. Of note, the HAS-BLED score was statistically higher in the patients with minor bleeding in the Apix group.

Further, we used the Cox proportional Hazard model to adjust for the outcomes according to the age, BW, Cr, and CHA_2DS_2-VASc scores, which had statistically significant differences in the univariate analysis. Table 3 shows the results of the adjusted HR between each DOAC for the minor bleeding events. Apix still had a higher minor bleeding risk than Riva [HR: 3.170, 95% confidential interval (CI): 1.762–5.703, $p < .001$] and Edox [HR 4.379, 95%CI: 1.919–9.992, $p < .001$].

To avoid any selection bias, we also performed propensity score matching using the age, BW, Cr, and CHA_2DS_2-VASc scores. Table S1 shows the baseline characteristics after the propensity score

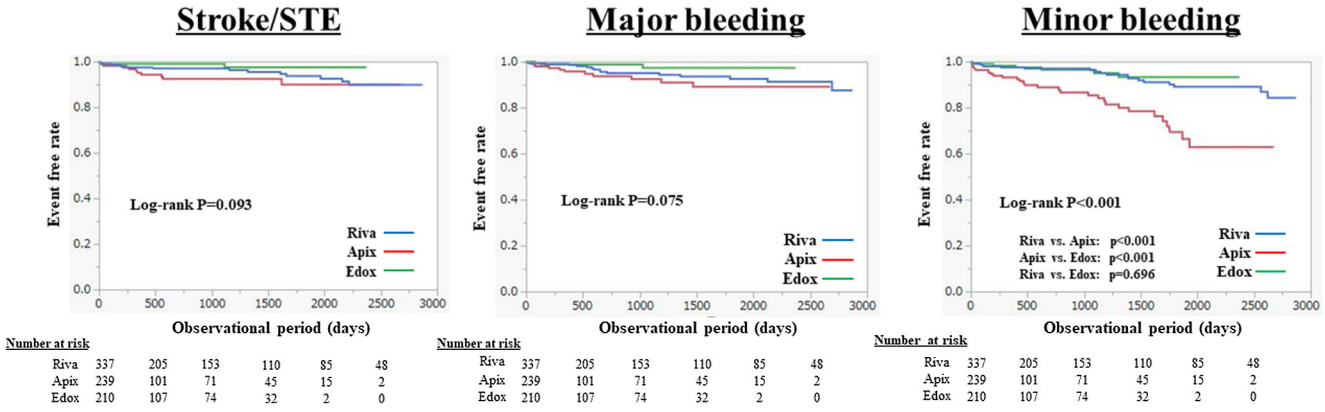

FIGURE 2 Overall results of the Kaplan–Meier analysis of strokes/systemic thromboembolisms (STEs) and major and minor bleeding among the three anti-Xa direct oral anticoagulant. Strokes/STEs (left) and major bleeding (middle) events were not significantly different among the groups; however, minor bleeding events were significantly higher in the Apix group (right).

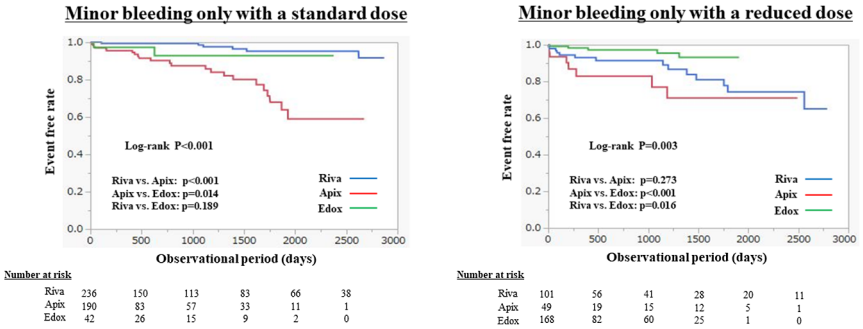

FIGURE 3 Kaplan–Meier analysis of minor bleeding among the three anti-Xa direct oral anticoagulants (DOACs) for standard or reduced doses. In the subgroup analysis, minor bleeding events were evaluated with standard (left) or reduced (right) doses of the three anti-Xa DOACs. The standard dose of Apix showed a higher rate of minor bleeding events.

