Prevalence and Clinical Characteristics of Patients With Atrial Fibrillation — Analysis of 20,000 Cases in Japan —

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In Japan, data on the epidemiological and clinical features of atrial fibrillation (AF) are rather sparse; even less data are available on the risk of thromboembolism in nonvalvular AF. The present study enrolled 19,825 patients who visited the cardiovascular clinics of the 13 hospitals in Hokkaido, Japan, between March and July 1995. The prevalence of AF, the clinical characteristics of AF patients, and the occurrence of ischemic events were examined during the 2 year follow-up period. The prevalence of AF increased with age, and the overall prevalence was 14%. Antithrombotic therapy was used in 57% of AF patients and the incidence of ischemic events during the follow-up period was 4.6% in all AF patients. Warfarin reduced the risk of ischemic events in both the valvular and nonvalvular AF groups. A history of cerebrovascular accidents, advanced age, and the presence of underlying heart disease were each associated with a significantly increased risk of ischemic events in the nonvalvular AF group. These results show a lower incidence of ischemic events and more frequent use of antiplatelet drugs in the nonvalvular AF group. Further prospective studies are needed to determine the best preventive methods for thromboembolic complications in Japanese patients with nonvalvular AF. (*Jpn Circ J* 2000; 64: 653–658)

Key Words: Antithrombotic therapy; Aspirin; Nonvalvular atrial fibrillation; Thromboembolism; Warfarin

Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice and not only does it reduce quality of life due to symptoms, but it also increases the risk of thromboembolism and heart failure. In the past, rheumatic valvular heart disease, especially mitral stenosis, accounted for the majority of cases of AF (valvular AF). More recently, the etiology of AF has shifted to hypertension, congestive heart failure and ischemic heart disease, and the proportion of AF cases in which no evidence of valvular heart disease was found (nonvalvular AF) has increased^{1,2}

The high risk of thromboembolism in cases of AF associated with mitral stenosis and prosthetic valves has long been accepted. Furthermore, even in the absence of these valvular diseases AF carries a substantially increased risk of thromboembolism, and the risk ratio for stroke has been shown to be 4 to 8 for patients with nonvalvular AF³. Recently, several large-scale randomized trials of antithrombotic therapy in nonvalvular AF have been published, providing valuable data for stratifying patients according to their risk of ischemic stroke^{4–10}

In Japan, however, data on the epidemiological and clinical

features of AF are rather sparse, with even less data available on the risk of thromboembolism, and there is not a consensus on the role of antithrombotic therapy for the prevention of ischemic stroke in nonvalvular AF. The present study was conducted to (1) clarify the prevalence and clinical characteristics of AF in patients visiting cardiovascular clinics, and (2) in patients with AF, to investigate the incidence of thromboembolism and the relationship between thromboembolism and clinical variables or antithrombotic therapy. The study was carried out at 13 hospitals in Hokkaido, Japan, that have cardiovascular medicine departments.

Methods

Study I

All patients who visited the cardiovascular clinics of the 13 hospitals between March and July 1995 were included. First we examined the prevalence of AF; then, for AF cases we also examined clinical characteristics as follows: (1) type of AF (paroxysmal or chronic), (2) underlying heart diseases, (3) New York Heart Association (NYHA) functional class, (4) complications, (5) history of cerebrovascular accidents, and (6) the use of antithrombotic therapy.

All patients underwent a physical examination, 12-lead ECG, and chest X-rays to evaluate their cardiovascular condition. The presence of AF was confirmed by 12-lead ECG or Holter ECG. Chronic AF was diagnosed when AF had lasted more than 6 months, and paroxysmal AF was the diagnosis when AF had occurred at least twice in the previous 6 months. Heart diseases included valvular heart disease, ischemic heart disease, cardiomyopathy, hypertension, and

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Fig 1. Number of patients (graph A) and prevalence of AF (graph B) at various ages.

