Present Status of Anticoagulation Treatment in Japanese Patients With Atrial Fibrillation

– A Report From the J-RHYTHM Registry –

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Background: Underuse and an inadequate range for the international normalized ratio (INR) for warfarin use are still problems in the management of the patients with atrial fibrillation (AF) in Japan.

Methods and Results: From January to July 2009, a total of 7,937 AF patients [5,468 men (68.6±10.0 years) and 2,469 women (72.2±9.0 years)] were registered from 158 institutions for the J-RHYTHM Registry. Overall, 34.2% of the patients were over the age of 75. The associated cardiovascular diagnoses were hypertension in 59.1%, coronary artery disease in 10.1%, cardiomyopathy in 8.3%, valvular heart disease in 13.7% and artificial cardiac valves in 3.1% of the patients. The type of AF was paroxysmal in 37.1%, persistent in 14.4%, and permanent in 48.5%. Overall, 87.3% of patients were taking warfarin (2.9±1.2 mg/day), of whom 66.0% had an INR between 1.6 and 2.6, and 35.4% were in the INR range from 2.0 to 3.0 at the time of registration. Aspirin was prescribed in 22.3% of cases. The CHADS2 score was 0 in 15.7% of patients, 1 in 34.0%, and ≥2 in 50.3%.

Conclusions: At present, warfarin is used extensively in patients with AF whose stroke risk is relatively low (ie, in Japan) and half of them had CHADS2 scores of 0 to 1 (UMIN Clinical Trials Registry UMIN000001569). (*Circ J* 2011; **75**: 1328–1333)

Key Words: Atrial fibrillation; CHADS2 score; International normalized ratio (INR); Multicenter registry; Warfarin

Although antithrombotic therapy by vitamin K antagonists to prevent thromboembolism in patients with atrial fibrillation (AF) has been recommended in clinical guidelines,^{1,2} the restrained use of warfarin is still part of general practice. At present, it is widely accepted that maximum protection against ischemic stroke in an AF patient is probably achieved in an international normalized ratio (INR) range of 2.0–3.0. However, 1 clinical report has stated that the optimal intensity of an INR was 1.6–2.6 in elderly Japanese AF patients³ in their second treatment to prevent stroke. According to reports on racial differences in the safety of warfarin use, it may increase the risk of intracranial hemorrhage among AF patients in Asia.^{4–6} According to Shen et al,⁴ non-white patients, especially Asians, with AF are at risk of such hemorrhages due to warfarin use. There have been no

large-scale investigations to demonstrate an appropriate INR for Japanese AF patients. The J-RHYTHM Registry is the first prospective, observational accumulation of data employed in the investigation of the optimal intensity of anticoagulation in Japanese AF patients and of the present status of anticoagulation treatment in Japan.⁷

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Methods

The purpose of this study was firstly to demonstrate the status of anticoagulation treatment in Japanese AF patients in 2009. Details of the overall study design of the J-RHYTHM Regis-

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Table 1. Baseline Characteristics of Registered Patients

