Target Intensity of Anticoagulation With Warfarin in Japanese Patients With Valvular Atrial Fibrillation
– Subanalysis of the J-RHYTHM Registry –

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on behalf of the J-RHYTHM Registry Investigators

Background: Warfarin is widely used for prevention of thromboembolism in patients with valvular atrial fibrillation (AF), and an international normalized ratio (INR) of prothrombin time between 2.0 and 3.0 is recommended. Optimal intensity of anticoagulation with warfarin in Japanese patients with valvular AF, however, has not been clarified thoroughly as yet.

Methods and Results: We evaluated the status of anti-thrombotic therapy and incidence rates of events in 410 patients with mitral stenosis and/or mechanical valve replacement (valvular AF) among 7,816 patients with AF followed in the J-RHYTHM Registry. Patients were divided into 5 groups based on INR (<1.6, 1.6–1.99, 2.0–2.59, 2.6–2.99, and ≥3.0) at the time of event or at the end of follow-up in order to determine the target INR for patients with valvular AF: Warfarin was prescribed in 407 (99.3%) of valvular AF patients. During a 2-year follow-up period, thromboembolism and major hemorrhage occurred in 12 (2.9%) and in 15 (3.7%) patients, respectively. Among patients receiving warfarin, 2-year incidence rates of thromboembolism were 10.3%, 1.6%, 0.6%, 3.0%, and 0.0% (P=0.003 for trend), and those of major hemorrhage were 1.5%, 1.6%, 3.2%, 6.1%, and 21.1% (P<0.001 for trend), respectively.

Conclusions: INR between 1.6 and 2.6 could be optimal to prevent thromboembolism without increasing major hemorrhage in Japanese patients with valvular AF. INR 2.6–2.99 would also be effective, but is associated with a modestly increased risk of major hemorrhage. (Circ J. 2015; 79: 325–330)

Key Words: Anticoagulation; Atrial fibrillation; International normalized ratio; Valvular disease; Warfarin

Valvular heart disease is an underlying etiology of atrial fibrillation (AF). Prosthetic heart valve replacement is performed in approximately 300,000 patients each year worldwide. Although mechanical valves are more durable than bioprosthetic valves, mechanical prostheses present a persistent risk of thromboembolic complications. Therefore, lifelong anticoagulation therapy is required to prevent the development of valve thrombosis, stroke, and systemic embolism in patients with mechanical valve replacement. Given that AF is also a risk of cardiogenic ischemic stroke, patients with AF who undergo valve replacement should be considered at higher risk for thromboembolic complications.

Vitamin K antagonists (VKA) are the only oral anticoagulant approved for long-term treatment of patients with valve replacement. The use of VKA has shown excellent protection against thromboembolic events in patients with mechanical heart valves. Warfarin is the VKA available in Japan, and currently used most frequently worldwide in patients with valvular AF; an international normalized ratio (INR) of prothrombin time between 2.0 and 3.0 is recommended for these patients. The optimal intensity of anticoagulation with warfarin in Japanese patients with valvular AF, however, was still...
Definition of Valvular AF

Valvular AF has been defined as AF in patients with rheumatic valvular diseases (predominantly mitral stenosis) or prosthetic heart valves; in the present study, however, it was defined as AF in patients with mitral stenosis or mechanical heart valve replacement according to the 2008 Guidelines for Pharmacotherapy of Atrial Fibrillation of the Japanese Circulation Society. Patients with bioprosthetic valve replacement for treatment of valvular diseases other than mitral stenosis were defined as having non-valvular AF.

Follow-up and Definition of Endpoints

The patients were followed for 2 years or until a defined endpoint, whichever occurred first. The thromboembolic endpoints consisted of symptomatic stroke, transient ischemic attack, and systemic embolism. Major hemorrhage including intracranial hemorrhage, gastrointestinal bleeding, and others requiring hospitalization were selected as the safety endpoints. All-
Table 2. Anti-Thrombotic Therapy at Enrollment