Table 1 Age-Specific Number of Patients and Prevalence of Atrial Fibrillation (AF)

Age (years)	All AF (n=2,667)	VAF (n=494)	NVAF (n=2,173)
<40 (n=1,186)	41 (3.5%)	5 (0.5%)	36 (3.0%)
40-50 (n=2,156)	149 (6.9%)	36 (1.6%)	113 (5.3%)
50-60 (n=4,335)	453 (10.4%)	117 (2.7%)	335 (7.7%)
60-70 (n=6,427)	868 (13.5%)	139 (2.2%)	729 (11.3%)
70-80 (n=4,422)	827 (18.7%)	135 (3.1%)	692 (15.6%)
≥80 (n=1,296)	329 (25.4%)	61 (4.7%)	268 (20.7%)

VAF, valvular atrial fibrillation; NVAF, nonvalvular atrial fibrillation.

Table 2 Clinical Characteristics of Patients With Atrial Fibrillation (AF)

	n (%)
Sex	
Male	1,659 (62)
Female	1,008 (48)
Age	
<60	643 (24)
60-80	1,695 (64)
≥80	329 (12)
Type of AF	
Chronic	1,713 (64)
Paroxysmal	954 (36)
Underlying heart disease	
Valvular heart disease	494 (19)
Nonvalvular heart disease	1,290 (48)
Hypertension	765 (29)
Ischemic heart disease	290 (11)
Cardiomyopathy	136 (5)
SSS	57 (2)
WPW syndrome	27 (1)
Others	138 (5)
No heart disease	883 (33)
NYHA functional class	
I	1,535 (58)
≥II	1,132 (42)
Diabetes	293 (11)
Cerebrovascular accidents	484 (18)
Cerebral infarction	391 (15)
Transient ischemic attack	72 (3)
Cerebral bleeding	21 (0.8)

SSS, sick sinus syndrome; WPW, Wolff-Parkinson-White.

other disorders such as sick sinus syndrome (SSS), Wolff-Parkinson-White (WPW) syndrome and congenital heart disease. Valvular heart disease was diagnosed when stenosis or regurgitation greater than grade III was found in any

valve by echocardiography, or there was a history of valve surgery. Antithrombotic drugs were warfarin, aspirin, ticlopidine and other drugs.

Study II

Approximately 2 years after Study I, we investigated the occurrence of ischemic events and the prognosis in patients with AF in Study I. Ischemic events included cerebral infarction, transient ischemic attack, and peripheral artery occlusion. No attempt was made to differentiate between cardioembolic and noncardioembolic events. Follow-up data were obtained through clinical records or telephone-calls. This follow-up study was performed between January and June 1997.

Statistical Analysis

Data are presented as mean ± SD. Continuous data were compared by Student's unpaired t test. Categorical data were compared by Fisher's exact test or chi-square test. Differences with $p < 0.05$ were considered significant.

Results

Study I

Study Patients Although a total of 19,888 patients were enrolled, 63 patients were excluded because their age or sex was not known. Thus, 19,825 patients (10,004 men and 9,821 women; mean age, 63 ± 13 years old) were selected as study subjects. Of the 19,825 patients, 2,667 had AF (1,659 men and 1,008 women), and the prevalence of AF was 14% (17% in men and 10% in women). The patients with AF (67 ± 11 years old) were significantly older than the patients without AF (62 ± 14 years old; $p < 0.0001$). Fig 1 and Table 1 show the age distribution of the patients and the age-specific prevalence of AF. The prevalence of AF clearly increased

Table 3 Antithrombotic Therapy

	All AF (n=2,667)	VAF (n=494)	NVAF (n=2,173)
(-)	1,148 (43%)	129 (26%)	1,019 (47%)
(+)	1,519 (57%)	365 (74%)	1,154 (53%)
Warfarin	362 (14%)	188 (38%)	174 (8%)
Aspirin	475 (18%)	70 (14%)	405 (19%)
Ticlopidine	682 (26%)	111 (22%)	571 (26%)
Others	20 (0.7%)	7 (1.4%)	13 (0.5%)

AF, atrial fibrillation; VAF, valvular AF; NVAF, non valvular AF.

