Beneficial Effect of Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation
– Results of the J-RHYTHM Registry 2 –
Eitaro Kodani, MD, PhD; Hirotsugu Atarashi, MD, PhD; Hiroshi Inoue, MD, PhD; Ken Okumura, MD, PhD; Takeshi Yamashita, MD, PhD; Hideki Origasa, PhD
on behalf of the J-RHYTHM Registry Investigators

**Background:** The J-RHYTHM Registry 2 was a multicenter, prospective observational study that extended the follow-up period of the J-RHYTHM Registry in order to investigate long-term outcomes and effects of non-vitamin K antagonist oral anticoagulants (NOACs) in Japanese patients with atrial fibrillation (AF).

**Methods and Results:** Among 6,616 patients with nonvalvular AF (NVAF) (men 71.0%, 69.7±9.9 years, CHADS\textsubscript{2} score 1.7±1.2), event rates were compared among patients receiving warfarin (n=3,964), NOACs (n=923), and no anticoagulation therapy (No-OAC, n=753) at the end of follow-up, except for 976 patients lacking anticoagulant data. During the 5-year follow-up period, thromboembolism occurred in 196 (4.9%), 19 (2.1%), and 45 (6.0%) patients, respectively; major hemorrhage in 233 (5.9%), 22 (2.4%), and 36 (4.8%); all-cause death in 230 (5.8%), 13 (1.4%), and 105 (13.9%), (P<0.001 for each). After adjusting for the components of the CHA\textsubscript{2}-DS\textsubscript{2}-VASc score and antiplatelet drug use, the odds ratio (OR) in the Warfarin group was significantly lower for all-cause death compared with that in the No-OAC group (OR 0.30, 95% confidence interval [CI] 0.23–0.39, P<0.001), whereas ORs in the NOACs group were significantly lower for all events (OR 0.42, 95% CI 0.24–0.74, P=0.003 for thromboembolism; OR 0.53, 95% CI 0.31–0.93, P=0.027 for major hemorrhage; and OR 0.10, 95% CI 0.06–0.18, P<0.001 for all-cause death, respectively).

**Conclusions:** NOACs could be beneficial for reducing event rates of all types in Japanese NVAF patients. (Circ J 2016; 80: 843–851)

**Key Words:** Anticoagulation; Atrial fibrillation; J-RHYTHM Registry; Non-vitamin K antagonist oral anticoagulants (NOACs); Warfarin

Atrial fibrillation (AF) is a potent risk factor for cardioembolic stroke by 60–70%.

Because oral anticoagulation (OAC) therapy can reduce the risk of AF-related ischemic stroke by 60–70%, vitamin K antagonists, mainly warfarin, have been used worldwide for more than 50 years. In order to investigate appropriate warfarin-based anticoagulation therapy for prevention of stroke in Japanese patients with AF, we previously conducted the J-RHYTHM Registry, which included more than 7,000 patients with AF.

The status of anticoagulation therapy and the 2-year incidence of events in Japanese AF patients have been reported. We demonstrated that more than 85% of AF patients were taking warfarin and the controlled international normalized ratio of prothrombin time (PT-INR) was slightly lower than the 2.0–3.0 recommended for management of AF in Western countries.

PT-INR of 1.6–2.5 may be optimal for preventing thromboembolism without increasing major hemorrhage in Japanese AF patients, even those with valvular AF, prior stroke or transient ischemic.
was selected as the safety endpoint. All-cause and cardiovascular deaths were also determined. Information on event type and antithrombotic therapy, including anticoagulant and antiplatelet drugs, were obtained for any event that occurred during the follow-up period. The diagnostic criteria for each event have been described elsewhere.

Patient Groupings
To clarify the event rates in patients receiving NOACs, the patients were divided into 3 groups according to the final status of anticoagulation therapy at the time of the event or at the end of follow-up: patients taking warfarin (Warfarin group), any NOAC (NOACs group), and no anticoagulant (No-OAC group). Event rates were compared among these 3 groups. In addition, event rates in subgroups based on the final status of antiplatelet therapy in each group were determined. Event rates according to the baseline PT-INR value (<1.6, 1.6–1.99, 2.0–2.59, 2.6–2.99, and ≥3.0) in patients who continued warfarin throughout the follow-period were also evaluated as reported previously.