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Valvular</th>
<th>Non-valvular</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>7,816</td>
<td>410</td>
<td>7,406</td>
<td></td>
</tr>
<tr>
<td>Anticoagulation therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>6,811 (87.1)</td>
<td>407 (99.3)</td>
<td>6,404 (86.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dosage (mg/day)</td>
<td>2.9±1.2</td>
<td>2.9±1.2</td>
<td>2.9±1.2</td>
<td>1.000</td>
</tr>
<tr>
<td>INR</td>
<td>1.9±0.5</td>
<td>2.1±0.5</td>
<td>1.9±0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;1.6</td>
<td>1,728 (25.4)</td>
<td>58 (14.3)</td>
<td>1,670 (26.1)</td>
<td></td>
</tr>
<tr>
<td>1.6–1.99</td>
<td>2,481 (36.4)</td>
<td>133 (32.7)</td>
<td>2,348 (36.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2.0–2.59</td>
<td>2,018 (29.6)</td>
<td>164 (40.3)</td>
<td>1,854 (29.0)</td>
<td></td>
</tr>
<tr>
<td>2.6–2.99</td>
<td>394 (5.8)</td>
<td>31 (7.6)</td>
<td>363 (5.7)</td>
<td></td>
</tr>
<tr>
<td>≥3.0</td>
<td>190 (2.8)</td>
<td>21 (5.2)</td>
<td>169 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Antiplatelet</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any antiplatelet</td>
<td>2,028 (25.9)</td>
<td>91 (22.2)</td>
<td>1,937 (26.2)</td>
<td>0.085</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1,749 (22.4)</td>
<td>74 (18.0)</td>
<td>1,675 (22.6)</td>
<td>0.036</td>
</tr>
<tr>
<td>Others</td>
<td>455 (5.8)</td>
<td>22 (5.4)</td>
<td>433 (5.8)</td>
<td>0.767</td>
</tr>
<tr>
<td>Warfarin+antiplatelet</td>
<td>1,447 (18.5)</td>
<td>89 (21.7)</td>
<td>1,358 (18.3)</td>
<td>0.100</td>
</tr>
</tbody>
</table>

Data given as n (%) or mean ±SD. †Valvular vs. non-valvular. INR, international normalized ratio.

Table 3. Incidence Rates During 2-Year Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Valvular AF</th>
<th>Non-warfarin</th>
<th>Warfarin</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. patients</td>
<td>410</td>
<td>396</td>
<td>154</td>
<td>33</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>13 (3.2)</td>
<td>11 (2.8)</td>
<td>7 (1.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>10 (2.4)</td>
<td>2 (0.5)</td>
<td>6 (1.7)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>TIA</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>2 (0.5)</td>
<td>2 (0.5)</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>15 (3.7)</td>
<td>14 (3.5)</td>
<td>1 (1.5)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>5 (1.2)</td>
<td>5 (1.2)</td>
<td>0 (0.0)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>6 (1.2)</td>
<td>6 (1.5)</td>
<td>0 (0.0)</td>
<td>2 (0.0)</td>
</tr>
<tr>
<td>Others</td>
<td>4 (1.0)</td>
<td>4 (1.1)</td>
<td>3 (0.7)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Thromboembolism+major hemorrhage</td>
<td>28 (6.8)</td>
<td>25 (6.3)</td>
<td>8 (1.8)</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>11 (2.7)</td>
<td>8 (2.0)</td>
<td>1 (0.3)</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>6 (1.5)</td>
<td>4 (1.0)</td>
<td>1 (0.3)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Data given as n (%). †Comparison among the 5 INR groups receiving warfarin (chi-squared test, [ ] for trend). ‡At the time of event or at end of follow-up. Abbreviations as in Tables 1,2.

cause death and cardiovascular death were also identified. If any event occurred during the follow-up period, it was mandatory that the final clinical data, including INR at the time closest to the event, be collected. The diagnostic criteria for each event have been described previously. Statistical Analysis

Data are presented as mean±SD. Patients receiving warfarin were divided into subgroups according to INR (<1.6, 1.6–1.99, 2.0–2.59, 2.6–2.99, and ≥3.0) or time in therapeutic range (TTR). Statistical significance of differences in the means was analyzed using Student’s t-test or ANOVA as appropriate. Frequencies of parameters or events were compared with chi-squared test or Fisher’s exact test as appropriate. Odds ratios (ORs) were calculated with multivariate logistic regression analysis using the group with INR for which the combined event rate (thromboembolism plus major hemorrhage) was the lowest as a reference. CHADS2 score (1 point each for the presence of congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus and 2 points for history of stroke or transient ischemic attack) was included as an explanatory variable in the multivariate logistic regression analysis to determine OR. P<0.05 was considered to be statistically significant. All statistical analysis was done with SPSS version 15.0 (SPSS Inc, Chicago, IL, USA).

