

Development of Congestive Heart Failure in Japanese Patients With Atrial Fibrillation

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Background Atrial fibrillation (AF) and congestive heart failure (CHF) are frequently coexistent, but their temporal relationship in Japanese patients is unclear.

Methods and Results 248 AF patients (63.6 ± 10.0 years old) without a history of CHF were enrolled for analysis of the development of CHF during the follow-up period of 49.7 ± 29.8 months. Of them, 195 did not have structural heart disease, 22 had dilated or hypertrophic cardiomyopathy, 18 had an old myocardial infarction, and 15 had valvular heart disease. During the follow-up period, 16 patients (6.5%) developed CHF requiring hospitalization (2.0% per patient-year). Although age, gender, fractional shortening, left atrial diameter, hypertension and diabetes mellitus were not associated with CHF development, existence of structural heart disease and left ventricular hypertrophy by Cornell voltage criteria on ECG were significantly associated with CHF development. Cox-Hazard regression analysis revealed that the existence of structural heart disease was the only independent risk factor (hazard ratio 3.50, 95% confidence interval 1.21–10.1).

Conclusions In the present group of Japanese AF patients, CHF requiring hospitalization occurred at a rate of 2% per year. The existence of structural heart disease was the only independent risk factor in this population. (*Circ J* 2007; 71: 308–312)

Key Words: Atrial fibrillation; Congestive heart failure; Hypertrophy

Atrial fibrillation (AF) is the most common type of arrhythmia and is responsible for substantial morbidity and mortality.^{1,2} Although AF-associated stroke is the major problem in the aged, congestive heart failure (CHF) related to AF can also impair quality of life, thus leading to increasing numbers of hospitalization. Because it has been proved that the overall prognosis of patients with AF, including stroke and heart failure, can not be improved simply by using the antiarrhythmic agents available at present;³ a new therapeutic approach is required.

Conversely, AF is still one of the major causes of CHF and therefore is more prevalent in patients with CHF than in the general population.^{4–6} Because AF and CHF are known to promote each other in a vicious cycle,^{7–10} AF remains an important therapeutic target for management and also prevention of CHF. In fact, it has been reported that in the United States patients with AF develop CHF at a high rate of approximately 3% per year.¹¹ Therefore, because AF is known to have characteristics peculiar to race and country,¹² the temporal relationships between AF and CHF should be also determined in Japanese AF patients for whom it remains unclear. The purpose of the present study was to investigate the incidence of CHF and its independent risk factors in Japanese AF patients to provide a valuable basis for prevention of CHF in Japan.

Methods

Study Population

Patients were enrolled in the present study, if they had visited the hospital for AF as a new patient from April 1995 to March 2003 and were thereafter followed up as an outpatient to March 2005. Patients with a history of CHF and/or dominant atrial flutter were excluded. All the patients were followed up monthly and treated by the attending physicians according to their judgments.

Data Collection

All data were entered into a computerized database. It included the following variables at the date of the initial visit to the hospital: gender, age, the presence of hypertension, diabetes mellitus, and underlying structural heart diseases, including myocardial infarction, dilated or hypertrophic cardiomyopathy, and valvular diseases. In the present study, persistent AF was defined clinically from the history and the 12-lead ECG when AF had continued for more than 6 months (so-called “chronic AF”). In each patient, left ventricular hypertrophy (LVH) was identified from the ECG with Cornell voltage criteria, which is the sum of the amplitudes of the R wave in lead aVL and the S wave in lead V3, adjusted by the addition of 800 μ V for females.^{13,14} The echocardiographic parameters, including the fractional shortening (FS) and left atrial dimension (LAd) recorded within 3 months after the initial visit, were also entered into the database. Valvular diseases were identified by echocardiography according to the following criteria: mitral/aortic regurgitation \geq grade 3, mitral valve area $< 2.0 \text{ cm}^2$ and/or aortic valve area $< 1.5 \text{ cm}^2$. During the follow-up period, medications and history of defibrillation were monitored. The development of CHF requiring hospitalization was

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Table 1 Baseline Characteristics of the Study Population

	Total	HF (+)	HF (–)	p value
<i>n</i>	248	16	232	
Age (years)	63.6±10.0	66.6±11.2	63.4±9.9	0.20 [#]
Male	192	11	181	0.39
Persistent AF	104	8	96	0.50
HT	94	5	89	0.57
DM	34	3	31	0.54
Structural heart diseases	53	8	45	0.0039*
HCM	15	2	13	
DCM	7	2	5	
MI	18	2	16	
VD	15	2	13	
LVH (cornell voltage criteria)	25	4	21	0.040*
Echocardiographic parameters				
FS <40%	158	11	147	0.66
LAD >40 mm	143	13	130	0.048*

HF, heart failure; AF, atrial fibrillation; HT, hypertension; DM, diabetes mellitus; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; MI, myocardial infarction; VD, valvular diseases; LVH, left ventricular hypertrophy; FS, fractional shortening; LAD, left atrial diameter.

