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Changes in plasma concentrations of edoxaban and coagulation biomarkers according to thromboembolic risk and atrial fibrillation type in patients undergoing catheter ablation: Subanalysis of KYU-RABLE

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Abstract

Background: Catheter ablation (CA) for atrial fibrillation (AF) can be associated with a risk of thromboembolism and bleeding. We recently demonstrated that uninterrupted edoxaban with one dose delayed on the CA procedural day is associated with a low risk of periprocedural complications. Previous reports have indicated that some specific subgroups of patients undergoing CA have an increased risk of bleeding and thromboembolic complications. This subanalysis of the KYU-RABLE study assessed the changes in plasma concentrations of edoxaban and coagulation biomarkers during the periprocedural period of CA in subgroups stratified by the risk of thromboembolism assessed by $CHADS_2$ score (<2 or ≥2) and AF type (paroxysmal AF [PAF] or non-PAF).

Methods: We evaluated changes in plasma concentrations of edoxaban and coagulation biomarkers (D-dimer and prothrombin fragment F1+2), by subgroup, during the periprocedural period of CA. Measurements were made prior to CA (procedure day).

Results: This subanalysis evaluated data from 343 patients with $CHADS_2$ score <2 and 134 patients with $CHADS_2$ score ≥2, and from 280 patients with PAF and 197 patients with non-PAF. Plasma edoxaban concentration decreased with time on the day of CA, while plasma concentrations of coagulation biomarkers remained unchanged. No significant differences were observed according to $CHADS_2$ score or type of AF.

Conclusions: The changes in plasma concentrations of edoxaban and coagulation biomarkers in each subgroup were similar to those of the whole analysis, regardless of the thromboembolic risk ($CHADS_2$ <2 or ≥2) or AF type (PAF or non-PAF).

KEYWORDS

atrial fibrillation, catheter ablation, edoxaban, hemorrhage, thromboembolism

Data from this subanalysis of the KYU-RABLE study were presented at the European Society of Cardiology Congress, 31 August–4 September 2019, Paris, France.

1 | INTRODUCTION

Catheter ablation (CA) is a procedure that is extensively performed for the treatment of atrial fibrillation (AF), particularly in symptomatic patients as an alternative to pharmacologic management, or when available treatment has been ineffective or not tolerated.[1,2] Although CA is an effective treatment strategy for AF, it can be associated with a risk of thromboembolism and major bleeding.[3,4]

Administration of uninterrupted vitamin K antagonists[5] and, more recently, direct oral anticoagulants (DOACs)[1,5] has been recommended during the periprocedural period of CA for AF. An analysis of almost 5000 patients undergoing CA found that uninterrupted periprocedural OACs were associated with a generally low risk of bleeding and thromboembolic complications.[6] Some published reports assessing the role of warfarin therapy for the prevention of periprocedural thromboembolic and hemorrhagic events have indicated that there may be specific subgroups of patients undergoing CA for AF who have an increased risk of occurrence of adverse coagulation events.[7,8] A prospective analysis of 732 CAs in 585 consecutive patients with AF found that a $CHADS_2$ score ≥2 was an independent predictor of left atrial thrombus.[7] Similarly, a prospective randomized trial of 1584 patients with AF undergoing CA found that thromboembolic events were more frequent in patients with non-paroxysmal AF (non-PAF), particularly in those with long-standing persistent AF.[8] Notably, for patients with AF undergoing CA while using periprocedural uninterrupted DOACs, data are limited on the effects of $CHADS_2$ score, type of AF, and coagulation biomarkers on the occurrence of thromboembolic and bleeding events. Specifically, for edoxaban, a previous study evaluated correlations between bleeding events and patient background characteristics, but no significant associations were detected.[9]

Recent studies have indicated that the CA procedure is associated with changes in the coagulation cascade,[10] with levels of prothrombotic biomarkers such as D-dimer and prothrombin fragment F1+2 showing significant alterations during treatment and affecting the efficacy of OACs to prevent the occurrence of silent thromboembolic events.[11-13] However, there are limited data available on the effects of $CHADS_2$ score and AF type on levels of coagulation biomarkers.

The open-label KYU-RABLE study was conducted in AF patients undergoing CA to evaluate the safety and efficacy of uninterrupted edoxaban administered once daily in the morning (with one dose delayed on the procedural day).[14] In KYU-RABLE, very few events were reported. One major bleeding event was observed (cardiac tamponade); no stroke or systemic embolism events occurred, and no deaths were reported.[14] Based on the low event occurrence, it was not possible to conclusively determine whether the $CHADS_2$ score or type of AF directly influenced thromboembolism during CA, and we elected instead to explore changes in perioperative coagulation biomarkers according to risk. Thus, the objectives of this subanalysis of the KYU-RABLE study were to comparatively assess changes in plasma concentrations of edoxaban and coagulation biomarkers during the periprocedural period of CA in subgroups stratified by $CHADS_2$ score and AF type.

2 | METHODS

2.1 | Study design and patients

Full details of the KYU-RABLE study have been published.[14] In brief, this prospective, multicenter, single-arm, interventional study was conducted between December 2017 and September 2018 at 23 Japanese institutions. Eligibility criteria included age ≥20 years and AF scheduled for CA. Key exclusion criteria were patients with any contraindication for edoxaban or CA, or renal impairment (creatinine clearance [CrCL] <30 mL/min).