Statistical Analysis
Data are presented as mean ± standard deviation (SD). The statistical significance of differences in the mean values was analyzed using Student’s t-test or analysis of variance (ANOVA), as appropriate. Frequencies of parameters or events were compared using chi-square or Fisher’s exact test, as appropriate. Kaplan-Meier curves for time to events were compared with log-rank tests. A Cox proportional hazard model was used to investigate the influence of warfarin therapy. Odds ratios (ORs) for each event in the Warfarin and NOACs groups were calculated by multivariate logistic regression analysis adjusted for the components of the CHA2DS2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, history of ischemic stroke or TIA, vascular disease [coronary artery disease], age 65–74 years, and female sex) and antiplatelet use, using the No-OAC group as a reference. Two-sided P-values <0.05 were considered statistically significant. All statistical analyses were performed with the IBM SPSS.
Statistics for Windows, version 23.0 (IBM Corp, Armonk, NY, USA).

Results

Of the 7,027 patients with AF who had been enrolled in this extended study, 364 were excluded for valvular AF, including mitral stenosis and/or mechanical prosthetic valves. Of the remaining 6,663 patients with NVAF, 47 (0.7%) were lost to follow-up. Therefore, a total of 6,616 patients with NVAF were included in the analyses (Figure 1).

Baseline Characteristics and Antithrombotic Therapy

The baseline characteristics of the patients and their antithrombotic therapy at baseline in the 3 groups are shown in Table 1. Mean age, CHADS2 score, and prevalence of permanent AF, coronary artery disease, cardiomyopathy, and heart failure were significantly different among the 3 groups, with the lowest CHADS2 score (1.4±1.1) in the NOACs group (Table 1). The frequency of baseline warfarin therapy was, of course, highest (95.5%) in the Warfarin group. By contrast, antiplatelet use was most frequent at baseline in the No-OAC group, and 332 patients (44.1%) in this group discontinued warfarin because of any reason. In the NOACs group, 776 patients (84.1%) switched from warfarin, while 147 (15.9%) newly started anticoagulation therapy with NOAC during the extended follow-up period (Table 1). Consequently, 3,786 patients who were taking warfarin at baseline continued warfarin and 421 patients did not receive any anticoagulation therapy throughout the follow-up period. The characteristics of these 4,207 patients are shown in Table S1.
Event Rates and Final Anticoagulation Therapy

During the 5-year follow-up period (median 1,935 days, 28,933 person-years), thromboembolic events occurred in 271 patients (4.1%), major hemorrhage in 303 (4.6%), and all-cause death in 430 (6.5%), including cardiovascular death in 115 (1.7%) (Table 3). The overall incidence rate of each event was 0.9, 1.0, 1.5, and 0.4/100 person-years, respectively.

Event rates in the 3 groups according to the final anticoagulation therapy are shown in Table 3. There were significant differences in all events among the groups (P<0.001 for each, Table 3). Notably, all event rates in the NOACs group were lower than those in the No-OAC and Warfarin groups. There were no significant differences in the event rates among the 3 NOAC groups (Table 3). When patients were divided into 2 subgroups according to the final status of antiplatelet therapy, antiplatelet use did not influence any event rate in the NOACs group (Figure 2). Unexpectedly, antiplatelet use was associated

Changes in Antithrombotic Therapy During Follow-up

During the 3-year extended follow-up period, NOAC use increased year by year, in parallel with decreasing warfarin use. In the last follow-up year (2014), the frequency of NOAC use was 20% among 4,404 patients. Rivaroxaban was administered most frequently, followed by dabigatran and apixaban (Table 2). No patient was receiving edoxaban at the end of the follow-up period in 2014. Finally, as shown in Table 1 and Table 2, 3,964 (59.9%) of 6,616 patients were taking warfarin (Warfarin group), while 923 (14.0%) received any NOAC at the time of an event or at the end of the follow-up period (NOACs group). In contrast, 753 (11.4%) were not on any anticoagulation therapy (No-OAC group). Unfortunately, information regarding anticoagulation therapy at the time of an event or at the end of follow-up was lacking in 976 patients (Table 2); these patients were therefore excluded from the subsequent analysis.

