Time in Therapeutic Range and Disease Outcomes in Elderly Japanese Patients With Nonvalvular Atrial Fibrillation

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Background: The relationship between warfarin treatment quality and prognosis for Japanese patients with nonvalvular atrial fibrillation (NVAF) has not been studied thoroughly.

Methods and Results: Data from the J-RHYTHM Registry were used to determine the time in therapeutic range (TTR) of the international normalized ratio (INR) of prothrombin time in elderly patients (≥ 70 years). Target INR was 1.6–2.6. Of 7,406 patients with NVAF in the database, 3,832 elderly patients (mean $\pm$ SD age 77.0 ± 5.0 years) constituted the study group. Of these patients, 459 did not receive warfarin and 3,373 received warfarin. Patients on warfarin were subdivided into 4 TTR groups: $<40\%$, 40–59.9%, 60–79.9%, and $\geq 80\%$. During the 2-year follow-up, the incidence of thromboembolism and all-cause death was lower in patients with higher TTR (Ptrend <0.001); however, the incidence of major hemorrhage was higher in patients with TTR $<40\%$. In multivariate analysis, compared with the no-warfarin group, TTR 60–79.9% and $\geq 80\%$ were associated with lower thromboembolic risk, with hazard ratios (HR) of 0.34 (95% confidence interval [CI] 0.17–0.67; $P=0.002$) and 0.35 (95% CI 0.18–0.68; $P=0.002$), respectively, and lower all-cause death (HR 0.37 [95% CI 0.22–0.65; $P<0.001$] and 0.43 [95% CI 0.26–0.71; $P=0.001$], respectively). TTR $<40\%$ was associated with major hemorrhage (HR 5.57; 95% CI 2.04–15.25; $P=0.001$).

Conclusions: In elderly Japanese patients with NVAF, TTR should be maintained $\geq 60\%$ to prevent thromboembolism and all-cause death. TTR $<40\%$ should be avoided to prevent major hemorrhage.

Key Words: Atrial fibrillation; Elderly patients; Outcomes; Warfarin control

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.^{1–3} A switch from warfarin to a DOAC may not be necessarily recommended in patients who are stable on warfarin.⁴ 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^{5,6} and of 1.6–2.6 for elderly patients in Japan⁷). 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,⁸ and it has been reported that TTR should

be maintained $>60\%$ to prevent thromboembolism in patients with NVAF.^{9–14} Morgan et al clearly showed that patients with NVAF and lower TTR (i.e., $<30\%$ or $\leq 40\%$) manifested with poor outcomes compared with patients receiving no warfarin.¹⁴ In Japan, this kind of analysis is still limited.^{11,15} 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.^{16,17} 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,⁷ thereby resulting in unpredictably lower TTR in patients aged <70 years.¹⁶

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Table 1. Baseline Patient Characteristics and Medications

