Received: 13 September 2017 | Accepted: 20 November 2017

DOI: 10.1002/joa3.12024

ORIGINAL ARTICLE

WILEY Journal of Arrhythmia Open Access

Comparison of uninterrupted anticoagulation with dabigatran etexilate or warfarin in the periprocedural period for atrial fibrillation catheter ablation: Results of the Japanese subgroup of the RE-CIRCUIT trial

Yukihiko Yoshida[1] | Masato Watarai[2] | Kenshi Fujii[3] | Wataru Shimizu[4] | Kazuhiro Satomi[5] | Yasuya Inden[6] | Yoshimasa Murakami[7] | Masato Murakami[8] | Atsushi Iwasa[9] | Masaomi Kimura[10] | Nobuko Yamada[11] | Tomofumi Nakagawa[11] | Matias Nordaby[12] | Ken Okumura[13]

[1]Department of Cardiology, Japanese Red Cross Nagoya Daini Hospital, Nagoya, Aichi, Japan

[2]Department of Cardiology, Aichi Prefectural Welfare Federation of Agricultural Co-operative Associations, Anjo-kosei Hospital, Anjo, Aichi, Japan

[3]Cardiovascular Division, Sakurabashi Watanabe Hospital, Osaka, Japan

[4]Department of Cardiovascular Medicine, Nippon Medical School Hospital, Bunkyo-ku, Tokyo, Japan

[5]Department of Cardiology, Tokyo Medical University, Shinjyuku-ku, Tokyo, Japan

[6]Department of Cardiology, Nagoya University Hospital, Nagoya, Aichi, Japan

[7]Division of Cardiology, Nagoya City East Medical Center, Nagoya, Aichi, Japan

[8]Department of Cardiology, Shonan Kamakura General Hospital, Kamakura, Kanagawa, Japan

[9]Department of Cardiology, New Tokyo Hospital, Matsudo, Chiba, Japan

[10]Department of Cardiology and Nephrology, Hirosaki University Hospital, Hirosaki, Aomori, Japan

[11]Nippon Boehringer Ingelheim Co., Ltd., Shinagawa-ku, Tokyo, Japan

[12]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany

[13]Division of Cardiology, Saiseikai Kumamoto Hospital, Kumamoto, Japan

Correspondence
Ken Okumura, Division of Cardiology, Saiseikai Kumamoto Hospital, Minami-ku, Kumamoto, Japan.
Email: okumura@hirosaki-u.ac.jp

Funding information
This study was funded by Boehringer Ingelheim. The sponsor was involved in the study design; in the collection, analysis, and interpretation of the data; and in the decision to submit the article for publication. Nippon Boehringer Ingelheim funded the publication fee for this manuscript.

Abstract

Background: There are limited data on uninterrupted anticoagulation with direct oral anticoagulants during catheter ablation for atrial fibrillation (AF), particularly in Japan. We planned a subgroup analysis of the RE-CIRCUIT study, comparing the use of uninterrupted dabigatran therapy with warfarin therapy during catheter ablation among the Japanese subgroup and with that in the total population.

Methods: The RE-CIRCUIT study utilized a prospective, randomized, open-label, blinded endpoint design, and the primary endpoint was the incidence of major bleeding events (MBEs). Patients were randomized to uninterrupted dabigatran 150 mg twice daily or warfarin. In this study, we analyzed the results in Japanese patients.

Results: Of 704 enrolled patients in the study, 112 Japanese patients were randomized to dabigatran (n = 65) or warfarin (n = 47). MBEs were experienced by two

patients: one in the dabigatran group (1.6%, cardiac tamponade) and one in the warfarin group (2.2%, groin hematoma) (risk difference vs warfarin −0.6%; 95% CI −5.8, 4.7). Within the Japanese subgroup, there were no thromboembolic events in both groups.

Conclusion: While not designed to show statistical difference between two treatment groups, our results from the Japanese subgroup supported those from the overall population. Furthermore, this study provided clinical information regarding MBE, especially cardiac tamponade, in Japanese patients.

KEYWORDS
catheter ablation, dabigatran, Japanese, nonvalvular atrial fibrillation, uninterrupted anticoagulation

1 | INTRODUCTION

Atrial fibrillation (AF) affects 1.5%–2% of the population globally,[1] and the prevalence is as high as 9%–14% in people aged >80 years in Western countries.[2] Catheter ablation is now a standard-of-care treatment for drug-refractory AF, but major bleeding and thromboembolic risks are treatment concerns. A prospective, randomized study of patients with interrupted or uninterrupted treatment with a vitamin K antagonist (VKA) during catheter ablation for AF revealed that uninterrupted VKA significantly decreases the incidence of stroke, transient ischemic attacks (TIA), and minor bleeding.[3] A meta-analysis comparing uninterrupted and interrupted VKA therapy in patients undergoing AF ablation showed that uninterrupted VKA had a favorable effect on the occurrence of stroke or TIA and major bleeding.[4] Prior studies have shown that performing AF ablation with uninterrupted VKA anticoagulation therapy helps to minimize the risk of these complications, and it is now a well-established anticoagulation strategy at the time of AF ablation.[1,5,6]

