Efficacy of Antiarrhythmic Drug Therapy in Preventing Recurrence of Atrial Fibrillation and Long-Term Cardiovascular Prognosis in Patients With Asymptomatic Paroxysmal Atrial Fibrillation

Comparison to Patients With Symptomatic Atrial Fibrillation

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Summary

We evaluated the efficacy of antiarrhythmic drug therapy (AAD) and long-term cardiovascular prognosis in patients with asymptomatic paroxysmal atrial fibrillation (AF). This retrospective study included 334 patients (229 men and 105 women, mean age, 69 ± 11 years, mean follow-up, 60 ± 11 months) who were divided into two groups: patients with symptomatic AF (group I) and those with asymptomatic AF (group II) on the basis of subjective symptoms.

(1) Actuarial rates of patients without AF recurrence, those with AF recurrence and with electrical/pharmacological cardioversion to restore sinus rhythm, and those with conversion to permanent AF despite AAD were 40%, 41%, and 19%, respectively, in group I, and 22%, 24%, and 54%, respectively, in group II at the end of the follow-up period. At 60 months, the percentage of patients with conversion to the permanent form of AF was significantly greater in group II than in group I (P < 0.05, group I versus group II). (2) Survival rates free from symptomatic thromboembolism at 36, 60, and 120 months were 96%, 93%, and 88%, in group I, and 82%, 76%, and 71%, respectively, in group II (P < 0.05, group I versus group II). In patients not undergoing anticoagulant therapy, the annual rate of symptomatic thromboembolism was significantly greater in group II (5.3%) than in group I (2.3%) (P < 0.05), while in patients undergoing anticoagulant therapy there was no significant difference in the annual rate of symptomatic thromboembolism between group I (0.9%) and group II (1.8%).

The clinical course of asymptomatic paroxysmal AF is refractory to AAD when compared to symptomatic AF, meaning that anticoagulant therapy is required to prevent symptomatic thromboembolism in this group. (Int Heart J 2010; 51: 98-104)

Key words: Atrial fibrillation, Prophylactic efficacy, Prognosis, Antiarrhythmic therapy, Ischemic stroke

Methods

Subjects: The subjects in this study were 334 patients (229 men and 105 women, mean age, 69 ± 11 years) with paroxysmal AF who were monitored at hospital visits every 2-4 weeks and could be observed for at least 1 year. These patients were classified into a symptomatic AF group (n = 289) or an asymptomatic AF group (n = 45) according to the presence of symptoms such as palpitations, shortness of breath, and precordial discomfort during episodes of AF.

Noninvasive examinations, including chest X-rays, exercise testing, and transthoracic echocardiography were performed in all patients, while pulmonary function tests, computed tomographic examination of the brain and chest, and cardiac catheterization were performed at the discretion of attending physicians. Patients with severe bradyarrhythmia (sick sinus syndrome, atrioventricular block, or intraventricular conduction disorder), those with hepatic or renal dysfunction associated with laboratory abnormalities,
women with child-bearing potential, and patients receiving concomitant administration of β-blockers or T-type calcium antagonists were excluded from the study. This study was conducted between June 1995 and August 2006, and the mean observation period was 60 ± 35 months.

**Protocols for cardioversion and antiarrhythmic drug therapy:** In accordance with the AHA Guidelines, pharmacological or electrical cardioversion under intravenous thiopental anesthesia was performed immediately in patients in whom the duration of AF was less than 48 hours. Prior to release of the AHA Guidelines, cardioversion was performed and warfarin anticoagulant therapy was added where the duration of AF was 48 hours or more, after the absence of left atrial thrombus or spontaneous echo contrast was confirmed by transesophageal echocardiography. After the release of the AHA Guidelines, however, in patients in this group were treated with electrical cardioversion under anticoagulant therapy with warfarin for 3 weeks before cardioversion and 4 weeks after cardioversion. In accordance with the protocol for prevention of recurrence by antiarrhythmic therapy, in patients with a left ventricular ejection fraction ≥ 40% on echocardiography, medical or electrical cardioversion was performed to restore sinus rhythm. A class Ia or Ib drug (disopyramide at 300 mg/day, aprindine at 60 mg/day, or cibenzoline at 300 mg/day) was then selected randomly by the envelope method as first-line therapy and AF recurrence was carefully monitored. If recurrence of AF was noted during follow-up, cardioversion was performed again, a class Ic drug (flecainide at 150 mg/day or pilscainide at 150 mg/day) or bepridil (150 mg/day) was selected randomly for second-line therapy, and then recurrence of AF was carefully monitored. If AF still recurred despite second-line therapy, amiodarone was administered to patients who consented to use of this drug. In patients with a left ventricular ejection fraction < 40% on echocardiography, sinus rhythm was restored by electrical cardioversion and then either aprindine (60 mg/day) or bepridil (150 mg/day) was selected as first-line or second-line treatment. If recurrence of AF was detected after treatment with both drugs, amiodarone or a class I antiarrhythmic drug not used before was administered to patients giving consent for its use. Amiodarone was administered orally at a dose of 400 mg/day for 2 weeks and then at a maintenance dose of 200 mg/day, and patients were observed carefully for recurrence of AF. Antithrombotic therapy was added at the discretion of the attending physicians. As antiplatelet therapy, aspirin was administered orally at a dose of 80-100 mg/day. For anticoagulant therapy, the dose of warfarin was adjusted so that the international normalized ratio (PT-INR) was 1.6-3.0.