	Overall	Warfarin group	Non-warfarin group	P value
No. of patients	7,937	6,932	1,005	
Age (years)	69.7±9.9	70.0±9.5	67.8±11.8	<0.0001
≤49	267 (3.4)	193 (2.8)	74 (7.4)	
50–59	859 (10.8)	706 (10.2)	153 (15.2)	
60–69	2,514 (31.7)	2,198 (31.7)	316 (31.4)	<0.0001
70–79	3,031 (38.2)	2,735 (39.5)	296 (29.5)	
≥80	1,266 (16.0)	1,100 (15.9)	166 (16.5)	
No. of men (%)	5,468 (68.9)	4,763 (68.7)	705 (70.2)	0.36
Age of men (years)	68.6±10.0	68.9±9.7	66.4±11.9	<0.0001
Age of women (years)	72.2±9.0	72.3±8.8	71.0±10.7	0.022
Type of atrial fibrillation				
Paroxysmal	2,947 (37.1)	2,338 (33.7)	609 (60.6)	
Persistent	1,144 (14.4)	1,036 (15.0)	108 (10.8)	<0.0001
Permanent	3,846 (48.5)	3,558 (51.3)	288 (28.7)	
Comorbidities				
Hypertension	4,691 (59.1)	4,155 (59.9)	536 (53.3)	<0.0001
Coronary artery disease	805 (10.1)	711 (10.3)	94 (9.4)	0.38
Cardiomyopathy	656 (8.3)	609 (8.8)	47 (4.7)	<0.0001
HCM	269 (3.4)	250 (3.6)	19 (1.9)	0.0050
DCM	387 (4.9)	359 (5.2)	28 (2.8)	0.0010
Congenital heart disease	100 (1.3)	89 (1.3)	11 (1.1)	0.62
COPD	136 (1.7)	121 (1.8)	15 (1.5)	0.56
Hyperthyroidism	138 (1.7)	120 (1.7)	18 (1.8)	0.89
Valvular disease	1,086 (13.7)	996 (14.4)	90 (9.0)	<0.0001
Mitral stenosis	274 (3.5)	271 (3.9)	3 (0.3)	<0.0001
Prosthetic valve	247 (3.1)	247 (3.6)	0 (0)	<0.0001
Diabetes mellitus	1,445 (18.2)	1,309 (18.9)	136 (13.5)	<0.0001
Stroke/TIA	1,110 (14.0)	1,043 (15.1)	67 (6.7)	<0.0001
CHADS2 score				
0	1,242 (15.6)	950 (13.7)	292 (29.1)	
1	2,697 (34.0)	2,322 (33.5)	375 (37.3)	
2	2,210 (27.8)	2,004 (28.9)	206 (20.5)	
3	1,145 (14.4)	1,065 (15.4)	80 (8.0)	<0.0001
4	455 (5.7)	420 (6.1)	35 (3.5)	
5	161 (2.0)	147 (2.1)	14 (1.4)	
6	27 (0.3)	24 (0.4)	3 (0.3)	
Heart rate (beats/min)	72.5±13.2	72.6±13.1	72.0±13.7	0.20
SBP (mmHg)	125.7±16.1	125.6±16.1	127.0±16.5	0.0083
DBP (mmHg)	73.1±11.1	73.0±11.2	73.9±10.6	0.0077

Data are expressed as no. of patients (%) or mean±SD.

HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; SBP, systolic blood pressure; DBP, diastolic blood pressure.

try have been published.⁷ Briefly, we enrolled a consecutive series of patients with AF of all types under clinical observation in the outpatient clinic, but those patients who had maintained sinus rhythm for more than 1 year, as well as inpatients, were excluded from the study.

Patient registration was conducted in proportion to the population density from each of the following 10 geographical divisions of Japan: Hokkaido area, Tohoku area (including Aomori, Akita, Yamagata, Iwate, Fukushima), Hokuetsu area (including Niigata, Toyama, Ishikawa, Fukui), North Kanto area (including Tochigi, Ibaraki, Saitama, Gunma, Yamanashi), South Kanto area (including Chiba, Tokyo, Kanagawa), Chubu area (including Shizuoka, Nagano, Aichi, Mie, Gifu), Kansai area (including Osaka, Shiga, Hyogo, Nara, Wakayama), Chugoku area (Okayama, Hiroshima, Yamaguchi, Tottori,

Shimane), Shikoku area and Kyushu area.⁷

The risk of stroke was evaluated by the CHADS2 score⁸ and clinical background data were obtained from each outpatient's clinical chart. The presence of diabetes was diagnosed using HbA_{1c} 6.5% as the standard⁹ or was assumed if the patient was taking medication for the treatment of diabetes. Hypertension was diagnosed if peripheral blood pressure was >140/90 mmHg,¹⁰ if the patient was taking medication for hypertension, or there was a history of hypertension.

The study protocol was approved by each of the participating institutions, and all participants were required to give written informed consent. Clinical background, including underlying disease and medications for the prevention of thromboembolism, INR and daily dosage of warfarin, was investigated for each patient. In each institution, collected

Table 2. Drugs Used for Atrial Fibrillation and INR at Registry

No. of patients	Overall	<70 years of age	≥70 years of age
	7,937	3,640	4,297
Type of medication			
Antithrombotic therapy			
Warfarin	6,932 (87.3)	3,097 (85.1)	3,835 (89.2)
Dosage, mg/day	2.9±1.2	3.2±1.2	2.6±1.1
INR	1.9±0.5	1.9±0.5	1.9±0.5
<1.60	1,760 (25.4)	786 (25.4)	974 (25.4)
1.60–1.99	2,525 (36.4)	1,080 (34.9)	1,445 (37.7)
2.00–2.59	2,050 (29.6)	957 (30.9)	1,093 (28.5)
2.60–2.99	403 (5.8)	188 (6.1)	215 (5.6)
≥3.00	194 (2.8)	86 (2.8)	108 (2.8)
Antiplatelet agents	2,052 (25.9)	822 (22.6)	1,230 (28.6)
Aspirin	1,770 (22.3)	736 (20.2)	1,034 (24.1)
Ticlopidine	228 (2.9)	74 (2.0)	154 (3.6)
Clopidogrel	86 (1.1)	31 (0.9)	55 (1.3)
Others	153 (1.9)	41 (1.1)	112 (2.6)
Warfarin plus antiplatelet agents	1,471 (18.5)	538 (14.8)	933 (21.7)
Antihypertensive agents	5,714 (72.0)	2,471 (67.9)	3,243 (75.5)
ACEI/ARB	4,195 (52.9)	1,838 (50.5)	2,357 (54.9)
Others	3,745 (47.2)	1,558 (42.8)	2,187 (50.9)
ACEI/ARB plus others	2,226 (28.0)	925 (25.4)	1,301 (30.3)
Statins	1,910 (24.1)	871 (23.9)	1,039 (24.2)