TABLE 2 Baseline characteristics in the patients with or without minor bleeding events

	All			Riva			Apix			Edox		
	(+)	(-)		(+)	(-)		(+)	(-)		(+)	(-)	
Minor bleeeding	***n* = 59**	***n* = 727**	***p* value**	***n* = 20**	***n* = 317**	***p* value**	***n* = 32**	***n* = 207**	***p* value**	***n* = 7**	***n* = 203**	***p* value**
Age, y.o.	75 ± 9	72 ± 10	.100	74 ± 9	71 ± 10	.144	75 ± 9	74 ± 10	.426	74 ± 13	73 ± 11	.884
Female: *n* (%)	119 (32.2)	241 (33.2)	.882	6 (30.0)	98 (30.9)	.931	12 (37.5)	63 (31.4)	.429	1 (14.3)	80 (39.4)	.150
BW, kg	56.5 [48.0-64.5]	58.7 [50.6-67.3]	.220	54.3 [50.1-63.1]	60.0 [51.8-67.9]	.161	57.0 [48.2-64.3]	60.0 [51.0-68.9]	.140	66.6 [42.4-74.6]	55.2 [47.5-63.6]	.580
Cr, mg/dl	0.98 [0.75-1.16]	0.89 [0.74-1.08]	.110	1.13 [0.80-1.29]	0.85 [0.72-1.00]	.008	0.97 [0.73-1.07]	0.93 [0.78-1.09]	.970	0.96 [0.68-1.24]	0.94 [0.76-1.19]	.987
CCr, ml/min	48.0 [40.6-65.5]	59.6 [43.1-74.8]	.010	46.0 [36.3-65.8]	65.6 [48.6-79.8]	.003	51.6 [43.9-64.5]	58.2 [45.1-72.0]	.159	44.8 [33.2-67.5]	46.7 [35.9-67.5]	.709
HF: *n* (%)	23 (39.0)	277 (38.1)	.893	7 (35.0)	108 (34.7)	.932	13 (40.6)	78 (38.1)	.750	3 (42.9)	91 (44.8)	.918
HT: *n* (%)	40 (67.8)	451 (62.0)	.380	12 (60.0)	203 (64.0)	.717	25 (78.1)	135 (65.2)	.136	3 (42.9)	113 (55.7)	.504
Age ≧75 y.o.: *n* (%)	36 (61.0)	333 (45.8)	.024	11 (55.0)	122 (38.5)	.148	19 (59.4)	104 (50.2)	.335	6 (85.7)	107 (52.7)	.068
Age 65–74 y.o.: *n* (%)	17 (28.8)	254 (34.9)	.341	7 (35.0)	117 (36.9)	.863	10 (31.3)	70 (33.8)	.774	0 (0)	67 (33.0)	.019
DM: *n* (%)	15 (25.4)	171 (23.5)	.741	5 (25.0)	82 (25.9)	.931	7 (21.9)	50 (24.2)	.776	3 (42.9)	39 (19.2)	.161
Stroke/TIA: *n* (%)	12 (20.3)	130 (17.9)	.637	5 (25.0)	44 (13.9)	.204	6 (18.8)	55 (25.6)	.331	1 (14.3)	31 (15.3)	.943
Vascular disase: *n* (%)	17 (28.8)	146 (20.1)	.112	7 (35.0)	66 (20.8)	.158	8 (25.0)	43 (20.8)	.593	2 (28.6)	37 (18.2)	.513
Liver/kidney disease: *n* (%)	3 (5.1)	23 (3.2)	.074	1 (5.0)	0 (0)	.034	1 (3.1)	6 (2.9)	.944	1 (14.3)	8 (3.94)	.285
Bleeding tendency: *n* (%)	5 (8.5)	24 (3.3)	.077	2 (10.0)	7 (2.2)	.036	3 (9.4)	5 (2.4)	.080	0 (0)	12 (5.9)	.360
Antiplatelets co-prescpription: *n* (%)	13 (22.0)	102 (14.0)	.113	3 (15.0)	58 (18.3)	.704	9 (28.1)	23 (11.1)	.016	1 (14.3)	21 (10.3)	.749
Standard dose prescription: *n* (%)	32 (54.2)	436 (60.0)	.39	6 (30.0)	230 (72.6)	<.001	24 (75.0)	116 (80.0)	.500	2 (28.6)	40 (19.7)	.564
$CHADS_2$ score	2 [1-3]	2 [1-3]	.035	2 [1-3]	2 [1-3]	.126	2 [1-3]	2 [1-3]	.684	2 [2-3]	2 [1-3]	.191
$CHADS_2$-VA_2Sc score	4 [3-5]	3 [2-4]	.013	4 [3-5]	3 [2-4]	.034	4 [3-5]	4 [2-5]	.667	4 [3-4]	3 [2-4]	.483
HAS-BLED score	2 [2-3]	2 [1-2]	.007	2 [1-3]	2 [1-2]	.176	2 [2-3]	2 [1-3]	.033	2 [1-2]	2 [1-2]	.949