However, there are limited data assessing the safety and effectiveness of uninterrupted anticoagulation therapy with direct oral anticoagulants (DOACs) during catheter ablation for AF, including in the Japanese population. A meta-analysis comparing DOAC with uninterrupted VKA therapy in patients undergoing AF ablation found no significant differences between the groups in the occurrence of stroke or TIA and major bleeding.[7] The VENTURE-AF trial was a prospective, randomized clinical trial that compared uninterrupted factor Xa inhibitor rivaroxaban treatment with uninterrupted VKA therapy.[8] This trial found no differences between the two treatments in thromboembolic events or major bleeding events (MBEs) and demonstrated the feasibility of uninterrupted use of factor Xa inhibitors during catheter ablation. No country-specific analyses of the data from this study have been published to date. In Japan, another prospective randomized study of patients treated with the factor Xa inhibitor apixaban during catheter ablation for AF revealed that uninterrupted factor Xa inhibitor therapy has similar safety and effectiveness to warfarin during the AF ablation periprocedural period.[9] A Japanese Catheter Ablation Registry of Atrial Fibrillation study showed that the incidence of complications including pericardial effusion in DOAC-treated patients was lower than that in patients receiving uninterrupted warfarin therapy.[10] Furthermore, a prospective registry study conducted in Japan revealed that the rates of thromboembolism and MBE during the AF ablation perioperative period in Japanese patients treated with the factor Xa inhibitor rivaroxaban were as low as those in patients treated with warfarin.[11]

The RE-CIRCUIT study evaluated the safety and efficacy of uninterrupted dabigatran therapy versus warfarin for periprocedural anticoagulation in patients with AF undergoing catheter ablation.[12] The overall results found that the incidence of MBE was significantly lower with dabigatran treatment than with warfarin. Here, we report the results of the Japanese subgroup of the RE-CIRCUIT study.

2 | METHODS

2.1 | Study overview

The RE-CIRCUIT study was a prospective, randomized, open-label, blinded endpoint (PROBE[13]), multicenter clinical trial. The study design has previously been published[12] and is shown in Figure 1. It included a screening period during weeks 0 to 2, a pre-ablation treatment period during weeks 4 to 8, a postablation treatment period of 8 weeks (starting with the ablation procedure), and a follow-up period of 1 week.

2.1.1 | Ethics and study oversight

The trial was carried out in compliance with the ethical principles outlined in the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice (GCP), and the Japanese GCP regulations in Japan. The protocol was approved by an institutional review board or independent ethics committee at each participating center, and all patients provided written informed consent before entering the trial. The trial was conducted under the guidance of a steering committee. Adjudicated and nonadjudicated data were checked by an independent data and safety monitoring committee,

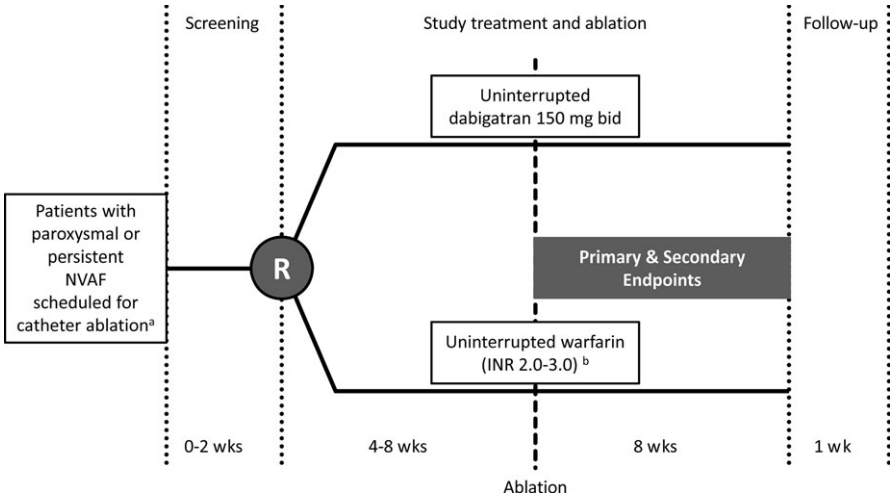

FIGURE 1 Study design. A, ablation; bid, *bis in die* (twice daily); INR, international normalized ratio; ISTH, International Society of Thrombosis and Hemostasis; NVAF, nonvalvular atrial fibrillation; R, randomization. [a]Also eligible for oral dabigatran treatment (150 mg bid) according to local prescribing information. [b]The target INR was 2.0–2.6 for Japanese patients aged 70 years or older

and all primary and secondary endpoints were adjudicated by a blinded independent adjudication committee. The authors adhered to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

2.1.2 | Protocol amendments

The following changes to the original protocol were made for the Japanese subgroup: the lower limit of the patient age range was increased from 18 to 20 years to meet Japanese regulatory requirements. The target international normalized ratio (INR) for patients aged 70 years and older was changed from 2.0–3.0 to 2.0–2.6 to meet Japanese scientific guideline recommendations. The serious adverse event (AE) reporting process for several outcome events (all deaths, bleeds, and pericardial tamponade events) was changed in response to a Japanese Pharmaceuticals and Medical Devices Agency request.

2.2 | Patients

The main inclusion criteria were as follows: male or female patients aged ≥20 years; eligible for treatment with dabigatran 150 mg twice daily (according to local label); with paroxysmal or persistent nonvalvular AF; and undergoing catheter ablation. Both treatment-naïve patients and patients on oral anticoagulant (OAC) treatment with a VKA or DOAC were included.

