Oral anticoagulation therapy with warfarin is effective at reducing thromboembolic events in patients with atrial fibrillation (AF). Although the proportion of nonvalvular AF (NVAF) patients taking warfarin has been decreasing worldwide after the introduction of direct oral anticoagulants (DOAC) in clinical practice, warfarin is still prescribed in a substantial number of patients. A switch from warfarin to a DOAC may not be necessarily recommended in patients who are stable on warfarin. However, a major limitation of warfarin is its narrow therapeutic range (i.e., international normalized ratio [INR] of prothrombin time of 2.0–3.0 in Western countries and of 1.6–2.6 for elderly patients in Japan). Moreover, the quality of anticoagulation with warfarin is critical for the prevention of thromboembolic events without increasing hemorrhagic events. Time in therapeutic range (TTR) is an index used to assess the quality of warfarin treatment, and it has been reported that TTR should be maintained >60% to prevent thromboembolism in patients with NVAF. Morgan et al clearly showed that patients with NVAF and lower TTR (i.e., <30% or ≤40%) manifested with poor outcomes compared with patients receiving no warfarin. In Japan, this kind of analysis is still limited. Therefore, in the present study we analyzed the association between TTR and disease outcomes to determine a critical TTR for effective prevention of thromboembolic events without increasing hemorrhagic events in elderly patients with NVAF using the J-RHYTHM Registry dataset.

Patients aged <70 years were excluded from the present subanalysis, because approximately 60% of these patients had baseline INR values lower than those recommended by the Japanese guidelines, thereby resulting in unpredictably lower TTR in patients aged <70 years.
Methods

Study Protocol

The J-RHYTHM Registry (UMIN Clinical Trials Registry UMIN000001569) is a prospective observational investigation that enrolled patients with AF from January to July 2009 after obtaining written informed consent. The study design and baseline characteristics of the patients have been reported elsewhere. Briefly, the study protocol conformed to the Declaration of Helsinki and was approved by the ethics committee of each participating institution. A consecutive series of outpatients with AF of any type was enrolled. Patients who presented with mitral stenosis, underwent mechanical valve replacement, or missed the follow-up examinations were excluded from the present analysis. Antithrombotic drugs and dosages were selected at the discretion of treating physicians. Anticoagulation intensity was determined by assessing the INR values, at least bimonthly.

Endpoints

Patients were followed-up for 2 years or until the occurrence of an adverse event, whichever occurred first. Primary endpoints were thromboembolism (including symptomatic

### Table 1. Baseline Patient Characteristics and Medications

<table>
<thead>
<tr>
<th>Group</th>
<th>TTR (%)</th>
<th>P&lt;sup&gt;rend&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No-warfarin group (n=459)</td>
<td>40–59.9 (n=485)</td>
<td>60–79.9 (n=1,008)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>78.0±5.7</td>
<td>78.2±5.0</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>173 (37.7)</td>
<td>125 (36.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.1±3.4</td>
<td>22.4±3.6</td>
</tr>
</tbody>
</table>

Data are given as the number of patients (%) or as the mean ± SD. The target INR of prothrombin time was 1.6–2.6. AF, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CHADS<sub>2</sub>, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and history of stroke or TIA; CHA2DS<sub>2</sub>-VASc, CHADS<sub>2</sub> components plus vascular disease (coronary artery disease), age 70–74 years in the present analysis, and female sex; HAS-BLED, hypertension (systolic blood pressure ≥140 mmHg), abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR (episodes of INR ≥3.5), elderly (age >70 years in the present analysis), drugs (use of antiplatelet drugs)/alcohol concomitantly; INR, international normalized ratio; TIA, transient ischemic attack; TTR, time in therapeutic range; TSupraTR, time in supratherapeutic range (INR >2.6); TSubTR, time in subtherapeutic range (INR <1.6).
ischemic stroke, transient ischemic attack [TIA], and systemic embolic events), major hemorrhagic events (including intracranial hemorrhage, gastrointestinal hemorrhage, and other hemorrhages requiring hospitalization), or all-cause death. A composite endpoint of thromboembolism, major hemorrhage, and all-cause death was also evaluated. The diagnostic criteria for each event have been described elsewhere.¹⁷