Abbreviations: BW, body weight; Cr, serum creatinine; CCr, creatinine clearance; DM, diabetes mellitus; HF, heart failure; HT, hypertension; TIA, transient ischemic attack.

TABLE 3 Adjusted cox regression analysis for minor bleeding events (age, BW, Cr, and CHA_2DS_2-VASc score)

Variables	Hazard ratio [95% CI]	*p*-value
Apix vs. Riva	3.170 [1.762-5.703]	<.001
Apix vs. Edox	4.379 [1.919-9.992]	<.001
Riva vs. Edox	1.381 [0.567-3.365]	.477
Age	1.015 [0.980-1.501]	.400
Body weight	0.984 [0.961-1.007]	.167
Cr	1.721 [0.848-3.495]	.133
CHA_2DS_2-VASc score	1.062 [0.890-1.268]	.508

Abbreviations: BW, body weight; Cr, creatinine; CI, confidential interval.

matching between Riva versus Apix and Apix versus Edox, respectively. Those were well matched except for a history of a stroke in the Riva versus Apix matching. The Kaplan–Meier analyses after the propensity score matching are shown in Figure 4. Even after the propensity score matching, the Apix group showed significantly higher minor bleeding events than the Riva ($p < .001$) and Edox ($p = .002$) groups, respectively.

3.3 | Relationship between bleeding events and the dose reduction criteria

According to the dose reduction criteria on the bleeding outcomes, we evaluated the dose changes for each DOAC. Focusing on the patients with a standard dose of Apix, 23.2% and 51.6% of those patients were fulfilled with the dose-reduction criteria of Riva and Edox. In the patients who were fulfilled with the dose-reduction criteria of Riva, the incidence rate of minor bleeding events was 13.0%/patient-year. Likewise, that was 9.2%/patient-year in the patients who were fulfilled with Edox. Those event rates were significantly higher than those who were not fulfilled with those criteria in the patients with the standard dose of Apix (5.3%/patient-year, Log-lank $p = .046$). On the other hand, the stroke/STE event rates were 1.1, 2.8, and 3.3%/patient-year in the patients fulfilled with Riva, Edox, and not fulfilled, respectively, and did not statistically differ among those sub-groups (Log-lank $p = .222$).

