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 –

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**Background:** Catheter ablation (CA) is a common treatment for atrial fibrillation (AF). Although rivaroxaban is increasingly used as a substitute for warfarin, its safety and efficacy during CA have not been established in Japanese patients. In the present study we explored the efficacy/safety of rivaroxaban during the CA perioperative period.

**Methods and Results:** We prospectively enrolled Japanese AF patients scheduled for CA who had received either rivaroxaban (rivaroxaban cohort, JACRE-R) or warfarin (warfarin cohort, JACRE-W) during the perioperative period. Primary outcome was a composite of thromboembolism and major bleeding within 30 days after CA. In JACRE-R and JACRE-W, 1,118 (median age, 65 years) and 204 patients (median, 69 years) were enrolled from 42 and 22 institutions, respectively. In JACRE-R, the primary outcome occurred in 7 patients (0.6%), comprising thromboembolism in 2 and major bleeding in 5. Non-major bleeding occurred in 27 patients (2.4%), and the incidence was significantly lower in patients without heparin bridging (n=572) than in those with heparin bridging (n=546). In JACRE-W, the primary outcome occurred in 3 patients (1.5%), all of which were major bleeding. After adjustment for patients’ characteristics, no significant difference was observed between the JACRE-R and JACRE-W cohorts for the primary outcome.

**Conclusions:** The rates of thromboembolism and major bleeding events during the AF ablation perioperative period in Japanese patients treated with rivaroxaban was as low as in those treated with warfarin. (Circ J 2016; 80: 2295–2301)

**Key Words:** Atrial fibrillation; Catheter ablation; Rivaroxaban; Thromboembolism

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Catheter ablation (CA) is now a standard-of-care treatment of drug-refractory atrial fibrillation (AF), but it can be associated with major bleeding and thromboembolic risks. The 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation recommended 3 weeks of systemic anticoagulation prior to the CA procedure and ≥2 months systemic anticoagulation following the procedure. As an optimal anticoagulation regimen, uninterrupted warfarin is widely accepted because it reduces the incidence of both stroke and non-major bleeding compared with interrupted warfarin with heparin bridging. Direct oral anticoagulants (DOACs) have been approved since 2011 for nonvalvular AF (NVAF), and have often been preferred over warfarin because of their efficacy and safety profiles. Several meta-analyses of observational studies and 1 randomized controlled trial of warfarin vs. DOACs in the CA perioperative period have confirmed that DOACs are non-inferior to warfarin in terms of efficacy and are associated with a lower risk of major bleeding. In Japan, it is standard practice to prescribe warfarin for patients scheduled for CA, but rivaroxaban has gained increasing use as an alternative to warfarin. The present study aimed to assess the efficacy and safety of rivaroxaban during the CA perioperative period in Japanese patients.
period have suggested similar safety and efficacy of DOACs to uninterrupted warfarin.\textsuperscript{8,13}

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The incidence of warfarin-induced bleeding, especially intracranial hemorrhage, is known to be higher in East Asians than in the non-East Asians.\textsuperscript{14-17} The dosage of rivaroxaban approved in Japan was reduced to 15 mg once daily because of the smaller body size and higher bleeding risk of Asians. Limited data, however, are available on the efficacy and safety for Japanese patients during the CA perioperative period with the reduced dosage of rivaroxaban approved in Japan. Thus, the current study prospectively enrolled Japanese NVAF patients scheduled for CA and receiving rivaroxaban or warfarin during the perioperative period and performed follow-up evaluation to determine the efficacy/safety of the perioperative dosage.

**Methods**

**Japanese Anti-Coagulation Regimen Exploration in AF Catheter Ablation Registry-Rivaroxaban Cohort (JACRE-R)**

This prospective registry was conducted in 42 Japanese high-volume CA institutions from July 2014 to September 2015 (Appendix S1). The study enrolled consecutive NVAF patients ≥20 years who received rivaroxaban for ≥3 weeks before a scheduled CA and followed them up for 30 days. The exclusion criteria included CA contraindication, history of thromboembolism or myocardial infarction within 2 months of enrollment, contraindication to rivaroxaban, and participation in another clinical study involving intervention. The study protocol was approved by the ethical committees of the participating institutions, and all patients gave written informed consent.

