Target International Normalized Ratio Values for Preventing Thromboembolic and Hemorrhagic Events in Japanese Patients With Non-Valvular Atrial Fibrillation – Results of the J-RHYTHM Registry –

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**Background:** Target anticoagulation levels for warfarin in Japanese patients with non-valvular atrial fibrillation (NVAF) are unclear.

**Methods and Results:** Of 7,527 patients with NVAF, 1,002 did not receive warfarin (non-warfarin group), and the remaining patients receiving warfarin were divided into 5 groups based on their baseline international normalized ratio (INR) of prothrombin time ($\leq 1.59$, $1.6-1.99$, $2.0-2.59$, $2.6-2.99$, and $\geq 3.0$). Patients were followed-up prospectively for 2 years. Primary endpoints were thromboembolic events (cerebral infarction, transient ischemic attack, and systemic embolism), and major hemorrhage requiring hospital admission. During the follow-up period, thromboembolic events occurred in 3.0% of non-warfarin group, but at lower frequencies in the warfarin groups (2.0, 1.3, 1.5, 0.6, and 1.8%/2 years for INR values of $\leq 1.59$, $1.6-1.99$, $2.0-2.59$, $2.6-2.99$, and $\geq 3.0$, respectively; $P=0.0059$). Major hemorrhage occurred more frequently in warfarin groups (1.5, 1.8, 2.4, 3.3, and 4.1% for INR values $\leq 1.59$, $1.6-1.99$, $2.0-2.59$, $2.6-2.99$, and $\geq 3.0$, respectively; $P=0.0041$) than in non-warfarin group (0.8%/2 years). These trends were maintained when the analyses were confined to patients aged $\geq 70$ years.

**Conclusions:** An INR of 1.6–2.6 is safe and effective at preventing thromboembolic events in patients with NVAF, particularly patients aged $\geq 70$ years. An INR of 2.6–2.99 is also effective, but associated with a slightly increased risk in major hemorrhage. (UMIN Clinical Trials Registry UMIN000001569)

**Key Words:** Atrial fibrillation; Hemorrhage; International normalized ratio; Thromboembolism; Warfarin
Anticoagulation treatment with warfarin is effective at preventing ischemic stroke and peripheral embolism in patients with atrial fibrillation (AF). The guidelines used in Western countries for the management of AF recommend target anticoagulation levels, as measured by the international normalized ratio (INR) of prothrombin time, of 2–3. The investigators in the ATRIA study reported that a target INR of between 2 and 3 is optimal for preventing thromboembolic and hemorrhagic events in patients with non-valvular AF (NVAF). In the present analysis of the J-RHYTHM Registry, target INR values for preventing both thromboembolic and hemorrhagic events in patients with NVAF were determined.

Methods

The details of the study design and the subjects’ baseline characteristics have been reported elsewhere. Briefly, consecutive AF patients were recruited at the outpatient clinic of each participating institution. All participating physicians were cardiologists who had been selected by the local members of the Steering Committee of the J-RHYTHM Registry. To avoid particular geographic regions being over- or underrepresented among the study population, enrollment targets that reflected the population densities of 10 geographical regions of Japan were set. The antithrombotic drugs and their dosages were selected by the participating physicians. A total of 7,937 AF patients (mean age, 69.7 years) were enrolled in the J-RHYTHM Registry. Of these, 410 patients had mitral stenosis or had undergone mechanical valve replacement, and so the remaining 7,527 patients with NVAF comprised the present study group.

The patients were followed for 2 years or until an endpoint occurred. The endpoints consisted of thromboembolic events, including symptomatic cerebral infarction (Cl), transient ischemic attack (TIA), and systemic embolism; major hemorrhage requiring hospital admission; and death. The diagnostic criteria for Cl and TIA have been reported previously.

