Long-Term Prognosis of Patients With Paroxysmal Atrial Fibrillation Depends on Their Response to Antiarrhythmic Therapy

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Background The rhythm control treatment strategy for persistent atrial fibrillation (AF) has been shown not to improve quality of life or prognosis any more than rate control. It is unclear whether the prognosis of the patients with paroxysmal AF (PAF) is influenced by the response to antiarrhythmic drug therapy (AAT).

Methods and Results The relationship between the response to AAT and long-term prognosis was evaluated in 290 patients with PAF (mean age, 69 years). During a mean follow-up period of 51 months, 114 patients (39%) had no recurrence of AF (Group 1), 113 (39%) had repeated AF recurrence (Group 2), and the remaining 63 (22%) had permanent AF despite AAT (Group 3). The survival rate without any cardiovascular deaths at 60 months was 99% in Group 1, 95% in Group 2 and 94% in Group 3 (p=NS among 3 groups). Survival rate without symptomatic ischemic stroke was 99% in Group 1, 88% in Group 2 and 76% in Group 3 (p<0.05 Group 1 vs Groups 2 and 3). The annual rate of stroke in the patients with warfarin treatment was similar among the 3 groups, whereas that in the patients without warfarin was higher in Groups 2 and 3 than in Group 1.

Conclusions Long-term prognosis of patients with PAF varies with the response to AAT: When sinus rhythm is maintained, the prognosis is good even without anticoagulation therapy. (Circ J 2004; 68: 729–733)

Key Words: Antiarrhythmic therapy; Atrial fibrillation; Prognosis; Stroke

Atrial fibrillation (AF) is not a fatal arrhythmia, but seriously affects the prognosis of the patient, especially those with underlying heart disease and advanced age.1-7 In patients with paroxysmal and persistent AF, antiarrhythmic drug therapy (AAT) has been widely performed to maintain sinus rhythm (rhythm control), but it is unclear whether this therapy improves the survival and reduces ischemic stroke. Recently, 2 large clinical trials (AFFIRM8 and RACE9) demonstrated that rhythm control therapy in patients with persistent AF does not improve either quality of life or long-term prognosis any more than rate control and in fact may increase the rate of mortality or any other cardiovascular event. It is unclear whether these results can be applied to patients with PAF and normal or minimally impaired cardiac function because these trials mainly included patients at high risk for ischemic stroke and cardiovascular death. It is also unclear whether the prognosis of the patient is affected by the results of the therapy.

Since 1993, we have treated 290 patients with symptomatic PAF and normal or minimally impaired left ventricular function with antiarrhythmic drugs. We found that there is a limitation to the maintenance of sinus rhythm, and AF recurred or became permanent during follow-up in more than half of the patients.10-12 The aim of the present study was to clarify the long-term prognosis of the patients with PAF in relation to the results of AAT by retrospectively analyzing the survival curves of the patients.

Methods

Study Patients

This study was performed from June 1993 to March 2003, and included 290 patients with symptomatic PAF who underwent AAT according to the protocol described for 12 months or more in order to maintain sinus rhythm (191 men, 99 women; mean age, 69 years (range 24–92)). The patients were divided into 3 groups according to their response to AAT: Group 1 consisted of 114 patients (39%) who were considered to have not had any recurrence of AF; Group 2 consisted of 113 patients (39%) who had repeated recurrence of AF; Group 3 consisted of 63 patients (22%) who had repeated recurrence of AF which eventually became permanent despite the therapy. The mean follow-up period was 51±29 months (mean±SD) (range 12–115) for all patients.

All patients underwent chest radiography, ECG recording, exercise ECG testing, echocardiography, and head computed tomography scanning before the initiation of AAT. Of the 290 patients, 93 had underlying heart diseases such as coronary artery disease (42), valvular heart disease (17), hypertrophic cardiomyopathy (11), dilated cardiomyopathy (10), sick sinus syndrome (bradycardia–tachycardia syndrome) (6), atrial septal defect (4), cardiac syndrome X (2), and myocarditis (1); 28 patients had pulmonary diseases such as healed tuberculosis (11), bronchial asthma (8), chronic bronchitis (5), pulmonary silicosis (3) and pulmonary emphysema (1). Patients with congestive heart failure,
left ventricular ejection fraction <40%, which was determined by echocardiography, bradycardia <40 beats/min, severe intraventricular conduction disturbance, severe liver or renal dysfunction and other serious complications were excluded.