4 | DISCUSSION

In this study, we evaluated the incidence of strokes/STEs and bleeding complications with anti-Xa DOACs, focusing on the dose reduction criteria. Our findings in this study were (1) the incidence of minor bleeding complications was higher in the Apix group than Riva and Edox groups even after an adjustment for the age, BW, Cr, and CHA_2DS_2-VASc score, or after performing propensity score matching, (2) the incidences were higher in the Apix group with a standard dose, and (3) focusing on the dose of Apix, 23.2% and 51.6% of the patients with the standard dose of Apix were fulfilled with the dose reduction criteria for Riva or Edox, and those patients showed the higher incidence rate of minor bleeding events than those who were not fulfilled. Those differences may be associated with higher bleeding events in the Apix group.

4.1 | Impact of the dose reduction criteria for each DOAC on the bleeding events

All four DOACs have different dose reduction criteria. Since that for Dabi is a recommendation, the choice of two doses, 110 mg or 150 mg twice daily, is at the discretion of the physicians. On the other hand, the other anti-Xa DOACs have strict criteria that have to be observed; however, they are all different. Therefore, we also evaluated the prescribed dose proportions of standard/reduced doses for each DOAC in 920 patients prescribed anti-Xa DOACs (Figure S1-1) in clinical practice. Upper graphs show the actually prescribed doses of the three DOACs, and lower graphs show the proportions of the authorized dose that we should have prescribed in accordance with the dose reduction criteria for each DOAC. The ratio of standard and reduced doses on each DOAC significantly differed among the three groups ($p < .001$) in both the actual and authorized dose prescriptions. Although the incidence of stroke and thromboembolic events was comparable among the three groups (Figure 2 left) and even in separate evaluations of the two different doses (Figure S2), the patients in the Apix group had more minor bleeding events than the others (Figure 2 right). Moreover, patients with a standard dose of Apix had a higher bleeding rate than the others (Figure 3 left). As shown in Table 2, there were no statistical differences in the

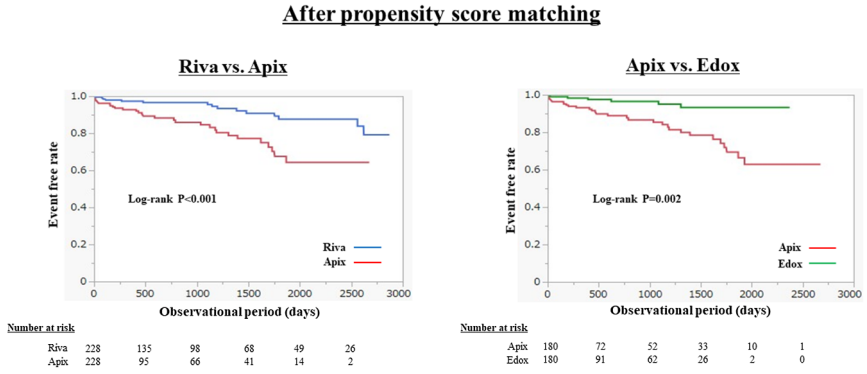

FIGURE 4 Kaplan–Meier analysis of minor bleeding after the propensity score matching. After the propensity score matching, the minor bleeding events were also greater in the Apix than Riva ($p < .001$) and Edox groups ($p = .002$).

proportion of dose selections in the Apix group. Only the HAS-BLED score was statistically higher in the patients with minor bleeding in the Apix group; therefore, the HAS-BLED score would also be helpful for predicting minor bleeding events. According to the detailed bleeding sites, gastro-intestinal bleeding was most prevalent in the Apix group (Table S2).

Since the present study was a retrospective analysis, some factors of the patient background were significantly different among the groups (Table 1), posing a selection bias. In fact, the Apix group had insignificant but numerically higher HAS-BLED scores than the other groups, which may have been associated with the results. In this study, only 22.7% of the patients in the Apix group matched the dose reduction criteria, which was significantly lower than that of the others (Figure S1-1).