Two to four weeks after commencement of or alteration in an oral antiarrhythmic drug, standard 12-lead ECG and ambulatory 24-hour monitoring were recorded in all patients. In addition, at every visit to our outpatient clinic, maintenance or otherwise of sinus rhythm was confirmed with the use of a portable ECG monitor (IEC-1101 “Heart Mate” manufactured by Nihon Kohden Corporation). For measurement of human atrial natriuretic peptide (ANP) during sinus rhythm, venous blood was collected from an upper limb after the patient had rested in the supine position if no palpitations had been noted since the start of drug therapy and sinus rhythm was confirmed on ECG at each hospital visit. Whenever palpitations occurred, an ambulatory 24-hour monitoring was recorded at the discretion of the attending physicians to determine whether AF had recurred or not.

**Definitions:** Based on symptoms and ambulatory 24-hour monitoring, paroxysmal AF was defined as transient AF terminating spontaneously within 1 week of onset. The history of AF was the period from the initial episode of AF to the time of the initiation of antiarrhythmic therapy. Permanent AF was defined as AF that was refractory to pharmacological and electrical cardioversion and did not convert to sinus rhythm for a period greater than 6 months. Asymptomatic AF was defined as an AF episode in which patients had none of the symptoms associated with arrhythmic symptoms such as palpitations, dizziness, light-headedness, fast heartbeat or syncope, and heart failure symptoms such as dyspnea, edema, orthopnea, or paroxysmal nocturnal dyspnea at the time of their initial hospital visit. Cerebral thromboembolism was diagnosed in all cases based on typical neurological symptoms and the development of a new low-density lesion greater than 3 mm on brain computed tomographic examination or magnetic resonance imaging, which was performed in all patients. Hypertension was diagnosed where ambulatory systolic pressure was ≥ 140 mmHg or diastolic pressure was ≥ 90 mmHg. Onset of paroxysmal AF was classified as diurnal type (07:00 to 17:00), nocturnal type (17:00 to 07:00 next morning), or mixed (symptoms appearing at any time) based on standard 12-lead ECG and ambulatory 24-hour monitoring findings. In patients with atrial fibrillation at the time of a hospital visit, classification was based on the time when symptoms commenced. Recurrence of AF was not determined from subjective symptoms, but was defined as the time when ECG first revealed AF during antiarrhythmic drug therapy. Death from a cardiovascular event was defined as sudden death, death from heart failure, or death from thromboembolism. In the pulmonary function test, we regarded FEV1.0 ≤ 70% as a diagnostic criterion for chronic obstructive pulmonary disease. Risk factors for thromboembolism were defined as a history of cerebral infarction or transient ischemic attack, hypertension, diabetes mellitus, coronary artery disease, and recent heart failure.

**Statistical analysis:** Demographic data on patients and frequency of recurrence of AF are expressed as the mean ± standard deviation. For statistical comparison between the two groups, clinical characteristics and number of AF recurrences in individual patients were compared between the two groups using the unpaired t-test for continuous variables and the chi-square test for categorical ones. Survival curves were estimated by the Kaplan-Meier method and were compared by the log-rank test (Cox-Mantel). A P < 0.05 was considered to indicate statistical significance.