Study treatment was uninterrupted edoxaban with one dose delayed. Patients received edoxaban 60 mg (or 30 mg if dose adjustment criteria were met: weight ≤60 kg, CrCL ≤50 mL/min, or concomitant use of P-glycoprotein inhibitor) once daily in the morning for ≥4 weeks prior to CA. On the day of CA, edoxaban was administered immediately after confirmation of hemostasis following the removal of the sheath. On the day after CA, edoxaban was administered ≥12 h after the edoxaban administration on the day of CA. Subsequently, edoxaban was administered in the morning for 4 weeks ± 7 days.[14]

The study was approved by the ethics committee of Oita University Faculty of Medicine (approval number B17-021, dated 12 December 2017), and by the appropriate review board at each participating center. All study procedures were conducted in accordance with the principles of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013) and the International Council for Harmonisation Good Clinical Practice Guidelines. All patients provided written informed consent. The study was registered in the University hospital Medical Information Network Clinical Trials Registry under the identifier UMIN000029693.

2.2 | Study outcomes

In this subanalysis, we assessed the changes in plasma concentrations of edoxaban and coagulation biomarkers (D-dimer and F1+2) during the periprocedural period of CA in subgroups stratified by $CHADS_2$ score (<2 or ≥2) and AF type (PAF or non-PAF). Measurements were made immediately prior to CA (procedure day). In this study, PAF was defined as AF returning to sinus rhythm within 7 days of onset.

As previously described,[14] solid-phase extraction using a liquid chromatography–tandem mass spectrometry system (SCIEX; Framingham, MA, USA) was used to measure plasma edoxaban concentrations, with assays being conducted at Shin Nippon Biomedical Laboratories, Ltd. (Wakayama, Japan). A latex immunoturbidimetric assay using LATECLE D-dimer reagent (KAINOS Laboratories, Inc, Tokyo, Japan) was used to measure D-dimer levels. This D-dimer reagent had a coefficient of variation of 10% or less when the control sample was measured five times simultaneously.[15] Enzyme-linked immunosorbent assays using Enzygnost F1+2 monoclonal antibody (Siemens Healthineers AG, Erlangen, Germany) was used to measure F1+2; both assays were conducted

at SRL Medisearch Inc (Tokyo, Japan). This assay had a coefficient of variation of 15% or less when each sample for control with known concentration was measured three times simultaneously.[16]

2.3 | Statistical methods

The calculation of the target sample size was previously reported.[14] Between-group differences in baseline variables were calculated using the Student's t-test for continuous values and the Chi-square test for categorical values.

Plasma concentrations of edoxaban and coagulation biomarkers were analyzed in the per-protocol set (PPS). Changes in the plasma concentrations of edoxaban and coagulation biomarkers were assessed according to the time of CA procedure (morning or afternoon), hours from last administration of edoxaban to ablation (<24, 24–<27, 27–<30, or ≥30), $CHADS_2$ score (<2 or ≥2), and type of AF (PAF or non-PAF). The comparison between the morning and afternoon was verified using the two-sided Mann-Whitney test. The comparison of the time from last administration of edoxaban to ablation was verified using the Jonckheere-Terpstra test. A $P < .05$ was considered statistically significant. The selected categories of hours between last administration of edoxaban and ablation were founded on surgical timings; the anticipated last dose ablation duration was 30 hours, and this was subsequently refined to the four stated categories based on the number of patients and the information collected. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC, USA).

3 | RESULTS

3.1 | Patients

In total, 477 patients were included in the PPS (36 were excluded from the full analysis set for protocol violations). At baseline, 28.1% of patients had a $CHADS_2$ score ≥2, while 41.3% had non-PAF (Table 1). Factors with a significant difference between $CHADS_2$ <2/≥2 groups included age, body mass index, CrCL, $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores, and the presence of some comorbidities (hypertension, hyperlipidemia, diabetes, and congestive heart failure). There were significant differences between the PAF and non-PAF groups, mainly in the type and treatment of AF, and the presence of congestive heart failure.

In the PPS, the proportion of patients treated with edoxaban 60 mg and 30 mg was 63.9% and 36.1%, respectively, and there were no significant differences between $CHADS_2$ groups or between AF groups. The usual reasons for administering a reduced dose are reduced CrCL, weight <60 kg, and concomitant use of P-glycoprotein inhibitors. However, more patients in the $CHADS_2$ ≥2 group had CrCL <50 mL/min compared with the $CHADS_2$ <2 group; there were no differences between the PAF and non-PAF groups. Furthermore, no between-group differences in either weight category or P-glycoprotein usage were observed. Regarding the duration between edoxaban last administration and the time of CA, patients in the $CHADS_2$ score ≥2 group had a significantly longer interval than did the $CHADS_2$ score <2 group ($P = .0016$). There was no significant difference between the PAF and non-PAF groups.

