ased on evidence accumulated mainly in the 1990s, recent guidelines on the management of atrial fibrillation (AF) published in the United States, Europe, and Japan recommend anticoagulation therapy for patients with non-valvular AF and risk factor(s) for ischemic stroke and systemic thromboembolism. Warfarin has been the only drug used for anticoagulation therapy for the past half century until the oral direct thrombin inhibitor, dabigatran, was recently demonstrated to be as effective as or more effective than warfarin in preventing ischemic stroke and thromboembolism in patients with non-valvular AF, and subsequently approved for clinical use. A recent focused guideline update recommended dabigatran as a class I drug that is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in AF patients with risk factors for stroke or systemic embolization. This guideline update also noted that because of the twice-daily dosing and greater risk of non-hemorrhagic side effects with dabigatran, patients already taking warfarin with excellent control of the international normalized ratio of prothrombin time (PT-INR) may have little to gain by switching to dabigatran.

**Background:** Time in the therapeutic range (TTR) assesses the appropriateness of international normalized ratio of prothrombin time (PT-INR) control during warfarin therapy. We examined the status of and the factors influencing TTR in Japanese patients with non-valvular atrial fibrillation (AF).

**Methods and Results:** We enrolled 501 AF patients (mean age, 70±10 years; males 66%; mean CHADS2 score 2.0±1.2) taking warfarin for ≥2 years from 5 prefectures. The PT-INR therapeutic range was set up according to the 2008 Japanese Guideline. TTR was 64±25% for all patients and varied from 56% to 74% with the institution. Time below and above TTR was 31±26% and 5±7%, respectively. TTR was not affected by gender or antiplatelet co-administration. TTR in patients <70 and ≥70 years old was 46±23% and 77±17%, respectively (P<0.0001). TTR in patients with CHADS2 score ≤1 and ≥2 was 59±27% and 68±23%, respectively (P<0.0001). TTR in patients with warfarin doses <2.0, 2.0–4.9, and ≥5.0 mg/day was 72±22%, 63±25% and 48±24%, respectively (all P<0.001). Multivariate analysis revealed age and warfarin dose as independent predictors of TTR.

**Conclusions:** TTR is generally high in Japan, although it varies with institutions. Most of the time spent out of therapeutic range is below the range. TTR is influenced by age presumably because of the low range recommendation for elderly patients, and by warfarin dose presumably because of physicians’ anxiety about the hemorrhage risk. (Circ J 2011; 75: 2087–2094)

**Key Words:** Anticoagulants; Atrial fibrillation; Stroke

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and between 1.6 and 2.6 in those equal to or older than 70 years.\(^4\) The PT-INR value represents the level of control at the time of measurement, and 1 measurement at 1 time does not necessarily reflect the appropriateness of long-term warfarin therapy in the individual patient. Recently, analysis of time in the therapeutic range (TTR) has been used to assess the appropriateness of PT-INR.\(^9\) This technique is based on the assumption that anticoagulation intensity during warfarin therapy shifts linearly between any 2 consecutive measurements,\(^10\) and TTR for an individual is calculated from the entire duration of observation. Subanalyses of recent large-scale clinical studies revealed that TTR >60–65% is associated with reduced risk for stroke.\(^11,12\) However, the status of TTR in Japan where the recommended therapeutic range for elderly patients is different from that in Western countries is not well known. The factors known to influence PT-INR include patient adherence and age, foods, concomitant drugs, and management by the physician.\(^13-17\) However, the factors influencing TTR in Japanese AF patients undergoing long-term warfarin therapy are not fully understood. We considered that identifying the factors related to a low TTR value (ie, poor PT-INR control and increased risk of stroke) may be useful in the decision of whether to continue with warfarin or switch to dabigatran in Japanese patients with non-valvular AF undergoing long-term warfarin therapy.

**Methods**

This multicenter study was conducted in 6 institutions and 1 clinic from 5 prefectures in Japan. The study protocol was approved by the ethics committee of each institution. Written informed consent was given by each patient.