Statistical Analysis

Data are presented as percentage or mean±SD values. The patients in the warfarin group were divided into subgroups according to their baseline antithrombotic therapy status and baseline INR values (≤1.59, 1.6–1.99, 2.0–2.59, 2.6–2.99, and ≥3.0). As the Japanese guidelines recommend different INR values according to the patient’s age, the patients were also divided into 2 age groups (ie, <70 years and ≥70 years). Vari-

### Table 1. Clinical Characteristics of the Japanese Patients With Non-Valvular AF in the J-RHYTHM Registry

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>n</th>
<th>Men (%)</th>
<th>Paroxysmal AF (%)</th>
<th>Heart failure (%)</th>
<th>Diabetes (%)</th>
<th>Hypertension (%)</th>
<th>Prior CI or TIA (%)</th>
<th>CHADS2 score</th>
<th>Antiplatelet (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>29.1</td>
<td>15.7</td>
<td>13.5</td>
<td>12.8</td>
<td>10.7</td>
<td>10.7</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>1</td>
<td>37.2</td>
<td>34.0</td>
<td>33.0</td>
<td>35.7</td>
<td>34.4</td>
<td>27.2</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>2</td>
<td>20.5</td>
<td>27.4</td>
<td>30.1</td>
<td>26.8</td>
<td>32.2</td>
<td>33.1</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>≥3</td>
<td>13.2</td>
<td>22.9</td>
<td>23.4</td>
<td>24.7</td>
<td>22.7</td>
<td>29.0</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Mean 1.2±1.2 1.7±1.2 1.7±1.2 1.8±1.2 1.8±1.1 1.9±1.2 <0.0001

### Table 2. Clinical Characteristics of the Japanese Patients With Non-Valvular AF in the J-RHYTHM Registry

<table>
<thead>
<tr>
<th>INR level</th>
<th>n</th>
<th>Age (years)</th>
<th>Men (%)</th>
<th>Paroxysmal AF (%)</th>
<th>Heart failure (%)</th>
<th>Diabetes (%)</th>
<th>Hypertension (%)</th>
<th>Prior CI or TIA (%)</th>
<th>CHADS2 score</th>
<th>Antiplatelet (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1.59</td>
<td>1,002</td>
<td>67.8±11.8</td>
<td>70±1±10.0</td>
<td>70±4±9.4</td>
<td>69.6±9.5</td>
<td>69.6±9.3</td>
<td>71.5±8.6 &lt;0.0001</td>
<td>0.66</td>
<td>0.00001</td>
<td>0.00001</td>
</tr>
<tr>
<td>1.6–1.99</td>
<td>1,670</td>
<td>66.7±11.7</td>
<td>71±1±9.4</td>
<td>69.6±9.5</td>
<td>69.6±9.3</td>
<td>71.5±8.6</td>
<td>0.00001</td>
<td>0.00001</td>
<td>0.00001</td>
<td></td>
</tr>
<tr>
<td>2.0–2.59</td>
<td>2,348</td>
<td>67.1±11.2</td>
<td>70.3±9.7</td>
<td>70.3±9.7</td>
<td>70.3±9.7</td>
<td>70.3±9.7</td>
<td>0.00001</td>
<td>0.00001</td>
<td>0.00001</td>
<td></td>
</tr>
<tr>
<td>2.6–2.99</td>
<td>1,854</td>
<td>67.6±11.1</td>
<td>70.3±9.6</td>
<td>70.3±9.6</td>
<td>70.3±9.6</td>
<td>70.3±9.6</td>
<td>0.00001</td>
<td>0.00001</td>
<td>0.00001</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>363</td>
<td>68.2±11.0</td>
<td>71.0±9.4</td>
<td>71.0±9.4</td>
<td>71.0±9.4</td>
<td>71.0±9.4</td>
<td>0.00001</td>
<td>0.00001</td>
<td>0.00001</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean±SD. AF, atrial fibrillation; CI, cerebral infarction; INR, international normalized ratio; TIA, transient ischemic attack.
Target INR in NVAF

Patients, 1,002 were not taking warfarin at the time of enrollment (non-warfarin group). The patients in this group were younger and had lower CHADS2 scores than the warfarin group; that is, the non-warfarin group was at low risk of thromboembolism; more than half of them had paroxysmal AF and were taking antiplatelet drugs instead of warfarin. Of the warfarin group, 36.7% had baseline INR values of 1.6–1.99, and 29.0% displayed baseline INR values of 2.0–2.59. Only 2.6% of the warfarin group had an INR ≥3 at the time of enrollment.