Data are expressed as no. of patients (%) or mean±SD.

INR, international normalized ratio; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blockade.

data are sent automatically by e-mail using a formatted USB memory to the data center (Medisket Co, Tokyo) for storage in the Electronic Data Capture (EDC) System after completion of the registry.

Statistical Analysis

Data collected at the Registry were expressed as mean±SD, and baseline differences between any 2 groups were evaluated with χ^2 tests for categorical variables, and with Student's t-test for continuous variables. To compare the average value of the CHADS2 score in each group and the differences in the CHADS2 scores among the types of AF, the Wilcoxon rank-sum test and the Kruskal-Wallis test, respectively, was used. For all the analyses, a 2-sided probability value <0.05 was considered statistically significant. Analysis was performed with SAS version 9.1 statistical software.

Results

Patient Registry

The Registry was established in January 2009, and by July 2009 a total of 7,937 AF patients from 158 institutions in Japan were enrolled (Appendix). After the number enrolled in each area was confirmed, the data accumulation for the Registry was terminated on July 23, 2009.

Baseline Characteristics of Registered Patients

The baseline clinical characteristics of all registered AF patients are summarized in Table 1. The warfarin group was significantly older than the non-warfarin group ($P<0.0001$). The paroxysmal type of AF was significantly more frequent in the non-warfarin group ($P<0.0001$). There were significant differences between the warfarin group and the non-warfarin

group in the frequency of hypertension ($P<0.0001$), cardiomyopathy ($P<0.0001$), valvular heart disease ($P<0.0001$), diabetes mellitus ($P<0.0001$) and stroke/transient ischemic attack (TIA) ($P<0.0001$), but not of coronary artery disease ($P=0.38$).

Almost half of the registered patients were at low risk for stroke (CHADS2 score, 0 or 1), and they were seen more frequently in the non-warfarin group. Patients with a CHADS2 score >2 were more common in the warfarin group.

There were also significant differences in peripheral blood pressure, but not in heart rate.

Drugs Used in AF Patients and the INR at Registry

Table 2 shows the drugs prescribed at baseline in this series of patients. More than 25% of warfarin-prescribed patients had an INR <1.6, 66.0% had an INR between 1.6 and 2.6 and 35.4% had an INR between 2.0 and 3.0. There was no significant difference between the 2 age groups (<70 years; ≥70 years).

Antiplatelet drugs, including aspirin, were prescribed for a total of 25% of the patients in the Registry.

Age Groups and Types of AF

The prevalence of the types of AF varied between the age groups. Paroxysmal AF was the most frequent, and affected more than half of the registered patients in the younger age group (<60 years), but in the older group (≥60 years), permanent AF was the most frequent (Figure).

CHADS2 Score and Type of AF

Table 3 shows the relationship between the CHADS2 score and the type of AF. In paroxysmal AF, 59.3% of patients were at lower risk (CHADS2 score 0 or 1); this proportion

Table 3. CHADS2 Score and Type of Atrial Fibrillation

CHADS2 score	Atrial fibrillation			
	Overall	Paroxysmal	Persistent	Permanent
	1.7±1.2	1.4±1.1	1.6±1.2	1.9±1.2
0	1,242 (15.7)	614 (20.8)	222 (19.4)	406 (10.6)
1	2,697 (34.0)	1,135 (38.5)	371 (32.4)	1,191 (31.0)
2	2,210 (27.8)	739 (25.1)	300 (26.2)	1,171 (30.5)
3	1,145 (14.4)	301 (10.2)	163 (14.3)	681 (17.7)
4	455 (5.7)	127 (4.3)	68 (5.9)	260 (6.8)
5	161 (2.0)	27 (0.9)	18 (1.6)	116 (3.0)
6	27 (0.3)	4 (0.1)	2 (0.2)	21 (0.6)

Data are expressed as no. of patients (%) or mean±SD.

