

Safety and Efficacy of Underdosing Non-vitamin K Antagonist Oral Anticoagulants in Patients Undergoing Catheter Ablation for Atrial Fibrillation

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Background: Some patients with atrial fibrillation (AF) received underdoses of non-vitamin K antagonist oral anticoagulants (NOACs) in the real world. Underdosing is defined as administration of a dose lower than the manufacturer recommended dose.

Objectives: To identify the efficacy and safety of underdosing NOACs as perioperative anticoagulation for atrial fibrillation ablation.

Methods: We retrospectively analyzed patients who received rivaroxaban or dabigatran etexilate according to dosage: adjusted low dosage (reduced by disturbed renal function; n = 30), underdosage (n = 307), or standard dosage (n = 683). Non-vitamin K antagonist oral anticoagulants and dosing decisions were at the discretion of treating cardiologists.

Results: Patients who received underdosed NOACs were older, more often female, and had lower body weight and lower renal function than those who received standard dosages. Activated clotting time at baseline in patients who received adjusted low dosage or underdosages was slightly longer than that in patients receiving standard dosages (156 ± 23 , 151 ± 224 , and 147 ± 24 seconds, respectively). Meaningful differences were not observed in other coagulation parameters. Adjusted low-, under-, and standard-dosing regimens did not differ in perioperative thromboembolic complications (0/30, 0.0%; 1/307, 0.3%; and 0/683, 0%,

respectively) or major (0/30, 0.0%; 2/307, 0.6%; 3/683, 0.4%) and minor (1/30, 3.3%; 13/307, 4.2%; 25/683, 3.6%) bleeding episodes. When comparisons were performed for each NOAC, similar results were observed.

Conclusions: With consideration of patient condition, age, sex, body weight, body mass index, and renal function, underdosing NOACs was effective and safe as a perioperative anticoagulation therapy for atrial fibrillation ablation. The therapeutic range of NOACs is potentially wider than manufacturer recommendations.

Key Words: atrial fibrillation, catheter ablation, pulmonary vein isolation, non-vitamin K antagonist oral anticoagulant, follow-up studies

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INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia and has a significant impact on morbidity and mortality.^{1,2} Applying radiofrequency (RF) energy to circumferentially isolate the pulmonary veins (PVs) from the left atrium (LA), known as PV atrium isolation (PVAI), is the most effective treatment for AF, with a cure rate between 50% and 90%.¹

Atrial fibrillation ablation is one of the most complex interventional electrophysiologic procedures and is thus associated with several important complications. One such complication is thromboembolism. Despite the introduction of novel ablation technologies, such as open irrigated catheters, and the widespread use of systemic anticoagulation with heparin, the risk of periprocedural thromboembolism remains notable, reaching approximately 1%–2% in large series.^{1,3,4}

Over the past 5 years, NOACs, such as rivaroxaban and dabigatran etexilate, have been approved for long-term oral anticoagulation, all of which have demonstrated safety, efficacy, and suitability for anticoagulation in patients with nonvalvular AF.⁵ Non-vitamin K antagonist oral anticoagulants offer several advantages over traditional anticoagulants: they have short half-lives, are easy to administer, have few interactions, and do not require laboratory monitoring. Patients at cardiovascular risk undergoing major procedures may require heparin bridging.⁶ All intraprocedural

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The authors report no conflict of interests.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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anticoagulation strategies use systemic unfractionated heparin guided by activated clotting time (ACT), with a recommended target within 300–350 seconds.¹

Drug manufacturers provide recommended dosages for NOACs, which are determined primarily by renal function. Dosages of NOACs can be divided into three categories: adjusted low dosage is a dose reduced according to renal function, as stipulated by the manufacturer. Standard dosage is the recommended dose for patients without renal disturbance. Underdosage can be defined as a dose lower than a standard dose in patients without renal disturbance. Few studies have reported on the efficacy of underdosing dabigatran for anticoagulation in AF ablation.^{7,8} The recommended dosage of rivaroxaban is reduced for Asian patients because of relatively low body weights when compared to Western populations.⁹ The efficacy of rivaroxaban for deep vein thrombosis has been validated over a wide range of dosages, from 20 to 40 mg/d.¹⁰ Such results indicate that underdosing NOACs is not necessarily associated with a loss of efficacy. Therefore, this study sought to identify the safety and efficacy of underdosing NOACs for perioperative anticoagulation in patients undergoing AF ablation.