NVAF Patients Aged ≥70 Years (Table 2)

There were 4,041 patients who were aged ≥70 years (mean age: 77.0 years), and approximately two-thirds of them were men. Of these patients, 459 did not receive anticoagulation therapy. Compared with the warfarin group, the non-warfarin group had a higher prevalence of AF, heart failure, and diabetes. The mean CHADS2 score was higher in the non-warfarin group than in the warfarin group. Antiplatelet therapy was more common in the non-warfarin group than in the warfarin group.

Baseline Characteristics of the Study Patients

Entire NVAF Patient Population (Table 1)

Of the 7,406 patients, 5,976 were taking warfarin at the time of enrollment (warfarin group). The patients in this group were younger and had lower CHADS2 scores than the non-warfarin group; that is, the warfarin group was at low risk of thromboembolism; more than half of them had paroxysmal AF and were taking antiplatelet drugs instead of warfarin. Of the warfarin group, 36.7% had baseline INR values of 1.6–1.99, and 29.0% displayed baseline INR values of 2.0–2.59. Only 2.6% of the warfarin group had an INR ≥3 at the time of enrollment.

Results

Of the 7,527 patients with NVAF, 121 (1.6%) were lost to follow-up. Therefore, the data for remaining 7,406 patients were used in the subsequent analyses.

Baseline Characteristics of the Study Patients

Entire NVAF Patient Population (Table 1)

Of the 7,406 patients, 1,002 were not taking warfarin at the time of enrollment (non-warfarin group). The patients in this group were younger and had lower CHADS2 scores than the warfarin group; that is, the non-warfarin group was at low risk of thromboembolism; more than half of them had paroxysmal AF and were taking antiplatelet drugs instead of warfarin. Of the warfarin group, 36.7% had baseline INR values of 1.6–1.99, and 29.0% displayed baseline INR values of 2.0–2.59. Only 2.6% of the warfarin group had an INR ≥3 at the time of enrollment.

NVAF Patients Aged ≥70 Years (Table 2) There were 4,041 patients who were aged ≥70 years (mean age: 77.0 years), and approximately two-thirds of them were men. Of these patients, 459 did not receive anticoagulation therapy. Compared with the warfarin group, the non-warfarin group had a higher prev-
and 195 patients died.

In the warfarin group, the incidence of thromboembolic events decreased as the INR value increased (P=0.0059 for trend) and was significantly lower in each warfarin group than in the non-warfarin group. In contrast, the frequency of hemorrhagic events increased significantly as the INR value rose (P=0.0041 for trend). In addition, all-cause mortality was lowest at an INR of between 2.0 and 2.99. Analyses based on the Cox proportional hazard model showed that thromboembolic risk was significantly lower at an INR of between 1.6 and 2.99 than that in the non-warfarin group, whereas hemorrhagic risk increased along with the rise in the INR value (Table 5). This suggested that an INR of 1.6–2.6 was safe and effective at preventing thromboembolic events in Japanese patients with NVAF, as Yasaka et al reported previously.

An INR of 2.6 to 2.99 was also effective but associated with a slightly increased risk of major hemorrhage.

The elderly patients group (≥70 years old) displayed similar results to those for the whole patient group (Tables 4, 5). Thromboembolic risk was lowest at an INR of 1.6–2.6 and 1.7–2.6, whereas hemorrhagic risk increased along with the rise in the INR value. This suggested that an INR of 1.6–2.6 was safe and effective at preventing thromboembolic events in Japanese patients with NVAF, as Yasaka et al reported previously.