Changes in Antithrombotic Therapy During Follow-up

During the 3-year extended follow-up period, NOAC use increased year by year, in parallel with decreasing warfarin use. In the last follow-up year (2014), the frequency of NOAC use was 20% among 4,404 patients. Rivaroxaban was administered most frequently, followed by dabigatran and apixaban (Table 2). No patient was receiving edoxaban at the end of the follow-up period in 2014. Finally, as shown in Table 1 and Table 2, 3,964 (59.9%) of 6,616 patients were taking warfarin (Warfarin group), while 923 (14.0%) received any NOAC at the time of an event or at the end of the follow-up period (NOACs group). In contrast, 753 (11.4%) were not on any anticoagulation therapy (No-OAC group). Unfortunately, information regarding anticoagulation therapy at the time of an event or at the end of follow-up was lacking in 976 patients (Table 2); these patients were therefore excluded from the subsequent analysis.

Changes in Antithrombotic Therapy During Follow-up

During the 3-year extended follow-up period, NOAC use increased year by year, in parallel with decreasing warfarin use. In the last follow-up year (2014), the frequency of NOAC use was 20% among 4,404 patients. Rivaroxaban was administered most frequently, followed by dabigatran and apixaban (Table 2). No patient was receiving edoxaban at the end of the follow-up period in 2014. Finally, as shown in Table 1 and Table 2, 3,964 (59.9%) of 6,616 patients were taking warfarin (Warfarin group), while 923 (14.0%) received any NOAC at the time of an event or at the end of the follow-up period (NOACs group). In contrast, 753 (11.4%) were not on any anticoagulation therapy (No-OAC group). Unfortunately, information regarding anticoagulation therapy at the time of an event or at the end of follow-up was lacking in 976 patients (Table 2); these patients were therefore excluded from the subsequent analysis.

Changes in Antithrombotic Therapy During Follow-up

During the 3-year extended follow-up period, NOAC use increased year by year, in parallel with decreasing warfarin use. In the last follow-up year (2014), the frequency of NOAC use was 20% among 4,404 patients. Rivaroxaban was administered most frequently, followed by dabigatran and apixaban (Table 2). No patient was receiving edoxaban at the end of the follow-up period in 2014. Finally, as shown in Table 1 and Table 2, 3,964 (59.9%) of 6,616 patients were taking warfarin (Warfarin group), while 923 (14.0%) received any NOAC at the time of an event or at the end of the follow-up period (NOACs group). In contrast, 753 (11.4%) were not on any anticoagulation therapy (No-OAC group). Unfortunately, information regarding anticoagulation therapy at the time of an event or at the end of follow-up was lacking in 976 patients (Table 2); these patients were therefore excluded from the subsequent analysis.

Changes in Antithrombotic Therapy During Follow-up

During the 3-year extended follow-up period, NOAC use increased year by year, in parallel with decreasing warfarin use. In the last follow-up year (2014), the frequency of NOAC use was 20% among 4,404 patients. Rivaroxaban was administered most frequently, followed by dabigatran and apixaban (Table 2). No patient was receiving edoxaban at the end of the follow-up period in 2014. Finally, as shown in Table 1 and Table 2, 3,964 (59.9%) of 6,616 patients were taking warfarin (Warfarin group), while 923 (14.0%) received any NOAC at the time of an event or at the end of the follow-up period (NOACs group). In contrast, 753 (11.4%) were not on any anticoagulation therapy (No-OAC group). Unfortunately, information regarding anticoagulation therapy at the time of an event or at the end of follow-up was lacking in 976 patients (Table 2); these patients were therefore excluded from the subsequent analysis.

