Progression to the Persistent Form in Asymptomatic Paroxysmal Atrial Fibrillation

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Background: This study investigated the progression of paroxysmal atrial fibrillation (AF) to the persistent form in Japanese asymptomatic AF patients.

Methods and Results: Data were derived from a single hospital-based cohort in the Shinken Database 2004–2012 (n=19,994), in which 1,176 patients were diagnosed as having paroxysmal AF. AF progression occurred in 115 patients (6.0%/year) during the mean follow-up period (1,213±905 days). Although patients who were asymptomatic at the initial visit (n=468) had a low-risk profile compared with symptomatic patients, they had greater AF progression at follow-up (unadjusted hazard ratio, 1.611; 95% CI: 1.087–2.389; P=0.018). Absence of symptoms, male sex, and cardiomyopathy were independent predictors for AF progression in the multivariate model. It was noted that asymptomatic patients were less likely to undergo pulmonary vein isolation (PVI). In addition, the interaction term between asymptomatic AF and absence of PVI could be another independent predictor for AF progression. Prognosis was similar between asymptomatic and symptomatic patients with AF.

Conclusions: Irrespective of low-risk profile, patients with asymptomatic paroxysmal AF had greater progression of AF compared with symptomatic patients. This paradoxical result appeared to be the result of less intensive clinical management, including invasive rhythm control. (*Circ J* 2014; **78**: 1121–1126)

Key Words: Asymptomatic atrial fibrillation; Atrial fibrillation; Epidemiology; Progression

Atrial fibrillation (AF) is the most common clinically significant arrhythmia in clinical practice.¹ AF is associated with increased morbidity and mortality that primarily occur as a result of 2 complications: stroke and heart failure.²

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In clinical practice, 1 should distinguish between paroxysmal AF (episodes of arrhythmia that terminate spontaneously) and persistent AF (episodes that are sustained for >7 days and are not self-terminating).³ Paroxysmal AF often progresses into persistent AF.^{4,5} Independent predictors of AF progression include older age and heart disease, which cause atrial structural remodeling.⁶ Although AF causes symptoms in most patients, it can be diagnosed when patients are asymptomatic.⁷ In our previous report, patients with symptomatic AF were older, had a frequent incidence of heart failure, and had large left atrial dimension, suggesting progression of atrial structural remodeling.⁸ Further-

more, it is generally believed that frequent AF symptoms lead to an increased incidence of AF episodes, and could thus predict AF progression. An epidemiological study, however, recently reported that asymptomatic AF is associated with future AF progression compared with symptomatic AF.⁹

Current evidence is scarce, and the impact of asymptomatic AF on AF progression and its clinical implication in the Japanese clinical setting remain unclear. The present study was designed to investigate AF progression and clinical outcome in asymptomatic Japanese patients with paroxysmal AF compared with symptomatic patients in a large, single hospital-based cohort study from the Shinken Database.

Methods

Subjects

The Shinken Database consists of all new patients visiting the Cardiovascular Institute Hospital in Tokyo, Japan ("Shinken" is an abbreviated name in Japanese for the name of the hospital).

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Table 1. Subject Characteristics