**Follow-up**

All patients were followed up once or twice each month at the outpatient clinic of Iwate Prefectural Iwai Hospital and at every visit it was established from the patient's symptoms and ECG findings whether or not sinus rhythm was being maintained without AF recurrence or if AF had recurred. Ambulatory 24-h ECG recording was repeated at 3-month intervals or whenever it was considered to be necessary by the physician. When AF recurred and did not terminate spontaneously, pharmacological and/or electrical cardioversion was attempted.

As antithrombotic therapy, aspirin (81 mg/day) was administered in 99 patients and warfarin in 63 patients. The dose of warfarin was set to an international normalized ratio (INR) between 1.6 and 2.6. There was no difference in the prevalence of the risk factors for ischemic stroke between the patient groups with and without warfarin treatment (age >65 years, 75% vs 66%; history of heart failure, 13% vs 7%; history of ischemic stroke, 8% vs 4%; hypertension, 46% vs 45%; and diabetes mellitus, 16% vs 14%).

**Protocols of AAT and Results of Therapy**

After sinus rhythm was restored spontaneously or by cardioversion, one of the following class I drugs, disopyramide (300 mg/day), cibenzoline (300 mg/day) or aprindine (60 mg/day), was selected by an envelope method (the first drug) and administered orally. When AF recurred, sinus rhythm was restored and one of the following drugs, flecainide (150 mg/day), pilsicainide (150 mg/day) or bepridil (150 mg/day), was selected by an envelope method (the second drug). When AF recurred, amiodarone or a class I antiarrhythmic drug that had not been used before was administered (the third drug). The selection of the third drug was left to the decision of the physician.

The details of the results of these protocols have been reported previously.10–12 Briefly, after 1 year of treatment with the first drug, 51%, 47% and 35% of the patients treated with disopyramide, cibenzoline and aprindine, respectively, were free from AF recurrence; after 1 year of the second drug, 33%, 33% and 21% of the patients treated with flecainide, pilsicainide and bepridil, respectively, were free from AF recurrence; and after 1 year of the third drug, 43% and 18% of the patients treated with amiodarone and a class I antiarrhythmic drug that had not been previously used, respectively, were free from AF recurrence. The patients who had permanent AF despite therapy (Group 3) were treated with digoxin, β-blocker, or Ca-antagonist to control ventricular rate during AF.

**Definitions and Statistical Analysis**

Paroxysmal AF was defined as AF that terminated spontaneously within 7 days after onset. Permanent AF was defined as AF that was refractory to pharmacological and electrical cardioversion and did not convert to sinus rhythm for a period >6 months. The duration of AF morbidity was the period from the initial episode of PAF to the time of the initiation of AAT. Hypertension was defined as blood pressures >160 mmHg at systole and >90 mmHg at diastole. Ischemic stroke was diagnosed by the typical symptoms and the development of a new, low-density lesion on the CT scan. The etiology of ischemic stroke (embolism or thrombosis) could not be clarified in each patient in this study. Cardiovascular deaths included death from heart failure, or ischemic or hemorrhagic stroke, and sudden cardiac death. All data are shown as mean ± SD. The clinical profiles of the patients were compared among Groups 1, 2 and 3 by one-way ANOVA for continuous variables and chi-square test for categorical ones. Survival curves were estimated by the Kaplan-Meier method and were compared by the log-rank test. A p-value <0.05 was considered to show statistical significance.

**Results**

**Comparisons of Clinical Profiles and Antithrombotic Therapy**

There were no differences in age, gender, percentage of the patients with coronary risk factors, and distributions of underlying heart and pulmonary diseases among the 3 groups (Table 1). The duration of morbidity of AF was longer in Group 3 than in Groups 1 and 2 (p<0.05) (Table 2). The follow-up period was longer in Groups 2 and 3 than in Group 1 (p<0.05). There was no difference in the left ventricular ejection fraction or end-diastolic left ventricular dimension determined by echocardiography among the 3 groups. The left atrial dimension was greater in Group 3 than in Groups 1 and 2 (p<0.05). The percentage of patients treated with aspirin was not different among the 3 groups. The percentage of the patients treated with war-
farin was greater in Groups 2 and 3 than in Group 1 (p<0.01). The INR ranged from 1.3 to 3.9 (mean value, 2.6) for all warfarin-treated patients during the study period.