The main exclusion criteria were as follows: patients with permanent AF or AF secondary to an obvious reversible cause; left atrial size ≥60 mm; contraindications (or known allergy) to systemic anticoagulation with heparin, warfarin, or dabigatran; mechanical or biological heart valve prosthesis; stroke within 1 month prior to screening; history of intracranial hemorrhage, intraocular, spinal, retroperitoneal or atraumatic intra-articular bleeding; or history of gastrointestinal hemorrhage within 1 month prior to screening.

2.3 | Treatment and procedure

Patients were randomized 1:1 to oral treatment with 150 mg dabigatran etexilate (Boehringer Ingelheim, Ingelheim, Germany) twice daily or warfarin sodium (Teva UK Ltd, Castleford, UK) in a combination of 1, 3, and 5 mg to achieve a target INR of 2.0–3.0 (2.0–2.6 for patients aged ≥70 years). Randomization was carried out centrally by an interactive, computerized response system using computer-generated sequences. Following a pre-ablation transesophageal echocardiography to rule out left atrial thrombi, ablation was performed with concomitant, uninterrupted anticoagulation treatment, which was continued for 8 weeks after the procedure. The morning dose of dabigatran was taken on the day of the ablation at the patient's scheduled time. Dabigatran was taken again in the evening of the procedure day at the scheduled time, with a minimum delay of 3 hours after sheath removal and achievement of hemostasis. The AF ablation procedure was performed according to the recommendations of a 2012 expert consensus statement.[5] All types of ablation technique, technology, and tools were permitted except for investigational ablation procedures. Radiofrequency energy was typically used, but cryoablation and hot balloon ablation were also allowed. All patients were scheduled to have a follow-up visit 1 week after the trial medication ended.

Compliance with the dabigatran treatment regime was assessed by capsule count. This was calculated as the number of capsules taken, divided by the number of capsules that should have been taken according to the scheduled period, multiplied by 100. Warfarin treatment compliance was assessed by the time that each patient's INR fell within the therapeutic range (TTR) using the Rosendaal

method.[14] This method gives a more accurate measure of the pharmacodynamic effect than pill counts.

2.4 | Primary and secondary endpoints

The primary endpoint was the incidence of MBEs according to the International Society on Thrombosis and Hemostasis (ISTH) definition[15] during the ablation procedure and up to 8 weeks postablation. The secondary endpoints were the incidence of the following during the ablation procedure and up to 8 weeks postablation: stroke, systemic embolism (SE), and TIA events; minor bleeding events; and a composite of MBE and thromboembolic events (stroke, SE, or TIA). Congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or TIA or thromboembolism, vascular disease, and sex scores (CHA_2DS_2-VASc) were used to assess stroke risk.[1] Body mass index (BMI) data were calculated for all patients.

2.5 | Adverse events

An AE was defined as any untoward medical occurrence in a patient administered a trial treatment. A severe AE was defined as an incapacitating event or one resulting in an inability to work or perform usual activities. Serious AEs were defined as any AE that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, resulted in a congenital anomaly/birth defect, or was to be deemed serious for any other reason.

2.6 | Statistical analysis

The trial was exploratory because the sample required to provide sufficient power to establish formal noninferiority with an acceptable upper limit of the 95% confidence interval (e.g., 1.5) would have made the trial unfeasible (>2000 patients per group). On the basis of multiple scenarios, it was decided that a minimum of 290 evaluable patients per treatment group would be enough to provide clinically meaningful information. Any subgroup analysis is therefore also only of a descriptive nature and presents two-sided 95% confidence intervals (CIs). The primary and secondary endpoint analyses were based on the ablation set, which included all randomly assigned patients who had taken at least one dose of trial drug, and who had undergone the ablation procedure. The treated set data (i.e., all randomly assigned patients who had taken ≥1 dose of trial drug) were used for the safety analysis, and AEs were analyzed descriptively.

3 | RESULTS

3.1 | Patient characteristics

In the overall study, 704 patients were enrolled from 104 centers in 11 countries between April 2015 and July 2016, 678 patients were randomized (dabigatran, n = 339; warfarin, n = 339), and 635 patients underwent ablation (n = 317 and 318, respectively). In the Japanese subgroup, 115 patients were enrolled from 10 centers in Japan and 112 were randomized and received the study drug