Changes in Antithrombotic Therapy During Follow-up

During the 3-year extended follow-up period, NOAC use increased year by year, in parallel with decreasing warfarin use. In the last follow-up year (2014), the frequency of NOAC use was 20% among 4,404 patients. Rivaroxaban was administered most frequently, followed by dabigatran and apixaban (Table 2). No patient was receiving edoxaban at the end of the follow-up period in 2014. Finally, as shown in Table 1 and Table 2, 3,964 (59.9%) of 6,616 patients were taking warfarin (Warfarin group), while 923 (14.0%) received any NOAC at the time of an event or at the end of the follow-up period (NOACs group). In contrast, 753 (11.4%) were not on any anticoagulation therapy (No-OAC group). Unfortunately, information regarding anticoagulation therapy at the time of an event or at the end of follow-up was lacking in 976 patients (Table 2); these patients were therefore excluded from the subsequent analysis.

Changes in Antithrombotic Therapy During Follow-up

During the 3-year extended follow-up period, NOAC use increased year by year, in parallel with decreasing warfarin use. In the last follow-up year (2014), the frequency of NOAC use was 20% among 4,404 patients. Rivaroxaban was administered most frequently, followed by dabigatran and apixaban (Table 2). No patient was receiving edoxaban at the end of the follow-up period in 2014. Finally, as shown in Table 1 and Table 2, 3,964 (59.9%) of 6,616 patients were taking warfarin (Warfarin group), while 923 (14.0%) received any NOAC at the time of an event or at the end of the follow-up period (NOACs group). In contrast, 753 (11.4%) were not on any anticoagulation therapy (No-OAC group). Unfortunately, information regarding anticoagulation therapy at the time of an event or at the end of follow-up was lacking in 976 patients (Table 2); these patients were therefore excluded from the subsequent analysis.

Changes in Antithrombotic Therapy During Follow-up

During the 3-year extended follow-up period, NOAC use increased year by year, in parallel with decreasing warfarin use. In the last follow-up year (2014), the frequency of NOAC use was 20% among 4,404 patients. Rivaroxaban was administered most frequently, followed by dabigatran and apixaban (Table 2). No patient was receiving edoxaban at the end of the follow-up period in 2014. Finally, as shown in Table 1 and Table 2, 3,964 (59.9%) of 6,616 patients were taking warfarin (Warfarin group), while 923 (14.0%) received any NOAC at the time of an event or at the end of the follow-up period (NOACs group). In contrast, 753 (11.4%) were not on any anticoagulation therapy (No-OAC group). Unfortunately, information regarding anticoagulation therapy at the time of an event or at the end of follow-up was lacking in 976 patients (Table 2); these patients were therefore excluded from the subsequent analysis.

Changes in Antithrombotic Therapy During Follow-up

During the 3-year extended follow-up period, NOAC use increased year by year, in parallel with decreasing warfarin use. In the last follow-up year (2014), the frequency of NOAC use was 20% among 4,404 patients. Rivaroxaban was administered most frequently, followed by dabigatran and apixaban (Table 2). No patient was receiving edoxaban at the end of the follow-up period in 2014. Finally, as shown in Table 1 and Table 2, 3,964 (59.9%) of 6,616 patients were taking warfarin (Warfarin group), while 923 (14.0%) received any NOAC at the time of an event or at the end of the follow-up period (NOACs group). In contrast, 753 (11.4%) were not on any anticoagulation therapy (No-OAC group). Unfortunately, information regarding anticoagulation therapy at the time of an event or at the end of follow-up was lacking in 976 patients (Table 2); these patients were therefore excluded from the subsequent analysis.
Event Rates and Long-Term Warfarin Therapy