3.2 | Plasma concentration of edoxaban and coagulation biomarkers

Figure 1 displays plasma concentrations of edoxaban (Figure 1A), D-dimer (Figure 1B), and F1+2 (Figure 1C) according to $CHADS_2$ score and timing of the CA procedure. Overall, the levels of edoxaban and coagulation biomarkers were similar in patients with a $CHADS_2$ score ≥2 and in patients with a score of <2. The plasma edoxaban concentration was lower in patients who underwent CA in the afternoon than in those who underwent CA in the morning, regardless of $CHADS_2$ score ($P < .0001$, Figure 1A). Conversely, the plasma levels of coagulation biomarkers did not differ between the groups undergoing CA in the morning and those undergoing CA in the afternoon, irrespective of $CHADS_2$ score (Figure 1B,C).

Figure 2 shows plasma concentrations of edoxaban (Figure 2A), D-dimer (Figure 2B), and F1+2 (Figure 2C) according to the type of AF and timing of the CA procedure. Edoxaban concentration decreased with time on the day of CA, while the plasma levels of coagulation biomarkers remained unchanged. No statistically significant differences were observed according to type of AF in each period (morning or afternoon).

Figures 3 and 4 show plasma concentration of edoxaban and coagulation biomarkers by hours from the last administration of edoxaban to ablation, according to $CHADS_2$ score and type of AF, respectively. In both $CHADS_2$ and AF subgroups, edoxaban concentrations decreased according to the duration between the last dose of edoxaban and CA, but biomarker levels remained constant regardless of the intervening time.

4 | DISCUSSION

The efficacy and safety of uninterrupted edoxaban with one dose delayed in NVAF patients undergoing CA (KYU-RABLE study) has been shown previously.[14] In this subanalysis, edoxaban concentration and the plasma levels of coagulation biomarkers were found to be comparable with those of the whole population, regardless of thromboembolic risk as assessed by $CHADS_2$ score (<2 or ≥2) or AF type (PAF or non-PAF). Furthermore, and in agreement with the results from the main KYU-RABLE analysis,[14] although the plasma edoxaban concentration decreased gradually after the last dose before CA, the levels of coagulation biomarkers remained unchanged, irrespective of the patient's thromboembolic risk or type of AF.

An elevated $CHADS_2$ score[7] and presence of the long-standing persistent type of AF[8] have previously been reported to be associated with a higher risk of periprocedural thrombosis during CA for AF among patients undergoing oral anticoagulation treatment with

TABLE 1 Patient characteristics

	PPS N = 477	$CHADS_2$ <2 n = 343	$CHADS_2$ ≥2 n = 134	P-value[a]	PAF n = 280	Non-PAF n = 197	P-value[b]
Age, years	64.7 ± 9.9	62.5 ± 9.4	70.1 ± 9.1	**<.0001**	64.8 ± 10.2	64.4 ± 9.5	.6593
Male Gender	334 (70.0)	247 (72.0)	87 (64.9)	.1290	184 (65.7)	150 (76.1)	**.0144**
Weight, kg	66.8 ± 13.4	66.3 ± 12.6	68.1 ± 15.1	.1751	65.7 ± 12.4	68.4 ± 14.4	**.0337**
≤60	154 (32.3)	113 (32.9)	41 (30.6)	.6221	98 (35.0)	56 (28.4)	.1306
BMI, kg/m^2	24.6 ± 4.0	24.0 ± 3.5	26.0 ± 4.9	**<.0001**	24.4 ± 3.6	24.8 ± 4.6	.2745
CrCL, mL/min	82.4 ± 26.0	85.5 ± 25.2	74.5 ± 26.6	**<.0001**	83.1 ± 26.6	81.3 ± 25.2	.4432
≤50	37 (7.8)	16 (4.7)	21 (15.7)	**<.0001**	25 (8.9)	12 (6.1)	.2540
$CHADS_2$ score	1.1 ± 0.9	0.7 ± 0.5	2.4 ± 0.6	**<.0001**	1.1 ± 0.9	1.2 ± 0.9	.0898
≥2	134 (28.1)	0 (0.0)	134 (100.0)	**<.0001**	73 (26.1)	61 (31.0)	.2417
CHA_2DS_2-VASc score	2.0 ± 1.3	1.5 ± 0.9	3.5 ± 1.0	**<.0001**	2.0 ± 1.3	2.0 ± 1.3	.8995
≥2	295 (61.8)	161 (46.9)	134 (100.0)	**<.0001**	174 (62.1)	121 (61.4)	.8731
HAS-BLED score	1.2 ± 0.7	1.1 ± 0.7	1.5 ± 0.7	**<.0001**	1.2 ± 0.8	1.3 ± 0.6	.4572
≥3	15 (3.3)	7 (2.2)	8 (6.3)	**.0290**	14 (5.4)	1 (0.5)	**.0044**
Type of AF							
Paroxysmal	280 (58.7)	207 (60.3)	73 (54.5)	.5036	280 (100.0)	0 (0.0)	**<.0001**
Persistent	145 (30.4)	100 (29.2)	45 (33.6)		0 (0.0)	145 (73.6)	
Long-standing persistent / Permanent	52 (10.9)	36 (10.5)	16 (11.9)		0 (0.0)	52 (26.4)	
Treatment of AF	297 (62.3)	203 (59.2)	94 (70.1)	**.0264**	177 (63.2)	120 (60.9)	.6098
Rate control	176 (36.9)	118 (34.4)	58 (43.3)	.0708	84 (30.0)	92 (46.7)	**.0002**
Rhythm control	176 (36.9)	123 (35.9)	53 (39.6)	.4526	132 (47.1)	44 (22.3)	**<.0001**
Previous treatment of ablation	71 (14.9)	45 (13.2)	26 (19.4)	.0854	43 (15.4)	28 (14.2)	.7176
Catheter ablation							
Radiofrequency	360 (75.5)	251 (73.2)	105 (78.4)	.7075	176 (62.9)	180 (91.4)	**<.0001**
Cryoballoon	108 (22.6)	79 (23.0)	25 (18.7)		88 (31.4)	16 (8.1)	
Hot balloon	5 (1.0)	4 (1.2)	1 (0.7)		5 (1.8)	0 (0.0)	
Laser balloon	8 (1.7)	6 (1.7)	2 (1.5)		8 (2.9)	0 (0.0)	
Dose of edoxaban 4 weeks before CA, mg							
60	305 (63.9)	225 (65.6)	80 (59.7)	.2281	179 (63.9)	126 (64.0)	.9945
30	172 (36.1)	118 (34.4)	54 (40.3)		101 (36.1)	71 (36.0)	
Duration between edoxaban last administration and the time of CA, hour	36.2 ± 4.6	35.8 ± 4.2	37.3 ± 5.4	**.0016**	36.2 ± 4.6	36.3 ± 4.5	.9210