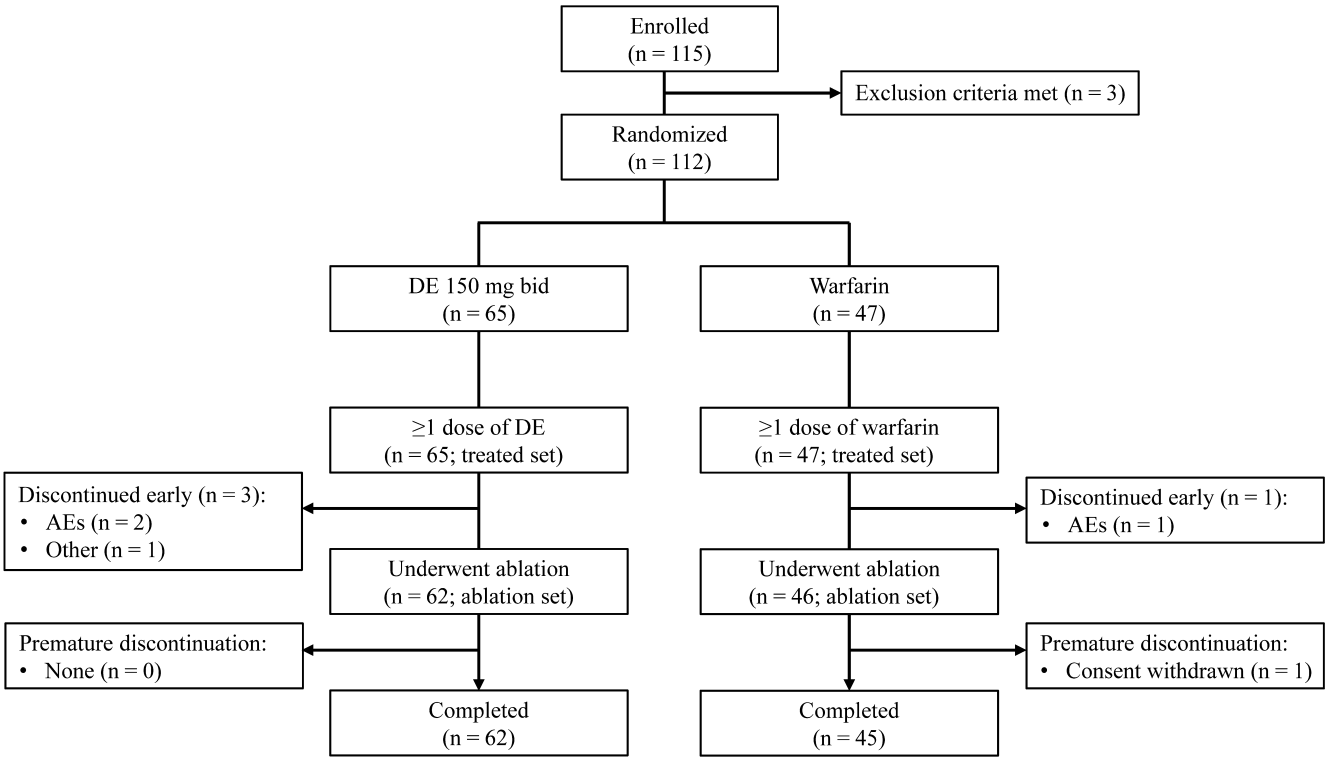

FIGURE 2 Patient disposition. AE, adverse event; DE, dabigatran etexilate

(dabigatran, n = 65; warfarin, n = 47). Of these, 108 patients underwent ablation (n = 62 and 46, respectively) and 107 patients completed the study (n = 62 and 45, respectively) (Figure 2).

The baseline characteristics of the Japanese subgroup are shown in Table 1. The mean age was 59.7 years (range 25-84) in the dabigatran group and 58.1 years (range 31-73) in the warfarin group, with 91.9% and 82.6% of patients, respectively, being male. The mean CHA_2DS_2-VASc scores were 2.1 and 1.8 in the dabigatran and warfarin groups, respectively. The BMI was 24.0 kg/m^2 in both groups. The AF types in the dabigatran vs warfarin groups were paroxysmal (51.6% vs 60.9%), persistent (33.9% vs 19.6%), and long-standing persistent (14.5% vs 19.6%). Fewer patients in the dabigatran group than in the warfarin group had coronary artery disease (1.6% vs 8.7%), a history of percutaneous coronary intervention (0.0% vs 6.5%) or previous GI bleeding, ulcerative GI disease or gastritis (9.7% vs 23.9%).

3.2 | Primary and secondary endpoints

Regarding the primary endpoint, in the Japanese subgroup, one patient in the dabigatran group (1.6%) and one in the warfarin group (2.2%) had an MBE (risk difference vs warfarin −0.6%; 95% CI −5.8, 4.7) (Table 2). The MBE occurring in the dabigatran group was cardiac tamponade, which occurred on the day of ablation. The patient was an 84-year-old female who underwent pulmonary vein isolation ablation with radiofrequency, during which she became hypotensive.

TABLE 1 Baseline patient characteristics (ablation set[a])

Characteristics	Dabigatran 150 mg bid (n = 62)	Warfarin (n = 46)
Male, n (%)	57 (91.9)	38 (82.6)
Mean age (standard deviation), years	59.7 (11.12)	58.1 (11.25)
Mean body mass index (kg/m^2)	24.0	24.0
CHA_2DS_2-VASc score[b], mean	2.1	1.8
Mean activated clotting time, sec	336.2	348.3
Atrial fibrillation, n (%)		
Paroxysmal	32 (51.6)	28 (60.9)
Persistent	21 (33.9)	9 (19.6)
Long-standing persistent	9 (14.5)	9 (19.6)
Medical history, n (%)		
Congestive heart failure	4 (6.5)	1 (2.2)
Left ventricular dysfunction	3 (4.8)	2 (4.3)
Hypertension	28 (45.2)	22 (47.8)
Coronary artery disease	1 (1.6)	4 (8.7)
Diabetes mellitus	6 (9.7)	4 (8.7)
Renal disease	2 (3.2)	2 (4.3)
Percutaneous coronary intervention	0 (0.0)	3 (6.5)
Previous stroke	5 (8.1)	0 (0.0)
Previous myocardial infarction	0 (0.0)	1 (2.2)
Previous major bleeding or predisposition	0 (0.0)	0 (0.0)
Previous GI bleeding, ulcerative GI disease or gastritis	6 (9.7)	11 (23.9)
Medication use, n (%)		
Warfarin	15 (24.2)	8 (17.4)
Dabigatran	10 (16.1)	9 (19.6)
Rivaroxaban	6 (9.7)	2 (4.3)
Apixaban	6 (9.7)	5 (10.9)
Edoxaban	1 (1.6)	0 (0.0)
Acetylsalicylic acid	3 (4.8)	2 (4.3)
Clopidogrel	0 (0.0)	1 (2.2)
Beta-blockers	22 (35.5)	17 (37.0)

bid, *bis in die* (twice daily); GI, gastrointestinal.