**Statistical Analysis**

Data are presented as the mean±SD. The significance of differences in mean values was analyzed using analysis of variance (ANOVA). Frequencies of parameters or events were compared using the Chi-squared test or Fisher’s exact test, as appropriate. Kaplan-Meier curves were used to compare the time of the events by applying log-rank tests. The cut-off values for TTR for predicting the disease outcomes were determined with the receiver operating characteristic (ROC) curve. Cox proportional hazards model was used to investigate the effects of TTR on the events. Hazard ratios (HRs) and 95% confidence interval (CI) of the 4 TTR groups were calculated with the no-warfarin group as a reference. Explanatory variables used in multivariate analyses were well-known risk factors, namely components of the CHA₂DS₂-VASc score (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, history of stroke or TIA, vascular disease [coronary artery disease in the present study], and female sex), antiplatelet drug use, and type of AF. Two-tailed P<0.05 was considered significant. All statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

**Results**

Of 7,937 patients with AF enrolled in the Registry, follow-up data were available for 7,406 patients with NVAF.¹⁸ Of these patients, TTR was available for 6,064 (2,691 patients aged <70 years and 3,373 patients aged ≥70 years). Warfarin was not administered in 459 patients aged ≥70 years. Therefore, 3,832 elderly patients (mean age 77.0±5.0 years, 64.3% males) with TTR or without warfarin treatment constituted the study group.

**Patients’ Clinical Characteristics**

The characteristics of the patients are given in Table 1. Although the prevalence rates of most of the comorbidities were comparable among the groups, patients belonging in the TTR <40% group were older and had a lower body mass index. Thromboembolic (CHADS₂: and CHA₂DS₂-VASc) risk scores¹⁹,²¹ did not differ among the 5 groups, but hemorrhagic risk (HAS-BLED) scores²² did. Daily doses of warfarin and baseline INR values were lower in the TTR
<40% group. The mean TTR values differed significantly among the 4 TTR groups for the study design. The number of the INR determinations also differed significantly among the 4 TTR groups ($P_{\text{trend}}<0.001$), with the lowest number of determinations in the TTR <40% group. Concomitant use of antiplatelet drugs was more frequent in the no-warfarin group.

**Event Rates**
During the 2-year follow-up period, 91 patients experienced thromboembolic events, 94 patients experienced major hemorrhagic events, and 144 patients died (Table 2). Incidence rates differed significantly for thromboembolism and all-cause death among the 5 groups, but not for major hemorrhages. Consequently, the rate of composite events differed among the 5 groups.

The cut-off values for TTR to predict disease outcomes are given in Table 3. When patients on warfarin were divided into 2 groups based on a TTR cut-off value of 66%, the TTR <66% group did not show any benefit for the prevention of thromboembolism and composite events compared with the no-warfarin group (Table 4; Figures S1, S2).

The Kaplan-Meier curves for the disease outcome were compared among the 5 groups (Figures 1, 2). Notably, the event-free survival rates for thromboembolism, major hemorrhages, and composite events were lower in the TTR <40% group than in the no-warfarin group.

In univariate analysis (Table 5), TTR <40% was associated with a higher risk for major hemorrhages and composite events compared with the no-warfarin group. TTR ≥60% was associated with a lower risk of thromboembolism, all-cause death, and composite events. As expected, an increase in time in the supratherapeutic range (i.e., INR values >2.6) was associated with a higher risk of major hemorrhages (Table S1). In contrast, an increase in time in the subtherapeutic range (i.e., INR values <1.6) was associated with a higher risk of thromboembolism (Table S1). In multivariate analysis (Table 6), TTR <40% and ≥60% was associated with outcome events, as in the univariate analysis. Several other comorbidities were associated with outcome events.

![Figure 1](https://example.com/figure1.png)  
**Figure 1.** Kaplan-Meier curves for the incidence of (A) thromboembolism, (B) major hemorrhage, and (C) all-cause death according to warfarin use and the 4 time in TTR strata. TTR, time in therapeutic range.
Time in Therapeutic Range and Outcomes of NVAF

In addition to the INR value itself, it has been reported that the TTR (which is an index of the quality of INR control) needs to be maintained above 60–75% for a significant reduction in stroke and systemic embolism. In a subanalysis of SPORTIF-III and IV, patients with NVAF on warfarin were divided into 3 groups considering INR values. 

### Discussion

We examined the relationship between the quality of warfarin treatment and the prognosis for elderly NVAF patients aged ≥70 years in whom target INR values between 1.6 and 2.6 are recommended by the Japanese guidelines. The major findings of the present study were that TTR was independently associated with the disease outcomes compared with the no-warfarin group and that TTR <40% was associated with a higher rate of major hemorrhage, but, in contrast, TTR ≥60% was associated with better prognosis in terms of thromboembolism, all-cause death, and composite events. 