Characteristics	Paroxysmal AF		P-value	Overall (n=1,176)
	Asymptomatic (n=468)	Symptomatic (n=708)		
Age (years)	61.2±12.6	61.5±13.5	0.709	61.4±13.1
Male	373 (79.3)	502 (70.9)	0.001	875 (74.4)
BMI	23.8±3.2	23.4±3.3	0.095	23.6±3.2
Hypertension	179 (38.2)	318 (44.9)	0.026	497 (42.3)
Dyslipidemia	120 (25.6)	175 (24.7)	0.732	295 (25.1)
Diabetes mellitus	48 (10.3)	85 (12.0)	0.397	133 (11.3)
Cardiovascular disease				
Structural heart disease	91 (19.4)	130 (18.4)	0.648	221 (18.8)
Ischemic heart disease	36 (7.7)	48 (6.8)	0.565	84 (7.1)
Valvular disease	33 (7.1)	49 (6.9)	1.0	82 (7.0)
Cardiomyopathy	31 (6.6)	45 (6.4)	0.904	76 (6.5)
History of congestive heart failure	42 (9.0)	77 (10.9)	0.324	119 (10.1)
History of TIA/stroke	14 (3.0)	30 (4.2)	0.346	44 (3.7)
CHADS₂ score	0.8±1.0	0.9±1.0	0.015	0.9±1.0
0	232 (49.6)	296 (41.8)	0.032	528 (44.9)
1	138 (29.5)	240 (33.9)		378 (32.1)
≥2	98 (20.9)	172 (24.3)		270 (23.0)
CHA₂DS₂-VASc score	1.4±1.5	1.7±1.5	0.05	1.6±1.5
0	160 (34.2)	188 (26.6)	0.012	348 (29.6)
1	121 (25.9)	187 (26.4)		308 (26.2)
≥2	187 (40.0)	333 (47.0)		520 (44.2)
Medication at discharge				
Antiplatelet agents	177 (40.9)	291 (39.2)	0.579	468 (39.8)
Anticoagulants	158 (33.8)	300 (42.4)	0.006	458 (39.0)
Warfarin	150 (32.1)	234 (33.1)	0.751	384 (32.7)
Dabigatran	8 (1.7)	66 (9.3)	<0.001	74 (6.3)
β-blockers	130 (27.8)	229 (32.3)	0.106	359 (30.5)
Calcium channel blocker	58 (12.4)	90 (12.7)	0.929	148 (12.6)
Digitalis glycosides	25 (5.3)	42 (5.9)	0.702	67 (5.7)
Diuretics	42 (9.0)	79 (11.2)	0.241	121 (10.3)
RAS inhibitors	91 (19.4)	161 (22.7)	0.191	252 (21.4)
Class Ia/Ic	205 (43.8)	317 (44.8)	0.764	522 (44.4)
Echocardiogram parameters†				
LVEF (%)	64.9±9.6	65±10.8	0.830	65±10.3
Left atrial dimension (mm)	37.8±6.6	37.6±6.8	0.531	37.7±6.7
Holter recording parameters‡				
Paroxysmal AF (%)	57 (33.1)	63 (30.4)	0.581	120 (31.7)
All-day AF during recording	7 (4.1)	7 (3.4)	0.788	14 (3.7)

Data given as mean±SD or n (%). †Obtained for 412, 617 and 1,029 patients in asymptomatic, symptomatic and overall groups, respectively. ‡Obtained for 172, 207 and 379 patients in asymptomatic, symptomatic and overall groups, respectively. AF, atrial fibrillation; BMI, body mass index; CHADS₂ score, congestive heart failure, hypertension, age >75, diabetes mellitus, stroke or TIA; CHA₂DS₂-VASc score, congestive heart failure, hypertension, age >75, diabetes mellitus, stroke or TIA, vascular disease, age 65–74 years and sex category (female gender); LVEF, left ventricular ejection fraction; RAS, renin-angiotensin system; TIA, transient ischemic attack.

It excludes patients with active cancer and foreign travelers. The principal aim of this hospital-based database is surveillance of the prevalence and prognosis of cardiovascular disease in the urban areas of Japan.^{10–14} The registry began in June 2004, and thereafter, patients have continually been registered to the database every year. Health status, incidence of cardiovascular events, and mortality are updated in the database by linking to the medical records of the hospital and by mailings sent to patients approximately once or twice per year.

The data in the present study were derived from this database between 2004 and 2012 (Shinken Database 2004–2012), con-

sisting of 19,994 new visiting patients. In the database, 2,333 patients were diagnosed with AF, of whom 1,176 patients had paroxysmal AF and had a mean follow-up period of 1,213±905 days. These patients comprised the present study group.