	No-warfarin group (n=459)	TTR (%)				P _{trend}
		<40 (n=342)	40–59.9 (n=485)	60–79.9 (n=1,008)	≥80 (n=1,538)	
Age (years)	78.0±5.7	78.2±5.0	77.2±5.0	76.7±4.9	76.6±4.7	<0.001
Sex (female)	173 (37.7)	125 (36.5)	156 (32.2)	382 (37.9)	532 (34.6)	0.417
BMI (kg/m ²)	23.1±3.4	22.4±3.6	23.1±7.2	23.0±3.5	23.3±3.2	0.001
Type of AF						<0.001
Paroxysmal	254 (55.3)	117 (34.2)	140 (28.9)	341 (33.8)	485 (31.5)	
Persistent	39 (8.5)	50 (14.6)	73 (15.1)	141 (14.0)	207 (13.5)	
Permanent	166 (36.2)	175 (51.2)	272 (56.1)	526 (52.2)	846 (55.0)	
Comorbidities						
Coronary artery disease	64 (13.9)	43 (12.6)	74 (15.3)	140 (13.9)	179 (11.6)	0.148
Cardiomyopathy	21 (4.6)	23 (6.7)	32 (6.6)	87 (8.6)	94 (6.1)	0.334
Hypertrophic	8 (1.7)	13 (3.8)	9 (1.9)	47 (4.7)	47 (3.1)	0.171
Dilated	13 (2.8)	10 (2.9)	23 (4.7)	40 (4.0)	47 (3.1)	0.999
COPD	12 (2.6)	14 (4.1)	10 (2.1)	21 (2.1)	33 (2.1)	0.179
Hyperthyroidism	5 (1.1)	2 (0.6)	3 (0.6)	19 (1.9)	20 (1.3)	0.255
Risk factors for stroke						
Heart failure	103 (22.4)	154 (45.0)	164 (33.8)	331 (32.8)	442 (28.7)	0.528
Hypertension	287 (62.5)	208 (60.8)	326 (67.2)	674 (66.9)	1,012 (65.8)	0.091
Age ≥75 years	308 (67.1)	247 (72.2)	318 (65.6)	616 (61.1)	942 (61.2)	<0.001
Diabetes mellitus	75 (16.3)	73 (21.3)	110 (22.7)	174 (17.3)	309 (20.1)	0.496
Stroke/TIA	54 (11.8)	60 (17.5)	74 (15.3)	179 (17.8)	245 (15.9)	0.109
CHADS ₂ score	1.9±1.2	2.3±1.2	2.2±1.2	2.1±1.2	2.1±1.2	0.423
CHA ₂ DS ₂ -VASc score	3.4±1.4	3.8±1.3	3.7±1.3	3.7±1.4	3.5±1.4	0.160
HAS-BLED score	2.1±0.8	2.0±0.9	2.0±0.9	1.9±0.9	1.7±0.8	<0.001
Warfarin dose (mg/day)	–	2.3±1.1	2.5±1.0	2.6±1.1	2.7±1.0	<0.001
INR	–	1.71±0.65	1.84±0.55	1.93±0.52	1.95±0.38	<0.001
No. INR determinations	–	10.8±5.8	13.6±5.2	14.7±5.1	14.1±5.5	<0.001
TTR ^a (%)	–	21.9±13.4	51.8±5.6	71.1±5.6	91.4±6.3	<0.001
TSupraTR (%)	–	13.1±25.1	13.6±15.8	11.0±10.4	3.5±4.8	<0.001
TSubTR (%)	–	65.0±29.5	34.5±16.8	17.9±11.2	5.0±5.6	<0.001
Antiplatelet drugs	295 (64.3)	100 (29.2)	145 (29.9)	245 (24.3)	337 (21.9)	<0.001
Aspirin	252 (54.9)	75 (21.9)	116 (23.9)	214 (21.2)	286 (18.6)	<0.001
Others	70 (15.3)	33 (9.6)	48 (9.9)	57 (5.7)	79 (5.1)	<0.001

Data are given as the number of patients (%) or as the mean ± SD. ^aThe target INR of prothrombin time was 1.6–2.6. AF, atrial fibrillation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CHADS₂, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and history of stroke or TIA; CHA₂DS₂-VASc, CHADS₂ 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).

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.¹⁷ The study design and baseline characteristics of the patients have been reported elsewhere.^{16,17} 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.¹⁷ The TTR was determined as an index of the quality of warfarin treatment by using the method developed by Rosendaal et al.⁸ For determination of TTR, the target INR level was set at 1.6–2.6 for elderly patients aged ≥70 years based on a previous study by Yasaka et al.¹⁸ and the Japanese guidelines.⁷ The time in INR >2.6 or <1.6 was also determined. Patients were divided into 5 groups based on warfarin use and 4 TTR values (i.e., no-warfarin and TTR <40%, 40–59.9%, 60–79.9%, and ≥80%).

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 2. Two-Year Event Rates in the No-Warfarin Group and 4 TTR Groups

	No-warfarin group (n=459)	TTR (%)				P _{trend}
		<40 (n=342)	40–59.9 (n=485)	60–79.9 (n=1,008)	≥80 (n=1,538)	
Thromboembolism	19 (4.1)	18 (5.3)	13 (2.7)	13 (1.3)	28 (1.8)	<0.001
Major hemorrhage	5 (1.1)	19 (5.6)	8 (1.6)	23 (2.3)	39 (2.5)	0.836
All-cause death	29 (6.3)	21 (6.1)	23 (4.7)	33 (3.3)	38 (2.5)	<0.001
Composite events ^A	53 (11.5)	58 (17.0)	44 (9.1)	69 (6.8)	105 (6.8)	<0.001

Data are given as number of patients (%). ^AComposite of thromboembolism, major hemorrhage, and all-cause death. TTR, time in therapeutic range.

Table 3. Receiver Operating Characteristic Curve Analysis

	AUC (95% CI)	P value	Cut-off TTR ^B (%)	Sensitivity (%)	Specificity (%)
Thromboembolism	0.582 (0.503–0.662)	0.017	65.9	69.3	51.4
Major hemorrhage	0.525 (0.455–0.596)	0.414	51.1	84.0	27.0
All-cause death	0.574 (0.514–0.634)	0.007	66.4	68.8	50.4
Composite events ^A	0.564 (0.523–0.605)	<0.001	66.8	68.9	46.7

^AComposite of thromboembolism, major hemorrhage, and all-cause death. ^BValues at maximum Youden's index (=sensitivity+specificity–1). AUC, area under the curve; CI, confidence interval; TTR, time in therapeutic range.