[a]The ablation set included all randomly assigned patients who had taken at least one dose of trial drug and who had undergone the ablation procedure.

[b]The CHA_2DS_2-VASc score reflects the risk of stroke in patients with atrial fibrillation. Scores range from 0 to 9, with higher scores indicating greater risk.

The transthoracic echocardiogram confirmed pericardial effusion of 2 cm. On the onset day, the patient underwent pericardial drainage and approximately 150 mL of blood was drained. The cardiac tamponade was associated with a decrease in hemoglobin and a 22% decrease from baseline in the hematocrit level. The patient received protamine for the cardiac tamponade, and the bleed required medical attention. Idarucizumab was not available at that time and therefore not administered. Dabigatran was temporarily interrupted. The following day, the patient recovered and the dabigatran was restarted on the same day. The patient was discharged from hospital three days later. The MBE in the warfarin group was a groin hematoma, occurring on the day following ablation. The incidence of MBE in the total population was lower with dabigatran than warfarin (five patients [1.6%] vs. 22 patients [6.9%]; absolute risk difference, −5.3%; confidence interval, −8.4% to −2.2%, $P < .001$).[12]

In terms of secondary endpoints in the subgroup analysis, there were no strokes, SE, or TIA in either treatment group. The incidence of minor bleeding events was similar between treatments, with 13 (21.0%) patients in the dabigatran group and 9 (19.6%) in the warfarin group (Table 2). There were no deaths, myocardial infarctions, or strokes in this Japanese subgroup.

3.3 | AEs

A total of 77 (68.8%) patients reported any AEs, 39 (60.0%) in the dabigatran group and 38 (80.9%) in the warfarin group (Table 3). Gastrointestinal disorders were the most common and were reported in 12 (18.5%) patients in the dabigatran group and 17 (36.2%) in the warfarin group, followed by infections and infestations (8 [12.3%] vs 13 [27.7%], respectively), and cardiac disorders (8 [12.3%] vs 12 [25.5%], respectively). Seven patients (10.8%) in the dabigatran group and 7 (14.9%) in the warfarin experienced serious AEs. Twelve patients (18.5%) in the dabigatran group and 12 (25.5%) in the warfarin group experienced investigator-defined treatment-related AEs.

TABLE 2 Primary and secondary endpoints (ablation set[a])

Event, n (%)	Dabigatran 150 mg bid (n = 62)	Warfarin (n = 46)
Primary endpoint		
ISTH MBEs	1 (1.6)	1 (2.2)
Secondary endpoints		
Stroke, systemic embolism, or TIA	0 (0.0)	0 (0.0)
Minor bleeding events	13 (21.0)	9 (19.6)
Composite of ISTH, MBEs, and thromboembolic events	1 (1.6)	1 (2.2)

bid, *bis in die* (twice daily); ISTH, International Society of Thrombosis and Hemostasis; MBE, major bleeding event; TIA, transient ischemic attack.
[a]The ablation set included all randomly assigned patients who had taken at least one dose of trial drug and who had undergone the ablation procedure.

TABLE 3 Summary of adverse events (treated set[a])

Event, n (%)[b]	Dabigatran 150 mg bid (n = 65)	Warfarin (n = 47)	Total (n = 112)
Any AEs	39 (60.0)	38 (80.9)	77 (68.8)
Gastrointestinal disorders	12 (18.5)	17 (36.2)	29 (25.9)
Infections and infestations	8 (12.3)	13 (27.2)	21 (18.8)
Cardiac disorders	8 (12.3)	12 (25.5)	20 (17.9)
Severe AEs	1 (1.5)	2 (4.3)	3 (2.7)
Investigator-defined drug-related AEs	12 (18.5)	12 (25.5)	24 (21.4)
Other significant AEs (according to ICH E3)	1 (1.5)	3 (6.4)	4 (3.6)
AEs leading to discontinuation of study drug	2 (3.1)	2 (4.3)	4 (3.6)
Serious AEs	7 (10.8)	7 (14.9)	14 (12.5)
Fatal AEs	0 (0.0)	0 (0.0)	0 (0.0)
Immediately life−threatening	0 (0.0)	1 (2.1)	1 (0.9)
Disability/incapacity	0 (0.0)	0 (0.0)	0 (0.0)
Requiring hospitalization	3 (4.6)	2 (4.3)	5 (4.5)
Resulting in prolonged hospitalization	3 (4.6)	5 (10.6)	8 (7.1)
Other[c]	1 (1.5)	1 (2.1)	2 (1.8)

AE, adverse event; bid, *bis in die* (twice daily); ICH, International Council for Harmonization.
[a]The treated set included all randomly assigned patients who had taken at least one dose of trial drug.
[b]Percentages were calculated with the total number of patients per treatment as the denominator.
[c]The "Other" category includes events deemed to be serious by the investigator in that they were important medical events that, after appropriate medical judgment, may have required medical or surgical intervention to prevent any of the outcomes mentioned previously.

The details of serious AEs are shown in Table 4, and those of treatment-related AEs in Table 5.