(Continues)

TABLE 1 (Continued)

	PPS N = 477	$CHADS_2$ <2 n = 343	$CHADS_2$ ≥2 n = 134	P-value[a]	PAF n = 280	Non-PAF n = 197	P-value[b]
Concomitant use of P-glycoprotein inhibitor	45 (9.4)	27 (7.9)	18 (13.4)	.0618	30 (10.7)	15 (7.6)	.2541
Comorbidities							
Hypertension	276 (57.9)	162 (47.2)	114 (85.1)	**<.0001**	159 (56.8)	117 (59.4)	.5705
Hyperlipidemia	152 (31.9)	90 (26.2)	62 (46.3)	**<.0001**	85 (30.4)	67 (34.0)	.3992
Diabetes	72 (15.1)	13 (3.8)	59 (44.0)	**<.0001**	40 (14.3)	32 (16.2)	.5564
Arrhythmia other than AF	49 (10.3)	30 (8.7)	19 (14.2)	.0790	37 (13.2)	12 (6.1)	**.0116**
Congestive heart failure	38 (8.0)	12 (3.5)	26 (19.4)	**<.0001**	10 (3.6)	28 (14.2)	**<.0001**
Ulcer/reflux esophagitis	30 (6.3)	19 (5.5)	11 (8.2)	.2804	21 (7.5)	9 (4.6)	.1941
Angina pectoris	26 (5.5)	17 (5.0)	9 (6.7)	.4466	17 (6.1)	9 (4.6)	.4765
Renal disease	25 (5.2)	15 (4.4)	10 (7.5)	.1736	12 (4.3)	13 (6.6)	.2643

Note: Data are shown as n (%) or mean ± SD. Bold values indicate statistical significance ($P < .05$).

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CrCL, creatinine clearance; PAF, paroxysmal atrial fibrillation; PPS, per protocol set; SD, standard deviation.

[a]Between $CHADS_2$ groups.

[b]Between PAF/non-PAF groups.

Student's *t* test was used for continuous values. Chi-squared test was used for categorical values.

warfarin. While recent studies comparing the efficacy and safety of uninterrupted DOACs versus vitamin K antagonists reported equivalent safety and efficacy profiles,[17-23] other studies comparing uninterrupted DOACs with warfarin for AF patients undergoing CA did not find that type of AF, particularly PAF,[24] and $CHADS_2$ score[25] were associated with the use of periprocedural uninterrupted DOACs. In the AXAFA-AFNET 5 trial, the type of AF was not associated with thromboembolic event rates in apixaban-treated patients.[26] Additionally, in a study of continuous periprocedural rivaroxaban during CA, neither $CHADS_2$ score nor type of AF were associated with thromboembolic events.[23] A very recent study comparing the safety and efficacy of uninterrupted edoxaban or warfarin during CA analyzed interactions between background factors, including $CHADS_2$ score and type of AF; no significant associations with these factors were identified.[9] We suspect that these results were attributable to the small sample size and bias in the distribution of background factors in that study. The present subanalysis also demonstrated that neither high thromboembolic risk nor type of AF was associated with the incidences of thromboembolism and bleeding during uninterrupted edoxaban treatment during CA. However, as the occurrence of events was low in the entire KYU-RABLE study,[14] it was not possible to conclusively determine how $CHADS_2$ score and AF type influence event occurrence. Therefore, we focused instead on plasma edoxaban concentrations and coagulation biomarker levels in subgroups of KYU-RABLE patients stratified according to potential risk.