**Results**

**Comparison of clinical profiles:** Table I shows the clinical profiles of the asymptomatic and symptomatic AF groups. Diabetes mellitus was present in 31% (14 patients) of the asymptomatic AF group and 10% (28 patients) of the symptomatic AF group, being significantly more common in the
asymptomatic group \((P < 0.01)\). The mixed type of AF occurred in 73\% (33 patients) of the asymptomatic AF group and 47\% (137 patients) of the symptomatic AF group, being significantly more common in the asymptomatic group \((P < 0.01)\). The nocturnal type was found in 7\% (3 patients) of the asymptomatic AF group and 35\% (104 patients) of the symptomatic AF group, being significantly less common in the asymptomatic group \((P < 0.01)\). The CHADS2 score was also significantly greater in the asymptomatic AF group (1.63 \(\pm\) 1.27) than in the symptomatic AF group (1.14 \(\pm\) 1.18, \(P < 0.05\)). Other demographic data showed no significant differences, including the incidence of administration of angiotensin-converting enzyme inhibitors (ACEI) or statins, and the percentage of patients treated with and without antithrombotic therapy also showed no significant differences between the asymptomatic and symptomatic AF groups.

Long-term prophylactic efficacy of antiarrhythmic drug therapy: Figure 1 summarizes the results of antiarrhythmic drug therapy in the asymptomatic and symptomatic AF groups. Patients were classified as the nonrecurrence group if there was no AF recurrence during follow-up after the start of antiarrhythmic drug therapy to maintain sinus rhythm. They were classified as the recurrence group if AF recurrence occurred during follow-up, but sinus rhythm could be restored by medical or electrical cardioversion, and they were classified as the permanent group if sinus rhythm could not be confirmed on ECG findings even once during 6 months despite therapy. The percentages of patients with recurrence and nonrecurrence were 22\% (10 patients) and 24\% (11 patients), respectively, in the asymptomatic AF group, and 40\% (115 patients) and 41\% (118 patients), respectively, in the symptomatic group, both being significantly lower in the asymptomatic group than in the symptomatic group (both, \(P < 0.05\)). On the other hand, the percentage of the permanent patient group was 54\% (24 patients) in patients with asymptomatic AF and 19\% (56 patients) in those with symptomatic AF. There was also a significant difference in the percentage between the asymptomatic and symptomatic AF groups (\(P < 0.05\)).

Comparison of the survival rates free from thromboembolism: Figures 2A and 2B show the survival curves free from thromboembolism between the asymptomatic and symptomatic AF groups. Of all patients, the survival rates free from thromboembolism at 12, 36, 60, 90, and 120 months after the start of observation were 100\%, 84\%, 80\%, 78\%, and 78\% in the asymptomatic AF group and 100\%, 97\%, 94\%, 92\%, and 90\%, respectively, in the symptomatic AF group, being significantly lower in the asymptomatic group at 120 months (Figure 2A, \(P < 0.05\)). In patients who were analyzed with the Kaplan-Meier method, the survival rates free from thromboembolism at 60 months were 100\% in the asymptomatic AF group and 90\% in the symptomatic AF group, and 80\% and 78\% at 90 months, respectively. The Kaplan-Meier method was used to analyze the survival rates free from thromboembolism, and the Log-rank test was used to determine the statistical significance of the differences in survival rates. The asymptomatic group had a significantly better survival rate than the symptomatic group (\(P < 0.05\)).
not receiving oral anticoagulant therapy (warfarin), the survival rates free from thromboembolism at 12, 36, 60, 90, and 120 months after the start of observation were 100%, 82%, 74%, and 71% in the asymptomatic AF group and 100%, 96%, 93%, 91%, and 88%, respectively, in the symptomatic AF group, being significantly lower in the asymptomatic group at 120 months, \( P < 0.05 \), Figure 2B.

Comparison of annual rates of thromboembolism stratified by antithrombotic therapy: Table II shows the annual rate of thromboembolism in the asymptomatic and symptomatic AF groups. The rate was 4.4% in the asymptomatic AF group and 2.0% in the symptomatic AF group, being significantly higher in the asymptomatic group \( P < 0.05 \).

Comparison of the survival rates free from cardiovascular death: Figure 3 shows the survival curves free from cardiovascular death between the asymptomatic and symptomatic AF groups. The survival rates free from cardiovascular death at 12, 36, 60, 90, and 120 months after the start of observation were 100%, 98%, 96%, 96%, and 93% in the asymptomatic AF group and 100%, 98%, 97%, 97%, and 96% in the symptomatic AF group, showing no significant difference between the two groups.