**Study Patients**

We enrolled patients with non-valvular AF undergoing warfarin therapy for \(\geq 2\) years in principle who had been followed up by each institution and visited an outpatient clinic between June 1, 2010, and July 31, 2010. The maximal number of enrollments from each institution was 100. The indication for prophylactic warfarin therapy, especially in patients with CHADS\(_2\) score of 0 or 1, was left to the decision of the attending physician. From a review of the patients’ charts, we collected the data including the patient profiles, warfarin dose, concomitant antiplatelet drug use, and PT-INR determined monthly or bimonthly in principle for the past 2 years. Warfarin dose during follow-up was adjusted according to TTR proposed by the Japanese Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS2008); that is, between 2.0 and 3.0 for patients <70 years and between 1.6 and 2.6 for those \(\geq 70\).\(^4\) In this study, the PT-INR value measured after at least 3 months after initiation of warfarin was used. Patients with stroke or systemic thromboembolism or major hemorrhage during the study period were excluded from analysis.

**Study Protocol**

Using specially programmed software (Medi-Skette Corporation, Tokyo, Japan), we input the successive PT-INR values of each patient and calculated the TTR. This software automatically draws lines successively between any 2 consecutive PT-INR values during the observation period, and calculates the percentage of the total time within the preset therapeutic range (ie, between 2.0 and 3.0 for patients <70 years and between 1.6 and 2.6 for those \(\geq 70\)) over the entire period. Because this software was not designed to alter TTR in accordance with an increase in age from 69 to 70 during the 2-year period.
study period, the range between 2.0 and 3.0 was used throughout the period to calculate TTR in patients who were younger than 70 years at the initiation of PT-INR collection and got closer to ≥70 during the study period.

First, we analyzed the status of PT-INR control for all patients and for the patients from each institution. There were 3 institutions participating from Aomori Prefecture, so to simplify the comparative analysis of institutions from the 5 prefectures, the data for the patients from Aomori were combined and grouped as “A”. The patient data from Iwate Medical University Hospital, Cardiovascular Institute, Osaka General Medical Center, and Ube Industry Central Hospital were grouped as B, C, D and E, respectively. To examine the chronological change in TTR, we compared the TTR determined in the first year and for the second year for all patients. Also, any seasonal effect on TTR was examined.

Second, we analyzed the possible influential factors of TTR, including age, gender, warfarin dose at the last visit, co-administration of antplatelet drug, and CHADS: score consisting of congestive heart failure (1 point), hypertension (1 point), age ≥75 years (1 point), diabetes mellitus (1 point) and previous stroke or transient ischemic attack (2 points).¹⁸

Statistical Analysis
All data are expressed as mean±1 standard deviation. For comparison of TTR between 2 groups, and for the assessment of TTR change from the first to the second year, a 2-tailed paired t-test was used. For comparison of TTR among 3 or more groups, 1-way analysis of variance (ANOVA) was used followed by post-hoc Bonferroni test. After these univariate analyses, multiple stepwise regression analysis with the use of SPSS Version 19 (SPAA Japan Inc, Tokyo, Japan) was performed to detect the independent predictors of TTR. P<0.05 was considered significant.

Results

Patients’ Clinical Characteristics
From 7 institutions in the 5 prefectures we enrolled 501 AF patients undergoing warfarin therapy: 134 patients enrolled in Group A (Aomori), 100 in Group B (Iwate), 100 in Group C (Tokyo), 67 in Group D (Osaka) and 100 in Group E (Yamaguchi). Mean follow-up period was 706±58 days (1.9±0.2 years) for all patients. Mean interval of PT-INR measurements was 45±13 days.

There were 331 male and 170 female patients, and their mean age was 70±10 years, ranging from 29 to 92. The mean age of the male and female patients was 69±10 and 73±9 years, respectively (P<0.0001). Mean CHADS: score was 2.0±1.2 (median 2), ranging from 0 to 6. Mean warfarin dose administered at the last visit was 3.0±1.2 mg/day (median 3.0 mg/day), ranging from 0.5 to 8.5 mg/day. Antiplatelet drugs were co-administered in 172 patients (34%).