Comparison of Long-Term Prognoses
Cardiovascular death occurred in 11 of the 290 patients (3.8%) during a mean follow-up period of 51 months. Fig 1 shows the survival curves without any cardiovascular deaths for the 3 groups. At 60 months, the survival rate was 99% in Group 1, 95% in Group 2 and 94% in Group 3 (p=NS among 3 groups). The cause of death was sudden cardiac death (1 patient) in Group 1, sudden cardiac death (2 patients), heart failure (2 patients) and stroke (2 patients) in Group 2, and heart failure (3 patients) and stroke (1 patient) in Group 3. Fig 2 shows the survival curves without fatal or nonfatal symptomatic ischemic stroke. At 60 months, survival rate was 99% in Group 1, 88% in Group 2 and 76% in Group 3 (p<0.05 Group 1 vs Groups 2 and 3).

Comparison of the Annual Rates of Ischemic Stroke
As shown in Table 3, the annual rate of ischemic stroke was significantly greater in Groups 2 and 3 than in Group 1. In patients in whom any antithrombotic therapy was not performed during the follow-up period, the annual rate of ischemic stroke was significantly greater in Groups 2 and 3 than in Group 1. In the patients with aspirin treatment, the annual rate was significantly greater in Groups 2 and 3 than in Group 1. In the patients with warfarin treatment, ischemic stroke occurred in 2 patients (one in Group 2 and the other in Group 3). The INR measured before the onset of stroke
in these 2 patients was 1.4 and 1.5. There was no significant difference in the annual rate among the 3 groups.

**Discussion**

In order to clarify the long-term prognosis of patients with PAF and the influence AAT on it, we retrospectively analyzed the survival curves of 3 groups of patients: Group 1 consisted of patients in whom sinus rhythm was maintained without AF recurrence, Group 2 consisted of patients in whom AF recurred during therapy, requiring a change in therapy, and Group 3 consisted of the patients in whom AF converted to a permanent form despite therapy. The results showed that cardiovascular death occurred in only 1% in Group 1 at 60 months whereas it was 5% and 6% in Groups 2 and 3, respectively. Fatal or nonfatal ischemic stroke occurred in only 1% in Group 1 at 60 months compared with 12% and 24% in Groups 2 and 3, respectively. Anticoagulation therapy with warfarin was done in only 10% of Group 1 patients. Thus, the long-term prognosis of the patients varied with their response to AAT: if sinus rhythm was maintained with antiarrhythmic therapy, the prognosis was good even if anticoagulation therapy was not performed. When AF repeatedly recurred or converted to permanent AF despite therapy, the prognosis became worse and ischemic stroke occurred at an increased rate especially when anticoagulation therapy was not performed.

**Long-Term Prognosis of PAF**

The total mortality rate in patients with AF is approximately double that of patients with sinus rhythm, and mortality is closely related to the severity of the underlying heart disease. In addition to this increased mortality rate, the annual rate of ischemic stroke among patients with nonvalvular AF, which is approximately 5%, is 2–7-fold that in the subjects without AF. The risk of stroke increases with age; a previous Framingham study showed that it was 1.5% in participants aged 50–59 years and 23.5% in those aged 80–89 years. Thus, though not fatal directly, AF does seriously affect the prognosis, especially of those with underlying heart disease and advanced age.

To improve survival and reduce the incidence of ischemic stroke in patients with paroxysmal and persistent AF, AAT to maintain sinus rhythm has been widely performed (rhythm control therapy), but it remains unclear whether such a treatment strategy achieves its aims.

Recently, 2 large clinical trials, which compared the long-term effects of 2 strategies, rhythm control vs rate control, in patients with persistent AF have reported their findings. Both studies found that rhythm control therapy did not improve either quality of life or long-term prognosis any more than rate control, but rather increased the incidence of mortality or any cardiovascular event. These adverse effects of rhythm control therapy might be related to the interruption of anticoagulant therapy in many patients and the use of potent antiarrhythmic drugs such as amiodarone. It should be noted that these trials mainly included patients at high risk for the development of ischemic stroke or cardiovascular death. It is therefore unclear whether the results can be applied to patients with PAF and normal or minimally impaired cardiac function. It is also unclear whether the prognosis of the patients in whom sinus rhythm is maintained without recurrence of AF is improved compared with those in whom AF recurred or converted to permanent form.