Predictors of thromboembolism during antiarrhythmic drug therapy: In Cox-Hazard model analysis, independent risk factors associated with thromboembolism on multivariate logistic regression analysis were CHADS2 score (odds ratio [OR], 6.641; 95% confidence interval [CI], 2.077-21.08), hypertension (OR, 7.322;95% CI, 2.156-24.86), the mixed type of AF (OR, 4.932;95% CI, 1.851-13.14), diabetes mellitus (OR, 8.254;95% CI, 2.259-30.16), (OR per one year, 1.072;95% CI, 1.027-1.119), and warfarin therapy (OR, 0.217;95% CI, 0.085-0.554). Asymptomatic AF, however,

<table>
<thead>
<tr>
<th>Follow-up period (months)</th>
<th>Without antithrombotic therapy</th>
<th>With antithrombotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>26 (21.7%)</td>
<td>3 (9.1%)</td>
</tr>
<tr>
<td>Annual rate (%/year)</td>
<td>2.3%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation.
Table III. Multivariate Predictors of Thromboembolism in the Atrial Fibrillation Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2 score</td>
<td>6.641 (2.077-21.08)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.322 (2.156-24.86)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mixed type of AF</td>
<td>4.932 (1.851-13.14)</td>
<td>0.005</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8.254 (2.259-30.16)</td>
<td>0.007</td>
</tr>
<tr>
<td>Age (per one year)</td>
<td>1.072 (1.027-1.119)</td>
<td>0.013</td>
</tr>
<tr>
<td>Warfarin therapy</td>
<td>0.217 (0.085-0.554)</td>
<td>0.040</td>
</tr>
<tr>
<td>Asymptomatic AF</td>
<td>2.040 (1.317-3.160)</td>
<td>0.216</td>
</tr>
<tr>
<td>Suffering period (per one month)</td>
<td>1.904 (1.002-1.006)</td>
<td>0.443</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.378 (1.132-1.678)</td>
<td>0.564</td>
</tr>
<tr>
<td>Organic heart disease</td>
<td>0.963 (0.941-0.986)</td>
<td>0.945</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation.

was not found to be an independent predictor of thromboembolism during antiarrhythmic drug therapy in this study (Table III).

**Discussion**

**Main point of this study:** The efficacy of antiarrhythmic therapy for preventing recurrence of AF and maintaining sinus rhythm was significantly inferior in the asymptomatic AF group compared to the symptomatic AF group. Among patients not receiving oral anticoagulant therapy (warfarin), the incidence of thromboembolism was significantly higher in the asymptomatic AF group than in the symptomatic AF group. Among the group receiving anticoagulant therapy (warfarin), however, there was no significant difference between the two groups. Cardiovascular prognosis also showed no significant difference between the asymptomatic and symptomatic AF groups.

**Determinants of asymptomatic AF:** It has been reported that demographic factors such as age and sex, as well as hypertension and diabetes mellitus, influence the onset of asymptomatic AF. According to a multicenter joint study performed in Canada, young age, female sex, and hypertension were related to the occurrence of symptomatic AF. A multicenter study performed in France showed that the incidence of asymptomatic AF increases with age. Several studies suggested that hyperesthesia and cognitive disorders due to diabetic neuropathy may result in a decrease of subjective symptoms in patients with diabetic mellitus. In this study, the CHADS2 score was also significantly greater in patients with asymptomatic AF than in those with symptomatic AF due to their incidence of diabetes mellitus. According to a subanalysis of the recent AFFIRM study, the percentage of men was lower and the incidence of other complications (including ischemic heart disease, heart failure, peripheral vascular disease, pulmonary disease, and thyroid disease) was lower in patients with asymptomatic AF.

The onset of asymptomatic AF may be influenced by arrhythmia-related factors, including heart rate during AF and duration, pattern of onset, and time of onset of arrhythmia. When the effect of antiarrhythmic drug therapy was evaluated by an ambulatory 24-hour monitoring analysis, it was confirmed that new asymptomatic AF had an incidence of approximately 22-27% during treatment with antiarrhythmic drugs that had pharmacological effects such as inhibition of atrioventricular conduction (propafenone and propranolol), and the effects were considered to be due to slow ventricular contraction and shortening of AF duration. When the prophylactic efficacy of flecainide on paroxysmal AF was assessed by transtelephonic electrocardiography before and after flecainide administration, it was observed that new asymptomatic AF had an incidence of 11% after administration. However, according to the French multicenter study, the incidence of asymptomatic AF in patients with chronic (permanent) AF was 16.2%, which was higher than that (5.4%) for paroxysmal AF. It has also been reported that symptoms tend to disappear if AF lasts for 24 hours or more in patients with a high frequency of drug-resistant episodes. In other words, if AF lasts long enough or occurs frequently, patients may become accustomed to the tachycardia and progression to asymptomatic AF may occur. Attention should be paid to this point.