3.4 | Compliance

The compliance data were summarized for the entire treated set. In the dabigatran group, the mean compliance rate was 97.7% (standard deviation [SD], 3.17%). In the warfarin group, the mean TTR during the study was 64.7% (SD, 41.54%). The mean postablation duration of exposure was 60.2 days (SD, 4.2) in the dabigatran group and 58.1 days (SD, 9.34) in the warfarin group. Fifty-three (85.5%) patients in the dabigatran group and 37 (80.4%) in the warfarin group received the trial medication for at least 8 weeks following the ablation. Table 6 shows a summary of exposure to the study medications in the postablation period in the ablation set.

4 | DISCUSSION

In the total population from the RE-CIRCUIT study, the incidence of MBE was significantly lower in the dabigatran group than in the warfarin group. Both treatment groups had a similar incidence of minor bleeding events, and one thromboembolic event occurred in the warfarin group.[12]

In the Japanese subgroup of the RE-CIRCUIT study, the incidence of MBE was one patient in the dabigatran group (1.6%) and one in the warfarin group (2.2%) during the ablation and the 8-week post-ablation period. The event in the dabigatran group was cardiac tamponade. Because this event is of great concern for patients with DOAC treatment, we described the event and its outcome in detail. For secondary endpoints, the incidence ratios of stroke, SE, TIA, and minor bleeding were identical in the two groups, with no stroke, SEs, or TIA in either.

As a result, there were no major differences in findings between the total population and the Japanese subgroup from the RE-CIRCUIT study. The results in the Japanese subgroup revealed no major differences between dabigatran and warfarin groups.

A study in 363 Japanese patients comparing uninterrupted dabigatran treatment (n = 173) with warfarin (n = 190) showed a similar incidence of bleeding events in both groups.[16] In that study, MBEs occurred in 2 patients (1%) in each treatment group, and the minor bleeding events included groin hematoma (dabigatran, 5%; warfarin, 5%) and thromboembolic complications (dabigatran, 0%; warfarin, 1%). A randomized, controlled study was also conducted in Japan

TABLE 4 Serious adverse events by treatment group, system organ class, and preferred term (treated set[a])

Event, n (%)[b]	Dabigatran 150 mg bid (n = 65)	Warfarin (n = 47)	Total (n = 112)
Total patients with serious adverse event	7 (10.8)	7 (14.9)	14 (12.5)
Cardiac disorders	4 (6.2)	1 (2.1)	5 (4.5)
Sinus node dysfunction	2 (3.1)	0 (0.0)	2 (1.8)
Pericarditis	0 (0.0)	1 (2.1)	1 (0.9)
Cardiac failure	1 (1.5)	0 (0.0)	1 (0.9)
Cardiac tamponade	1 (1.5)	0 (0.0)	1 (0.9)
Vascular disorders	0 (0.0)	2 (4.3)	2 (1.8)
Hematoma	0 (0.0)	1 (2.1)	1 (0.9)
Peripheral artery occlusion	0 (0.0)	1 (2.1)	1 (0.9)
General disorders and administration site conditions	0 (0.0)	1 (2.1)	1 (0.9)
Pyrexia	0 (0.0)	1 (2.1)	1 (0.9)
Injury, poisoning and procedural complications	0 (0.0)	1 (2.1)	1 (0.9)
Vascular pseudoaneurysm ruptured	0 (0.0)	1 (2.1)	1 (0.9)
Investigations	0 (0.0)	1 (2.1)	1 (0.9)
Bleeding time prolonged	0 (0.0)	1 (2.1)	1 (0.9)
Musculoskeletal and connective tissue disorders	1 (1.5)	1 (2.1)	2 (1.8)
Compartment syndrome	0 (0.0)	1 (2.1)	1 (0.9)
Intervertebral disk protrusion	1 (1.5)	0 (0.0)	1 (0.9)
Nervous system disorders	1 (1.5)	1 (2.1)	2 (1.8)
Phrenic nerve paralysis	0 (0.0)	1 (2.1)	1 (0.9)
Facial paralysis	1 (1.5)	0 (0.0)	1 (0.9)
Gastrointestinal disorders	1 (1.5)	0 (0.0)	1 (0.9)
Colitis ulcerative	1 (1.5)	0 (0.0)	1 (0.9)

bid, *bis in die* (twice daily).

[a]The treated set included all randomly assigned patients who had taken at least one dose of trial drug.

[b]Percentages were calculated with the total number of patients per treatment as the denominator.

TABLE 5 Treatment-related adverse events by treatment group, system organ class, and preferred term (treated set[a])