Paroxysmal AF often occurs in patients without any underlying heart disease, causing symptoms such as palpitation, chest discomfort and dizziness in many patients and therefore requiring treatment. In the present study, during a mean follow-up period of 51 months, we found that sinus rhythm was maintained without AF recurrence in 39% of the patients, but that AF recurred or converted to permanent form despite therapy in the remaining 61%. This finding is consistent with previously reported results and indicates that there is a limitation to the treatment of PAF with the antiarrhythmic drugs currently available in Japan.

When the long-term prognosis of these patients was analyzed in relation to the preventive effects of AAT on AF recurrence, we found that the prognosis varied with the response to therapy. Thus, when sinus rhythm was maintained, the prognosis was found to be good even if anticoagulation therapy was not performed, whereas if AF recurred or converted to permanent AF, the prognosis became worse and ischemic stroke occurred at an increased rate especially when anticoagulation therapy was not performed.

A recent STAF study could not find any difference in prognosis between rhythm control and rate control strategies in patients with persistent AF, but most of the endpoints (death, cardiopulmonary resuscitation, cerebrovascular event and systemic embolism) occurred during AF. Thus, the maintenance of sinus rhythm in patients with AF will improve their prognosis. A rhythm control strategy with antiarrhythmic drugs is therefore the choice of treatment for PAF in patients with normal or minimally impaired cardiac function because it will improves their long-term prognosis.

Sudden cardiac death occurred in 3 of the 227 Group 1 and 2 patients (1.3%) in whom AAT was continued. Although the precise cause(s) of death was not clarified, the possibility of a proarrhythmic effect of the drug administered could not be excluded and care should be taken with long-term treatment with antiarrhythmic drugs.

**Importance of Anticoagulation Therapy in Preventing Ischemic Stroke**

Our results showed that in 62 of the 114 Group 1 patients (54%) did not undergo any antithrombotic therapy and symptomatic ischemic stroke did not occur in any of the patients. In the other 52 patients, aspirin or warfarin was administered and ischemic stroke occurred in one patient during follow-up. The clinical characteristics, including age, the prevalence of hypertension, diabetes...
mellitus, organic heart disease and cardiac function, were similar among the 3 groups, and therefore the risk for ischemic stroke in Group 1 patients was not lower than in the other groups. The results indicate that in patients with PAF, ischemic stroke is prevented if AF recurrence is prevented by AAT. However, in patients with asymptomatic or minimally symptomatic AF, it may not be easy to judge if AAT has prevented recurrence of AF.

On the other hand, in the Group 2 and 3 patients, the annual rate of ischemic stroke was >4%, which is consistent with that reported previously for patients not undergoing any anticoagulation therapy.14-17 When comparing the annual rate between the patient groups treated with aspirin and warfarin, it was approximately 5-7-fold higher in patients treated with aspirin than in those with warfarin. Actually, the annual rate in patients treated with warfarin was less than 1% in both Groups 2 and 3. Thus, in patients with PAF that is refractory to AAT, aspirin did not prevent ischemic stroke whereas warfarin did. Aspirin has been shown to be effective in preventing ischemic stroke in relatively young patients and in those with hypertension.20-24 The present study included many patients with advanced age (mean age in Groups 2 and 3, 70 years), which may explain the ineffectiveness of aspirin. Therefore, when treating the patients with PAF and age similar to that in the present patients, anticoagulation therapy is required to prevent AF recurring or converting to permanent form.

**Study Limitations**

This was a retrospective, observational study, and the prognosis of the patients was not compared with that of patients who did not receive either AAT or rate control therapy. All of the patients, however, were asymptomatic and were considered to need rhythm control therapy. Further studies comparing rhythm and rate control therapies are needed to clarify the role of AAT in the management of symptomatic PAF. For this purpose, the J-RHYTHM (Japanese Rhythm Management Trial for Atrial Fibrillation) study is currently being performed.25

Page et al reported that in patients with PAF, sustained asymptomatic AF occurs far more frequently than symptomatic AF.26 In the present study, Group 1 patients were considered not to have AF recurrence, based on their symptoms and ECG findings recorded periodically at the outpatient clinic, but the possibility of asymptomatic episodes of AF in these patients cannot be excluded completely.

**References**