In this study, edoxaban was orally administered once a day in the morning for 4 weeks or more before catheter ablation. Therefore, regardless of the time from the last administration of edoxaban, biomarker increases might be suppressed, resulting in stable levels. Changes in the plasma edoxaban concentration were also found to be similar between subgroups, regardless of $CHADS_2$ score or AF type, and were consistent with the results of the main KYU-RABLE analysis.[14] Plasma edoxaban concentrations were also in agreement with previously reported data from AF patients with normal renal function or mild renal impairment, in which the median (minimum–maximum) levels were 9.7 (3.9-23.2) ng/mL with edoxaban 30 mg and 18.2 (6.9-29.5) ng/mL with edoxaban 60 mg.[27] Although no test for significance was performed, edoxaban concentrations were numerically higher in the population of patients with $CHADS_2$ score ≥2 compared with those in patients with a score of <2. Plasma levels of edoxaban are known to be affected by body weight, renal function, and use of P-glycoprotein inhibitors, but in this subanalysis, only CrCL differed between $CHADS_2$ <2/≥2 subgroups. Mean CrCL was significantly lower and the proportion of patients with impaired renal function (CrCL < 50 mL/min) was higher in the $CHADS_2$ ≥2 subgroup, which may account for the higher levels of plasma edoxaban concentrations on the day of CA, although this was not tested for significance. No significant differences in weight, renal function, and use of P-glycoprotein inhibitors was observed between the PAF and non-PAF subgroups.

The coagulation biomarkers used in this subanalysis were chosen based on published analyses in which levels of D-dimer or F1+2 were demonstrated to correlate with thromboembolic and

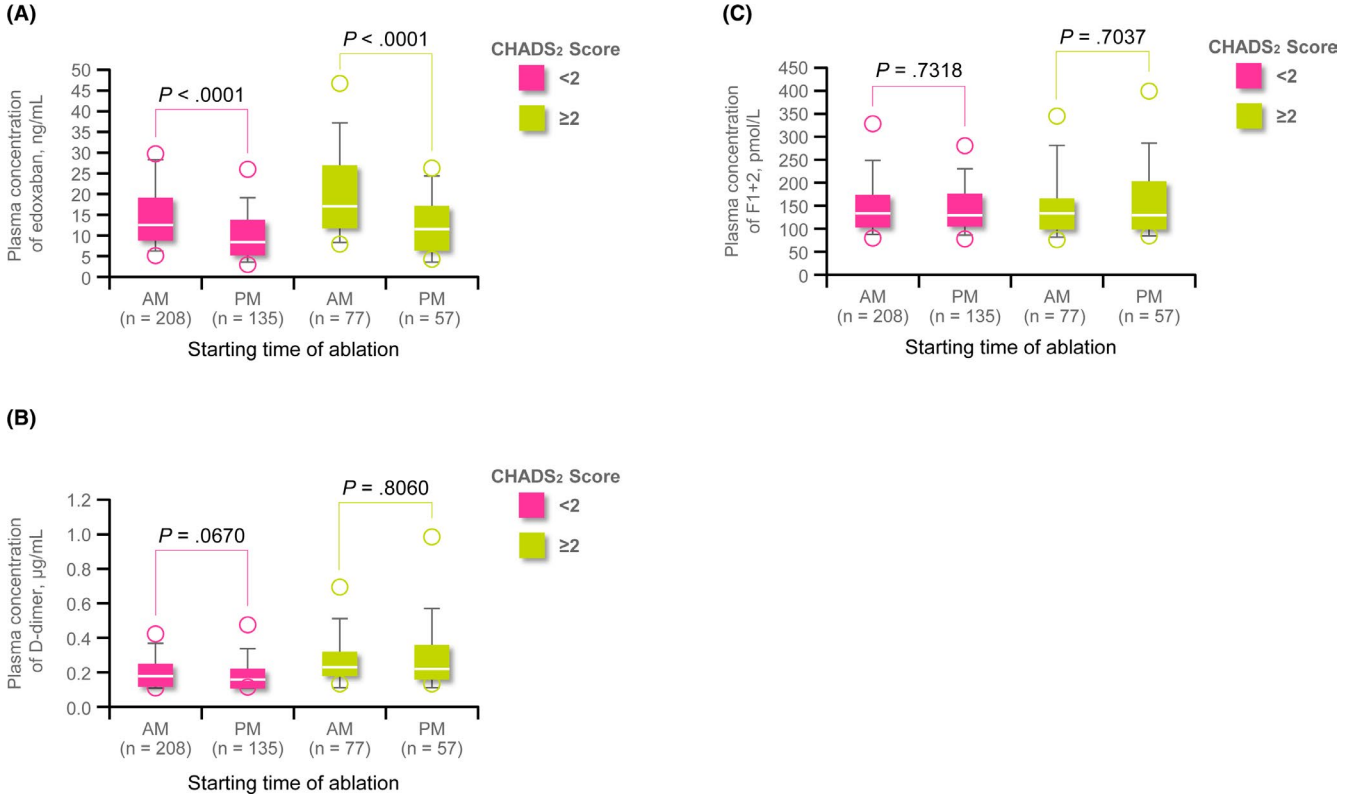

FIGURE 1 Plasma concentration of edoxaban and coagulation biomarkers in the morning and afternoon according to $CHADS_2$ score. A, Edoxaban; B, D-dimer; and C, F1+2. *Note:* Data are presented as box-and-whisker plots, in which the boxes represent medians (Q1;Q3), bars represent 90th and 10th percentiles, and dots represent 95th and 5th percentiles. *P*-values were calculated using the two-sided Mann-Whitney test. Abbreviations: AM, morning; PM, afternoon