Data Collection

After electrocardiogram (ECG) and chest X-ray, cardiovascular status was evaluated for each patient using echocardiography, exercise test, 24-h Holter recordings, and blood laboratory data from the initial visit, as determined by the attending physicians. From the database, the following information was collected:

(1) patient data, including sex, age, height, and weight; (2) cardiovascular risk factors, including hypertension (use of anti-hypertensive agents, systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure 90 mmHg on admission) and diabetes mellitus (use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin $\geq 6.5\%$); (3) cardiovascular disease, including structural heart disease, congestive heart failure, or a history of a disabling cerebral infarction or transient ischemic attack (TIA); and (4) use of medication. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

Definitions

In the present study, paroxysmal AF at the initial visit was defined as (1) sinus rhythm on ECG and previous diagnosis of paroxysmal AF by referring physicians; (2) symptomatic AF on ECG at the initial visit and duration of AF estimated as < 7 days according to symptoms or ECG recordings; and (3) asymptomatic AF on ECG at the initial visit and no AF 1 week prior. Patients whose AF was estimated to continue for > 7 days after the initial visit, were considered to have persistent AF originally and were excluded from the analysis.

Asymptomatic AF was defined as AF documented on 12-lead ECG during a visit, in the absence of any new symptoms such as palpitations, tachycardia, fatigue, malaise, shortness of breath on exertion, dyspnea, chest pain, syncope, or presyncope related to AF and other illnesses.

During the follow-up period, the onset of persistent AF was defined as the first time in which all ECG indicated AF after ≥ 3 consecutive ECG at an interval ≥ 1 week after the initial examination. When an ECG could not be obtained thrice during the period, the physicians made a clinical judgment regarding the onset time of AF progression. When electrical cardioversion

was performed after > 7 days continuing from AF onset, it was also considered as AF progression.

We calculated the CHADS₂ score¹⁵ (congestive heart failure, hypertension, age ≥ 75 years], diabetes mellitus, and history of stroke or TIA; 2 points). Also, the CHA₂DS₂-VASc score was determined, adding vascular disease (previous myocardial infarction, complex aortic plaque, and peripheral artery disease [PAD]), age 65–74, and female sex to the factors of the original CHADS₂ score.¹⁶

Statistical Analysis

For baseline characteristics, continuous variables and categorical variables are expressed as mean $\pm$ SD and as absolute numbers (percentages), respectively. Chi-squared test and unpaired Student's t-test were used for the comparison of categories and continuous variables between 2 groups, respectively. Cumulative progression-free survival (ie, without progression to persistent AF) was estimated using the Kaplan-Meier method. Univariate and multivariate Cox regression analyses were performed to identify predictors of AF progression. In the multivariate model, cofactors that were significantly associated with AF progression in the univariate models were analyzed using the stepwise method (model 1). The multivariate model 2 was specially developed to determine whether the interaction between asymptomatic AF and the effect of treatment intervention on AF progression was significant. The incidence of adverse events (eg, AF progression, ischemic stroke, cardiovascular death, and all-cause death) was calculated by the person-year method. All statistical analysis was done using SPSS version 19.0 (SPSS, Chicago, IL, USA) for Windows (Microsoft Corp, Redmond, WA, USA). Statistical significance was set at $P < 0.05$.

Table 2. Predictors of Progression to Persistent AF

	HR	95% CI	P-value
Univariate model			
Age	1.014	0.998–1.031	0.082
Sex (male)	2.063	1.217–3.500	0.007
Asymptomatic AF	1.611	1.087–2.389	0.018
Hypertension	0.963	0.661–1.402	0.844
Dyslipidemia	1.117	0.751–1.662	0.585
Diabetes mellitus	1.472	0.889–2.439	0.133
Structural heart disease	1.329	0.893–1.979	0.161
Ischemic heart disease	1.038	0.542–1.988	0.911
Valvular disease	0.95	0.532–1.697	0.863
Cardiomyopathy	2.125	1.265–3.568	0.004
History of stroke or TIA	1.901	0.833–4.336	0.127
History of heart failure	1.304	0.812–2.095	0.273
Absence of PVI	1.703	0.983–2.948	0.057
Multivariate model 1			
Asymptomatic AF	1.461	1.007–2.119	0.046
Cardiomyopathy	1.882	1.117–3.173	0.018
Sex (male)	1.872	1.009–3.190	0.021
Multivariate model 2			
Asymptomatic AF×absence of PVI [†]	1.490	1.020–2.175	0.039
Cardiomyopathy	1.849	1.095–3.120	0.021
Sex (male)	1.904	1.119–3.241	0.018

[†]Interaction term. AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; PVI, pulmonary vein isolation. Other abbreviations as in Table 1.