Table 4. Incidence of Thromboembolic and Major Hemorrhagic Events During the 2-Year Follow-up of Japanese Patients With Non-Valvular AF in the J-RHYTHM Registry

<table>
<thead>
<tr>
<th>INR level</th>
<th>Non-warfarin</th>
<th>Warfarin</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.59</td>
<td>30 (3.0%)</td>
<td>33 (2.0%)</td>
<td>0.0059</td>
</tr>
<tr>
<td>1.6–1.99</td>
<td>27 (2.6%)</td>
<td>31 (1.3%)</td>
<td></td>
</tr>
<tr>
<td>2.0–2.59</td>
<td>27 (2.1%)</td>
<td>23 (1.5%)</td>
<td></td>
</tr>
<tr>
<td>2.6–2.99</td>
<td>27 (1.5%)</td>
<td>1 (0.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>27 (1.3%)</td>
<td>3 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>27 (1.5%)</td>
<td>2 (0.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

NVAF Patients Aged <70 Years (Table 3) There were 3,365 patients aged <70 years (mean age: 61.0 years), and approximately three-quarters of them were men. Of these patients, 543 did not receive anticoagulation therapy. The mean CHADS2 score of the non-warfarin group was slightly lower than that of the warfarin group.

Thromboembolic and Hemorrhagic Events, and Mortality (Tables 4, 5) During the 2-year follow-up, 126 patients suffered thromboembolic events (CI, TIA, or systemic embolism), 140 patients suffered major hemorrhagic events requiring hospitalization,
the risk of hemorrhagic events was significantly increased at an INR $\geq 2.0$. Again, these findings suggested that the optimal target INR for Japanese elderly patients with NVAF ranges from 1.6 to 2.6. An INR of 2.6–2.99 was associated with a trend toward an increase in major hemorrhage.

The results for the younger patient group (<70 years old) were somewhat different from those of the whole group and the elderly group (Table 4). The frequencies of thromboembolic and major hemorrhagic events were very low, and thromboembolic events did not occur at an INR $\geq 2.6$. The incidence of major hemorrhagic events did not differ significantly among the non-warfarin and warfarin groups.

### Discussion

**Major Findings**

The major findings of the present observational study were as follows. First, in the whole warfarin group, INR $\geq 1.6$ was effective at reducing the frequency of thromboembolic events among Japanese patients with NVAF. However, the frequency of major hemorrhagic events increased as the INR value increased and was higher in each warfarin group than in the non-warfarin group. Second, for elderly Japanese patients ($\geq 70$ years old) with NVAF, the risk of thromboembolic events was lowest at an INR of 1.6–2.99. At an INR $\geq 2.6$, the risk of hemorrhagic events was 4-fold higher than that of the non-warfarin group. These findings support the Japanese guidelines for target anticoagulation levels among elderly patients with NVAF (ie, target INR between 1.6 and 2.6). An INR of 2.6–2.99 was effective at reducing thromboembolic events, but associated with a slight increase in major hemorrhagic events as compared with an INR of 1.6–2.59. Third, in the younger patient group (<70 years old), the optimal target INR values for preventing thromboembolic and major hemorrhagic events could hardly be determined, which might be related to younger patients with NVAF being at lower risk of thromboembolic and hemorrhagic events.

**Anticoagulation Levels**

An INR between 2 and 3 is recommended in the guidelines used in Western countries for the management of AF. Previous studies from Western countries have revealed that the risk of stroke increased among patients with INR values between 1.5 and 2.1. Even in patients $\geq 75$ years of age, an INR of 2–3 were found to be effective at reducing the frequencies of fatal stroke and non-fatal disabling stroke in the primary care setting. The investigators in the ATRIA study reported that an INR of between 2 and 3 were effective at preventing thromboembolism and major hemorrhage in patients with NVAF, irrespective of their age and CHADS2 score. However, their results suggested that increased intracranial hemorrhage would occur in patients $\geq 70$ years old at an INR $\geq 2.6$. A meta-analysis involving patients with various pathological conditions that required anticoagulation treatment with warfarin also showed that an INR of between 2 and 3 was optimal for preventing thromboembolic events without increasing the risk of hemorrhagic events. Taken together, studies from Western countries have repeatedly suggested that the optimal target INR for managing patients with AF ranges from 2 to 3.