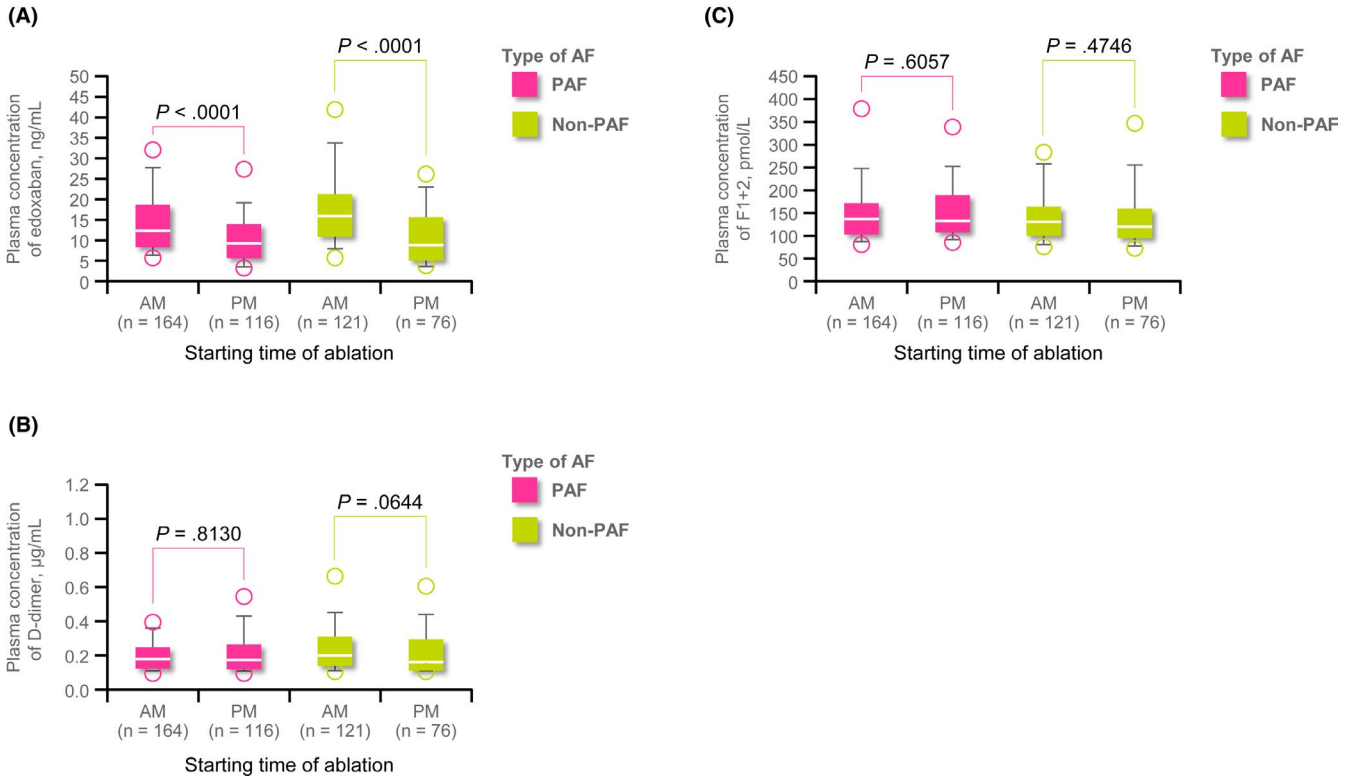

FIGURE 2 Plasma concentration of edoxaban and coagulation biomarkers in the morning and afternoon according to type of AF. A, Edoxaban; B, D-dimer; and C, F1+2. *Note:* Data are presented as box-and-whisker plots, in which the boxes represent medians (Q1;Q3), bars represent 90th and 10th percentiles, and dots represent 95th and 5th percentiles. *P*-values were calculated using the two-sided Mann-Whitney test. Abbreviations: AM, morning; PAF, paroxysmal atrial fibrillation; PM, afternoon