METHODS

Patients

A single-center, retrospective study was conducted at the Okayama Heart Clinic, Okayama, Japan, and included patients who underwent AF ablation between April 2011 and December 2014. Data from 120 days of anticoagulation therapy (from 30 days before to 90 days after) were analyzed. Examination and analysis procedures complied with the rules of the Declaration of Helsinki,¹¹ and the study was approved by the Institutional Ethics Committee for Human Research of Okayama Heart Clinic. Written informed consent for the use of data without personally identifiable information was obtained from all participants.

Patient Classification and Anticoagulation Therapy Regimens

A total of 1020 patients (age, 64 ± 10 years; 736 men, 284 women; 658 with paroxysmal AF, 362 with non-paroxysmal AF) were included. Non-vitamin K antagonist oral anticoagulant selection and dosages were at the discretion of the treating physician. Administered dosages were defined as follows: adjusted low dosage was a reduction in dose according to renal function, as stipulated by the drug manufacturer; standard dosage was the manufacturer recommended dose for patients with creatinine clearance >50 mL/min; and

underdosage was defined as a dosage lower than the manufacturer recommended dose for patients with creatinine clearance >50 mL/min (Table 1).

First, patients were divided into three groups according to dosage (adjusted low dosage, underdosage, or standard dosage). Subsequently, patients were divided into two subgroups according to the NOAC type (rivaroxaban or dabigatran etexilate). Comparisons were made for each subgroup.

The anticoagulant regimens of the two groups are shown in Figure 1. Rivaroxaban was administered once daily, in the morning, and was initiated at least 30 days before AF ablation. Dabigatran etexilate was administered twice daily, in the morning and evening, and was initiated at least 30 days before AF ablation. Non-vitamin K antagonist oral anticoagulants were not administered before the ablation procedure on the day of AF ablation. In all patients, a single dose of each NOAC was resumed three hours after AF ablation, without any additional dose on the day of the AF ablation procedure. Each NOAC was restarted the next morning as usual.

After completing AF ablation, heparin was discontinued and protamine sulfate was administered intravenously at a dose of 20 mg or 30 mg, depending on whether the ACT was 300–350 or >350 seconds, respectively. When bleeding at the puncture site did not stop after the initial administration of protamine sulfate, additional doses (10–30 mg, dependent on bleeding status) were administered at 4 minutes intervals until the bleeding stopped.

Catheter Placement

All patients underwent transesophageal echocardiography immediately before ablation as a means of examining the LA and LA appendage (LAA) for thrombi. When AF ablation was performed in the afternoon, heparin (5000 U) was administered subcutaneously the same morning.¹² Before transseptal catheterization, an intravenous heparin bolus (100–130 U/kg) was administered.¹² After transseptal catheterization, heparinized saline was infused continuously via a peripheral vein (400 U/h) to maintain the ACT within 300–350 seconds to avoid thrombus formation.

Five venous accesses were obtained as follows. Two standard electrophysiology catheters were positioned: a 4-F catheter (Japan Lifeline Co, Ltd, Tokyo, Japan) in the His bundle region via the femoral vein and a 6-F catheter in the coronary sinus via the right intrajugular vein. Three 8-F SL0 sheaths (St. Jude Medical Inc, St. Paul, MN) were advanced to the LA using the Brockenbrough technique, with all sheaths over 1 puncture site. Three catheters were positioned in the LA: two decapolar ring catheters (Japan Lifeline Co, Ltd) and one ablation catheter.

