Combination Therapy With Amiodarone and Enalapril in Patients With Paroxysmal Atrial Fibrillation Prevents the Development of Structural Atrial Remodeling

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SUMMARY

The purpose of this study was to examine the relationship between long-term efficacy of amiodarone therapy (100-200 mg/day) combined with angiotensin converting enzyme inhibitor (ACEI; enalapril 5 mg/day) administration, and the development of structural atrial remodeling in patients with paroxysmal atrial fibrillation (AF). Fifty-eight patients (40 men, 18 women, mean age, 68 ± 8 years, mean follow-up period, 43 ± 18 months) with AF refractory to ≥ two class I antiarrhythmic drugs were divided into two groups; those treated with enalapril on amiodarone (group A, n = 25) and those treated with amiodarone alone (group B, n = 33), to evaluate the efficacy of combination therapy.

1) At 12 and 24 months, the survival rates for patients free from AF recurrence were 80% and 64% in group A, and 45% and 30% in group B, respectively (P < 0.05, group A versus group B). The percentage of patients with conversion to permanent AF despite amiodarone therapy was 20% in group A and 48.5% in group B (P < 0.05, group A versus group B). 2) In group B, left atrial dimension (LAD) was significantly greater after amiodarone therapy (40.2 ± 6.3 mm) than at baseline (35.2 ± 6.6 mm) (P < 0.01), whereas there was no significant difference in LAD between baseline and after amiodarone therapy in group A (39.1 ± 5.0 mm versus 41.0 ± 5.0 mm, respectively).

In patients with paroxysmal AF, ACE-I appears to enhance the efficacy of amiodarone therapy in maintaining sinus rhythm and preventing the development of structural remodeling in atria. (Int Heart J 2008; 49: 435-447)

Key words: Atrial fibrillation, Amiodarone, Prevention, Remodeling, Angiotensin converting enzyme inhibitor

Atrial fibrillation (AF) is the most commonly encountered tachyarrhythmia in daily medical practice. As the incidence of AF increases rapidly with age, the number of patients with AF is predicted to increase in the Japanese population.1)
AF not only decreases quality of life, but also complicates thromboembolism or heart failure. In addition, it worsens prognosis among patients with cardiac dysfunction or the elderly. AF is recognized as a disease requiring long-term treatment and follow-up.

We have previously reported a therapeutic limitation with class I antiarrhythmic drugs in preventing recurrence of AF. However, it has been reported that the efficacy of amiodarone in preventing recurrence of paroxysmal and persistent AF is superior to that of the class I antiarrhythmic drugs and dl-sotalol in two large clinical trials. It has also been reported recently that amiodarone is effective not only in preventing the development of atrial remodeling but also in reversing atrial remodeling established by rapid atrial pacing.

On the other hand, angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor blockers, and statins prevent the electrophysiological changes seen in AF such as reduction in conduction velocity and development of structural remodeling such as fibrosis of the atrial myocardium. It has been suggested that combination therapy with amiodarone and ACEI constitutes a superior strategy for preventing recurrence of AF and development of structural remodeling. However, it remains unclear whether this combination therapy is beneficial in Japanese patients with paroxysmal and persistent AF.

In the present study, we examined the long-term efficacy of combination therapy with amiodarone and ACEI (enalapril 5 mg/day) in preventing recurrence of AF and development of structural remodeling in patients with paroxysmal and persistent AF.

**METHODS**

**Subjects:** We recruited a total of 58 patients (40 men and 18 women, mean age, 68 ± 8 years) with paroxysmal AF who visited our department with subjective symptoms that interfered with their daily lives and who received amiodarone for treatment of AF which had relapsed after treatment using not less than two class I antiarrhythmic drugs. Subjects were required to visit the department periodically (every 2-4 weeks) and were followed up for at least 12 months. Each subject underwent transthoracic echocardiography (TTE) before and after antiarrhythmic therapy. Subjects were divided into two groups: group A (25 subjects) receiving amiodarone plus ACEI (enalapril 5 mg/day) and group B (33 subjects) receiving amiodarone alone. All subjects underwent noninvasive examinations, such as investigation of medical history, chest X-rays, exercise tolerance test, pulmonary function tests, and chest CT. In addition, TTE was performed for a mean duration of 37.4 ± 21.7 months from baseline until the completion of treatment. Prior to the initiation of treatment with amiodarone, we explained the necessity for use of
an antiarrhythmic drug and possible adverse drug reactions before obtaining oral or written informed consent from each subject.