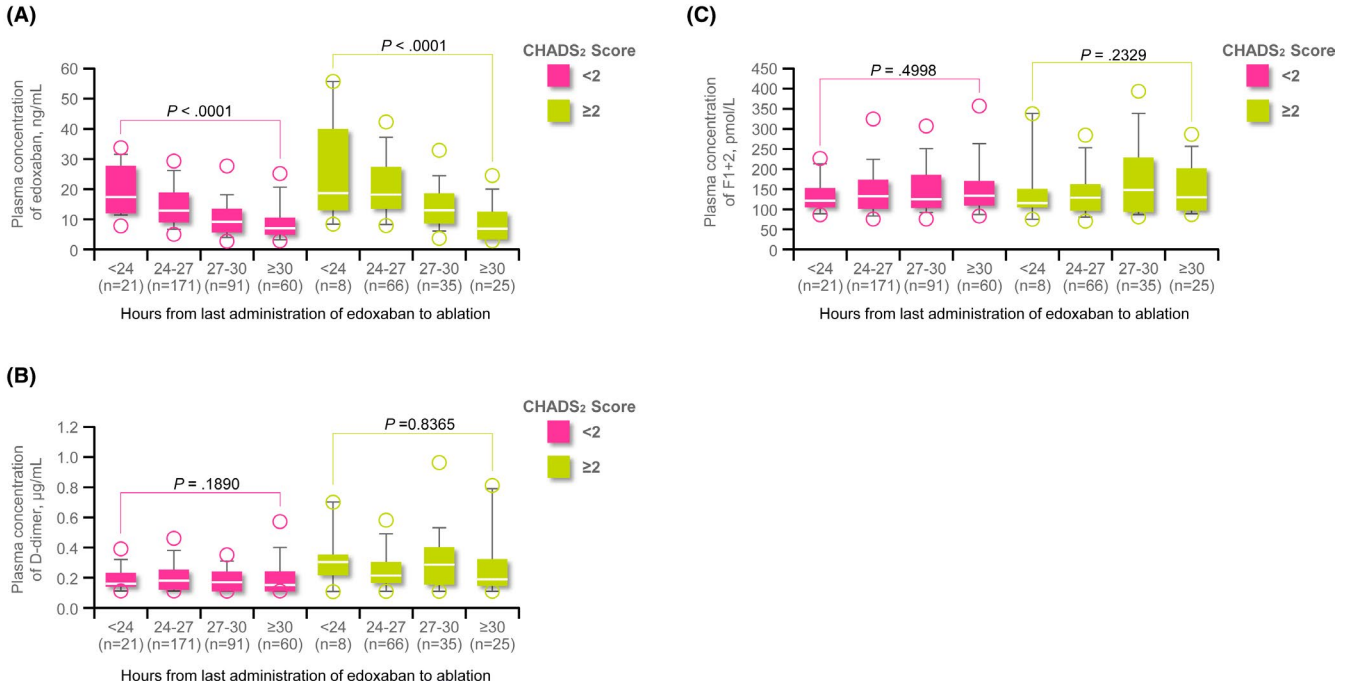

FIGURE 3 Plasma concentration of edoxaban and coagulation biomarkers, by hours from last administration of edoxaban to ablation, according to $CHADS_2$ score. A, Edoxaban; B, D-dimer; and C, F1+2. *Note:* Data are presented as box-and-whisker plots, in which the boxes represent medians (Q1;Q3), bars represent 90th and 10th percentiles, and dots represent 95th and 5th percentiles. *P*-values were calculated using the Jonckheere-Terpstra test

