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

Hirosuke Yamaji, MD,* Takashi Murakami, MD,* Kazuyoshi Hina, MD,* Shunichi Higashiyama, MD,* Hiroshi Kawamura, MD,* Masaaki Murakami, MD,* Shigeshi Kamikawa, MD,* Issei Komatsubara, MD,† and Shozo Kusachi, MD*†

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 (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

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 non-valvular 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
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 Eteixlate  |
|------------------|----------------------|-----------------------|
| 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.
Radiofrequency Ablation

The ablation strategy was the same in all groups, and PVAI was performed in all patients. Electrophysiological mapping was performed using a 3.5-mm-tip ablation catheter (CoolFlex; St. Jude Medical Inc, CoolPath Duo; St. Jude Medical Inc, or Safire BLU; St. Jude Medical Inc) inserted via the transseptal sheath. Each PV ostium was identified using an electroanatomic integration mapping system (Ensite NavX system; St. Jude Medical Inc.). After LA reconstruction, each PV ostium was identified by selective venography and tagged on the electroanatomic map.

Two decapolar ring catheters were placed within the ipsilateral superior and inferior PVs or within the superior and inferior branches of a common PV during radiofrequency delivery. Irrigated radiofrequency energy was delivered with a target temperature of 43°C, a maximal power limit of 35 W (20–30 W for posterior wall ablation and 30–35 W for anterior wall ablation), and an infusion rate of 8–13 mL/min via the irrigated ablation catheter. Radiofrequency energy was applied for 30 seconds, until the maximal local electrogram amplitude decreased by 70%. Irrigated radiofrequency ablation was performed in the posterior and anterior walls at 5–10 mm and 5 mm, respectively, from the angiographically or electrophysiologically defined PV ostia. The temperature of the esophagus during ablation was continuously monitored by a catheter with a temperature sensor (SensiTherm; St. Jude Medical Inc,) to avoid esophageal damage from the high energy supplied. When the temperature exceeded 39°C, energy supply was discontinued.

The end point of PVAI was defined as: (1) elimination of PV potentials, as recorded by 2 ring catheters within the ipsilateral PVs, and lack of LA capture during intra-PV, isthmus, and PV atrial pacing at least 30 minutes after isolation; and (2) no recurrence of PV spikes within any of the PVs after intravenous administration of 20–40 mg of adenosine triphosphate during sinus rhythm or coronary sinus pacing.

In patients with paroxysmal AF, only PVAI was performed. In patients with persistent and long-standing persistent AF, additional ablations were performed in combination with PVAI. After PVAI, a left atrial roof line was created, and subsequent ablation of fractionated atrial electrograms in the right atrium and LA and in the coronary sinus was performed. Further ablation at the superior vena cava and cavotricuspid isthmus was also performed. If the AF did not terminate after ablation procedures, direct current cardioversion was performed to restore normal sinus rhythm.

Postablation Care and Follow-up

After the ablation procedure, anticoagulation therapy was continued for at least three months in all groups. Patients were followed-up at our center every month for at least 90 days. The initial follow-up visit was three weeks after AF ablation. All previously ineffective antiarrhythmic drugs were withdrawn immediately after ablation. At follow-up, a surface electrocardiogram (ECG) was recorded, and transthoracic echocardiography was performed at our center. All patients were given a telemetry electrocardiogram recorder (Omron Co, Ltd, Kyoto, Japan) to document symptomatic arrhythmias or to transfer electrocardiogram data once per week if they remained asymptomatic for 6 months.

Complications and Safety Outcome

Cerebrovascular accidents and transient ischemic attacks were considered as thromboembolic complications once intracranial hemorrhage had been ruled out. Pulmonary embolism and deep venous embolism were also defined as thromboembolic complications. Cardiac tamponade, retroperitoneal bleeding, and groin hematoma requiring blood transfusion were defined as major bleeding episodes. Cardiac tamponade was defined by characteristic clinical features and the presence of a considerable pericardial effusion requiring
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

| No. patients | Adjusted Low-dosage NOAC | Underdosage NOAC | Standard-dosage NOAC | P | Adjusted Low-dosage Versus Underdosage, P | Underdosage Versus Standard Dose, P | Adjusted Low-dosage Versus Standard Dose, P |
|--------------|--------------------------|------------------|---------------------|---|-----------------------------------------|-------------------------------------|-----------------------------------------|
| 30           | 307                      | 683              |                     |   | <0.01                                   | <0.01                               | <0.01                                   |
| 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/m²   | 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                                   |
| CHADS2 score | 0.8 ± 1.0                | 0.6 ± 0.9        | 0.5 ± 0.8           | <0.01 | 0.24                                   | 0.037                               | 0.67                                    |
| CHA2DS2-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.