**Perioperative Anticoagulation Management**

The patients received 15 mg of rivaroxaban once daily, or 10 mg once daily when creatinine clearance was 30–49 ml/min. Perioperative rivaroxaban interruption and heparin use was at the investigators’ discretion.

**Ablation Procedures**

The JACRE Registry protocol neither defined nor restricted the ablation procedure or decisions over the interruption of perioperative anticoagulation management. Activated coagulation time was maintained >300 s during the ablation procedure by administering heparin at appropriate doses.

**Efficacy and Safety Endpoints**

Efficacy was evaluated by the incidence of thromboembolic complications, including transient ischemic attack (TIA), cerebral infarction, and other systemic embolisms. Safety was by bleeding complications occurring from CA procedure initiation to 30 days after completion. Major bleeding events were defined as pericardial effusion requiring cardiac drainage (cardiac tamponade), hematoma at the puncture site that required surgical treatment, and other hemorrhagic complications that required transfusion. Non-major bleeding events included complications not requiring invasive treatment. The primary endpoints of this study were a composite of thromboembolism and major bleeding events during follow-up, and the secondary endpoints were thromboembolism, major bleeding, and non-major bleeding.

An adjudication committee, consisting of 2 neurologists and 2 cardiologists independent of the steering committee (K.O., K.A., K.K. and K.H.), the protocol committee (K.I., M.K., Y.M. and E.T.) and Bayer Yakuhin, Ltd, judged the data from the case record forms masked by the primary investigators, and controlled and finally decided the primary and secondary endpoints. On-site sample source data verification was performed for 5% of the JACRE-R patients by professional monitors who were independent of clinical staff.

**JACRE-W (JACRE-Warfarin Cohort)**

This prospective registry involved 22 institutes also participating in JACRE-R from October 2014 to October 2015 (Appendix S1) with a protocol independent from that used in JACRE-R. The study enrolled consecutive NVAF patients who received warfarin for ≥3 weeks before a scheduled CA and were followed up for 30 days. The inclusion and exclusion criteria were the same as for JACRE-R. The prothrombin time-international normalized ratio (PT-INR) was controlled at 2.0–3.0 (or 1.6–2.6 for patients ≥70 years). The efficacy/safety endpoints were the same as for the rivaroxaban cohort. Although these cohorts were not from the same population, they were deemed to reflect the current use of rivaroxaban and warfarin in Japan.

We divided the warfarin cohort into interrupted and uninterrupted arms defined as follows. In the interrupted arm, warfarin administration was interrupted one or a few days before CA to make the PT-INR lower than the therapeutic range while intravenous heparin was continuously administered to keep the activated partial thromboplastin time between 1.5 and 2.0 of the control value (heparin bridging). In the uninterrupted arm, warfarin was continued while maintaining the PT-INR within the therapeutic range.

**Statistical Analysis**

The patients’ characteristics were compared by Pearson’s chi-square test or Fisher’s exact test for nominal variables and the Mann-Whitney U-test for ordered and continuous variables. The incidence of events was compared between groups using the log-rank test. In the comparison of incidence between the rivaroxaban and warfarin cohorts, we found differences in the patients’ characteristics. Thus, propensity scores were developed for clinically relevant items (age, sex, body weight, AF classification, left arterial dimension, antiplatelet use, CHADS\textsubscript{2} score, and HAS-BLED score), which were adjusted. Match-based adjustment predicted a substantial reduction in the number of patients evaluable for statistical analysis because of unmatched pairs. In this statistical analysis, multivariate Cox regression analysis was performed by using the Logit converted propensity score as a covariate, and results were evaluated with an adjusted hazard ratio. The sparseness of events caused a trend towards an unstable statistical model; thus, the assumption used Firth’s penalized likelihood method. The level of significance for all the tests was 2-sided at \( P < 0.05 \). Statistical analyses were carried out using IBM SPSS Statistics 22.0 (International Business Machines Corp, Armonk, New York, NY, USA) and R version 3.0.2 (http://www.R-project.org/; R Foundation for Statistical Computing, Vienna, Austria).

**Results**

**Rivaroxaban Cohort**

A total of 1,118 patients were enrolled in JACRE-R, and of them, 1,113 (99.6%) completed the follow-up. In the remaining 5, rivaroxaban was not resumed postoperatively because of a switch to another agent (n=2), or patient’s request, major bleeding, and death (n=1 of each). The patient who died had suffered from left atrial perforation of a catheter sheath and underwent emergency surgery for hemostatic treatment, which resolved the cardiac tamponade. Nevertheless, 3 days later, the patient developed non-occlusive mesenteric ischemia, leading to death.