In a prospective randomized study from Western countries have demonstrated the efficacy of slightly lower INR values in patients with NVAF. The BAATAF study used a target INR of between 1.5 and 2.7 in 420 patients with nonrheumatic AF (mean age, 68 years old), and the SPINAF study used a target INR of between 1.4 and 2.8 in 571 male patients with nonrheumatic AF (mean age, 67 years old). These 2 studies clearly demonstrated that lower INR values are effective at reducing the risk of thromboembolic events. In the SPINAF study, the utility of lower INR values for preventing ischemic stroke was evident, particularly in patients $\geq 70$ years of age.

As for Asian NVAF patients, only a few prospective studies have attempted to determine the optimal INR values for this patient group. Yasaka et al combined the results of 2 prospective secondary prevention trials to determine the optimal INR values for Japanese patients with NVAF. They found that major ischemic stroke and systemic embolism only occurred in patients with an INR $<1.6$, and major hemorrhage only developed in patients with an INR $\geq 2.6$ (mean, 2.81). Based on these findings, INR values between 1.6 and 2.6 were recommended as optimal for preventing embolic events and major hemorrhagic events in Japanese patients with NVAF. In a retrospective cohort study, Naganuma et al found that an INR of between 1.5 and 2.5 was associated with low incidences of thromboembolic and major bleeding events in 845 elderly Japanese NVAF patients ($\geq 70$ years old; mean, 74 years old) with CHADS2 scores $\geq 2$. In addition, they found that an INR $\geq 2.5$ was associated with a trend toward an increased risk of major hemorrhage.

Among Chinese patients receiving warfarin, lower INR values were also suggested to be optimal for preventing embolic and bleeding events. In a retrospective study involving
555 Chinese patients (mean age, 69.7 years) with valvular AF or NVAF who were taking warfarin, Cheung et al found that an INR range of 1.5–1.9 was associated with the lowest frequencies of thromboembolic and serious bleeding events. They concluded that an INR range of 1.5–3.0 was safe and effective at preventing stroke in Chinese AF patients. Another retrospective study by You et al enrolled 491 Chinese patients (mean age, 65.8 years) who had recently started taking warfarin for various indications with the aim of achieving a target INR of between 2 and 3. AF was the main indication for warfarin in 72% of the patients. The incidence of hemorrhagic or thromboembolic events was lowest at an INR of between 1.8 and 2.4. These studies from China and Japan, as well as the present study suggest that an INR slightly less than 2.0 (ie, 1.5 or 1.6–2.0) is effective at preventing embolic events in Japanese and Chinese patients with NVAF. It should be noted that the risk of major hemorrhagic events is increased at INR values exceeding 2.5 or 2.6. Based on an observational study, Suzuki et al reported that an INR of 2.27 or higher was the only significant predictor of major hemorrhage in patients receiving warfarin.

In a previous study, the effects of the INR value on hemostatic marker levels were analyzed in Japanese patients with NVAF. It was found that the reduction in D-dimer levels observed at an INR of between 1.5 and 1.99 was similar to that seen at an INR of 2.00 or higher. Therefore, an INR of between 1.5 and 1.99 is also effective at preventing thrombus formation in the cardiovascular system, which suggests that lower INR values (between 1.5 and 1.99) are as effective as INR values of between 2 and 3 at preventing embolic events in patients with NVAF.