There was a possibility that the different baseline characteristics would affect the dose selection; therefore, we presumably evaluated the differences in the dose selection if all patients were prescribed every single DOAC. Figure S1-2 shows the presumptive analysis of the dose proportions. Even in this presumptive analysis, the proportion of a reduced dose in the Apix group was significantly lower than that in the other groups ($p < .001$). Therefore, it was proposed that the dose reduction criteria for Apix would be too strict, and a standard dose of Apix would be chosen even in patients with a high bleeding risk. Concerning this issue, we evaluated the dose proportion changes from the standard dose of Apix to Riva or Edox, suggesting that the standard dose in the Apix group included patients who would be candidates for a reduced dose of Riva (23.2%) or Edox (51.6%). In fact, in the patients with the standard dose of Apix, the patients who were fulfilled with the dose reduction criteria of Riva and Edox experienced minor bleeding in 13.0 and 9.2%/patient-year, respectively, which was statistically higher than that in the patients who were not fulfilled with any other dose-reduction criteria (5.3%/patients-year, Log-lank $p = .046$). The patients with reduced doses of the other DOACs, especially for Edox, had lower event rates of minor bleeding than with Apix, whereas the Stroke/STE event rates were comparable even for the reduced doses of three DOACs (Figure S2). In this study, the patients with bleeding complications in the Apix group had a higher HAS-BLED score than those without (Table 2). Therefore, the standard dose of Apix might not be suitable for patients with higher HAS-BLED scores. In lean, small, and aged Japanese patients, the muscle volume would be small, so the sCr and CCr would apparently be preserved even in such patients. In contrast, patients with a low BW[19] or low body mass index[20,21] are also associated with a higher bleeding risk. These discrepancies might have affected the results of this study. In the J-ELD AF Registry,[22] a multicenter prospective cohort study in Japanese elderly AF patients >75 years taking apixaban, the proportion of the patients with a reduced dose was 57.6%, which was higher than those in the present study (22.7%) and previous reports.[17,23] That might have been just because the J-ELD AF Registry only included elderly patients >75 years, resulting in an average age of 81.7 years. An age ≥80 years is one of the dose reduction criteria for Apix; therefore, the reduced dose tended to be chosen in the J-ELD AF Registry. They concluded that there were no differences in the event rates between the patients with standard and reduced doses for 1 year of observation, although the total death and cardiovascular death were higher in the reduced-dose group than standard-dose group. In our present study, we included all generations prescribed anti-Xa DOACs, and 77.3% of the patients in the Apix group were prescribed the standard dose. Considering those results, the patients with a high bleeding risk but unmatched to the dose reduction criteria for Apix had experienced minor bleeding events in the present study.

4.2 | Reduced dose of DOACs

Due to the concern for bleeding complications, anticoagulation therapy tends to be less provided.[24–27] Even after the launch of DOACs, inappropriate underdoses were seen in 10%–30% of the patients.[10,25,28] In this study, inappropriate underdoses were also seen in 8%–12% of the patients (Figure S1-1), which was similar to the previous reports.[28,29] It has been reported[28] that an inappropriate underdose of DOACs causes higher mortality and a higher hospitalization rate; therefore, physicians should abide by the dose reduction criteria for choosing the appropriate dose of each DOAC. For the Asian population, Lee et al. reported from the Korean nationwide claims database[30] that the proportion of off-label underdoses of Apix was 41%, and the patients with off-label inappropriate underdoses of Apix had a significantly higher rate of ischemic strokes and all-cause death than those with the on-label standard dose, whereas the major bleeding events were not different between the two groups. This study suggested that an inappropriate underdose was also not uncommon in the Asian population and contributed to adverse clinical events.