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The JACRE-R patients’ baseline characteristics and anticoagulation management are presented in Table 1 and Table 2, respectively. There were 836 men (74.8%), and the median age was 65 years (interquartile range, 57–71). Paroxysmal AF was present in 699 patients (62.5%). Of all patients, 226 (20.2%) had a history of previous AF ablation. Most patients (87.1%) were administered a 15-mg dose rivaroxaban, the standard dose in Japan. Heparin bridging was performed in 546 patients (48.8%): before the procedure in 331 patients (29.6%) and after the procedure in 424 (37.9%).

The incidences of adverse events are shown in Table 3. The composite of thromboembolism and major bleeding occurred in 7 patients (0.6%). Both of the thromboembolic episodes (n=2) were TIA. Major bleeding (n=5) included pericardial effusion (cardiac tamponade) in 4 patients and puncture site hematoma in 1. Non-major bleeding events occurred in 27 patients (2.4%). As shown in Table 4, rivaroxaban was administered to 1,068 patients (95.5%) on the day before (day –1),
This study prospectively evaluated the efficacy/safety of rivaroxaban and warfarin in Japanese AF patients scheduled for CA. As represented by only 2 cases (0.2%) of thromboembolic episodes (TIA) in the entire rivaroxaban cohort (1,118 patients), the incidence of thromboembolism was found to be quite low in the present JACRE-R cohort. Also, the incidence of the major bleeding was low (0.4%). The incidences in the Japanese AF ablation registry (JACRE-W) were also low (0% and 1.5%, respectively). Further, there was no statistical difference in the incidence between the rivaroxaban and uninterrupted warfarin group, no significant differences were detected (Figure B). The event rates were also compared between the rivaroxaban cohort in which rivaroxaban was interrupted for >24 h (ie, the drug was withheld in the morning of the day of CA) and the uninterrupted warfarin cohort, and there were no differences between the 2 groups.

**Discussion**

The rivaroxaban and warfarin cohorts were recruited with independent protocols. As shown in Table 1, there were significant differences in the age, AF duration, prevalence of paroxysmal AF, incidences of heart failure, cardiomyopathy, chronic renal disease, and history of anemia and bleeding between the cohorts. For statistical comparison of the event incidences between cohorts, the patients’ characteristics were adjusted. Figure A shows the adjusted hazard ratios of the incidences of the primary and secondary endpoints, thromboembolism, non-major bleeding, and major bleeding in the rivaroxaban cohort compared with those in the warfarin cohort. None differed significantly between cohorts. When the event rates were compared between the rivaroxaban cohort and the uninterrupted warfarin group, no significant differences were detected (Figure B). The event rates were also compared between the rivaroxaban cohort in which rivaroxaban was interrupted for >24 h (ie, the drug was withheld in the morning of the day of CA) and the uninterrupted warfarin cohort, and there were no differences between the 2 groups.

**Warfarin Cohort**

For JACRE-W, a total of 204 patients were enrolled, and of them, 199 (97.5%) completed the follow-up. Warfarin was not resumed postoperatively in the remaining 5 patients because of a switch to DOAC (n=4) and the possibility of lung cancer treatment (n=1). Warfarin was interrupted before CA in 32 (16%) and not interrupted in the other 172 (84%). The baseline patients’ characteristics and anticoagulation management are presented in Table 1 and Table 2, respectively. There were 142 men (69.6%), and the median age was 69 years (interquartile range, 63–75). Paroxysmal AF was present in 115 patients (56.4%). Of all patients, 56 (27.5%) had a history of previous AF ablation. Heparin bridging was performed in 67 patients (32.8%) before and in 80 (39.2%) after the procedure.

The composite of thromboembolism and major bleeding occurred in 3 patients (1.5%), comprising 1 case each of pericardial effusion, puncture site hematoma and intracranial hemorrhage (Table 5). The secondary endpoints also had low incidence. The incidence of composite thromboembolism and major bleeding did not significantly differ between the uninterrupted and interrupted warfarin groups (Table 5).

**Comparison of Treatment Cohorts**

Data shown as n (%). *Log-rank test.