Status of PT-INR Control and Influential Factors
TTR was calculated for all patients and separately for each group. It was 64±25%, ranging from 0% to 100%, for all patients and in each group it varied from of 56% to 74% (P<0.001 by ANOVA) with significant low values in Groups A and D compared with the others (Figure 1). The distribution of the numbers of patients with TTR from 0 to 100% at the first and second observation years for all patients, for patients <70 years and those aged ≥70 is shown in Figure 2. In the total patient group, 303 (60.5%) had a TTR >60%. The distribution was quite different between the patient groups aged <70 and ≥70 years.

The TTR calculated for the first and second observation years for all patients was 63±29% and 65±28%, respectively (P=0.0737). To examine the effect of seasons, TTR was calculated separately for the periods from April to September.
and from October to May. As shown in Figure 3, no significant seasonal effect was observed, although TTR was slightly increased as the year changed from the first to the second. Time below and above TTR was 31±26% and 5±7%, respectively, for all patients. Groups with low TTR values showed longer times under TTR.

TTR was not affected by gender: in male and female patients it was 64±25% and 65±25%, respectively. Also, it was not affected by co-administration of antiplatelet drugs: TTR in patients with and without antiplatelet drugs was 64±25%
and 65±25%, respectively. Figure 4 shows TTR separately for patients aged ≤49, between 50 and 59, between 60 and 69, between 70 and 74, and ≥75 years. TTR values for the groups aged <70 years were all significantly low compared with TTR for the groups aged ≥70 (all P<0.0001). TTR in the groups aged <70 and ≥70 years was 46±23% and 77±17%, respectively (P<0.0001), and this significant difference was observed in each of groups A–E. Time below and above TTR in the patient group aged <70 years was 51±24% and 2±4%, respectively, while in the group aged ≥70 years it was 23±16% and 7±9%, respectively.

Figure 5 shows TTR separately for the patient groups with CHADS₂ scores from 0 to 6. TTR in the group with score 0 was 50±31% and was significantly lower than in the groups with scores of 2 or 3. When TTR was compared between the groups with CHADS₂ score ≤1 and ≥2, it was 59±27% and 68±23%, respectively (P<0.0001). The average age of the patients with CHADS₂ score ≤1 (n=198) was 65±11 years,
whereas that of the patients with a score ≥2 (n=303) was 73±8 years (P<0.0001). Of the 198 patients with CHADS2 score ≤1, 121 (61%) were younger than 70 years, and their TTR was 45±23%. Of the other 303 with a score ≥2, 87 (29%) were younger than 70 years, and their TTR was 48±22% (P=NS, vs. patients with the score ≤1). Thus, in patients younger than 70 years, TTR was low, irrespectively of CHADS2 score.

Figure 6 shows the effect of warfarin dose on TTR, separately for the patient groups with a dose <2.5 mg/day (mean 1.7±0.4), between 2.5 and 4.9 mg/day (mean 3.3±0.6), and ≥5.0 mg/day (mean 5.6±0.8). TTR in these 3 groups was 72±22%, 66±25% and 48±24%, respectively (all P<0.001). The mean dose in patients aged <70 years was 3.5±1.2 mg/day and in the elderly it was 2.7±1.0 mg/day (P=0.0001).

Multiple stepwise regression analysis revealed that age and warfarin dose were independent predictors of TTR (Table).

### Discussion

**Major Findings**

By analyzing the TTR of 501 patients enrolled from 5 prefectures in Japan, we found that PT-INR was well-controlled or moderately well-controlled, although it varied significantly with the institutions. Most of the time spent out of TTR was under the range, reflecting a tendency toward relatively weak PT-INR control in Japan. There were slight chronological changes in PT-INR control over the 2-year period. The factors influencing TTR included age, CHADS2 score and warfarin dose. Multivariate analysis indicated that age and warfarin dose were independent predictors of TTR. (Table)