### TTR Values and Prognosis

The intensity of anticoagulation with warfarin, measured in terms of INR values, is critical for the prevention of thromboembolic events among patients with NVAF receiving warfarin. According to guidelines in Europe, North America, and Japan, target INR values are in the range 2.0–3.0, except for elderly NVAF patients in Japan, for whom INR values in the range 1.6–2.6 are recommended. In addition to the INR value itself, it has been reported that the TTR (which is an index of the quality of INR control) needs to be maintained above 60–75% for a significant reduction in stroke and systemic embolism.

Masaki et al determined the relationship between TTR and the incidence of stroke in 188 elderly Japanese patients with AF. As in the present study, the target INR values in that study were set at 1.6–2.6. ROC curve analysis by Masaki et al revealed that the cut-off value for TTR was 68% to ensure anticoagulation benefit. The TTR ≤68% group did not show any benefit compared with the no-warfarin group. However, in that study the relationship between TTR and hemorrhagic events or mortality was not significant.

In a subanalysis of SPORTIF-III and IV, patients with NVAF on warfarin were divided into 3 groups considering
However, in these studies a no-warfarin group was not compared with the no-warfarin group, TTR groups receiving warfarin with those of the no-warfarin patients with a CHADS 2 score ≥3.14 Associated with a lower incidences of all-cause death, and TTR associated with a lower rate of all-cause death. Female sex was observed to be associated with a lower rate of stroke/TIA. In the multivariate analysis, some clinical variables associated with the incidence of thromboembolic major hemorrhage, and all-cause death. Vascular disease, coronary artery disease. Other abbreviations as in Tables 1, 5.

<table>
<thead>
<tr>
<th>TTR (%)</th>
<th>Thromboembolism</th>
<th>Major hemorrhage</th>
<th>All-cause death</th>
<th>Composite events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P value</td>
<td>HR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>&lt;40%</td>
<td>1.20 (0.59–2.41)</td>
<td>0.614</td>
<td>5.57 (2.04–15.25)</td>
<td>0.001</td>
</tr>
<tr>
<td>40–59.9%</td>
<td>0.51 (0.25–1.01)</td>
<td>0.554</td>
<td>1.35 (0.46–3.97)</td>
<td>0.583</td>
</tr>
<tr>
<td>60–79.9%</td>
<td>0.34 (0.17–0.67)</td>
<td>0.002</td>
<td>1.99 (0.74–5.36)</td>
<td>0.172</td>
</tr>
<tr>
<td>≥80%</td>
<td>0.35 (0.18–0.68)</td>
<td>0.002</td>
<td>2.40 (0.91–6.30)</td>
<td>0.076</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.79 (0.50–1.26)</td>
<td>0.325</td>
<td>1.39 (0.91–2.14)</td>
<td>0.129</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.94 (0.61–1.44)</td>
<td>0.769</td>
<td>1.66 (1.03–2.66)</td>
<td>0.037</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>1.74 (1.07–2.83)</td>
<td>0.025</td>
<td>1.66 (1.04–2.65)</td>
<td>0.035</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.22 (0.74–2.00)</td>
<td>0.444</td>
<td>0.95 (0.56–1.58)</td>
<td>0.848</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>1.68 (1.03–2.73)</td>
<td>0.039</td>
<td>1.38 (0.84–2.26)</td>
<td>0.199</td>
</tr>
<tr>
<td>Vascular diseases</td>
<td>0.92 (0.48–1.75)</td>
<td>0.797</td>
<td>1.11 (0.61–2.00)</td>
<td>0.739</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.85 (0.55–1.34)</td>
<td>0.488</td>
<td>0.57 (0.35–0.91)</td>
<td>0.020</td>
</tr>
<tr>
<td>Persistent AF²</td>
<td>1.28 (0.60–2.74)</td>
<td>0.525</td>
<td>1.22 (0.63–2.36)</td>
<td>0.560</td>
</tr>
<tr>
<td>Permanent AF²</td>
<td>2.00 (1.20–3.35)</td>
<td>0.008</td>
<td>1.21 (0.74–1.98)</td>
<td>0.444</td>
</tr>
<tr>
<td>Antiplatelet use</td>
<td>1.05 (0.65–1.71)</td>
<td>0.833</td>
<td>1.26 (0.78–2.03)</td>
<td>0.341</td>
</tr>
</tbody>
</table>

*Compared with no-warfarin. *Compared with paroxysmal AF. Composite of thromboembolism, major hemorrhage, and all-cause death.