* $p < 0.05$, [#]unpaired t-test.

diagnosed using the Framingham criteria:² presence of 2 major, or 1 major and 2 minor, criteria used to establish a diagnosis of CHF. Major criteria included paroxysmal nocturnal dyspnea or orthopnea, distended neck veins, rales, radiographic cardiomegaly, pulmonary edema, third heart sound, increased venous pressure, hepatojugular reflux, and weight loss on diuretic therapy. Minor criteria were ankle edema, night cough, dyspnea on exertion, hepatomegaly, pleural effusion, pulmonary vascular redistribution, decrease in vital capacity, and tachycardia. The present study was an observational one approved by the institutional review board.

Statistical Analysis

Statistical analysis was performed with StatView 5.0 (SAS Institute Inc, Cary, NC, USA). Parametric data are expressed as mean±SD. Survival curves were estimated by the Kaplan-Meier product-limit method¹⁵ and compared by means of Mantel (log-rank) test. The effect of prognostic factors on CHF development was evaluated with Cox models.¹⁶ We tested the following covariates: age (years), gender (female, male), FS (%), LAd (mm), history of hypertension (yes, no), diabetes mellitus (yes, no), structural heart diseases (yes, no), LVH (yes, no) and presence of persistent AF. All p-values were 2-tailed and values of <0.05 were considered statistically significant. All confidence intervals (CI) were calculated to the 95th percentile.

Results

Baseline Characteristics of the Study Population

From our database, we screened 798 AF patients from all the new patients (n=17,925) who visited the hospital between April 1995 and March 2003. Among them, 352 patients with a history of CHF and 198 patients with dominant atrial flutter were excluded, and 248 AF patients were included in the present study and followed up thereafter. The baseline characteristics of the population are shown in Table 1. The mean age was 63.6±10.0 years old, 23% of the patients were women and approximately 80% of the patients had no underlying structural heart diseases. The mean duration of follow-up was 49.7±29.8 months. At the initial visit, 104 patients (41.9%) were diagnosed as having

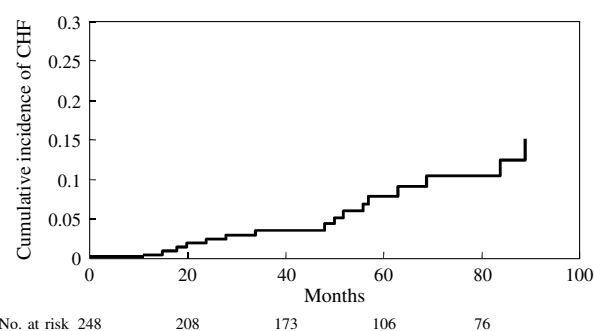


Fig 1. Time-course of new-onset congestive heart failure (CHF) in Japanese patients with atrial fibrillation. The average incidence rate of CHF development was 2% per year.

persistent AF. Structural heart diseases, LVH on electrocardiograms, and LAd >40 mm were more frequently observed in patients with new CHF events.

Defibrillation and Medications for AF

During the follow-up period, the drugs were changed according to the judgment of the attending physicians. At the initial visit, rhythm control strategy with class I drugs was undertaken in 88 patients (35%). During the follow-up period, defibrillation by direct current shock was undertaken in 99 patients (39.9%). For rhythm control, Vaughan Williams class I antiarrhythmic drugs were frequently used, which is the tendency of Japanese physicians.¹⁷

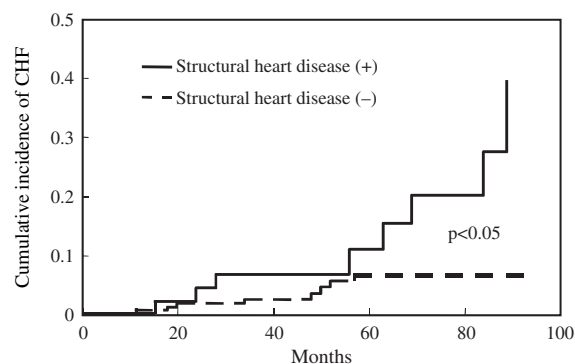
CHF Development during the Follow-up Period

Fig 1 shows the time course of the development of CHF requiring hospitalization during the follow-up period. Of the total patient group, 16 developed CHF that required hospital admission (6.5%, 2.0% per patient-year). All the patients needed intravenous infusion of diuretics to manage CHF.