Study Limitations
The present study had several limitations. First, the study design was observational, and the antithrombotic drugs were selected by the participating physicians, although the patients were followed-up prospectively for 2 years. In addition, the non-warfarin group consisted of patients who were at low risk of thromboembolism according to their CHADS2 scores (mean, 1.2). This could have hampered our ability to examine the utility of warfarin for preventing thromboembolic events, but this was not the case. The incidence of thromboembolic events was lower in the warfarin groups with INR values ≥1.6 than in the non-warfarin group. Second, our analyses only involved the subjects’ baseline antithrombotic therapy status and baseline INR values. The present study collected outpatients who were being treated by the participating physicians, and the antithrombotic treatment and dosage were selected by the participating physicians. Therefore, the baseline INR values were used as values that represented anticoagulation intensity. The effects of switching antithrombotic therapy were not taken into consideration in the present analyses. These limitations could have explained the slightly higher rate of thromboembolic events in patients with an INR ≥3.0. However, this could not be the case, because the hemorrhagic event rate was highest in these patients. More sophisticated analyses involving the time in the therapeutic range need to be done to determine the associations between the variation in INR values during the follow-up period and event frequencies. Third, 121 patients were lost to follow-up in the present study, which could lead to underreporting of endpoints. The incidence of CI among the elderly patients (≥70 years old) with baseline INR values of 2.0–2.59 (mean CHADS2 score of 2.2; Table 2) in the present study was 16/1,004 or 1.59%/2 years, a slightly lower rate as compared with the Japanese patients in the warfarin arm (mean CHADS2 score of 2.2; target INR 2.0–2.6 for elderly patients aged ≥70 years, and 2.0–3.0 for the remaining patients) in the RE-LY trial (1.33%/year). As for intracranial hemorrhage, the incidence was similar between the present study (14/1,004 or 1.39%/2 years for elderly patients with INR of 2.0–2.59) and the RE-LY trial (0.66%/year for Japanese patients receiving warfarin). Therefore, the effects of underreporting of endpoints because of a lack of follow-up data in a small proportion (1.6%) of the patients should be limited in the present study. Finally, the patients in the <70-year-old group were at low risk of thromboembolism (ie, the mean CHADS2 score was 0.7 in the non-warfarin group and ranged from 1.1 to 1.5 in the warfarin groups). Therefore, the incidence rates of thromboembolism and major hemorrhage were quite low in this age group and did not differ significantly among the non-warfarin group and the warfarin group (Table 4).

Conclusion
Although our study was affected by the stated limitations, it clearly demonstrated that an INR of 1.6–2.6 is a safe and effective target for the prevention of thromboembolic events in Japanese patients with NVAF, particularly those aged ≥70 years. An INR between 2.6 and 2.99 is also effective, but associated with a trend toward an increased risk of major hemorrhage. The management of Japanese patients with NVAF should be based on data obtained from Japanese patients.

Disclosures
Conflict of Interest: Dr Inoue received research funding from Boehringer Ingelheim and Daiichi-Sankyo, and remuneration from Daiichi-Sankyo, Bayer Healthcare and Boehringer Ingelheim; Dr Okamura received research funding from Boehringer Ingelheim and Daiichi-Sankyo, and remuneration from Boehringer Ingelheim, Bayer Healthcare, Daiichi-Sankyo, and Pfizer; Dr Atarashi received research funding from Daiichi-Sankyo and Boehringer Ingelheim, and lecture fees from Bayer Healthcare and Boehringer Ingelheim; Dr Yamashita received research funding from Boehringer Ingelheim and Daiichi-Sankyo, and remuneration from Boehringer Ingelheim, Daiichi-Sankyo, Bayer Healthcare, Pfizer, Bristol-Myers Squibb, and Eisai; Dr Origasa received lecture fees from Daiichi-Sankyo; Dr Kawamura received lecture fees from Boehringer Ingelheim; Dr Kubota received research funding from Daiichi-Sankyo; Dr Watanabe received lecture fees from Bayer Healthcare and Boehringer Ingelheim; Dr Kuretsume received remuneration from Boehringer Ingelheim, and lecture fees from Bayer Healthcare and Boehringer Ingelheim; Dr Shimizu received lecture fees from Boehringer Ingelheim and Daiichi-Sankyo; Dr Okuyama received lecture fees from Boehringer Ingelheim; and Dr Chishaki received lecture fees from Bayer Healthcare. No other potential conflict of interest relating to this article are reported.

References

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**Appendix**

The participating physicians are listed in references 12–14.