Event, n (%)[b]	Dabigatran 150 mg bid (n = 65)	Warfarin (n = 47)	Total (n = 112)
Total	12 (18.5)	12 (25.5)	24 (21.4)
General disorders and administration site conditions	7 (10.8)	2 (4.3)	9 (8.0)
Puncture site hemorrhage	4 (6.2)	1 (2.1)	5 (4.5)
Vessel puncture site hemorrhage	3 (4.6)	0 (0.0)	3 (2.7)
Puncture site induration	0 (0.0)	1 (2.1)	1 (0.9)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	4 (8.5)	4 (3.6)
Epistaxis	0 (0.0)	4 (8.5)	4 (3.6)
Gastrointestinal disorders	3 (4.6)	1 (2.1)	4 (3.6)
Diarrhea	0 (0.0)	1 (2.1)	1 (0.9)
Abdominal discomfort	1 (1.5)	0 (0.0)	1 (0.9)
Abdominal pain upper	1 (1.5)	0 (0.0)	1 (0.9)
Dyspepsia	1 (1.5)	0 (0.0)	1 (0.9)
Eye disorders	0 (0.0)	2 (4.3)	2 (1.8)
Conjunctival hemorrhage	0 (0.0)	1 (2.1)	1 (0.9)
Conjunctival hyperemia	0 (0.0)	1 (2.1)	1 (0.9)
Investigations	0 (0.0)	2 (4.3)	2 (1.8)
Bleeding time prolonged	0 (0.0)	1 (2.1)	1 (0.9)
International normalized ratio increased	0 (0.0)	1 (2.1)	1 (0.9)
Skin and subcutaneous tissue disorders	2 (3.1)	2 (4.3)	4 (3.6)
Hemorrhage subcutaneous	2 (3.1)	2 (4.3)	4 (3.6)
Vascular disorders	0 (0.0)	2 (4.3)	2 (1.8)
Hematoma	0 (0.0)	2 (4.3)	2 (1.8)
Renal and urinary disorders	2 (3.1)	1 (2.1)	3 (2.7)
Hematuria	2 (3.1)	1 (2.1)	3 (2.7)
Injury, poisoning and procedural complications	1 (1.5)	1 (2.1)	2 (1.8)
Vascular pseudoaneurysm ruptured	0 (0.0)	1 (2.1)	1 (0.9)
Traumatic hemorrhage	1 (1.5)	0 (0.0)	1 (0.9)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (2.1)	1 (0.9)
Pain in extremity	0 (0.0)	1 (2.1)	1 (0.9)
Reproductive system and breast disorders	0 (0.0)	1 (2.1)	1 (0.9)
Hematospermia	0 (0.0)	1 (2.1)	1 (0.9)
Cardiac disorders	1 (1.5)	0 (0.0)	1 (0.9)
Cardiac tamponade	1 (1.5)	0 (0.0)	1 (0.9)
Hepatobiliary disorders	1 (1.5)	0 (0.0)	1 (0.9)
Hepatic function abnormal	1 (1.5)	0 (0.0)	1 (0.9)
Metabolism and nutrition disorders	1 (1.5)	0 (0.0)	1 (0.9)
Decreased appetite	1 (1.5)	0 (0.0)	1 (0.9)

bid, *bis in die* (twice daily).
[a]The treated set included all randomly assigned patients who had taken at least one dose of trial drug, whether or not they underwent ablation.
[b]Percentages were calculated with the total number of patients per treatment as the denominator.

during 2011-2012 to compare the interrupted use of dabigatran and warfarin during ablation.[17] In this case, both anticoagulants were discontinued the day before the ablation and resumed after it. This study aimed to see the incidence of bleeding from any source within 48 hours after the ablation procedure. The result indicated that dabigatran was superior to warfarin in terms of rebleeding from the venipuncture site (20% vs 44%).

It is noteworthy that idarucizumab, a dabigatran-specific reversal agent, is now available in Japan, and can immediately, completely, and sustainably reverse the anticoagulant effect of dabigatran. This may further support the safety of uninterrupted dabigatran as a periprocedural anticoagulation therapy for catheter ablation. Although the incidence of MBE was low with dabigatran treatment, the availability of an antagonistic agent can enhance

TABLE 6 Summary of exposure to study medication in the post-ablation period (ablation set[a])

	Dabigatran 150 mg bid (n = 62)	Warfarin (n = 46)	Total (n = 108)
Post-ablation duration of exposure (days)			
Mean (SD)	60.2 (4.20)	58.1 (9.34)	59.3 (6.92)
Median	60.5	59.0	59.5
Categorized post-ablation duration of exposure, n (%)			
<2 weeks	0 (0.0)	1 (2.2)	1 (0.9)
2 weeks to <4 weeks	0 (0.0)	0 (0.0)	0 (0.0)
4 weeks to <6 weeks	0 (0.0)	0 (0.0)	0 (0.0)
6 weeks to <8 weeks	9 (14.5)	8 (17.4)	17 (15.7)
≥8 weeks	53 (85.5)	37 (80.4)	90 (83.3)

bid, *bis in die* (twice daily); SD, standard deviation.
[a]The ablation set included all randomly assigned patients who had taken at least one dose of trial drug and who had undergone the ablation procedure.

patients' safety and dispel their concerns over the ablation procedure.

The limitations of this study include the small patient numbers in the Japanese population, and the fact that the RE-CIRCUIT trial was an open-label trial. However, endpoints were adjudicated by the trial's independent adjudication committee. Furthermore, while our sample size was too small to enable meaningful statistical analysis, the Japanese subgroup had a similar profile to that of the global population. Therefore, the results support the use of uninterrupted dabigatran treatment during catheter ablation of AF in the Japanese population.

5 | CONCLUSION

This subgroup analysis was not designed to show a statistical difference between the two treatment groups, as this has already been suggested by the results of the main study.[12] However, our results from this Japanese subgroup do support the main study results in that they provide important clinical information regarding MBE, especially cardiac tamponade, in Japanese patients.

ACKNOWLEDGEMENTS

The authors thank all patients involved in this study; Kosuke Ishida, Medicine Department, Biostatistics and Data Sciences, Nippon Boehringer Ingelheim, for undertaking the statistical review; and Daisuke Kuroki, Medicine Department, Clinical Development and Medical Affairs, Nippon Boehringer Ingelheim, for publication management, review, and editorial support. The authors also thank Marion Barnett of Edanz Medical Writing for providing medical writing assistance, which was sponsored by Nippon Boehringer Ingelheim.