The 5-year incidence rates of thromboembolism and all-cause death were significantly lower in the 3,786 patients who continued warfarin therapy throughout the study compared with the 421 patients who did not receive any anticoagulation therapy (5.0% vs. 7.8%, P=0.021 and 5.8% vs. 10.2%, P<0.001, respectively). The incidence of major hemorrhage was higher in patients on warfarin therapy compared with those in the No-OAC group (5.9% vs. 2.6%, P=0.007) (Table S2). The Kaplan-Meier curves for these patients are shown in Figure 3.
Event-free rates of thromboembolism and all-cause death were significantly higher in patients on continuous warfarin therapy than in those without any OAC (P=0.002 and P<0.001, respectively, by log-rank test), whereas the event-free rate of major hemorrhage was lower in patients on continuous warfarin therapy than in those without any OAC (P=0.024 by log-rank test) (Figure 3).

Rates of thromboembolism decreased (P=0.006 for trend), but those of major hemorrhage increased (P<0.001 for trend) along with an increase in PT-INR values at baseline in the

---

**Table 4. Adjusted ORs for Events**

<table>
<thead>
<tr>
<th>Final status of OAC</th>
<th>No-OAC (reference)</th>
<th>Warfarin</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>NOACs</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism</td>
<td>1.00</td>
<td>0.90 (0.64–1.28)</td>
<td>0.553</td>
<td>0.42 (0.24–0.74)</td>
<td>0.003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>1.00</td>
<td>1.20 (0.83–1.73)</td>
<td>0.343</td>
<td>0.53 (0.31–0.93)</td>
<td>0.027</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolism+major hemorrhage</td>
<td>1.00</td>
<td>1.03 (0.79–1.34)</td>
<td>0.816</td>
<td>0.45 (0.30–0.68)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>1.00</td>
<td>0.30 (0.23–0.39)</td>
<td>&lt;0.001</td>
<td>0.10 (0.06–0.18)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>1.00</td>
<td>0.44 (0.27–0.70)</td>
<td>0.001</td>
<td>0.12 (0.04–0.40)</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ORs are adjusted for the components of the CHA2DS2-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, history of stroke or transient ischemic attack, vascular disease [coronary artery disease], age 65–74 years, and female sex) and antiplatelet use. CI, confidence interval; OR, odds ratio. Other abbreviations as in Table 1.

**Figure 3.** Kaplan-Meier curves for thromboembolism (A), major hemorrhage (B), all-cause death (C), and cardiovascular death (D) in 3,786 patients on continuous warfarin therapy and in 421 patients without any OAC treatment throughout the follow-up period. Insets show the magnified event-free curves with a 10-fold scale. See text for details. P-values: comparisons between patients with warfarin and without any OAC by log-rank test. OAC, oral anticoagulant.
Discussion

The major findings of the present study were as follows. First, the overall incidence of each event was quite low for the 5-year follow-up period in Japanese patients with NVAF. Second, all event rates in the NOACs group were extremely low compared with those in the No-OAC and Warfarin groups. In addition, NOAC use was an independent factor for reduction of all events. Third, the beneficial effects of warfarin lasted for 5 years when event rates were analyzed in patients who did not change anticoagulation therapy throughout the follow-up period (continuous Warfarin vs. continuous NOAC). Long-term warfarin therapy was effective at preventing thromboembolism, but was associated with an increased incidence of major hemorrhage. Fourth, the incidence of thromboembolism decreased, but that of major hemorrhage increased along with an increase in baseline PT-INR values compared with those for the No-OAC patients.