TABLE 1. Standard Dosage, Underdosage, and Adjusted Low Dosage for Each Non-vitamin K Antagonist Oral Anticoagulant

	Rivaroxaban	Dabigatran Etexilate
Standard dosage	15 mg, once daily (CCr > 50 mL/min)	150 mg, twice daily (CCr > 50 mL/min)
Underdosage	10 mg, once daily (CCr > 50 mL/min)	110 mg, twice daily (CCr > 50 mL/min)
Adjusted low dosage	10 mg, once daily (CCr 15–50 mL/min)	110 mg, twice daily (CCr 30–50 mL/min)

CCr, creatinine clearance.

drainage. Pericardial effusion, reduced hemoglobin without blood transfusion, and hematuria were defined as minor complications. A pericardial effusion was defined as an effusion identified in the pericardial space by routine follow-up echocardiography without hemodynamic disturbance (non-tamponade). Late cardiac tamponades were those occurring >48 hours after the procedure. The primary safety outcome measured was a composite of bleeding and thromboembolic complications. Miscellaneous non-anticoagulation-related events were also recorded.

Statistics

SPSS version 18 was used in all statistical analyses. Data were expressed as mean ± SD. When comparing two groups, Student *t*-tests and χ^2 tests were used for continuous and categorical variables, respectively. For multiple comparisons of continuous variables, including ACT levels among the three dosage groups, we used a one-way analysis of variance (ANOVA) or Kruskal–Wallis test, and the Scheffé *F* test or Mann–Whitney *U* test with Bonferroni correction as a post hoc test to compare two groups in multiple groups, when appropriate. The χ^2 test with multiple tables and two-tailed test for categorical variables were used to evaluate differences among the three dosage groups. Differences were considered significant at *P* < 0.05.

RESULTS

Patient Characteristics, Procedural Time, and Ablation Success

Patient characteristics are summarized in Tables 2 and 3. The average age of patients in the underdosage group was higher than that in the standard-dosage group and lower than that in the adjusted low-dosage group. The underdosage group also had a higher percentage of female patients than the standard-dosage group. Body weight and body mass index in the underdosage group were lower than those in the standard-dosage group and higher than those in the adjusted low-dosage group. Creatinine clearance in the underdosage group was lower than that in the standard-dosage group and higher than that in the adjusted low-dosage group. Sex, age, body weight, body mass index, and creatinine clearance exhibited significant correlations in all patients and in each NOAC group, with a few exceptions (Table 4).

CHADS₂ and CHA₂DS₂-VASc scores in the underdosage group were higher than those in the standard-dosage group and lower than those in the adjusted low-dosage group. When patient characteristics were compared among the three dosage categories for both rivaroxaban and dabigatran etexilate, identical results were obtained in each NOAC subcategory.

TABLE 2. Clinical and Arrhythmia Conditions, Activated Clotting Time, Heparin and Protamine Dosages, and Procedural Time According to Dosage

	Adjusted Low-dosage NOAC	Underdosage NOAC	Standard-dosage NOAC	<i>P</i>	Adjusted Low dosage Versus Underdosage, <i>P</i>	Underdosage Versus Standard Dosage, <i>P</i>	Adjusted Low-Versus Standard dosage, <i>P</i>
No. patients	30	307	683				
Age, yr	75 ± 6	71 ± 8	61 ± 9	<0.01	0.91	<0.01	<0.01
Sex (female)	14 (47)	130 (42)	140 (20)	<0.01	0.70	<0.01	<0.01
BW, kg	50 ± 8	62 ± 12	68 ± 13	<0.01	<0.01	<0.01	<0.01
BMI, kg/m ²	20.3 ± 2.8	23.8 ± 3.8	24.1 ± 3.5	<0.01	<0.01	<0.01	<0.01
CCr, mL/min	41 ± 7	81 ± 22	97 ± 28	<0.01	<0.01	<0.01	<0.01
CHADS ₂ score	0.8 ± 1.0	0.6 ± 0.9	0.5 ± 0.8	<0.01	0.24	0.037	0.67
CHA ₂ DS ₂ -VASc score	2.3 ± 1.4	1.8 ± 1.2	1.3 ± 1.2	<0.01	0.49	<0.01	<0.01
Type of AF							
PAF	25 (83)	190 (62)	443 (65)	0.06	0.45	0.74	0.60
PeAF	3 (10)	62 (20)	116 (17)				
LS-PeAF	2 (7)	40 (13)	96 (14)				
AT	0 (0)	15 (5)	28 (4)				
ACT, s							
Baseline	156 ± 23	151 ± 24	147 ± 24	<0.01	0.87	<0.01	0.32
15 min	315 ± 47	305 ± 42	301 ± 36	0.23	0.60	0.45	0.43
End of ablation	324 ± 57	315 ± 30	307 ± 28	<0.01	0.40	<0.01	0.018
Heparin							
Total dose, U	8268 ± 3271	9928 ± 2752	10,833 ± 3047	<0.01	0.055	<0.01	<0.01
U/kg	166 ± 43	159 ± 36	162 ± 37	0.57	0.014	0.058	0.048
Protamine, mg	31 ± 27	28 ± 30	25 ± 27	0.10	0.08	0.80	0.052
Procedural time, min	107 ± 28	113 ± 38	110 ± 38	0.63	0.12	<0.01	0.89