### Status of PT-INR Control in Japan

In Japan in the early 1990s, warfarin was used only in <20% of the patients with AF, but usage increased to 50% around year 2000. Currently, warfarin is used in approximately 90% of patients that are treated by cardiologists. To secure not only efficacy but also safety during warfarin therapy, Japanese guidelines recommended PT-INR control between 2.0 and 3.0 in patients aged <70 years and between 1.6 and 2.6 in those aged ≥70 years. TTR is the proportion of time during which PT-INR is supposed to be within the recommended therapeutic range for the observation period, and the higher TTR is, the better the PT-INR control. The analysis of the outcome of patients randomized to warfarin therapy in the SPORTIF III and V studies indicated that the risks of death, myocardial infarction, and stroke or systemic embolic event were lower in patients with TTR ≥60% than in those with TTR <60%. A post-hoc analysis of the ACTIVE W study showed that in patients treated at hospitals with a TTR below the median value (65%), no treatment benefit with warfarin was demonstrated compared with combined antiplatelet therapy, whereas in patients at hospitals with a TTR ≥65%, warfarin showed a marked benefit, reducing vascular events by >2-fold. The ACTIVE W study estimated the target threshold TTR to be between 58% and 65%, below which there is little benefit of warfarin over antiplatelet therapy. Masaki et al retrospectively analyzed 120 Japanese patients with AF and aged ≥70 years who were treated with warfarin according to the Japanese Guideline, and showed that TTR >68% was associated with reduced risk of stroke compared with ≤68%. They also showed that the average PT-INR was not an effective measure for risk stratification.

In this study, we calculated the TTR for PT-INR values measured over a 2-year period in 501 AF patients enrolled from 5 prefectures. We found that TTR calculated from the first- and second-year data was unchanged, and furthermore, TTR was not affected by the seasons. Thus, TTR is considered to be a stable and reliable marker of PT-INR control. The study results showed that the mean TTR for the 2-year period was 64% for all patients, varying from 56% to 74% among the institutions. In the ACTIVE W study, 29 different countries participated, and the country mean TTR was shown to vary from 46% to 78%. In the recent RELY study, 44 different countries participated, and the country mean TTR varied from 44% to 77%. The RELY study subanalysis demonstrated that the most important baseline characteristic associated with variability in TTR in the individual patient was the mean TTR of the institution. Although the present results may not necessarily reflect the status of PT-INR control in all Japanese institutions, PT-INR as a whole is considered to be well-controlled or moderately well-controlled in Japan.

This study showed that most of the time spent out of TTR was below the range. Importantly, the amount of time below therapeutic range was markedly high (51±24%) in the patient group aged <70 years. This finding reflects a tendency to relatively weak PT-INR control in Japan, especially in the patients aged <70 years, even though the recommended therapeutic range is between 2.0 and 3.0. Because there was little chronological change in PT-INR control during the 2-year period, this weak PT-INR control may be related to the conviction of the attending physicians. A Japan-specific, relatively low therapeutic range (1.6–2.6) set for patients aged ≥70 years may have affected the range set for patients aged <70, resulting in an increased proportion of time spent below therapeutic range in the younger patients.

### Factors Affecting TTR

There was no difference in TTR between male and female patients. There was also no difference by co-administration of antiplatelet drugs, although the combined use of warfarin and an antiplatelet drug has been shown to be associated with increased risk of severe bleeding events. Age strongly affected TTR: in patients aged ≥70 years, TTR was 77±17%, whereas in those aged <70, it was significantly decreased to 46±23%. As clearly shown in Figure 2, most of the patients aged <70 years had a TTR <60%, whereas most of the patients aged ≥70 had a TTR >60%. It should be emphasized that the difference in TTR by age was observed in all institutions. As discussed before, most of the time spent out of TTR (ie, >50% of the time) was below the range, especially in the patients aged <70 years. It should be noted that many of the patients aged <70 years had a low risk of stroke (CHADS2 score <2), which might have affected the level of PT-INR control maintained by the physicians. However, TTR was also low (48±22%) in patients aged <70 years and at high risk (CHADS2 score ≥2). Thus, adherence to the Japanese Guideline seems to be insufficient in many AF patients aged <70 years undergoing warfarin therapy. TTR between 1.6 and 2.6 for patients aged ≥70 years recommended by the guideline seems to have affected PT-INR control even in patients aged <70 in whom