Table 4. Two-Year Event Rates in the No-Warfarin Group and 2 TTR Groups

	No-warfarin group (n=459)	TTR (%)		P _{trend}
		<66 (n=1,058)	≥66 (n=2,315)	
Thromboembolism	19 (4.1)	37 (3.5)	35 (1.5)	<0.001
Major hemorrhage	5 (1.1)	32 (3.0)	57 (2.5)	0.334
All-cause death	29 (6.3)	55 (5.2)	60 (2.6)	<0.001
Composite events ^A	53 (11.5)	124 (11.7)	152 (6.6)	<0.001

Data are given as number of patients (%). ^AComposite of thromboembolism, major hemorrhage, and all-cause death. TTR, time in therapeutic range.

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),¹⁹ 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.²⁰ 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 (CHA₂DS₂ and CHA₂DS₂-VASc) risk scores^{19,21} 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

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.

<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.

Table 5. Univariate Analysis for Effects of TTR on Events								
	Thromboembolism		Major hemorrhage		All-cause death		Composite events ^A	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
No-warfarin group	Ref.	–	Ref.	–	Ref.	–	Ref.	–
TTR (%)								
<40	1.34 (0.69–2.60)	0.392	6.06 (2.26–16.23)	<0.001	1.06 (0.59–1.89)	0.851	1.63 (1.12–2.38)	0.011
40–59.9	0.58 (0.30–1.11)	0.098	1.41 (0.49–4.07)	0.521	0.68 (0.41–1.13)	0.139	0.71 (0.49–1.03)	0.074
60–79.9	0.36 (0.19–0.70)	0.002	1.95 (0.75–5.12)	0.174	0.39 (0.23–0.65)	<0.001	0.53 (0.37–0.76)	<0.001
≥80	0.39 (0.21–0.73)	0.003	2.38 (0.93–6.07)	0.070	0.43 (0.26–0.70)	0.001	0.60 (0.43–0.84)	0.003

^AComposite of thromboembolism, major hemorrhage, and all-cause death. CI, confidence interval; HR, hazard ratio; TTR, time in therapeutic range.

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.⁷ 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,⁵

North America,⁶ and Japan,⁷ 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.^{7,18} 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.^{9–14}

Masaki et al¹¹ 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 al¹¹ 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.¹¹ However, in that study the relationship between TTR and hemorrhagic events or mortality was not significant.

In a subanalysis of SPORTIF-III and IV,⁹ patients with NVAF on warfarin were divided into 3 groups considering

Table 6. Multivariate Analysis for Variables Associated With Clinical Events

	Thromboembolism		Major hemorrhage		All-cause death		Composite events ^c	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
TTR (%)								
<40 ^A	1.20 (0.59–2.41)	0.614	5.57 (2.04–15.25)	0.001	0.81 (0.44–1.47)	0.487	1.38 (0.93–2.04)	0.112
40–59.9 ^A	0.51 (0.25–1.01)	0.054	1.35 (0.46–3.97)	0.583	0.60 (0.35–1.01)	0.053	0.65 (0.44–0.96)	0.028
60–79.9 ^A	0.34 (0.17–0.67)	0.002	1.99 (0.74–5.36)	0.172	0.37 (0.22–0.65)	<0.001	0.52 (0.36–0.75)	0.001
≥80 ^A	0.35 (0.18–0.68)	0.002	2.40 (0.91–6.30)	0.076	0.43 (0.26–0.71)	0.001	0.59 (0.41–0.84)	0.004
Heart failure	0.79 (0.50–1.26)	0.325	1.39 (0.91–2.14)	0.129	2.79 (1.97–3.94)	<0.001	1.63 (1.30–2.05)	<0.001
Hypertension	0.94 (0.61–1.44)	0.769	1.66 (1.03–2.66)	0.037	0.75 (0.54–1.05)	0.096	0.99 (0.78–1.24)	0.895
Age ≥75 years	1.74 (1.07–2.83)	0.025	1.66 (1.04–2.65)	0.035	3.26 (2.03–5.25)	<0.001	2.18 (1.66–2.86)	<0.001
Diabetes mellitus	1.22 (0.74–2.00)	0.444	0.95 (0.56–1.58)	0.848	1.09 (0.74–1.62)	0.652	1.08 (0.83–1.41)	0.553
Stroke/TIA	1.68 (1.03–2.73)	0.039	1.38 (0.84–2.26)	0.199	1.51 (1.01–2.23)	0.042	1.51 (1.17–1.97)	0.002
Vascular diseases	0.92 (0.48–1.75)	0.797	1.11 (0.61–2.00)	0.739	2.19 (1.47–3.26)	<0.001	1.50 (1.12–2.00)	0.006
Female sex	0.85 (0.55–1.34)	0.488	0.57 (0.35–0.91)	0.020	0.62 (0.42–0.90)	0.012	0.66 (0.52–0.85)	0.001
Persistent AF ^B	1.28 (0.60–2.74)	0.525	1.22 (0.63–2.36)	0.560	0.89 (0.49–1.63)	0.705	1.08 (0.74–1.59)	0.697
Permanent AF ^B	2.00 (1.20–3.35)	0.008	1.21 (0.74–1.98)	0.444	1.21 (0.82–1.80)	0.336	1.39 (1.07–1.80)	0.015
Antiplatelet use	1.05 (0.65–1.71)	0.833	1.26 (0.78–2.03)	0.341	1.21 (0.83–1.77)	0.315	1.18 (0.92–1.52)	0.192