<table>
<thead>
<tr>
<th>Table 3. Incidence of Each Event in the Rivaroxaban Cohort and in the Subgroups With and Without Heparin Bridging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients (n=1,118)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Composite of thromboembolism and major bleeding</td>
</tr>
<tr>
<td>Thromboembolism</td>
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<tr>
<td>Major bleeding</td>
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<tr>
<td>Non-major bleeding</td>
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</table>

469 (41.9%) on the day of CA (day 0), and 1,094 (97.9%) on the day after CA (day +1). The dosing time on days –1 and +1 was mostly in the morning: in 955 (85.4%) of 1,068 patients on day –1 and in 958 (85.7%) of 1,094 on day +1. The dosing time on day 0 was before CA in 43 (3.8%) of 469 and after CA in the other 426 (38.1%). The 2 patients with thromboembolism were administered rivaroxaban on day –1, and one of them restarted it on day +1, while the other recommenced treatment on day 0 after CA. The 5 patients with major bleeding were administered the drug on day –1, and 2 of them also took it before CA on day 0, while the other 3 did not on day 0. Thus, 2 of 43 patients (4.7%) taking rivaroxaban before CA on day 0 had major bleeding event and one of them underwent an emergency surgery as hemostatic treatment; 3 of 1,075 (0.3%) patients not taking rivaroxaban before CA on day 0 had a major bleeding event (P<0.001).

When comparing the incidence of non-major bleeding between the subgroups with (n=546) and without heparin bridging before or after CA (n=572), it was significantly lower in the subgroup without bridging (Table 3). There was no difference between these subgroups in the incidence of composite thromboembolism and major bleeding. There was no difference in the event rates between the groups administered rivaroxaban at 15 and 10 mg.
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Table 5. Incidence of Each Event in the Warfarin Cohort and in the Subgroups With and Without Interruption

<table>
<thead>
<tr>
<th>Event</th>
<th>All patients (n=204)</th>
<th>Uninterrupted (n=172)</th>
<th>Interrupted (n=32)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of thromboembolism and major bleeding</td>
<td>3 (1.5)</td>
<td>2 (1.2)</td>
<td>1 (3.1)</td>
<td>0.372</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>–</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3 (1.5)</td>
<td>2 (1.2)</td>
<td>1 (3.1)</td>
<td>0.372</td>
</tr>
<tr>
<td>Non-major bleeding</td>
<td>7 (3.4)</td>
<td>5 (2.9)</td>
<td>2 (6.3)</td>
<td>0.313</td>
</tr>
</tbody>
</table>

Data shown as n (%). *Log-rank test.

Figure. Comparison of complications between the rivaroxaban and warfarin cohorts (A) and between the rivaroxaban cohort and uninterrupted warfarin group (B). CI, confidence interval; HR, hazard ratio.

Previous Studies
The prospective, randomized COMPARE study reported that uninterrupted warfarin was associated with reduced incidence of stroke/TIA and non-major bleeding compared with interrupted warfarin with heparin bridging. Other studies also reported better outcomes for uninterrupted warfarin.

As for the effects of DOACs, several retrospective and prospective observational studies have been performed. Hohnloser and Camm performed a meta-analysis of 10 studies of dabigatran, and concluded that dabigatran has similar efficacy and
safety compared with warfarin when used in the CA perioperative period. A more recent meta-analysis, on the other hand, demonstrated fewer thromboembolism events in the uninterrupted warfarin arm during the perioperative period than in the DOAC arm (relative risk [RR], 1.89) and fewer all bleeding events in the DOAC arm (RR: 0.78). 8 VENTURE-AF, a multicenter randomized study, showed that uninterrupted rivaroxaban was feasible and the incidence was comparable to uninterrupted warfarin administration. 13 Today, a DOAC is thought to be a reasonable option for perioperative oral anticoagulant; however, there have been few reports indicating efficacy and safety of perioperative rivaroxaban at a reduced dosage in East Asian populations who are known to have a higher risk of bleeding complications. 21