Copyright © 2016 The Author(s). Published by Wolters Kluwer Health, Inc.
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 | Dabigatran Exetilate | P Underdosage Versus Standard dosage |
|--------------------|-------------|----------------------|-------------------------------------|
|                    | Adjusted Low Dosage | Underdosage | Standard Dosage | P under Versus Standard | Adjusted Low Dosage | Underdosage | Standard Dosage | P under Versus Standard |
| 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/m²         | 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 |
| CHADS₂             | 0.7 ± 1.0 | 0.8 ± 0.9 | 0.6 ± 0.8 | 0.35 | 0.49 | 0.8 ± 0.9 | 0.6 ± 0.9 | 0.4 ± 0.7 | <0.01 | <0.01 |
| CHA₂DS²-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 | PeAF | LS-PeAF | AT | ACT, s | PAF | PeAF | LS-PeAF | AT | 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 PVI 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
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 4. Correlations Among Patient Characteristics

|                      | Sex          | Age          | BW           | BMI          | CCr          |
|----------------------|--------------|--------------|--------------|--------------|--------------|
| **All patients**     |              |              |              |              |              |
| 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       |              |              |
| **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       |              |              |
| **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.
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. Procedural times in all groups analyzed were comparable to or shorter than those in recent reports. Heparin was administered to maintain an ACT in the range 300–350 seconds, in accordance with generally accepted practice. 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. 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. 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. The efficacy and safety of a 15 mg/d dosage of rivaroxaban has been reported in the treatment of nonvalvular AF patients. 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.

---

**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.
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.1,6,17 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

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

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

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

REFERENCES

1. Raviele A, Natale A, Calkins H, et al. Venice Chart international consensus document on atrial fibrillation ablation: 2011 update. J Cardiovasc Electrophysiol. 2012;23:890–923.
2. Calkins H, Kuck KH, Cappato R, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace. 2012;14:528–606.
3. Scherr D, Sharma K, Dalal D, et al. Incidence and predictors of periprocedural cerebrovascular accident in patients undergoing catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol. 2009;20:1357–1363.
4. Hoyt H, Bhonsale A, Chihukuri K, et al. Complications arising from catheter ablation of atrial fibrillation: temporal trends and predictors. Heart Rhythm. 2011;8:1869–1874.
5. Mani H, Lindhoff-Last E. New oral anticoagulants in patients with non-valvular atrial fibrillation: a review of pharmacokinetics, safety, efficacy, quality of life, and cost effectiveness. Drug Des Dev Ther. 2014;8:789–798.
6. Beyer-Westendorf J, Gelbrich V, Forster K, et al. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J. 2014;35:1888–1896.
7. Nin T, Sairaku A, Yoshida Y, et al. A randomized controlled trial of dabigatran versus warfarin for periablation anticoagulation in patients undergoing ablation of atrial fibrillation. Pacing Clin Electrophysiol. 2013;36:172–179.
8. Efremidis M, Vlachos K, Letsas KP, et al. Low dose dabigatran versus uninterrupted acenocoumarol for peri-procedural anticoagulation in atrial fibrillation catheter ablation. J Electrocardiol. 2015;48:840–844.
9. Hori M, Matsumoto M, Tanahashi N, et al. Safety and efficacy of adjusted dose of rivaroxaban in Japanese patients with non-valvular atrial fibrillation: subanalysis of J-ROCKET AF for patients with moderate renal impairment. Circ J. 2013;77:632–638.
10. Buller HR, Lensing AW, Prins MH, et al. A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study. Blood. 2008;112:2242–2247.
11. World Medical Association Declaration of Helsinki ethical principles for medical research involving human subjects. JAMA. 2000;284:3043–3045.
12. Yamaji H, Murakami T, Hina K, et al. Adequate initial heparin dosage for atrial fibrillation ablation in patients receiving non-vitamin K antagonist oral anticoagulants. Clin Drug Investig. 2016;36:837–848.
13. Lee G, Sparks PB, Morton JB, et al. Low risk of major complications associated with pulmonary vein antral isolation for atrial fibrillation: results of 500 consecutive ablation procedures in patients with low prevalence of structural heart disease from a single center. J Cardiovasc Electrophysiol. 2011;22:163–168.
14. Tanigawa T, Kaneko M, Hahizume K, et al. Model-based dose selection for phase III rivaroxaban study in Japanese patients with non-valvular atrial fibrillation. Drug Metab Pharmacokinet. 2013;28:59–70.
15. Huisman MV, Lip GY, Diener HC, et al. Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: resolving uncertainties in routine practice. Thromb Haemost. 2012;107:838–847.
16. Santangeli P, Di Biase L, Sanchez JE, et al. Atrial fibrillation ablation without interruption of anticoagulation. Cardioil Res Pract. 2012:2011; 837841.
17. Lakkireddy D, Reddy YM, Di Biase L, et al. Feasibility and safety of dabigatran versus warfarin for periprocedural anticoagulation in patients undergoing radiofrequency ablation for atrial fibrillation: results from a multicenter prospective registry. J Am Coll Cardiol. 2012;59:1168–1174.
18. Cappato R, Calkins H, Chen SA, et al. Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation. 2005;111:1100–1105.
19. Lip GY, Larsen TB, Skjøth F, et al. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2012;60:738–746.
20. Becker WC, Phung OJ. Systematic review and adjusted indirect comparison meta-analysis of oral anticoagulants in atrial fibrillation. Circ Cardiovasc Qual Outcomes. 2012;5:711–719.