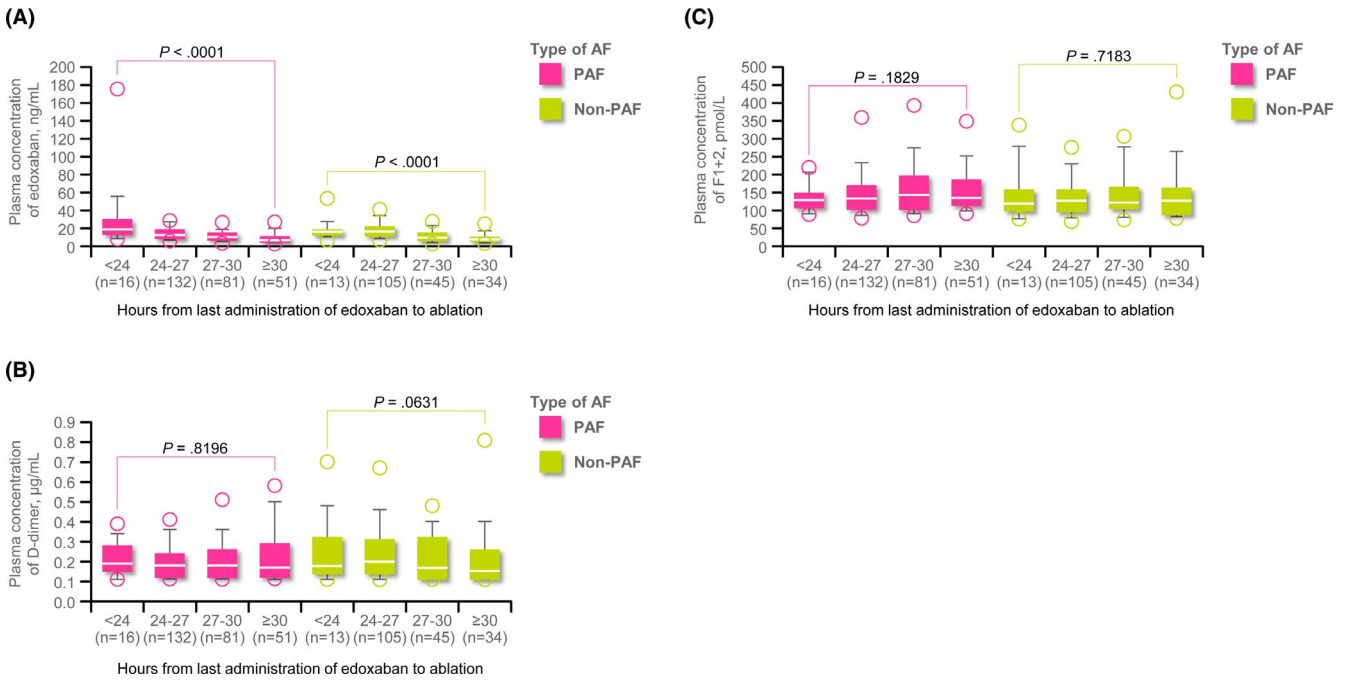

FIGURE 4 Plasma concentration of edoxaban and coagulation biomarkers, by hours from last administration of edoxaban to ablation, according to type of AF. A, Edoxaban; B, D-dimer, and C, F1+2. *Note:* Data are presented as box-and-whisker plots, in which the boxes represent medians (Q1;Q3), bars represent 90th and 10th percentiles, and dots represent 95th and 5th percentiles. *P*-values were calculated using the Jonckheere-Terpstra test. Abbreviations: PAF, paroxysmal atrial fibrillation

bleeding events in patients with AF.[28-31] D-dimer and F1+2 have also been evaluated as coagulation biomarkers in previous studies of CA-treated AF patients,[11-13] indicating their suitability and validity for use as surrogate markers in this study as an indicator of coagulation activation, which occurred too infrequently to be useful. As described above, the plasma levels of D-dimer and F1+2 in this subanalysis did not differ significantly between any of the subgroups evaluated, or between morning/afternoon CA procedures,

and the overall results were similar to those obtained in the main KYU-RABLE study.[14] Furthermore, the levels of D-dimer and F1+2 in this analysis were in line with those reported in previous studies in patients with AF undergoing CA.[11-13] In the total population, five (1.0%) patients exceeded the D-dimer cutoff value of 1 μg/mL, and the breakdown per subgroup was as follows: $CHADS_2$ <2, n = 2 (0.4%); $CHADS_2$ ≥2, n = 3 (0.6%); PAF, n = 1 (0.2%); and non-PAF, n = 4 (0.8%). Twenty-eight (5.9%) patients had values above the F1+2 cutoff value of 300 pmol/L and the breakdown per subgroups was as follows: $CHADS_2$ <2, n = 18 (3.8%); $CHADS_2$ ≥2, n = 10 (2.1%); PAF, n = 18 (3.8%); and non-PAF, n = 10 (2.1%). Additionally, although there were some patients who exceeded the biomarker cutoff values, no stroke or systemic embolism events, and no deaths were reported.

On the basis of these data, we can infer that even in patients with a high risk for thromboembolism and bleeding, changes in biomarkers were consistent with the results observed in the overall KYU-RABLE study population, and that one dose delayed administration of edoxaban on the CA procedural day may effectively suppress the incidences of bleeding and thromboembolism across the entire spectrum of patients with AF.

4.1 | Limitations

The limitations of this study include the open-label design and the relatively short 4-week follow-up period, with a single time point for measurement of plasma edoxaban and biomarker concentration. Only Japanese patients were included in the study, which may potentially restrict a broader generalization of the results. Additionally, the proportion of patients receiving edoxaban 60 mg rather than 30 mg was higher in both the PPS and subgroups; this ratio is the opposite of those reported in previous studies that included AF patients without CA.[32] Furthermore, the mean age of patients in this study was 64.7 years, which is younger than that of a previous study population;[33] therefore, it is possible that our study included many patients in relatively good health who did not meet the dose reduction criteria, again precluding the wider generalizability of our data to the clinical AF population. Most notably, this analysis was limited by the low number of events, which may have resulted in an underestimation of differences in risk between $CHADS_2$ and AF groups. Moreover, we did not analyze whether there were differences in the edoxaban concentration and incidence rate of each event between patients who exceeded the cutoff value of D-dimer or F1+2 and those who did not. Although it is well known that these biomarkers can be used as indicators of coagulation status, further verification is required in the future as to whether these will be alternative indicators of thromboembolic events. Finally, although we can postulate that systemic coagulation was not activated during CA for AF, irrespective of thromboembolic risk or type of AF, we were not able to definitively confirm this point using the data available from our study.

5 | CONCLUSIONS

In this subanalysis of the KYU-RABLE study in patients with high-risk scores ($CHADS_2$ ≥2) or non-PAF, plasma edoxaban concentrations and biomarker levels showed similar trends to those previously observed in the overall study population, suggesting the efficacy of edoxaban on coagulation biomarker activation, regardless of thromboembolic risk and AF type.

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CONFLICT OF INTEREST

NT has received remuneration from Daiichi Sankyo, Bristol-Myers Squibb, Pfizer Japan, and received research funding from Ono Pharmaceutical. YM has received remuneration from Daiichi Sankyo, Bristol-Myers Squibb, and Nippon Boehringer Ingelheim. KO has received remuneration from Nippon Boehringer Ingelheim, Daiichi Sankyo, Johnson & Johnson, and Medtronic. TK, KY, and AT are employees of Daiichi Sankyo. TS and HO have nothing to disclose. IRB Approval number: B17-021. IRB Approval date: 12 December 2017.

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