Factors Associated With CHF Development by Univariate Analysis

We determined the relationships between patient background at the initial visit and subsequent CHF development.

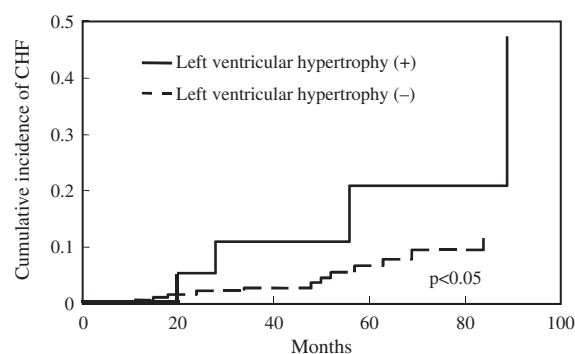
A



No. at risk 53 47 40 21 17
(Structural heart disease +)

No. at risk 195 161 133 85 59
(Structural heart disease -)

B



No. at risk 25 18 16 8 2
(Left ventricular hypertrophy +)

No. at risk 223 190 157 98 74
(Left ventricular hypertrophy -)

Fig2. (A) Incidence of congestive heart failure (CHF) in patients with and without structural heart disease. Patients with structural heart diseases (line) were more prone to develop CHF than those without (dotted line, $p < 0.05$). (B) Incidence of CHF in patients with and without left ventricular hypertrophy by Cornell voltage criteria. Patients with left ventricular hypertrophy (line) were more prone to develop CHF than those without (dotted line, $p < 0.05$).

When we compared patients with and without structural heart diseases, those with structural heart diseases were more prone to develop CHF than those without ($p < 0.05$, Fig 2A), which would imply a significant role of the underlying heart disease. Moreover, LVH based on Cornell voltage criteria was also significantly associated with CHF development ($p < 0.05$, Fig 2B). However, age, gender, hypertension, diabetes mellitus, echocardiographic parameters, persistent AF at initial visit, and history of defibrillation during follow-up were not associated with CHF development.

Cox Proportional Hazard Model

Factors Associated With CHF Development by Multivariate Analysis

In order to evaluate the individual hazards of factors for the development of CHF, a Cox proportional hazard model was established with the results detailed in Table 2. The existence of structural heart disease was the only independent risk factor for CHF (hazard ratio 3.50, 95% CI 1.21–10.1).

Table 2 Individual Hazards of Factors for the Development of CHF (Cox Proportional Hazard Model)

	Hazard ratio	95%CI
Age	1.02	0.97–1.09
Male	0.40	0.11–1.49
Persistent AF	1.13	0.40–3.24
HT	0.61	0.20–1.83
DM	1.28	0.34–4.90
Structural heart disease	3.50	1.21–10.1
LVH (cornell voltage criteria)	2.76	0.79–9.71
Echocardiographic parameters		
FS <40%	1.65	0.51–5.29
LAD >40 mm	2.26	0.61–8.26

CHF, congestive heart failure; CI, confidence interval. Other abbreviations see in Table 1.

In this model, however, age, gender, hypertension, diabetes mellitus, echocardiographic parameters, LVH by Cornell voltage criteria and presence of persistent AF at initial visit were not significantly related to the development of CHF.

Discussion

The major findings of the present study are that Japanese AF patients without a history of CHF develop new-onset CHF requiring hospitalization at a rate of 2.0% per year, and that the presence of structural heart disease and LVH on ECG are related to new CHF events with the former being the only independent predictor.

It is well known that prevention of stroke and CHF is primarily important for preventing mortality and morbidity in AF patients. In the US, the Framingham study revealed the high incidence of stroke and CHF in AF patients.² The rate of ischemic stroke among AF patients averages approximately 5% per year,¹⁸ and the rate of CHF is also high at approximately 3.3% per year.¹¹ A cohort study in France also reported a high incidence (4%) of CHF development in AF patients during a relatively short follow-up period of 8.6 months.¹⁹ Because AF aggravates CHF and CHF promotes AF,^{7–10} patients with either condition who develop the alternate condition are believed to have a poor prognosis. Therefore, to identify high-risk patients for CHF among AF patients is crucial, but in Japan even the annual rate of CHF development in AF has long remained unclear. The present study is the first to report that the incidence of new-onset CHF in Japanese AF patients is approximately 2% per patient-year, slightly lower than in the United States or France.