**Methods:** In line with the American Heart Association (AHA) guidelines, pharmacological or electrical cardioversion under intravenous anesthesia with thiopental was performed immediately for patients in whom the duration of AF was < 48 hours. Prior to introduction of the AHA guidelines, cardioversion was performed with subsequent warfarin anticoagulation therapy after confirmation that neither the existence of thrombus in the left atrium nor spontaneous echo contrast was detected on transesophageal echocardiography (TEE). For AF cases occurring after the AHA guidelines were issued, warfarin anticoagulation therapy was administered for 3 weeks prior to and 4 weeks after electrical cardioversion. The warfarin dose was set so as to obtain an international normalized ratio (INR) between 1.6 and 2.6. In the present study, 43 patients (74%) had paroxysmal AF and 15 patients (26%) had persistent AF.

Patients who had a left ventricular ejection fraction of at least 40% or more confirmed by echocardiography were given pharmacological or electrical cardioversion. After converting to sinus rhythm, these patients were given a class Ia or Ib agent (disopyramide 300 mg/day, aprindine 60 mg/day, or cibenzoline 300 mg/day) by randomized allocation as the first-choice drug and observed carefully for manifestation of recurrence. If AF recurred during follow-up, defibrillation was performed again. This was followed by randomized allocation of a class Ic agent (flecainide 150 mg/day, pilsicainide 150 mg/day) or bepridil 150 mg/day as the second-choice drug, and the patients were again observed carefully for AF recurrence. If patients relapsed during the period of observation after administration of the second-choice drug, amiodarone was administered to consenting patients.

Patients whose left ventricular ejection fraction was less than 40% confirmed by echocardiography underwent electrical cardioversion. After converting to sinus rhythm, these patients were given either aprindine 60 mg/day or bepridil 150 mg/day by randomized allocation as the first- and second-choice drug. If recurrence of AF was observed with both drugs, amiodarone was administered to consenting patients. These patients were loaded with oral amiodarone at a dose of 400 mg/day for 14 days. After the initial loading phase, a maintenance dose of 50-200 mg/day was adjusted while the efficacy and side effects were monitored, decreasing amiodarone at a dose of 50 mg/day step by step if recurrence of AF was not observed for 12 months. Patients were hospitalized for at least 2 weeks while undergoing the initial amiodarone loading and follow-up was continued at 1 month after discharge, and then at intervals of 1-3 months. Baseline 12-lead electrocardiography (ECG), echocardiography, thyroid and liver function tests, pulmonary function tests, ophthalmologic examination, and chest X-rays were performed for most patients before amiodarone therapy. Twelve-leading ECG was
performed several times during the initial loading phase and also at each outpatient visit. Thyroid and liver function testing, pulmonary function testing, and chest X-rays were used to access the adverse effects of amiodarone therapy at week 2, month 1 and 3, and then every 6 months after initiation. Ophthalmologic examination was performed every 6 months.

All patients underwent standard 12-lead ECG and ambulatory 24-hour ECG monitoring after 2 to 4 weeks of selected antiarrhythmic drug therapy or alteration of drug choice. Maintenance of sinus rhythm was confirmed at every visit using a portable ECG monitor (IEC-1101 ‘Heart Mate’, Nihon Koden Corp., Japan). Recurrence was determined as the time point when AF was first confirmed by ECG after the patient began taking oral amiodarone.

Once sinus rhythm was being maintained without recurrence of paroxysmal AF after administration of the antiarrhythmic agent, venous blood was collected from an upper extremity with the subject in a resting recumbent position to assay plasma concentrations of atrial natriuretic peptide (ANP) during sinus rhythm.

**Definitions and statistical analysis:** Paroxysmal AF was defined as AF terminating spontaneously within 7 days after onset. Persistent AF was defined as AF lasting from 7 days to 6 months, and also requiring pharmacological or electrical cardioversion for restoration of sinus rhythm. 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. 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 CT or MRI images of the head. Hypertension was defined as a casual blood pressure greater than 140 mm Hg at systole or 90 mm Hg at diastole. Paroxysmal AF was divided into 3 groups: diurnal type (7:00 AM to 5:00 PM), nocturnal type (5:00 PM to 7:00 AM) and mixed type (symptoms appearing at any time) based on the time of equivalent symptom onset on ECG recording. In the pulmonary function test, we regarded FEV1.0 ≤ 70% as a diagnostic criterion for chronic obstructive pulmonary disease.

Patients were excluded on the basis of the following: congestive heart failure, severe bradycardia (sick sinus syndrome, atrioventricular block, intraventricular conduction disturbance), left ventricular ejection fraction (LVEF) < 40% as determined by echocardiography, liver and/or renal dysfunction with abnormal laboratory test values, pregnancy, concomitant use of β-blockers and/or T-type calcium antagonists to assess the efficacy of combination therapy with ACEI alone on amiodarone in preventing recurrence development of structural remodeling in patients with paroxysmal and persistent AF.

All data are shown as the mean ± SD. Clinical characteristics and numbers
of recurrences of AF in individual patients were compared between the two groups by the unpaired $t$-test for continuous variables and by the chi-square test for categorical variables. The parameters determined by echocardiography were compared by the paired $t$-test for continuous variables. In all tests, a $P$ value of $< 0.05$ was considered significant.