Effectiveness of NOACs

In the present study, all event rates in the NOACs group were extremely low compared with those in the Warfarin group. After their approval for clinical use, several real-world reports on NOACs have been published. In a recent report from Hong Kong, the incidence of stroke and intracranial hemorrhage was 2.24 and 0.32/100 person-years, respectively, in 8,754 Chinese patients administered dabigatran. Another study from the United States, using Medicare data from 134,414 patients on dabigatran, reported the incidence of ischemic stroke and major hemorrhage as 1.13 and 4.27/100 person-years, respectively. In the Xarelto® for Prevention of Stroke in Patients with Atrial Fibrillation (XANTUS) study, the rates of these events in 6,784 patients, mostly European, on rivaroxaban therapy were 0.7 and 2.1/100 person-years, respectively. In other recent reports on rivaroxaban from the Dresden NOAC registry of 1,776 patients and real-world outcomes in the USA of 27,467 patients, the incidence of major hemorrhage was 3.1 and 2.86/100 person-years, respectively. In contrast, in the present study the overall rate of thromboembolism and major hemorrhage was 0.9 and 1.0/100 person-years, respectively, and those in the NOACs group were further lower. In addition, the incidence of major hemorrhage was rather higher in the No-OAC group than in the NOACs group (Table 3). Antiplatelet drug use was not the reason, because antiplatelet drugs were generally administered to patients who had any comorbidities such as a history of stroke/TIA, coronary artery disease, and/or other atherosclerotic diseases, thereby resulting in increased event rates in patients receiving antiplatelet drugs. It was difficult to rule out the possibility that the differences in potential bleeding risk, observation period, and unmeasured confounding factors between the NOAC and NOACs groups could have influenced the higher incidence of major hemorrhage in the No-OAC group, despite the OR for major hemorrhage being significantly lower in the NOAC group in contrast to that of thromboembolism (Figures 2A-B). It was difficult to rule out the possibility that the differences in potential bleeding risk, observation period, and unmeasured confounding factors between the NOAC and NOACs groups could have influenced the higher incidence of major hemorrhage in the No-OAC group, despite the OR for major hemorrhage being significantly lower in the NOACs group after adjusting for known confounding factors (Table 4). By contrast, the incidence of thromboembolism was higher in patients with than in those without taking antiplatelet drugs in the No-OAC and Warfarin groups (Figure 2A). All-cause and cardiovascular mortality rates were also higher in patients taking antiplatelet drugs in the Warfarin group (Figures 2C-D). We do not have a plausible explanation for these unexpected findings. A possible explanation is that antiplatelet drugs were generally administered to patients who had any comorbidities such as a history of stroke/TIA, coronary artery disease, and/or other atherosclerotic diseases, thereby resulting in increased event rates in patients receiving antiplatelet therapy.
The present study extended the follow-up period to investigate the long-term effects of warfarin therapy. Anticoagulation therapies were changed in more than 1,000 patients during the extended follow-up period (Table 3). One possible explanation for this observation was that warfarin was switched to NOAC, especially in low-risk patients in good clinical condition, since the risk for thromboembolism in the NOACs group was lower than that in the Warfarin group (Table 1). The present study extended the follow-up period to investigate the long-term effects of warfarin therapy. Anticoagulation therapies were changed in more than 1,000 patients during the extended follow-up period (Tables 1, 2). It therefore became more difficult to clearly determine the long-term effects of warfarin based on the baseline status of warfarin therapy. Therefore, we compared event rates and time-to-event curves in the limited number of patients who did not change anticoagulation therapy from baseline to the end of follow-up (ie, 3,786 patients with continuous warfarin and 421 without any anticoagulation therapy throughout the study period). As shown in Figure 3 and Table S2, the beneficial effects of warfarin to prevent thromboembolism lasted for 5 years. However, long-term use of warfarin was associated with an increasing incidence of major hemorrhage. Although these results were consistent with our previous report, they differed from the 1-year outcomes of the Fushimi AF Registry, in which anticoagulation therapy did not affect the incidence of either thromboembolism or major hemorrhage. This discrepancy could be explained by differences between study populations rather than follow-up period. In contrast to the J-RHYTHM Registry, the Fushimi AF Registry included a large number of patients from general hospitals in an urban community.