Table 4. Antithrombotic Agents for Initial Therapy Based on CHADS2 Score

CHADS2 score	Overall	W (W+AP)	AP (aspirin)	No therapy
0	1,242	950 (108)	133 (128)	159
1	2,697	2,322 (352)	211 (194)	164
2	2,210	2,004 (436)	145 (122)	61
3	1,145	1,065 (344)	51 (45)	29
4	455	420 (159)	26 (22)	9
5	161	147 (63)	14 (11)	0
6	27	24 (9)	1 (0)	2
Overall	7,937	6,932 (1,471)	581 (522)	424

Data are expressed as no. of patients
W, warfarin; AP, antiplatelet agent.

decreased to 51.8% in persistent AF, and to 41.6% in permanent AF.

CHADS2 Score and Warfarin/Aspirin Use

Of the moderate- and high-risk patients (CHADS2 score ≥ 2), more than 90% were taking warfarin, and even in the lowest risk group (CHADS2 score 0), more than 75% of patients were taking warfarin. Aspirin was prescribed in a total of 22% of patients, and the ratio increased with increasing CHADS2 score. This trend did not change when other antiplatelet drugs were included (Table 4). A combination of warfarin and anti-

platelet drugs was prescribed to a total of 18.5% of patients.

Discussion

The J-RHYTHM Registry⁷ is the first large-scale prospective investigation of anticoagulation in AF patients in Japan. From January 2009 to July 2009, a total of 7,937 AF patients were successfully registered from 158 institutions. The present study presents the clinical profile of Japanese AF patients. The prevalence of coronary artery disease as underlying heart disease in AF patients was only approximately 10%, whereas

hypertension was present in 59% of AF patients. Japanese AF patients characteristically show a low prevalence of coronary artery disease, which is a major difference from the US and European studies.^{11–13} Also, almost half of the registered patients were at low risk of stroke (CHADS2 score 0 or 1), a fact that may be related to the medical system in Japan, where it is easy to visit any hospital anywhere at uniform treatment charges.

The Japanese guideline² for the pharmacological management of AF recommends an INR of 2.0–3.0 for patients at moderate risk of stroke (CHADS2 score 2), but in patients aged 70 years old or older, a lower intensity of INR, namely, 1.6–2.6, is recommended because of the results of a small prospective study for the secondary prevention of stroke in which an INR >2.6 increased the number of hemorrhagic incidents.³ In Japan, to date, there has not been a large-scale prospective clinical investigation dealing with anticoagulation management of patients with AF. The present study covered a total of 87.3% of the AF patients who were taking warfarin in 2009 in Japan. The high rate of actual warfarin use may be due to the fact that selected institutions with cardiologists seeking to improve their understanding of anticoagulation treatment were devoting considerable energy to taking care of their AF patients. According to a previous report by Inoue et al almost 10 years ago,¹⁴ only 51.7% of their patients (non-valvular AF only) were taking warfarin, and the authors concluded that the low degree of warfarin use may have resulted mostly from the attitude of Japanese cardiologists at that time. However, in recent years in Japan, the attitude has been changing, and annual warfarin prescriptions are increasing. In the J-TRACE Study, prescription of warfarin increased approximately 73% without any intersexual difference.¹⁵ But in Western countries more than 10 years ago, fewer than 30% of AF patients received warfarin¹⁶ and this restrained use of warfarin persists in the West, being prescribed for only 40% of patients admitted with their first ischemic stroke and a known history of AF;¹⁷ however, in a recent clinical study, the percentage was as high as 90% in patients with heart failure.¹³ Newer Japanese guidelines for the pharmacological management of AF² do not recommend aspirin use, because of the results of the JAST study that found that aspirin was neither effective nor safe in patients with AF who had a history of stroke.¹⁸ Those results and the guideline's statement may also have led to the increase in the rate of warfarin use in Japan.