**Long-term efficacy of antiarrhythmic therapy for asymptomatic AF:** In general, if AF persists, a vicious cycle of “electrical/structural remodeling” is established, making recurrence of AF easier and, resulting in progression to chronic (permanent) AF. If sinus rhythm is not restored soon after the onset of AF, the efficacy of subsequent antiarrhythmic therapy will be reduced. It is possible that treatment was less effective in the asymptomatic AF group than in the symptomatic AF group because recurrence of AF may not have been detected during follow-up as it did not cause subjective symptoms in the asymptomatic group. Furthermore, since the time of initial onset was unclear in patients with asymptomatic AF, it is possible that some patients were already resistant to antiarrhythmic drug therapy at their first hospital visit because of a long interval since onset of AF. It is therefore necessary to establish a method for early and efficient detection of recurrence of asymptomatic AF when treating patients in whom maintenance of sinus rhythm is essential.

**Long-term cardiovascular prognosis in asymptomatic AF:** In patients with asymptomatic AF, episodes of tachycardia tend to be overlooked because the lack of subjective symptoms means these individuals do not present for medical attention. It is therefore possible that an AF episode may first be detected on ECG findings after the occurrence of thromboembolism as a complication of AF. Ischemic stroke associated with AF occurs at least once throughout life in approximately 30% of patients with AF, and the incidence for ischemic stroke in patients with AF accounts for approximately 20% of all patients with cerebral infarction. According to a subanalysis of the AFFIRM study, the incidence for ischemic stroke was significantly higher in the asymptomatic AF group than in the symptomatic AF group at the time of patient entry if adequate anticoagulant therapy was not being performed. In this study, the incidence for ischemic stroke was also higher in the asymptomatic AF group than in the symptomatic AF group if adequate anticoagulant therapy with warfarin was not provided. However, there was no significant difference in incidence for ischemic stroke between the two groups when anticoagulant therapy was adequate, thus confirming the possibility for importance of anticoagulant therapy.
On the other hand, according to the subanalysis of the AFFIRM study, the survival rate free from cardiovascular death did not differ significantly between the asymptomatic and symptomatic AF groups when adjusted for demographic data at the time of entry, and latent underlying heart disease was considered to have a stronger influence on survival rate than the presence of symptoms.10 In the present study, the long-term survival rate (mean observation period: 60 months) was investigated, with no significant difference in cardiovascular survival found between the asymptomatic and symptomatic AF groups, supporting the above-mentioned findings.

Limitations: The limitations of this study were as follows. First, the present study was a retrospective, observation study, and the demographic data were biased between the two groups. Second, antithrombotic therapy was initiated at the discretion of the attending physicians. Among the background factors of patients in this study, there were no significant differences between the two groups in terms of risk factors for thromboembolism and antithrombotic drugs selected. However, it is still possible that these factors may have had an influence on therapeutic efficacy because randomization of antithrombotic drugs to prevent ischemic stroke was not performed. Third, AF recurrence was defined by detection of AF on ECG. However, according to a study involving ambulatory 24-hour monitoring, even patients with paroxysmal AF and obvious symptoms were not aware of more than half of their tachycardic episodes.23,24 On the other hand, analysis by portable transtelephonic electrocardiography (cardiophone) showed that 30-70% of symptomatic AF patients developed sinus tachycardia or premature atrial contractions when they complained of palpitations.23,25 In other words, detection methods based on symptoms and ECG findings have their methodological limitations in accurately detecting recurrence of AF. Finally, the total number of patients was relatively small. More patients are required to draw a definite conclusion in terms of the efficacy of oral anticoagulant therapy (warfarin) in Japanese patients with asymptomatic AF.

It will therefore be necessary in the future to perform a prospective multicenter comparison within the Japanese population to re-evaluate the results of antiarrhythmic therapy for asymptomatic AF.

Conclusion: Since patients with asymptomatic paroxysmal AF appear to have a clinical course refractory to antiarrhythmic therapy for maintenance of sinus rhythm and also develop thromboembolism more frequently than those with symptomatic AF, anticoagulant therapy with warfarin is considered to be important for their cardiovascular prognosis even in AF patients without symptoms.

References

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