Values are n (%) and mean ± SD.

ACT, activated clotting time; AT, atrial tachycardia; BMI, body mass index; BW, body weight; CCr, creatinine clearance; AF, atrial fibrillation; LS-PeAF, long-standing persistent AF; NOACs, non-vitamin K antagonist oral anticoagulants; P, probability value; PAF, paroxysmal AF; PeAF, persistent AF.

TABLE 3. Clinical and Arrhythmia Conditions, Activated Clotting Time, Heparin and Protamine Dosages, and Procedural Time According to Non-vitamin K Antagonist Oral Anticoagulant Administered and Dosage

	Rivaroxaban			P	P under Versus Standard	Dabigatran Etxilate			P	P Underdosage Versus Standard dosage
	Once Daily					Twice Daily				
	Adjusted Low Dosage	Underdosage	Standard Dosage			Adjusted Low Dosage	Underdosage	Standard Dosage		
No. patients	18	110	394			12	197	289		
Age, yr	75 ± 7	74 ± 6	62 ± 9	<0.01	<0.01	75 ± 4	69 ± 8	59 ± 9	<0.01	<0.01
Sex (female)	8 (44)	56 (51)	93 (24)	<0.01	<0.01	6 (50)	74 (38)	47 (16)	<0.01	<0.01
BW, kg	50 ± 8	59 ± 11	67 ± 12	<0.01	<0.01	50 ± 8	64 ± 12	69 ± 13	<0.01	<0.01
BMI, kg/m ²	19.7 ± 3.4	23.3 ± 4.2	24.0 ± 3.5	<0.01	0.23	21.3 ± 1.4	24.0 ± 3.5	24.2 ± 3.6	<0.01	0.13
CCr, mL/min	41 ± 8	72 ± 19	95 ± 28	<0.01	<0.01	42 ± 5	86 ± 23	101 ± 29	<0.01	<0.01
CHADS ₂	0.7 ± 1.0	0.8 ± 0.9	0.6 ± 0.8	0.35	0.49	0.8 ± 0.9	0.6 ± 0.8	0.4 ± 0.7	<0.01	<0.01
CHA ₂ DS ₂ -VASc	2.5 ± 1.4	2.4 ± 1.2	1.5 ± 1.2	<0.01	<0.01	2.1 ± 1.4	1.6 ± 1.1	1.0 ± 1.1	<0.01	<0.01
Type AF										
PAF	15 (83)	72 (65)	275 (70)	0.28	0.20	10 (83)	118 (60)	168 (58)	0.30	0.96
PeAF	3 (17)	27 (25)	65 (17)			0 (0)	35 (18)	51 (18)		
LS-PeAF	0 (0)	5 (5)	37 (9)			2 (17)	35 (18)	59 (20)		
AT	0 (0)	6 (5)	17 (4)			0 (0)	9 (4)	11 (4)		
ACT, s										
Baseline	144 ± 18	140 ± 18	140 ± 21	0.74	0.23	176 ± 14	158 ± 26	159 ± 23	0.23	0.87
15 min	303 ± 29	304 ± 43	299 ± 35	0.58	0.81	330 ± 62	305 ± 42	305 ± 38	0.18	0.64
at end	311 ± 28	316 ± 28	306 ± 28	<0.01	<0.01	342 ± 80	314 ± 31	308 ± 29	0.16	0.01
Heparin										
Total, U	8992 ± 3744	9758 ± 2643	10,984 ± 3100	<0.01	<0.01	7304 ± 2318	10,022 ± 2814	10,626 ± 2965	<0.01	<0.01
U/kg	180 ± 42	160 ± 35	167 ± 37	0.16	0.97	147 ± 36	158 ± 37	155 ± 36	0.39	0.75
Protamine, mg	30 ± 23	25 ± 26	24 ± 27	0.30	0.13	33 ± 33	30 ± 31	26 ± 28	0.41	0.23
Procedural time, min	104 ± 26	111 ± 39	110 ± 37	0.95	0.15	109 ± 32	114 ± 38	111 ± 38	0.65	0.17