The results of the present study revealed that the baseline PT-INR level still influenced the incidence of thromboembolism and major hemorrhage (Figure S1), even after adjusting for multiple confounding factors (Figure 4). Importantly, the adjusted HRs for thromboembolism were significantly lower in all PT-INR subgroups, while those for major hemorrhage were significantly higher for PT-INR values ≥2.6 compared with the reference group not receiving any anticoagulation therapy. These results support our previous reports on target INR values in the J-RHYTHM Registry.11,12

Study Limitations

First, this registry study was performed in a single country and subjects were enrolled from 131 selected institutions in Japan. The clinical backgrounds of the patients in this registry may not be extrapolated to a general Japanese patient population with NVAF because most of the participating physicians and institutions specialized in cardiology. Second, although the original J-RHYTHM Registry started with 7,937 patients, the number of patients participating in the extended follow-up decreased to 6,616 patients with NVAF. Additionally, 976 patients were lacking data regarding anticoagulation status at the end of the study; therefore only 5,640 patients were available for on-treatment analysis at the end of follow-up. Third, the quality of warfarin therapy was evaluated using only baseline PT-INR values. Because PT-INR values were not recorded during each visit during the extended follow-up period, neither time in the therapeutic range (TTR) nor the intensity of anticoagulation during the extended follow-up period was determined in the present study. The TTR according to the Japanese guidelines34 was 59.3±29.2% in the first 2 years of the J-RHYTHM Registry.11,12 Finally, although we found that event rates in the NOACs group were quite low, the selection of antithrombotic drugs was not randomized, because of the observational nature of the study. In addition, the number of patients in the NOACs group was relatively small (n=923) and the follow-up period after starting NOACs was shorter than that for patients who continued to take warfarin. Further observations with larger real-world populations and longer follow-up periods are necessary to clarify the efficacy and safety of NOACs among Japanese patients with NVAF.

Conclusions

In Japanese NVAF patients, long-term use of warfarin may be beneficial for preventing thromboembolism at the expense of major hemorrhage. In contrast, NOAC use could be beneficial for reducing event rates of all types.

Disclosures

The J-RHYTHM registry and the J-RHYTHM registry 2 were supported by grants from the Japan Heart Foundation (12080025 and 12110015). This research is partially supported by the Practical Research Project for Life-Style related Diseases including Cardiovascular Diseases and Diabete Mellitus from the Japan Agency for Medical Research and Development (AMED, 15656344). The following co-authors have potential conflicts of interest: H.A. has received research funding from Boehringer Ingelheim, and remuneration from Bayer Healthcare, Boehringer Ingelheim, and Daiichi-Sankyo; H.I. has received research funding from Boehringer Ingelheim and Daiichi-Sankyo, and remuneration from Daiichi-Sankyo, Bayer Healthcare, and Boehringer Ingelheim; K.O. has received research funding from Boehringer Ingelheim and Daiichi-Sankyo, and remuneration from Boehringer Ingelheim, Bayer Healthcare, Daiichi-Sankyo, and Pfizer; T.Y. has received research funding from Daiichi-Sankyo, Bayer, Bristol-Meyers Squibb and remuneration from Nippon Boehringer, Bristol-Myers Squibb, Pfizer, Bayer, Daiichi-Sankyo, Tanabe-Mitsubishi, Ono Pharmaceutical, Eisai and Toa-Eiyo; H.O. has received lecture fees from Daiichi-Sankyo.

Acknowledgments

The present study was presented in part at the 80th Annual Scientific Meeting of the Japanese Circulation Society (Sendai, Japan, March 18, 2016). Executive Committee of the J-RHYTHM Registry 2 comprised Okumura K, Inoue H, Atarashi H, and Yamashita T. Local Executive Committee was as follows: Sakurai M, Kawamura Y (Hokkaido); Okumura K, Kobuta I (Tohoku); Kaneko Y, Matsumoto K (North Kanto); Ogasawara S, Atarashi H, Yamashita T (South Kanto); Inoue H, Chinsuhi M (Hokkaido); Kodama I, Watanabe E (Chiba); Kurotsune Y, Okumura Y (Kansai); Shimizu A, Adachi M (Chugoku); Bando S, Fukatani M (Shikoku); Saikawa T, Chishaki A (Kyushu). Statistical advisor: Otogasa H. Other investigators are listed in references 6 and 35.

References