### Table. Multiple Stepwise Regression Analysis of the Variables That Were Related to Time in the Therapeutic Range

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>SEM</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.063</td>
<td>0.113</td>
<td>9.378</td>
<td>0.000</td>
</tr>
<tr>
<td>CHADS2 score</td>
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<td>0.869</td>
<td>-0.320</td>
<td>0.749</td>
</tr>
<tr>
<td>Warfarin dose</td>
<td>-1.897</td>
<td>0.922</td>
<td>-2.057</td>
<td>0.040</td>
</tr>
</tbody>
</table>
the recommended range is between 2.0 and 3.0. CHADS: score also significantly affected TTR: in patients with a score ≤1, TTR was 59±27%, and in those with a score ≥2, it was significantly increased to 68±23%. In our multivariate analysis, however, CHADS: score was not an independent predictor of TTR, which may be explained by the fact that the age of the patients with a score ≥2 was significantly higher than that of the patients with a score ≤1, and many (72%) of the patients with a score ≥2 were ≥70 years old.

Warfarin dose significantly affected TTR: in the patient groups with a dose <2.5 mg/day or between 2.5 and 4.9 mg/day, TTR was 72±22% and 63±25%, respectively and in the group with a dose ≥5.0 mg/day TTR was significantly decreased to 48±24%. Thus, the higher the required dose of warfarin dose, the poorer the PT-INR control. It should be noted that the warfarin dose differed between the patient groups aged <70 and ≥70 years, and age might have affected the dose administered by the physician. In fact, the mean dose was higher in the younger patients than in the elderly. After multivariate analysis, however, warfarin dose remained an independent predictor of TTR. The dose adjustment needed to obtain optimal PT-INR may be difficult in the patients who require doses ≥5.0 mg/day. Or increasing the warfarin dose ≥5.0 mg/day may make physicians anxious about the risk of hemorrhage.

Study Limitations
We retrospectively analyzed the records of patients taking warfarin for ≥2 years. A prospective study may be associated with better PT-INR control. However, the data presented here seem to reflect the “real life” status of PT-INR control in Japan. This study did not include patients with stroke or systemic thromboembolism or major hemorrhage during the study period. The purpose of the study was to examine the status of TTR and identify the influential factors on TTR in AF patients undergoing long-term warfarin therapy, and not the relation of TTR to cardiovascular events, including ischemic and hemorrhagic stroke. A prospective study will be required to show the relation of TTR to the efficacy and safety of warfarin therapy. In this study, multivariate analysis revealed that age and warfarin dose were independent predictors of TTR. Because TTR used for calculating TTR may make physicians anxious about the risk of hemorrhage. The dose adjustment needed to obtain optimal PT-INR may be difficult in the patients who require doses ≥5.0 mg/day. Or increasing the warfarin dose ≥5.0 mg/day may make physicians anxious about the risk of hemorrhage.

Clinical Implications
This study revealed the influential factors on TTR in Japanese patients with AF undergoing long-term warfarin therapy. Age and warfarin dose were found to be independent predictors of TTR. PT-INR control was poor in the patients <70 years and taking warfarin ≥5.0 mg/day. Because this remained unchanged during the 2-year observation period, continuance of appropriate warfarin therapy may be difficult, at least in patients with these clinical characteristics in Japan. The new oral anticoagulant, dabigatran, could be considered in such patients. Finally, PT-INR control was excellent in the present patients aged ≥70 years, largely because TTR is set at a low level compared with the range for patients <70. The efficacy and safety of adjusting the warfarin dose to keep the PT-INR within this low range in patients aged ≥70 years are now being investigated by the J-RHYHTM registry. A proposal for selecting either warfarin or dabigatran in this high-risk patient group will be made after analysis of the results of J-RHYHTM.

Disclosure
The authors declare no financial conflicts of interest.

References