Values are n (%) and mean ± SD.

ACT, activated clotting time; AT, atrial tachycardia; BMI, body mass index; BW, body weight; CCr, creatinine clearance; AF, atrial fibrillation; LS-PeAF, long-standing persistent AF; NOACs, non-vitamin K antagonist oral anticoagulants; P, probability value; PAF, paroxysmal AF; PeAF, persistent AF.

Procedural times did not differ among patients who received adjusted low-, under-, and standard dosages of NOACs or among dosage subgroups for each NOAC (Tables 2 and 3). All patients reached the endpoint of PVAI, and the initial success rate was thus the same in all groups and subgroups.

Blood Clotting System Parameters, Heparin During Procedure, and Protamine After Ablation

Although ACT at baseline and at the completion of ablation in patients from the underdosage group was significantly longer than those in the standard-dosage group, differences were not clinically meaningful (Table 2). However, no differences in ACT were observed among all dosage groups at 15 minutes after the start of ablation. When analyses were performed separately for each NOAC subgroup, no dosage-related differences in ACTs before or after ablation could be identified. The total dosage of heparin per kilogram of body weight required during the procedure to maintain an ACT of 300–350 seconds did not differ among patients who received adjusted low-, under-, and standard-dosage NOACs. Similarly, in each NOAC subgroup, no significant differences

in the total dosage of heparin per kilogram of body weight required during the procedure were observed among dosage groups. The dosage of protamine required for hemostasis after termination of AF ablation also did not differ among patients receiving adjusted low-, under-, and standard-dosage NOACs, nor were there any differences when the analysis was performed for each NOAC separately (Table 3).

Complications and Safety Outcome

No patients in any group exhibited thromboembolic or bleeding complications in the 30 days before ablation. Transesophageal echocardiography performed immediately before ablation did not identify LA or LAA thrombosis in any patient.

During the procedural and periprocedural periods, only one patient (1/1020, 0.09%) experienced a transient ischemic attack, but recovered promptly (Table 5). Consequently, there were no significant differences in thromboembolic complications among the adjusted low-, under-, and standard-dosage patients, either overall (Table 5), or when analyzed separately for each NOAC (Table 6). Major bleeding episodes were observed in 8 of the 1020 patients (0.8%). No significant differences were noted in the incidence of major and minor