Results

A total of 7,937 patients with AF were enrolled in the J-RHYTHM Registry. Of these, 421 (5.3%) had valvular AF (274 with mitral stenosis, 214 with mechanical valves, and 67 with both). Eleven (2.6%) of 421 patients with valvular AF and 110 (1.5%) of 7,516 patients with non-valvular AF were lost to follow-up. Therefore, 410 patients with valvular AF (269 with mitral stenosis including 66 after replacement with mechanical valves and 6 with bioprosthetic valves, and 141
with mechanical valve replacement for treatment of valvular diseases other than mitral stenosis) constituted the study group for subsequent analyses.

**Baseline Characteristics and the Status of Anti-Thrombotic Therapy**

Prevalence of female gender, permanent AF and heart failure, and mean CHADS2 score were significantly higher in patients with valvular AF than in those with non-valvular AF. In contrast, prevalence of hypertension, coronary artery disease, and cardiomyopathy was lower in patients with valvular AF than in those with non-valvular AF (Table 1). In the valvular AF group, only 3 (0.7%) were not taking warfarin at the time of enrollment; the rate of warfarin treatment was significantly higher in valvular AF than in non-valvular AF (Table 2). In patients with valvular AF receiving warfarin, 47.9% had INR <2.0 at the time of enrollment. Mean INR was slightly but significantly higher in the valvular AF than in the non-valvular AF group at the time of enrollment, whereas daily warfarin dosage was not different between the valvular and non-valvular AF groups (Table 2).

**Thromboembolic Events and Major Hemorrhage**

During a 2-year follow-up period, thromboembolic events were observed in 13 (3.2%), major hemorrhage in 15 (3.7%), and all-cause death in 11 (2.7%) among 410 patients with valvular AF (Table 3). Incidence rates of thromboembolism and major hemorrhage were significantly higher in patients with valvular AF than in those with non-valvular AF (thromboembolism: 3.2% vs. 1.7%, P=0.046; major hemorrhage: 3.7% vs. 1.9%, P=0.022).12 This was also true when the analysis was confined to patients receiving warfarin at baseline, both rates were also significantly higher in patients with valvular AF than in those with non-valvular AF (thromboembolism: 2.9% vs. 1.5%, P<0.001; major hemorrhage: 3.7% vs. 2.1%, P=0.039).12 All-cause mortality was similar between patients with valvular AF and those with non-valvular AF.

When the analysis was done according to the INR at the time of event or at the end of follow-up, incidence rates of both thromboembolism and major hemorrhage had an obvious association with INR (P=0.003 and P<0.001 for trend, respectively, Table 3). Rate of combined events (thromboembolism plus major hemorrhage) was lower in groups with INR 1.6–2.59 (P=0.007, Table 3).

Characteristics of patients with events are summarized in Table S1. Mean INR at the event was 3.4±2.6 in patients with major hemorrhage and 1.6±0.6 in those with thromboembolism. When the patients were divided into 5 groups according to INR, there were no significant differences in incidence rates of either thromboembolism or major hemorrhage among the 5 groups (Table S2).

**Target INR for Valvular AF**

OR for each event showed a significant trend among the 5 INR groups. With INR 1.6–1.99 as the reference, INR <1.6 had a significantly higher OR for thromboembolism, while INR ≥3.0 did so for major hemorrhage (Table 4). Although statistically not significant, INR 2.6–2.99 had a 3-fold higher OR for combined events.

**Discussion**

The major findings of the present study were as follows. First, patients with valvular AF (mitral stenosis and/or mechanical valves) accounted for 5% of all the patients enrolled in the J-RHYTHM Registry. Second, warfarin was prescribed in >99% of patients with valvular AF. The prevalence of target INR between 2.0 and 3.0,7 however, was <50%, similar to that for INR <2.0. Third, the OR for thromboembolism was significantly higher at INR <1.6, while that for major hemorrhage were higher at INR ≥3.0. The combined event rate of thromboembolism and major hemorrhage was lower at INR between 1.6 and 2.6.

**Intensity of Anticoagulation and Events**

In the European guidelines of the management of valvular heart disease (version 2012),13 an optimal INR range between 2.5 and 4.0 is recommended for patients with mechanical valves due to the combination of prevention thrombogenicity (bileaflet, tilting disc, etc) and patient-related risk factors. The patient-related risk factors included AF, tricuspid or mitral valve replacement, previous thromboembolism, mitral stenosis of any degree, and left ventricular dysfunction. Other investigators noted that optimal INR for patients with mechanical valve replacement was between 2.5 and 2.9, given that the lowest incidence of all events was found at INR 2.5–2.9.14 In several
guidelines for management of AF including the Japanese guidelines, however, INR 2.0–3.0 was recommended for patients with valvular AF as well as for those with non-valvular AF.