Ethics

The ethics committee of the Cardiovascular Institute granted ethics permission for this study, and all patients provided written informed consent.

Results

Subject Characteristics

The baseline characteristics of the 1,176 patients with paroxysmal AF are listed in [Table 1](#). The mean age of all patients was 61.4±13.1 years. Mean BMI was 23.6±3.2. A total of 468 patients (38.9%) were asymptomatic. Among asymptomatic and symptomatic patients with AF, there were similar prevalences of dyslipidemia, diabetes mellitus, and cardiovascular diseases (eg, structural heart disease, congestive heart failure, and TIA/stroke). Asymptomatic patients with AF were more likely to be male and had a lower prevalence of hypertension, resulting in a greater prevalence of a CHADS₂ score of 0 and CHA₂DS₂-VASC score of 0 (both P<0.05). At baseline, fewer asymptomatic patients received anticoagulation than did symptomatic patients. Otherwise, there were no substantial differences in medication use (eg, antiplatelet and anti-arrhythmic drugs [class Ia/Ic]).

In addition, echocardiogram parameters and Holter recordings were compared between asymptomatic and symptomatic patients, although these parameters were obtained in a limited number of patients. Echocardiogram parameters, including left ventricular ejection fraction and left atrial dimension, were similar between asymptomatic and symptomatic AF patients. Moreover, short AF episodes and all-day AF during Holter recording were similarly documented between asymptomatic and symptomatic AF patients (detection rates of short AF episodes, 33.1% vs. 30.4%; P=0.581; all-day AF during Holter recording, 4.1% vs. 3.4%; P=0.788, respectively).

Follow-up

During the follow-up period of 1,213±905 days, AF progression occurred in 115 patients (6.0%/year). This was observed more in asymptomatic than in symptomatic patients (8.6% vs. 4.7%/year; log rank test, P=0.015; [Figure](#)). In the unadjusted model with Cox regression analysis, the hazard ratio (HR) of asymptomatic AF for AF progression was 1.611 (95% confidence interval [CI]: 1.087–2.389; P=0.018). In the multivariate model, which used all factors that were significantly associated with AF progression in univariate models (model 1), the independent predictors for AF progression included asymptomatic AF, male sex, and cardiomyopathy ([Table 2](#)). Moreover, multivariate model 2 was specially developed to determine whether the interaction between asymptomatic AF and the effect of treatment intervention on AF progression was significant. For this purpose, we used these models with the interaction term for asymptomatic AF in model 2, but the absence of treatment intervention (pulmonary vein isolation; PVI) was not significantly associated with AF progression (P=0.057). Accordingly, in model 2, the interaction term between the absence of PVI and asymptomatic AF was identified as an independent predictor for AF progression ([Table 2](#)).

The clinical outcome rates during follow-up are given in [Table 3](#) as the crude number of events per 100 patient-years. Of the patients who underwent PVI during the follow-up period, the prevalence was lower in patients who were asymptomatic compared to those who were symptomatic (69, 14.8% vs. 162, 22.8%, respectively; P=0.001), but there was no significant difference in other clinical outcomes (eg, ischemic stroke, cardiovascular death, and all-cause mortality) between asymptomatic and symptomatic patients with AF.

Table 3. Clinical Outcome

	Asymptomatic AF (n=468)	Symptomatic AF (n=708)	P-value	Overall (n=1,176)
AF progression	55 (8.6)	60 (4.7)	0.001	115 (6.0)
Ischemic stroke	9 (0.6)	25 (1.1)	0.113	34 (0.9)
CV death	4 (0.4)	8 (0.5)	0.772	12 (0.4)
All-cause death	10 (0.9)	18 (1.0)	0.701	28 (1.0)

Data given as no. events (crude rate for 100 patient-years). CV, cardiovascular. Other abbreviations as in Table 2.

Discussion

In the present study involving patients from a single cardiovascular hospital, patients with asymptomatic paroxysmal AF had greater AF progression into the persistent form compared to those with symptomatic AF, irrespective of the patients' low-risk profiles. When we considered the effect of treatment intervention during follow-up, the interaction term between the absence of PVI and asymptomatic AF was independently associated with AF progression. Furthermore, asymptomatic AF patients had similar mortality rates and incidence rates of ischemic stroke compared to symptomatic ones.