TABLE 4. Correlations Among Patient Characteristics

	Sex	Age	BW	BMI	CCr
All patients					
Sex					
Correlation coefficient	—	−0.185	0.480	0.152	−0.029
Probability value	—	<0.001	<0.001	<0.001	0.387
Age					
Correlation coefficient	−0.185	—	−0.329	−0.136	−0.613
Probability value	<0.001	—	<0.001	<0.001	<0.001
BW					
Correlation coefficient	0.480	−0.329	—	0.826	0.509
Probability value	<0.001	<0.001	—	<0.001	<0.001
BMI					
Correlation coefficient	0.152	−0.136	0.826	—	0.474
Probability value	<0.001	<0.001	<0.001	—	<0.001
CCr					
Correlation coefficient	−0.029	−0.613	0.509	0.474	—
Probability value	0.387	<0.001	<0.001	<0.001	—
Rivaroxaban					
Sex					
Correlation coefficient	—	−0.167	0.786	0.127	0.022
Probability value	—	<0.001	<0.001	0.004	0.616
Age					
Correlation coefficient	−0.167	—	−0.344	−0.129	−0.660
Probability value	<0.001	—	<0.001	0.004	<0.001
BW					
Correlation coefficient	0.486	−0.344	—	0.804	0.496
Probability value	<0.001	<0.001	—	<0.001	<0.001
BMI					
Correlation coefficient	0.126	−0.129	0.804	—	0.451
Probability value	0.004	0.004	<0.001	—	<0.001
CCr					
Correlation coefficient	−0.022	−0.660	0.496	0.451	—
Probability value	0.616	<0.001	<0.001	<0.001	—
Dabigatran etexilate					
Sex					
Correlation coefficient	—	−0.144	0.454	0.185	−0.090
Probability value	—	0.006	<0.001	<0.001	0.085
Age					
Correlation coefficient	−0.144	—	−0.253	−0.130	−0.506
Probability value	0.006	—	<0.001	0.012	<0.001
BW					
Correlation coefficient	0.455	−0.253	—	0.862	0.504
Probability value	<0.001	<0.001	—	<0.001	<0.001
BMI					
Correlation coefficient	0.185	−0.130	0.865	—	0.506
Probability value	<0.001	0.012	<0.001	—	<0.001
CCr					
Correlation coefficient	−0.009	−0.506	0.504	0.506	—
Probability value	0.085	<0.001	<0.001	<0.001	—

BMI, body mass index; BW, body weight; CCr, creatinine clearance.

bleeding among patients with adjusted low-, under-, and standard-dosage NOACs, either overall or in each NOAC subgroup analyzed separately.

During the 90-day follow-up period after AF ablation, neither thromboembolic nor bleeding complications were observed.

TABLE 5. Comparison of Complications Among Patients With Adjusted Low-, Under-, and Standard-dosage Non-vitamin K Antagonist Oral Anticoagulants

	Adjusted Low-dosage NOAC, n = 30	Underdosage NOAC, n = 30	Standard-dosage NOAC, n = 30	P
Thromboembolic complications, n				
Stroke	0	0	0	1
TIA	0	1	0	0.33
DVT	0	0	0	1
Pulmonary embolism	0	0	0	1
Bleeding complications, n				
Major bleeding				
Retroperitoneal bleeding	0	0	0	1
Cardiac tamponade	0	2	6	0.85
Groin hematoma requiring blood transfusion	0	0	0	1
Bleeding requiring blood transfusion	0	0	0	1
Minor bleeding and other minor complications				
Pericardial effusion	0	4	8	0.96
Reduced hemoglobin level >4 g/dL	0	0	0	1
Minor groin hematoma	0	4	9	0.96
Hematuria	1	4	8	0.96
Prolonged hospitalization	0	0	0	1
Safety outcome (the composite of thromboembolic and bleeding complications)	1	16	31	0.95

DVT, deep venous thrombosis; NOAC, non-vitamin K antagonist oral anticoagulant; P, probability value; TIA, transient ischemic attack.

As a whole, safety outcomes did not differ among adjusted low-, under-, and standard-dosage groups (Table 5), nor were there any differences when the analysis was performed for each NOAC separately (Table 6).

DISCUSSION

The present study demonstrated that underdosing the NOACs rivaroxaban and dabigatran etexilate, which involves administering a dosage lower than that recommended by the drug manufacturer, provided safe and effective anticoagulation for patients undergoing catheter ablation for AF. Dosages were selected according to the discretion of the treating cardiologist, with consideration of age, sex, body weight and body mass index, and creatinine clearance. Underdosage was considered to be clinically appropriate in a considerable number of patients, indicating that efficacy and safety exists over a wider range of doses than the drug manufacturer recommends.