Regarding an appropriately reduced dose of DOACs, there is not enough evidence for its efficacy and safety. In the randomized control phase III studies of DOACs, the RE-LY trial[14] of Dabi and the ENGAGE-AF trial[18] of Edox were evaluated with two different doses and compared with vitamin K antagonists (VKAs). On the other hand, in the ROCKET AF[16] and J-ROCKET AF[15] trials of Riva and the ARISTOTLE trial of Apix,[17] the outcomes for the two different doses were not separately analyzed, and the number of enrolled patients with a reduced dose was quite small (the J-ROCKET AF: $n = 141$ and the ARISTOTLE: $n = 428$). Therefore, we have to state that the evidence for a reduced dose of Riva and Apix was not robust. In the Denmark registry that focused on a reduced dose prescription, the appropriate underdoses of Riva and Apix showed a significantly higher mortality than the VKA or Dabi groups.[31] After that report, the recent European Heart Rhythm Association practical guide[4] recommends a reduced dose of Dabi (110 mg twice daily) or a reduced dose of Edox (30 mg once daily) for patients with concern for drug–drug interactions or a higher bleeding risk. In this study, the reduced dose subgroup with Riva and Apix had a higher rate of minor bleeding events than the Edox subgroup (Figure 3 right). We should also take note of whether the

reduced DOAC doses have the same efficacy and safety outcomes as the standard dose.

Because of the difference in the dose reduction criteria for each DOAC, the selected dose would be variable. It is crucial to avoid inappropriate underdose prescriptions; however, the outcomes of the standard dose were significantly different in the present study. We also evaluated the minor bleeding events after adjusting for some factors (age, BW, Cr, and CHA_2DS_2-VASc score), and a propensity score matching analysis was also performed to reduce the selection bias. Those results indicated that the Apix group still had a higher event rate of minor bleeding. Further, the patients with the standard dose of Apix who were matched with the other DOAC dose-reduction criteria had more minor bleeding events. Therefore, selecting DOACs with consideration of those results would provide safer outcomes in AF patients on anti-Xa DOACs.

5 | STUDY LIMITATIONS

Our investigation had several limitations. First, this study was a single-center retrospective analysis, so the number of patients was small. Further, selection bias could not be eliminated. The proportion of appropriately reduced doses in this study was higher (Riva: 27.3%, Apix: 22.7%, and Edox: 72.3%, respectively) than that in the Phase III studies (22.1%, 4.7%, and 25.3%, respectively).[15,18,32] In spite of this, in the reports of the Japanese post-market surveillance of those DOACs, the proportion of a reduced dose was reported as 21.2% (Riva), 26.8% (Apix), and 61.1% (Edox),[23,33,34] suggesting that our data were compatible with the Japanese real-world data. Second, we only evaluated the patients prescribed with DOACs, that is, those with VKAs were not included. Third, the efficacy and safety outcomes may have been underestimated because the patients with those events were not necessarily noticeable, and the observational periods were different for each DOAC. Further prospective studies are necessary to evaluate the relationship between the dose selection and efficacy/safety outcomes in real-world practice.

6 | CONCLUSION

The patients with a standard dose of Apix had a higher incidence of minor bleeding events than the other dosages. A reduced dose of apixaban was not prone to being chosen because of the dose reduction criteria, which may have been associated with a higher minor bleeding rate in patients with Apix.

ACKNOWLEDGMENT

We thank Mr. John Martin for kindly helping with the English editing of this paper.

CONFLICT OF INTEREST

HF received lecture fees from Nippon Boehringer Ingelheim and Daiichi-Sankyo, J.O., HN, TI, TF, NI, TY, AS, and JK have no conflict of interest. SN received lecture fees from Boehringer Ingelheim, Bayer, Bristol-Myers Squib, and Daiichi-Sankyo. JA received research funding from Bristol Meyers Squib, Pfizer, Boehringer Ingelheim, Bayer, and Daiichi-Sankyo and lecture fees from Sanofi, Bristol-Meyers, Pfizer, Boehringer Ingelheim, Bayer, and Daiichi-Sankyo.

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SUPPORTING INFORMATION

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How to cite this article: Fukaya H, Oikawa J, Nakamura H, Igarashi T, Fujiishi T, Ishizue N, Impact of different dose reduction criteria for anti-Xa direct oral anticoagulants on bleeding complications: A single center observational study. J Arrhythmia. 2022;38:386–394. https://doi.org/10.1002/joa3.12716