Table 4 Clinical Characteristics of Atrial Fibrillation (AF) Patients With or Without Antithrombotic Therapy

	No therapy (n=1,148)	Anticoagulant (n=362)	Antiplatelet (n=1,177)
Age (years)	67±12	63±9 [#]	68±10
Sex			
Male (%)	60.7	58.6	64.7
Type of AF			
Chronic (%)	54.4	83.1 [#]	67.8*
Underlying heart disease			
Present (%)	62.9	85.1 [#]	65.3
NYHA functional class			
≥II (%)	38.8	63.8 [#]	39.5
Diabetes			
Present (%)	10.5	11.3	12.0
Cerebrovascular accidents			
Present (%)	10.4	46.0 [#]	22.2*

[#]p<0.001 vs No antithrombotic therapy, *p<0.001 vs Antiplatelet, *p<0.001 vs No antithrombotic therapy.**Table 5 Incidence of Ischemic Events**

	All AF (n=2,457)	VAF (n=459)	NVAF (n=1,998)
Total	112 (4.6%)	24 (5.2%)	88 (4.4%)
Cerebral infarction	82	18	64
Transient ischemic attack	18	4	14
Peripheral artery occlusion	12	2	10

AF, atrial fibrillation; VAF, valvular AF; NVAF, non valvular AF.

with age and more than 70% of all AF patients were older than 60 years. Of the patients with AF, 19% had valvular heart disease (valvular AF) and 81% did not have valvular heart disease (nonvalvular AF). Compared with valvular AF, the age-related increase of prevalence was much clearer in nonvalvular AF.

Baseline Characteristics Table 2 shows the baseline characteristics of the patients with AF; 62% of these patients were men, and these men (66±11 years old) were significantly younger than the AF-diagnosed women (68±11 years old; p<0.0001). Most patients had had chronic AF (64%) for more than 1 year. For the patients with nonvalvular AF, hypertension was the disease most frequently diagnosed; other disorders included ischemic heart disease and cardiomyopathy; 18% of these patients, compared with 20% in valvular AF, had a history of cerebrovascular accident, most of which were ischemic events such as cerebral infarction and transient ischemic attack. The patients with a history of cerebrovascular accident (69±9 years old) were significantly older than those without a history of such accidents (66±12 years old; p<0.0001).

Antithrombotic Therapy Table 3 shows the use of antithrombotic therapy in patients with AF; 57% received antithrombotic therapy, and antiplatelet drugs (aspirin and ticlopidine) were used much more frequently than warfarin (several patients received 2 or more types of medication).

Compared with valvular AF, antithrombotic therapy was less frequently used (p<0.01) and the proportion of warfarin use was significantly lower (p<0.01) for the nonvalvular AF group.

Table 4 shows the baseline characteristics according to assigned treatment. The warfarin-treated group were younger and more of these patients had chronic AF, NYHA ≥II, a history of cerebrovascular disease, and underlying heart disease than the other 2 groups. The antiplatelet drugs-treated group contained more patients with chronic AF and a history of cerebrovascular accidents than the no antithrombotic-treated group.

In the nonvalvular AF group, warfarin was used only in 8.7% of patients with indications for warfarin therapy (high- or moderate-risk of thromboembolism) based on the Recommendation of the American Heart Association;¹¹ these are the patients older than 65 years, with prior ischemic stroke, hypertension, heart failure or diabetes.

Study II

Outcome Events Follow-up data were obtained from 2,457 patients (92% of all AF in Study I), and the mean follow-up period was 1.7±0.4 years. Of the 2,457 patients, 19% were diagnosed with valvular AF and 81% were diagnosed with nonvalvular AF, and the ratio of valvular to nonvalvular AF cases was the same as in Study I. During

Fig 2. Incidence of ischemic events in valvular AF (graph A) and nonvalvular AF (graph B). No, Asp, Tic, and War indicate the patients given no antithrombotic drugs, aspirin, ticlopidine, and warfarin, respectively. * $p < 0.05$ vs No.