^ACompared with no-warfarin. ^BCompared with paroxysmal AF. ^CComposite of thromboembolism, major hemorrhage, and all-cause death. Vascular disease, coronary artery disease. Other abbreviations as in Tables 1,5.

the quality of INR control (i.e., poor, moderate, and good control based on TTR). The findings of that study indicated that TTR calculated with target INR values of 2–3 should be maintained above 75% to prevent stroke and systemic embolism, and above 65% to decrease all-cause death and major hemorrhage.⁹ 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% was associated with lower rates for the events.²³ However, in these studies a no-warfarin group was not included as a reference.^{9,23}

In a systematic review, Wan et al²⁴ 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. Wan et al²⁴ recommended that anticoagulation processes aim for a TTR of 70–80% to optimize the benefits and reduce the harm in patients on warfarin. Morgan et al¹⁴ compared event rates of 6 TTR groups receiving warfarin with those of the no-warfarin group among patients with NVAF and found that, compared with the no-warfarin group, TTR ≥41% was associated with a lower incidence of all-cause death, and TTR ≥71% was associated with a lower incidence of stroke for patients with a CHADS₂ score ≥2. When all patients were included in the analysis, TTR ≥41% was observed to be associated with a lower rate of stroke and TTR ≥31% was associated with a lower rate of all-cause death.¹⁴ In the present study, the critical TTR values for better prognosis differed slightly from those suggested by Morgan et al;¹⁴ specifically, TTR ≥60% (or ≥66% as determined by ROC curve analysis) was required for a lower incidence of thromboembolism and all-cause death compared with the no-warfarin group. The difference in the association of

TTR values with outcome events between the present study and the study of Morgan et al¹⁴ could be attributed, at least in part, to differences in the clinical characteristics of the patients enrolled in the studies. For example, Morgan et al¹⁴ included younger as well as elderly patients (vs. only elderly patients in the present study), who had been hospitalized in 1995–2000 (vs. outpatients in 2009 in the present study). In addition, patients in the study of Morgan et al¹⁴ had a lower prevalence of hypertension (16.7%; vs. 65.4% in the present study), a lower mean CHADS₂ score (1.04; vs. 2.1 in the present study), and a higher rate of all-cause death (237.7/1,000 person-years for the no-warfarin group; vs. 6.3%/2 years in the present study).

TTR <40% was associated with major hemorrhagic events in the present study. This association seemed difficult to explain, because the TTR <40% group had a similar HAS-BLED score, as well as a similar time in the supratherapeutic range as the TTR 40–59.9% group. Some confounding factors not determined in the present analysis could have been involved in the association between TTR <40% and major hemorrhagic events.

In the multivariate analysis, some clinical variables in addition to age emerged as independent predictors of disease outcomes. Hypertension is a component of the bleeding risk score (i.e., HAS-BLED);²² therefore, it was associated with the incidence of major hemorrhage. In the case of thromboembolism, a previous history of stroke/TIA events emerged as an independent predictor, as expected from the risk scores.^{9,21} It seems likely that vascular diseases (coronary artery disease in the present analysis) and heart failure were associated with the incidence of all-cause death. Female sex was observed to be associated with a lower risk of major hemorrhage and all-cause death, as reported in the previous sub-analysis of the J-RHYTHM Registry.²⁵ Compared with paroxysmal AF, permanent

AF emerged as an independent predictor of thromboembolism, a finding consistent with other studies.^{26,27} 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.²⁸ 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 guidelines⁷ recommend lower target INR (1.6–2.6) 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.^{16,17} 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 Bristol-Myers Squibb. K.O. 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.

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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);
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