Catheter ablation of AF in this study was performed in essentially the same manner as improved methods described recently.^{2,3,13} Procedural times in all groups analyzed were comparable to or shorter than those in recent reports.^{3,13} Heparin was administered to maintain an ACT in the range 300–350 seconds, in accordance with generally accepted practice.^{2,13} All patients reached the endpoint of successful AF ablation, and the overall complication rate was comparable to or less than that described in recent reports.^{1,3} The

present procedural parameters and clinical outcomes indicate that these methods for AF ablation were satisfactory. Such considerations validate comparisons among the groups and open the door to further discussion.

The present study identified no differences in thromboembolic and bleeding complications between underdosage and standard-dosage patients. Further, no differences were observed between rivaroxaban and dabigatran etexilate. About rivaroxaban, research has noted that doses of 20, 30, and 40 mg/d appear to be equivalent in safety and efficacy for the treatment of deep venous thrombosis.¹⁰ In comparison, rivaroxaban dosages used in this study were lower, at 10 mg/d in the underdosage group. The reported results indicated that higher dosage of rivaroxaban exhibited safeness. This would account for the considerably low incidence of bleeding complications (0.8%) observed in the present study. The standard dosage of rivaroxaban in Asian patients is less than that of Western populations, typically between 20 and 15 mg/d, given differences in population pharmacokinetics and pharmacodynamics.¹⁴ The efficacy and safety of a 15 mg/d dosage of rivaroxaban has been reported in the treatment of nonvalvular AF patients.⁹ However, underdosing rivaroxaban in patients undergoing AF ablation is poorly researched, and the present study cannot be compared with reported studies. About dabigatran etexilate, one study in which comparisons were made with acenocoumarol noted that underdosages of 110 mg twice daily were safe and efficacious for perioperative anticoagulation in patients undergoing AF ablation.⁸

TABLE 6. Comparison of Complications Among Patients With Adjusted Low-, Under-, and Standard-dosage Non-vitamin K Antagonist Oral Anticoagulants

	Rivaroxaban			P	Dabigatran Etexilate			P
	Adjusted Low Dosage Once Daily, n = 18	Underdosage Once Daily, n = 110	Standard Dosage Once Daily, n = 394		Adjusted Low Dosage Twice Daily, n = 12	Under-dosage Twice Daily, n = 197	Standard Dosage Twice Daily, n = 289	
Thromboembolic complications, n								
Stroke	0	0	0	1	0	0	0	1
TIA	0	1	0	0.15	0	0	0	1
DVT	0	0	0	1	0	0	0	1
Pulmonary embolism	0	0	0	1	0	0	0	1
Bleeding complications, n								
Major bleeding								
Retroperitoneal bleeding	0	0	0	1	0	0	0	1
Cardiac tamponade	0	0	3	0.61	0	2	3	0.94
Groin hematoma requiring blood transfusion	0	0	0	1	0	0	0	1
Bleeding requiring blood transfusion	0	0	0	1	0	0	0	1
Minor bleeding and minor complications								
Pericardial effusion	0	2	4	0.70	0	2	4	0.87
Reduced hemoglobin level >4 g/dL	0	0	0	1	0	0	0	1
Minor groin hematoma	0	2	5	0.80	0	2	4	0.87
Hematuria	1	1	4	0.20	0	4	4	0.78
Prolonged hospitalization	0	0	0	1	0	0	0	1
Safety outcome (the composite of thromboembolic and bleeding complications)	1	6	16	0.80	0	10	15	0.72

DVT, deep venous thrombosis; NOAC, non-vitamin K antagonist oral anticoagulant; P, probability value; TIA, transient ischemic attack.