Table 6 Incidence of Ischemic Events based on Clinical Characteristics in Nonvalvular Atrial Fibrillation (AF)

Variable	n	Incidence (%)
Age (years)		
<60	445	3.0
60–80	1,360	4.6
≥80	246	6.0* (vs <60)
Sex		
Male	1,339	4.3
Female	658	4.6
Type of AF		
Chronic	1,165	5.0
Paroxysmal	832	3.6
Underlying heart disease		
Present	1,199	5.4**
Absent	798	2.9
Hypertension		
Present	727	5.0
Absent	1,270	4.1
Ischemic heart disease		
Present	286	6.2
Absent	1,711	4.2
Cardiomyopathy		
Present	138	8.6*
Absent	1,859	4.2
NYHA functional class		
I	1,275	6.2
≥II	722	5.1
Diabetes		
Present	234	5.8
Absent	1,763	4.3
Antithrombotic therapy		
No	922	4.5
Anticoagulant	185	3.8
Antiplatelet drugs	890	4.5
Cerebrovascular accidents		
Present	347	9.2***
Absent	1,650	3.4

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$.

the follow-up period, 112 patients (4.6%) had ischemic events: 5.2% for the valvular AF group and 4.4% for the nonvalvular AF group. In both valvular and nonvalvular AF cases, patients with a history of cerebrovascular accident had a significantly higher incidence of ischemic events compared with those without such a history. Of a total of 112 ischemic events, 100 (89%) were cerebrovascular accidents (82 cerebral infarction and 18 transient ischemic attack) and 12 (11%) were peripheral artery occlusion (Table 5). There were 24 deaths in the patients with ischemic events. Another 79 patients died during the follow-up period: 27 were due to cardiovascular diseases, 24 to cancer, 18 to

respiratory illness, 7 to renal failure and 3 to liver dysfunction. No major bleeding complications were observed during the follow-up period.

Effects of Antithrombotic Therapy in Primary Prevention
Fig 2 shows the incidence of ischemic events according to antithrombotic therapy in patients without a history of cerebrovascular accident. In valvular AF, the incidence of ischemic events were 6.3%, 6.3%, 7.1%, and 1.5% in the patients given no antithrombotic therapy, aspirin, ticlopidine, and warfarin, respectively. In nonvalvular AF, these incidences were 3.2%, 3.7%, 3.8% and 1.9%, respectively. In both the valvular and nonvalvular AF groups the patients treated with warfarin had a lower incidence of ischemic events compared with those who received no antithrombotic therapy, and this difference was statistically significant for the valvular AF group. Neither aspirin nor ticlopidine reduced the incidence of ischemic events in either the valvular or nonvalvular AF groups.

Risk Factors for Ischemic Events in Cases of Nonvalvular AF
Table 6 shows the incidence of ischemic events based on the baseline clinical characteristics of patients with nonvalvular AF. Univariate analysis of 8 clinical variables showed that a history of cerebrovascular accidents, advanced age and underlying heart disease were each associated with a significantly increased risk of ischemic events. Of the underlying heart diseases, cardiomyopathy posed the highest risk for ischemic events. Gender, type of AF, NYHA functional class, diabetes and antithrombotic therapy were not significantly related to the risk for ischemic events.

Discussion

Epidemiological studies have shown that the prevalence of AF increases with age, and in the United States 70% of AF patients are between the ages of 65 and 85 years and nearly one-third are older than 80!^{1,2} Most cases of AF in the elderly are nonvalvular, and hypertensive heart disease and ischemic heart disease are most commonly associated with nonvalvular AF. The results of the present study regarding the age-related prevalence of AF, the high frequency of nonvalvular AF and the types of associated heart diseases are consistent with the previous findings of population-based studies in the United States!^{1,2} However, it should be noted that the present results may not be representative of the general Japanese populations, because the data were obtained from clinical populations in Hokkaido, a northern part of Japan.

In the present study, antithrombotic therapy was used for more than half the patients in both the valvular and nonva-

lular AF groups. Antiplatelet drugs comprised the greater part of this therapy, whereas warfarin was prescribed for antithrombotic therapy in only 24%, 52%, and 15% of cases for all AF patients, valvular AF patients, and nonvalvular AF patients, respectively. Although the exact reasons for the less frequent usage of warfarin in nonvalvular AF patients are unclear, one may be that scant information on the risk of strokes and the role of antithrombotic therapy in the prevention of strokes is available for Japanese patients with nonvalvular AF. The difficulty of frequent monitoring of coagulation capacity and the close follow-up examinations needed for warfarin treatment may also affect this result.