Efficacy/Safety of Perioperative Rivaroxaban
In the present rivaroxaban cohort, most (95%) patients received the drug on the days before (day −1) and after CA (day +1), and 41.9% on the day of CA (day 0). The dosing time on days −1 and +1 was mostly (85%) in the morning, which is common for once-a-day drugs in Japan, but on day 0 it was mostly after CA. Because most of the present patients did not receive rivaroxaban before CA on day 0, the drug was withheld for at least 24 h of the beginning of the CA procedure. However, only 2 patients (0.2%) experienced thromboembolic events (TIA). A recent report from the Japanese Catheter Ablation Registry of AF (J-CARAF) showed that the incidence of post-procedural stroke/TIA was 0.3% (10 of 3,373 patients) for 3 survey periods in 2,011 and 2,012 during which warfarin was the dominant oral anticoagulant. 22 Recent prospective multicenter studies using uninterrupted rivaroxaban in the CA perioperative period reported 0.3% (1 of 321 patients) 23 and 0% (0 of 124 patients) 24 for thromboembolic events. The present result was comparable with those recent reports. It therefore seems to be appropriate to administer rivaroxaban in the morning of day −1, and resume it after CA on day 0 or in the morning of day +1.

Major bleeding occurred in 5 (0.4%) of the 1,118 patients, including 4 cases of cardiac tamponade (0.36%). J-CARAF reported that the incidence of pericardial effusion requiring drainage was 1.3% (43 of 3,373 patients), 22 which was similar to the incidence (1.31%) reported by the Updated Worldwide Survey. 23 Thus, the incidence of major bleeding in the present rivaroxaban cohort was low; in particular, those who did not take rivaroxaban before CA on day 0, the incidence of major bleeding was 0.3% (3 of 1,075).

Approximately one-half of the rivaroxaban cohort was treated with heparin bridging before and/or after CA. Heparin bridging was associated with increased non-major bleeding events, although there was no difference in the incidence of composite thromboembolism and major bleeding between the groups with and without heparin bridging. Some recent reports claim that heparin bridging may induce risks of bleeding and adverse events in patients with interrupted warfarin. 24-26 In patients with interrupted dabigatran for a procedure or surgery, use of heparin bridging anticoagulation increased the risk for major bleeding in the RE-LY trial. 27 Thus, heparin bridging before or after AF ablation procedure should be avoided or only performed in patients with a high risk for thromboembolism.

Comparison of Rivaroxaban and Warfarin Cohorts
The incidence of the composite of thromboembolism and major bleeding was 0.6% in the rivaroxaban and 1.5% in the warfarin cohort. Lakireddy et al showed a 2.5% and 1.9% incidence in their warfarin and rivaroxaban groups, respectively. 12

Providência et al showed respective incidences of 6.3% and 2.7%. 28 The results observed in this study may be comparable to or lower than those previous studies. 19,28

Direct comparison of the incidence in the present 2 cohorts cannot be made appropriately because of differences in the baseline patients’ characteristics (Table 1) and the number of the patients. We therefore adjusted the characteristics and found no significant differences between cohorts (Figure). The rivaroxaban group showed comparable efficacy and safety with not only the entire warfarin group but also the uninterrupted warfarin group. Recent studies reported that uninterrupted dabigatran, 29,30 rivaroxaban, 19,28 and apixaban 31 regimens can achieve similar effectiveness and safety as the uninterrupted warfarin regimen.

Study Limitations
The present study had 2 cohorts, rivaroxaban and warfarin, and did not randomly assign patients to one of the drugs before CA. To minimize the selection bias, consecutive patients receiving rivaroxaban or warfarin before CA were enrolled. However, some of the baseline characteristics were different between the cohorts (Table 1). Further, the number of patients enrolled was different between them (1,118 vs. 204). This was largely because of progressive reduction in the use of warfarin for patients undergoing AF ablation after the launch of DOACs in Japan. These differences in the baseline characteristics and number of patients might significantly affect interpretation of the results. Another limitation was the diverse dosing patterns of rivaroxaban. Most of the patients enrolled, however, were administered rivaroxaban in accordance with the common dosing pattern in Japan, that is, dosing a once-a-day drug in the morning. Our results seem to reflect the real-world efficacy/safety of rivaroxaban in the CA perioperative period. The study was conducted in the 42 high-volume institutions in Japan where the perioperative major complications were expected to occur at a decreased incidence. The low incidence of major complications may be partly explained by excellent technical experience with the CA procedure.

Conclusions
Perioperative anticoagulation management using rivaroxaban with the last dose 24 h prior to the procedure and with the dose resumed after the procedure or the next morning was found to be effective and safe in a Japanese population.

Acknowledgment
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Disclosures
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References
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Supplementary Files
Appendix S1. Participating Institutions and Investigators

Please find supplementary file(s)