However, the study in question included few patients who were young compared with the population observed here and had longer procedural times and higher complication rates, thereby making comparisons with present results difficult. Additionally, a randomized study has examined the comparative safety and efficacy of underdosing dabigatran against warfarin in patients undergoing AF ablation.⁷ Similarly, however, the study included few of patients (n = 45 in each group) and did not perform comparisons with standard doses of dabigatran etexilate. Despite such insufficiencies, previously reported results are largely consistent with those observed in this study. In clinical flowcharts for dabigatran etexilate in AF, a 110 mg dose is recommended in patients of advanced age, even with preserved creatinine clearance or low thromboembolic risk and high bleeding risk.¹⁵ Considered together, the present study suggests that underdosing NOACs, such as rivaroxaban and dabigatran etexilate, is safe and efficacious in the perioperative anticoagulation of patients undergoing AF ablation.

Overall, the rate of bleeding complications was less than or comparable to that reported in other studies.^{1,16,17} Bleeding complications are assumed to be related to a hemorrhagic tendency or to technical, procedural, and anatomical factors. Given that the ACT was controlled and there were no differences in the incidence of bleeding complications

between under- and standard-dosage groups, we may conclude that neither adjusted low-, under-, nor standard-dosage NOACs play a major role in bleeding complications. Furthermore, the accumulation of experience and improved methods, including ablation devices, has reduced the incidence of bleeding complications.¹³ Indeed, the incidence of cardiac tamponade in the present study was 0.5%, lower than that reported in previous studies.¹⁸ A thromboembolic complication was observed in just one patient who experienced a transient ischemic attack. This suggests that under- and standard-dosage NOACs are effective in the prevention of thromboembolic complications.

When selecting NOAC dosages, underdosing was associated with female sex, advanced age, lower body weight, and poorer renal function in all patients and in both NOAC subgroups. Pharmacokinetics generally indicated a significant correlation between serum drug concentration and body weight. Further, significant correlations among body weight, age, sex, and renal function were observed (Table 4). Theoretically, including such factors in the clinical consideration of dosing is reasonable. Risk scores for stroke (CHADS₂, CHA₂DS₂-VASc) were higher in the underdosage group than those in the standard-dosage group. In these risk score systems, female sex and advanced age contribute to a greater risk. The underdosage group exhibited a higher incidence of

both female sex and advanced age that would, at least partly, account for a higher risk score in the underdosage group than the standard-dosage group.

In each NOAC subgroup, the ACT immediately before the AF ablation procedure was slightly but significantly elevated; however, no significant differences were observed among patients receiving adjusted low-, under-, and standard dosages of NOACs. Further, the quantity of heparin per kilogram of body weight required to maintain an ACT in the range of 300–350 seconds did not differ between patients among under-, standard-, and adjusted low-dosages, nor were any differences observed in each NOAC subgroup considered separately. In addition, the dose of protamine needed for homeostasis also showed no differences among patients receiving under-, standard-, and adjusted low-dosage NOACs, overall or for each NOAC individually. Such results suggest that blood coagulation activity was suppressed equally and significantly by all NOAC dosages used in this study and account for observations about equivalent safety and efficacy.

An indirect comparison has previously suggested that significant differences exist in safety and efficacy among NOACs.^{19,20} However, the present study did not reveal any such differences: underdosing two different NOACs had no effect on their safety and efficacy in the context of anticoagulation. There have been no reports of thromboembolic or bleeding episodes in patients receiving underdosage NOACs compared to those with standard-dosage NOACs, and the present results suggest that underdosage of both rivaroxaban and dabigatran etexilate, at physician discretion, is safe and effective in the prevention of thromboembolism in AF patients.

The present study had several limitations. First, it included a relatively few patients. Second, the study was conducted in a retrospective manner and therefore lacks the power of a prospective randomized study. Although it appears that an increase in the number of patients would most likely not produce significant changes in results, multicenter studies with a greater number of patients are required to confirm the results observed in this study.

CONCLUSIONS

Underdosing NOACs, which involves administering a dosage lower than that recommended by the drug manufacturer (standard dose), is safe and efficacious for the perioperative anticoagulation of patients undergoing AF ablation, provided adequate consideration is given to patient condition, age, sex, body weight, body mass index, and renal function. The results of this study indicate that the therapeutic range of NOACs is wider than the manufacturer recommended dosage.

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