The risk of strokes, and the subsequent benefits of anticoagulant therapy, in patients with AF associated with mitral stenosis have been widely recognized. Results of large-scale, randomized clinical trials of antithrombotic therapy (anticoagulation with warfarin and/or antiplatelet therapy with aspirin) in patients with nonvalvular AF have been published⁴⁻¹⁰ and these show a 5-6-fold increase in the risk of stroke and an approximately 4-6% annual incidence of stroke in patients with nonvalvular AF.¹² Also, these studies have shown that anticoagulation with warfarin is highly effective in reducing ischemic stroke in nonvalvular AF patients. However, the efficacy of aspirin for stroke prevention is less clear, and aspirin alone or aspirin plus low-dose warfarin seems to be ineffective for high-risk patients.^{9,10,13}

The present study showed that the incidence of ischemic events was 4.6% during a 1.7-year follow-up period: 5.2% in valvular AF and 4.4% in nonvalvular AF cases. In nonvalvular AF patients, a history of cerebrovascular accidents, advanced age and underlying heart disease were each associated with a significantly increased risk for ischemic events. Furthermore, only warfarin (not aspirin or ticlopidine) reduced the occurrence of ischemic events in primary prevention. Data are insufficient regarding the incidence of thromboembolic complications and the effect of antithrombotic therapy in nonvalvular AF patients in Japan.¹⁴⁻¹⁷ The COOPAT (Cooperative Osaka Platelet Antiaggregation Trial) study, which prospectively evaluated the efficacy of warfarin and ticlopidine therapy for the prevention of ischemic strokes in nonvalvular AF patients, showed that there was 4.5% yearly incidence of stroke and that only warfarin (and not ticlopidine) was effective for preventing ischemic strokes.¹⁶ On the other hand, results from a research group for antiarrhythmic drug therapy have shown that the annual incidence of thrombotic complications in AF patients not receiving antithrombotic drugs was 0.9-2.7% depending on the underlying heart disease.¹⁷ That study also showed that antiplatelet agents as well as warfarin reduced the thrombotic complications.

It is widely accepted that antiplatelet agents such as aspirin and ticlopidine reduce the risk for stroke, myocardial infarction and vascular death compared with a placebo.^{18,19} However, the efficacy of aspirin for stroke prevention in AF patients is less clear and remains controversial.¹³ The mechanisms of increased thromboembolic risk in nonvalvular AF patients have not been fully elucidated, but are generally believed to be caused by cardioembolism subsequent to circulatory stasis in the left atrium.^{20,21} Furthermore, activation of the coagulation system because of abnormal stasis rather than platelet activation seems to predominantly influence thrombus formation in the left atrium,^{22,23} which may be one of the causes of the lowered effective-

ness of antiplatelet agents for stroke prevention in AF.

With regard to warfarin therapy, the need for periodic laboratory monitoring of anticoagulation and dosage adjustment, as well as the need for and potential difficulties with frequent communication between physician and patient, add to the inconvenience of warfarin therapy. In spite of the rather compelling evidence favoring anticoagulation for patients with nonvalvular AF, physicians remain reluctant to prescribe such therapy, especially for elderly patients who would derive the most benefit, albeit at a greater risk. The International Normalized Ratio (INR), which standardizes the prothrombin time ratio for varying types of thromboplastin with differing sensitivities, is now the accepted method of monitoring patients undergoing warfarin therapy and a target INR of 2.0-3.0 is the currently recommended intensity of anticoagulation to prevent thrombotic complications.¹²

For stroke prevention in patients with AF, the Subcommittee of the American Heart Association recommends warfarin for high- or moderate-risk patients (patients older than 65 years, with prior ischemic stroke, hypertension, heart failure or diabetes) and aspirin therapy for low-risk patients (patients without any of the aforementioned risks).¹¹ However, a target INR of 2.0-3.0 and an aspirin dosage of 325 mg/day are higher than the usual therapeutic ranges in Japan. We need more information regarding the role of antithrombotic therapy, depending on risk, in preventing ischemic events in nonvalvular AF patients.

In conclusion, the present results show a lower incidence of ischemic events and more frequent use of antiplatelet drugs in nonvalvular AF patients. There are ethnic differences in coagulation activity and Japanese have a higher hemorrhagic tendency compared with Caucasians. Further prospective studies are needed to determine the best preventive methods for thromboembolic complications in Japanese with nonvalvular AF.

Appendix

The institutions and investigators participating in the study.

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