CONFLICT OF INTEREST

YY received consulting/lecture fees from Boehringer Ingelheim, Daiichi Sankyo, Pfizer, Bristol-Myers Squibb, and Bayer. MW received consulting/lecture fees from Bayer, Pfizer, Bristol-Myers Squibb, Daiichi Sankyo, Boehringer Ingelheim, Astellas Pharma, Sanofi, Takeda, Ono, Kowa, Taisho Toyama, AstraZeneca, Toa Eiyo, Otsuka, Novartis, and Nippon Shinyaku. WS received consulting/lecture fees and/or research funding from Boehringer Ingelheim, Daiichi Sankyo, Bristol-Myers Squibb, Pfizer, Bayer, and Eisai. KS received consulting/lecture fees and/or research funding from Japan Lifeline, Abbott Japan, Medtronic, Johnson & Johnson, Boehringer Ingelheim, Bristol-Myers Squibb, Bayer, and Biotronik Japan. YI received consulting/lecture fees and/or research funding from Boehringer Ingelheim, Daiichi Sankyo, Pfizer, Bristol-Myers Squibb, and Bayer. MK received consulting/lecture fees from Boehringer Ingelheim, Medtronic, Johnson & Johnson, and Bayer. KO received consulting/lecture fees from Daiichi Sankyo, Bayer, Johnson & Johnson, and Medtronic. KF, YM, MM, and AI have no conflicts of interest to declare. NY and TN are employees of Nippon Boehringer Ingelheim, and MN is an employee of Boehringer Ingelheim.

REFERENCES

1. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of ESC Guidelines for the management of atrial fibrillation – an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Eur Heart J. 2012;33:2719–47.
2. JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). Circ J. 2014;78:1997–2021.
3. Di Biase L, Burkhardt JD, Santangeli P, et al. Periprocedural stroke and bleeding complications in patients undergoing catheter ablation of atrial fibrillation with different anticoagulation management: results from the role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation (AF) Patients Undergoing Catheter Ablation (COMPARE) randomized trial. Circulation. 2014;129:2638–44.
4. Nairooz R, Sardar P, Payne J, et al. Meta-analysis of major bleeding with uninterrupted warfarin compared interrupted warfarin and heparin bridging in ablation of atrial fibrillation. Int J Cardiol. 2015;187:426–9.
5. 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.

6. Wann LS, Curtis AB, January CT, et al., Writing on behalf of the 2006 ACC/AHA/ESC. Guidelines for the Management of Patients with Atrial Fibrillation Writing Committee. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;123:104–23.
7. Wu S, Yang Y, Zhu J, et al. Meta-analysis of efficacy and safety of new oral anticoagulants compared with uninterrupted vitamin K antagonists in patients undergoing catheter ablation for atrial fibrillation. Am J Cardiol. 2016;117:926–34.
8. Cappato R, Marchlinski FE, Hohnloser SH, et al. Uninterrupted rivaroxaban vs. uninterrupted vitamin K antagonists for catheter ablation in non-valvular atrial fibrillation. Eur Heart J. 2015;36:1805–11.
9. Kuwahara M, Abe M, Yamaki M, et al. Apixaban versus warfarin for the prevention of periprocedural cerebral thromboembolism in atrial fibrillation ablation: Multicenter prospective randomized study. J Cardiovasc Electrophysiol. 2016;27:549–54.
10. Murakawa Y, Nogami A, Shoda M, et al. Nationwide survey of catheter ablation for atrial fibrillation: The Japanese Catheter Ablation Registry of Atrial Fibrillation (J-CARAF)-A report on periprocedural oral anticoagulants. J Arrhythm 2015;31:29–32.
11. Okumura K, Aonuma K, Kumagai K, et al. Efficacy and safety of rivaroxaban and warfarin in the perioperative period of catheter ablation for atrial fibrillation – outcome analysis from a prospective multicenter registry study in Japan. Circ J. 2016;80:2295–301.
12. Calkins H, Willems S, Gerstenfeld EP, et al. Uninterrupted dabigatran versus warfarin for ablation in atrial fibrillation. N Engl J Med. 2017;76:1627–36.
13. Hansson L, Hedner T, Dahlöf B. Prospective randomized open blinded end-point (PROBE) study. A novel design for intervention trials. Prospective Randomized Open Blinded End-Point. Blood Press. 1992;1:113–9.
14. Rosendaal FR, Cannegieter SC, van der Meer FJM, et al. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993;69:236–9.
15. Schulman S, Kearon C, on behalf of the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in nonsurgical patients. Scientific and Standardization Committee communication. J Thromb Haemost. 2005; 3:692–4.
16. Nagao T, Inden Y, Shimano M, et al. Feasibility and safety of uninterrupted dabigatran therapy in patients undergoing ablation for atrial fibrillation. Intern Med. 2015;54:1167–73.
17. 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;36:172–9.

How to cite this article: Yoshida Y, Watarai M, Fujii K, et al. Comparison of uninterrupted anticoagulation with dabigatran etexilate or warfarin in the periprocedural period for atrial fibrillation catheter ablation: Results of the Japanese subgroup of the RE-CIRCUIT trial. *J Arrhythmia*. 2018;34:148–157. https://doi.org/10.1002/joa3.12024