To prevent the development of CHF in AF patients, it is essential to identify the high-risk patients as a first step. However, the risk factors for new-onset CHF in AF patients have not been fully evaluated, possibly because the temporal relationships differ from patient to patient. Although AF can be the result of CHF in some patients, AF and CHF might be occurring simultaneously in others. These various temporal relationships make the analysis complex. Therefore, in the present study, to focus on primary prevention of CHF in AF patients, we enrolled only those without a history of CHF, and we subsequently identified that the presence of structural heart diseases and LVH based on Cornell voltage criteria were related to the development of CHF after AF by univariate analysis, whereas the former was the only independent risk factor by multivariate analysis.

Although it is plausible that the presence of structural

heart disease is significantly associated with CHF development, the relationships of LVH to new-onset CHF deserves discussion, even though it was not an independent predictor in the present study. Recent epidemiological data have reported that approximately half of the patients with CHF present with preserved systolic function, implying an important role for diastolic dysfunction.²⁰ LVH on ECG might represent this diastolic dysfunction, which contributes to the development of CHF. In fact, in the LIFE study of hypertensive patients, LVH on ECG was identified as an important risk factor for CHF.²¹ Because diastolic dysfunction cannot be evaluated by routine echocardiography, particularly in those with persistent AF, the ECG findings might provide an important practical method of predicting CHF in AF cases, although the relationship between LVH on ECG and diastolic dysfunction remains to be precisely determined.

On the other hand, it should be questioned why the echocardiographic parameters evaluating systolic function were not independent predictors for CHF development. There are several explanations. First, prediction of diastolic CHF, which is affecting half of CHF patients in Japan's aged society,²² is difficult solely from the parameters of systolic function. Second, even when the present study enrolled AF patients without a history of CHF, the majority of the patients had low value of FS at the initial visit, possibly because of AF tachycardia, and this might lead to underestimation of the systolic function. Third, even if systolic function was truly impaired at the initial visit, it could be improved also by appropriate heart rate control during follow-up. This is well known as tachycardia-induced cardiomyopathy.⁸ Conversely, it should be noted that in clinical situations CHF can develop even when the systolic function is apparently preserved on echocardiography.

Persistent AF at initial visit was not an independent predictor for CHF in the present study, which is consistent with the ALFA study¹⁹ and the Framingham study;² both of which have reported that persistent AF prior to CHF did not affect the prognosis of AF patients.²³ In the present study, persistent AF was diagnosed at the initial visit when CHF was absent. The inclusion criteria of the present study might be related to the result, because persistent AF with prior or simultaneous CHF was excluded. However, defibrillation of AF during the follow-up also could not be a factor for decreasing the rate of CHF development. This suggests that a rate control strategy could adequately prevent new-onset CHF in the majority of AF patients, as in the AFFIRM study.³ Negative inotropic effects and/or insufficient efficacy of antiarrhythmic drugs after defibrillation might be related to the insignificant role of defibrillation in the prevention of CHF.

In the present study, we described a relatively benign prognosis of Japanese AF patients compared with American and European studies. There are several reasons for the difference. In the previous studies in the USA and Europe, patients with AF had structural heart disease more frequently than the Japanese patients in the present study.¹⁹ Because the presence of structural heart disease was an independent predictor in our study, the prevalence of basal diseases should explain the different prognosis. Moreover, medical circumstances, including hospital access and health insurance, are different and in Japan could facilitate frequent hospital visits, which might lead to a lowering of the incidence of hospitalization because of early intervention.

Study Limitations

First, the present study only included AF patients without a history of CHF. Therefore, the results can not be extrapolated to AF patients with a history of CHF and thus only refer to primary prevention of CHF. Second, the study was performed in both a retrospective and nonrandomized fashion in a single center specializing in cardiovascular diseases, which result in some biases that could not be precisely determined. Lastly, considering the relatively low incidence of new CHF in AF patients that has been clarified in the present study, the sample size, though small, was still adequate for precise determination of the independent risk factors. Despite these limitations, the present study reports for the first time the incidence of and independent risk factors for new-onset CHF in Japanese AF patients, and therefore provides a basis for primary prevention of CHF in AF in Japan.

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