In a systematic review, Wan et al indicated that an 8.3% increase in TTR significantly reduced the incidence of major hemorrhage by 1 event per 100 patient-years, and a 10.2% increase in TTR reduced the incidence of thromboembolic events by 1 event per 100 patient-years among patients on warfarin. In a subanalysis of the RE-LY, patients belonging to the warfarin group were divided into groups based on 4 individual TTR, and TTR ≥67.2% associated with lower rates for the events. However, in these studies a no-warfarin group was not included as a reference. In a systematic review, Wan et al indicated that an 8.3% increase in TTR significantly reduced the incidence of major hemorrhage by 1 event per 100 patient-years, and a 10.2% increase in TTR reduced the incidence of thromboembolic events by 1 event per 100 patient-years among patients on warfarin. In a subanalysis of the RE-LY, patients belonging to the warfarin group were divided into groups based on 4 individual TTR, and TTR ≥67.2% associated with lower rates for the events. However, in these studies a no-warfarin group was not included as a reference. In a systematic review, Wan et al indicated that an 8.3% increase in TTR significantly reduced the incidence of major hemorrhage by 1 event per 100 patient-years, and a 10.2% increase in TTR reduced the incidence of thromboembolic events by 1 event per 100 patient-years among patients on warfarin. In a subanalysis of the RE-LY, patients belonging to the warfarin group were divided into groups based on 4 individual TTR, and TTR ≥67.2% associated with lower rates for the events. However, in these studies a no-warfarin group was not included as a reference. In a systematic review, Wan et al indicated that an 8.3% increase in TTR significantly reduced the incidence of major hemorrhage by 1 event per 100 patient-years, and a 10.2% increase in TTR reduced the incidence of thromboembolic events by 1 event per 100 patient-years among patients on warfarin. In a subanalysis of the RE-LY, patients belonging to the warfarin group were divided into groups based on 4 individual TTR, and TTR ≥67.2% associated with lower rates for the events. However, in these studies a no-warfarin group was not included as a reference.

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AF emerged as an independent predictor of thromboembolism, a finding consistent with other studies. When the multivariate analysis was performed with different explanatory variables, permanent AF did not emerge as an independent predictor of thromboembolism, as reported in our previous subanalysis of the J-RHYTHM Registry. Therefore, the association of AF type with thromboembolic events should be interpreted with caution.

Study Limitations
The present subanalysis had several limitations. First, this subanalysis was a post hoc analysis of an observational study and was therefore hypothesis generating in nature. Second, younger patients (<70 years) were not included in the present analysis. The Japanese guidelines recommend lower target INR (1.6–2.0) for elderly patients (≥70 years) with NVAF. Therefore, the present results cannot be extrapolated to Japanese patients with NVAF who are aged <70 years or to patients with NVAF of other countries where different target INR values are recommended. 5,6

Conclusions
Among the elderly Japanese patients with NVAF in the present study, patients belonging to the TTR <40% group had a higher incidence of major hemorrhage than those in the no-warfarin group. In contrast, TTR ≥60% or ≥66% was associated with a good prognosis with regard to thromboembolism and all-cause death.

Acknowledgments
A list of the cardiologists participating in the J-RHYTHM Registry is available elsewhere. The J-RHYTHM Registry was supported by a grant from the Japan Heart Foundation (No. 12080025), Tokyo, Japan.

Conflict of Interest
H.I. reports receiving remuneration from Daiichi-Sankyo, Bayer Healthcare, Bristol-Myers Squibb, and Boehringer Ingelheim. E.K. has received remuneration from Boehringer Ingelheim, Bayer Healthcare, and Daiichi-Sankyo. T.Y. has received research funding from Bayer Healthcare, Bristol-Myers Squibb, and Daiichi-Sankyo, as well as remuneration from Boehringer Ingelheim, Daiichi-Sankyo, Bayer Healthcare, Pfizer, Bristol-Myers Squibb, and Eisai. Y.O. has received remuneration from Bristol-Myers Squibb and Pfizer. H.O. has helped collect data for trials sponsored by Daiichi-Sankyo. H.A. has received remuneration from Daiichi-Sankyo.

References


Supplementary Files

Supplementary File 1

Figure S1. Kaplan-Meier curves for the incidence of (A) thromboembolism, (B) major hemorrhage, and (C) all-cause death according to warfarin use and 2 TTR strata.

Figure S2. Kaplan-Meier curves for the incidence of the composite of thromboembolism, major hemorrhage, and all-cause death according to warfarin use and 2 TTR strata.

Table S1. Effects of TTR, time in supratherapeutic range (INR >2.6), and time in subtherapeutic range (INR <1.6) on events (univariate analysis)

Please find supplementary file(s):