It is generally considered that asymptomatic patients with AF have few cardiovascular comorbidities compared with symptomatic patients.¹⁷ It is natural to consider that asymptomatic paroxysmal AF would progress into the persistent form less frequently and would have a better prognosis than symptomatic AF. In the present study, asymptomatic AF patients had lower CHADS₂ and CHA₂DS₂-VASc scores compared with symptomatic ones, demonstrating the low-risk profile. Paradoxically, however, asymptomatic paroxysmal AF had a greater association with AF progression, and this association remained independent even after adjustment for various clinical patient characteristics. A similar paradoxical association has been reported previously.⁷ In a population-based study with first-detected AF, AF progression was observed in more patients with asymptomatic paroxysmal AF (41/79; 51.9%) compared to those with symptomatic AF (280/811; 34.5%), with a significant HR of 1.6 (95% CI: 1.1–2.2) in the multivariate model. The present results extend these results to Japanese AF patients in a single cardiovascular hospital. The annual incidence rate of AF progression (asymptomatic AF, 8.6% vs. symptomatic AF, 4.7%, respectively) and the HR of asymptomatic AF in the multivariate model (1.461) in the present patients are similar to those in the previous study.⁷

It is difficult to determine the reason as to why asymptomatic AF patients had a greater association with AF progression irrespective of low-risk profile. From a pathophysiological standpoint, left atrial dimension and left ventricular ejection fraction were similar between the present asymptomatic and symptomatic patients, suggesting that the progression of cardiac remodeling was similar. From a clinical standpoint, although the use of anti-arrhythmic agents (class Ia/Ic) was similar between asymptomatic and symptomatic patients (43.8% vs. 44.8%, respectively), the prevalence of PVI was lower among asymptomatic patients than among symptomatic ones (14.8% vs. 22.8%; $P=0.001$, respectively). Moreover, in the multivariate model, absence of PVI had a significant interaction with asymptomatic AF, and this interaction term had an independent association with AF progression. In this regard, it is assumed that the effect of asymptomatic AF on AF progression in the present study might be partly explained by a less-invasive intervention for rhythm control.

In the present study, the incidence rates of mortality or the development of ischemic stroke in asymptomatic AF patients were similar to those in symptomatic AF patients, irrespective of the low-risk profile. Consequently, the prognosis for AF appeared to be unrelated to the presence of symptoms. These results are consistent with the results of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study¹⁸ and other trials that support the concept that rate control is an acceptable strategy in the management of AF. Whether active invasive rhythm control, including catheter ablation, is beneficial for patients with asymptomatic paroxysmal AF remains to be investigated.

As with other studies on asymptomatic AF, we found that asymptomatic AF patients were more frequently male.^{6,8} This finding may simply reflect the greater risk for AF progression in male patients. A diagnosis of cardiomyopathy may reflect a variety of etiologies, including hypertension, which is not independently associated with a higher probability of progression. Cardiomyopathy will result in increased left atrial pressure and wall stress, which may be important stimuli for chronic atrial structural remodeling, enabling the maintenance of AF.¹⁹

Study Limitations

The present study has several limitations. Because this was a retrospective study, the definition of asymptomatic and paroxysmal AF was not completely accurate. This was especially true in asymptomatic AF patients, given that there remained a possibility that long AF persistence had already occurred before the initial hospital visit. We excluded, however, those patients in whom AF persisted for >7 days from the initial visit. We believe that this exclusion aided avoidance of misdiagnosis of progression into the persistent form at baseline. The present data were derived from a single hospital-based cohort in a cardiovascular hospital in an urban area of Japan. As a consequence, the present results cannot be easily extrapolated to other areas, countries, or population-based cohorts. Despite these limitations, the present data suggest the possibility that asymptomatic paroxysmal AF patients are not provided with adequate treatment, which partly contributes to disease progression and worsening of prognosis.

Conclusions

Irrespective of low-risk profile, asymptomatic paroxysmal AF patients were associated with greater AF progression to a sustained form compared to symptomatic patients. It is assumed that the paradoxical results are due to less intensive clinical management, including invasive rhythm control.

Acknowledgments

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