In the J-RHYTHM Registry, the prevalence of the currently recommended INR of between 2.0 and 3.0 was <50% among Japanese patients with valvular AF. INR 1.6–2.6, however, was found in 73.0% of patients at the time of enrollment. Japanese guidelines recommended slightly lower INR for elderly patients (≥70 years old) with non-valvular AF. Other Japanese physicians and cardiologists seemed to adopt this lower INR as the target intensity, even for patients with valvular AF as well as for those with non-valvular AF. Shen et al demonstrated that non-Caucasian patients, especially Asian patients, with AF were at risk for intracranial hemorrhage under warfarin treatment with a target INR 2.0–3.0. In Japanese patients with non-valvular AF, INR ≥2.27 was an independent risk factor for major hemorrhage. Other Japanese investigators also found that an INR range of 1.5–2.5 appeared to be optimal after prophylactic valve replacement, regardless of AF. Racial differences in drug response would be similar between patients with valvular AF and with non-valvular AF. Indeed, the OR for major hemorrhage was approximately 4-fold higher for INR ≥2.6 as compared with INR 1.6–1.99 in the present study. In addition, the combined rate of thromboembolism and major hemorrhage was lower for INR between 1.6 and 2.6. Therefore, INR 1.6–2.6 may be optimal to prevent thromboembolism without increasing major hemorrhage in Japanese patients with valvular AF. INR 2.6–2.99 was also effective at preventing thromboembolism, but associated with a modestly increased risk of major hemorrhage.

In the present post-hoc analysis, INR at the time of events or at the end of the follow-up period were used; the main analysis of the J-RHYTHM Registry, however, included baseline INR for analysis. This method using the baseline INR to determine target INR seemed not free from criticism, given that variation of INR and discontinuation or initiation of warfarin during the follow-up period were not taken into consideration. Therefore, the present post-hoc analysis utilized INR at the time of events or at the end of the follow-up period. TTR is a sophisticated method for determining quality of warfarin control. Therefore, in the present subanalysis TTR was calculated, but the results did not show a consistent trend (Table S2). Patients with TTR ≥290% had higher event rates for thromboembolism and major hemorrhage. A possible explanation for higher hemorrhagic event rate was that better quality of warfarin control at INR 2.6–2.99 could lead to higher TTR but higher risk for major hemorrhage among Japanese patients with valvular AF. In contrast, higher TTR but a sudden decrease in INR would lead to a thromboembolic event.

Study Limitations
The present study had several limitations. First, the present study was performed in a single country and the registry was established only in 158 selected institutions in Japan. The participating physicians included cardiologists but not general practitioners: thus, the patient clinical background may not be extrapolated to Japanese patients with AF. Second, although this registry was large, enrolling a total of 7,937 patients with AF, the number of patients with valvular AF accounted for only 5% of the whole group. Consequently, the number of patients having events was small. This might have reduced the statistical power of the present study. Third, the study design was prospective but observational. Anti-thrombotic agents and INR for individual patients were selected at the discretion of the participating physicians. Consequently, warfarin was prescribed in 99.3% of patients at the time of enrollment. Therefore, it was difficult to analyze the non-warfarin group as a control in the present subanalysis. Fourth, 2.6% of patients were lost to follow-up in the present study, which could lead to underreporting of endpoints. Finally, there was no information about prosthesis thrombosis, type of prosthetic valve (eg, bileaflet or other types), or position of prosthetic valve. This might affect the incidence of thromboembolic events.

Conclusions
Although oral anticoagulation with warfarin was frequently used in Japanese patients with valvular AF, achieved INR was lower than the recommended guideline level of 2.0–3.0 in approximately half of the patients. INR 1.6–2.6 may be optimal to prevent thromboembolism without increasing major hemorrhage in Japanese patients with valvular AF, as reported in elderly patients with non-valvular AF. INR 2.6–2.99 is also effective at preventing thromboembolism, but is associated with a modestly increased risk of major hemorrhage.

Acknowledgments
The summary of this study was presented at the 78th Annual Scientific Meeting of the Japanese Circulation Society (Tokyo, Japan, 21 March 2014). Investigators in the J-RHYTHM Registry are listed in references.

Disclosures
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References
7. JCS Joint Working Group. Guidelines for pharmacotherapy of atrial

Supplementary Files

Table S1. Patient characteristics vs. presence of valvular AF and events
Table S2. Incidence rates and TTR
Please find supplementary file(s); http://dx.doi.org/10.1253/circj.CJ-14-1057