At present, a relatively low intensity of INR (1.6–2.6) is recommended for patients aged 70 or older in Japan for 2 reasons. Firstly, in 1 prospective study, a low intensity of INR showed results as effective as those obtained in a patient group with a high intensity INR,¹⁹ and secondly, it appears that racial differences cause a tendency toward an increase in intracranial hemorrhage in Asians.^{4–6} The present study examined more than 60% of AF patients who were taking warfarin, in whom the INR ranged from 1.6 to 2.6, and this trend did not change even in patents older than 70 years. One very interesting result was that the intensity of INR was not adjusted by age. Antiplatelet drugs, including aspirin, were still being prescribed in more than 25% of patients, despite the elimination of aspirin therapy from the Japanese guideline.² The use of low-dose warfarin is still common practice in Japan. More than 25% of warfarin-treated patients had an INR <1.6, and 36% had an INR between 1.6 and 2.0. This may have been related to the physician's intention to avoid bleeding complications in aged patients. Only 35.4% of the patients were within the internationally recommended INR

intensity range (ie, 2.0–3.0). Antiplatelet drugs, including aspirin, were prescribed for a total of 25.9% of patients in the Registry, although this sometimes included aspirin use for the prevention of coronary artery disease. The combination of warfarin with antiplatelet drugs was prescribed in 18.5% of patients.

Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARB) were used in more than half (52.9%) of the registered patients, and statins in 24.1%, which was more than we expected. This situation may reflect the findings of recent studies of the reverse remodeling of the atrial myocardium while using ACEI or ARB.^{20,21}

More than one-third of the registered patients had paroxysmal AF, and this is the most frequent type of AF in patients seen in hospital care in Japan. The type of AF changed with increased age, and in the present study, the permanent type was the most common in those over the age of 75. The risk of stroke may also have been changed by the clinical course of the patients. In patients with paroxysmal AF, more than half had low CHADS2 scores (0 or 1), whereas in patients with permanent AF, the percentage of low-risk patients was less. These clinical findings seem to indicate that permanent AF leads to the highest risk of stroke, which contradicts the findings of a Swedish report that there was no significant difference between paroxysmal AF and permanent AF regarding the incidence of stroke in a 3.6-year follow-up.²²

It is interesting that the mean warfarin dose was 2.9 mg/day, and the mean INR was 1.9 in this series of AF patients, for these results may reflect the Japanese guideline² in which a lower INR for AF patient care is recommended than that used in the US and Europe.

In the present study, there is a very high rate of warfarin use. More than 75% of patients with CHADS2 scores of 0 or 1, and more than 90% of those with CHADS2 score >2, were taking warfarin. Aspirin was prescribed in less than 20%, even in low-risk patients, despite the newer Japanese guideline.² Fewer than 20% of the patients were taking any combination of warfarin and antiplatelet drugs. According to the SPAF III trial,²³ a combination of fixed-dose warfarin and aspirin had a higher rate of ischemic stroke or systemic embolism than adjusted doses of warfarin. Since that report, combination therapy has been withdrawn as a first-line therapy for preventing stroke. The relatively low rate of prescription of antiplatelet drugs may partially reflect the findings of the SPAF III trial.

This was a large-scale prospective observational study, but the Registry was established only in selected institutions and does not include general practitioner clinics where more aspirin and digoxin, but less warfarin, are generally prescribed. The clinical backgrounds of the patients were investigated only at registration, and so these clinical parameters may have changed during the 2 years of follow-up.

In this registry, we did not investigate the type of drug used for rate or rhythm control, because these drugs have already been investigated and reported in the J-RHYTHM Study.²⁴ In this J-RHYTHM Registry, the primary endpoint was described in the design paper,⁷ with further goals to explore the appropriate INR and bleeding risk score for Japanese AF patients. We also did not assess the risk of bleeding complications with anticoagulation treatment. Because it is important to elucidate an appropriate INR for the management of AF patients, and also to access the clinical factors related to bleeding risks, the J-RHYTHM Registry is going to explore the bleeding risk score for Japanese AF patients.⁷ In the evaluation of the risks for stroke and bleeding complications,

patients with prosthetic valves will be excluded because the pathophysiology of thrombus formation might be different.

In conclusion, almost half of registered Japanese AF patients were at low risk for stroke, had a high rate of warfarin use and a lower frequency of coronary artery disease as the underlying heart disease. We expect to complete the 2-year follow-up in most of the registered patients.

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Appendix

The following persons participated in this trial.

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Local Executive Committee: Sakurai M, Kawamura Y (Hokkaido); Okumura K, Kubota I (Tohoku); Kaneko Y, Matsumoto K (North Kanto); Ogawa S, Atarashi H, Yamashita T (South Kanto); Inoue H, Aizawa Y (Hokkaido); Kodama I, Watanabe E (Chubu); Koretsune Y, Okuyama Y (Kansai); Shimizu A, Igawa O (Chugoku); Bando S, Fukutani M (Shikoku); Saikawa T, Chishaki A (Kyushu).

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