**RESULTS**

1. **Comparison of patient baseline characteristics (Table):** The time zones of AF occurrence in the study population were classified as follows: daytime in 5 subjects (8.6%), nighttime in 3 subjects (5.2%), and mixed day/night in 50 subjects (86.4%). Thirty (54.5%) of 55 subjects had underlying heart disease, including ischemic heart disease ($n = 11$), dilated cardiomyopathy ($n = 9$), valvular disease ($n = 5$), hypertrophic cardiomyopathy ($n = 4$), and atrial septal defect ($n = 1$). On the other hand, 3 (5.5%) of 55 subjects had an underlying pulmonary disease, including old pulmonary tuberculosis ($n = 2$) and bronchial asthma ($n = 1$). There were no significant differences in age, sex, hypertension, diabetes, or time zone of onset between the two groups. Systolic blood pressures were $122 \pm 13$ mmHg in group A, $124 \pm 15$ mmHg in group B at baseline, and $123 \pm 14$ mmHg in group A, $126 \pm 16$ mmHg in group B after therapy, respectively. There were also no significant differences in systolic and diastolic blood pressure between the two groups during follow-up periods. However, the number of subjects with underly-

<table>
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<tr>
<th>Table. Clinical Characteristics of Patients</th>
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<tr>
<td>Enalapril (+) group ($n = 25$)</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Male/female</td>
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<tr>
<td>Hypertension</td>
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<td>Diabetes mellitus</td>
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<td>Underlying heart diseases</td>
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<td>Suffering period (months)</td>
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<td>At baseline</td>
</tr>
<tr>
<td>LVDD (mm)</td>
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<td>LAD (mm)</td>
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<td>LVEF (%)</td>
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<td>Time of Onset</td>
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<td>diurnal/nocturnal/mixed</td>
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Continuous values are the mean $\pm$ SD. Values in parentheses are %.
LVDD indicates left ventricular end-diastolic dimension; LAD, left atrial dimension; and LVEF, left ventricular ejection fraction.
ing heart disease and that of subjects with a medical history of heart failure were significantly higher in group A than in group B ($P < 0.01$). On the other hand, the duration of illness and left ventricular ejection fraction were significantly lower in group A than in group B (both; $P < 0.05$). Left ventricular end-diastolic diameter and left atrial diameter were significantly greater in group A than in group B ($P < 0.05$).

2. Survival rates free from AF recurrence in each group (Figure 1): The survival rates free from AF recurrence at 3, 6, 12, 18, and 24 months of follow-up were 88%, 84%, 80%, 68%, and 64% in group A, and 73%, 64%, 45%, 33%, and 30% in group B. The survival rate free from AF recurrence at month 24 of follow-up was significantly higher in group A than in group B ($P < 0.05$, Figure 1).

3. Rate of conversion to chronic AF in each group: AF became chronic in 5 subjects (20.0%) in group A and in 16 subjects (48.5%) in group B. The rate of conversion to chronic AF was significantly lower in group A than in group B ($P < 0.05$).

4. Changes from baseline in transthoracic echocardiographic parameters in each group (Figures 2 and 3): There was no statistically significant change from baseline in left ventricular end-diastolic dimension (LVDd), left atrial dimension (LAD), or left ventricular ejection fraction (LVEF) after therapy in group A. In

![Figure 1](image.png)
group B, no statistically significant change from baseline was seen in either LVDd or LVEF after therapy, but LAD was significantly greater after therapy.

Figure 2. Changes in TTE parameters in patients treated with Enalapril between baseline and after amiodarone therapy. TTE indicates transthoracic echocardiography. Note that there was no significant difference in left atrial dimension (LAD) between baseline and after amiodarone therapy in the Enalapril (+) group.

Figure 3. Changes in TTE parameters in patients treated without Enalapril between baseline and after amiodarone therapy. TTE indicates transthoracic echocardiography. Note that left atrial dimension (LAD) in the Enalapril (-) group after amiodarone therapy was significantly greater than that at baseline ($P < 0.05$; paired-$t$ test).
compared to the baseline value (35.2 ± 6.2 mm at baseline, 40.2 ± 6.3 mm after therapy; \( P < 0.01 \)).

5. Changes from baseline in LAD in each group (Figure 4): The patients in group A were divided into two groups; those with maintaining sinus rhythm (group I, \( n = 20 \)), and those with conversion to permanent AF despite therapy (group II, \( n = 5 \)). The patients in group B were also divided into two groups; those with maintaining sinus rhythm (group III, \( n = 17 \)), and those with conversion to permanent AF despite therapy (group IV, \( n = 16 \)). In groups I and II, there was no statistically significant change from baseline in LAD after therapy. In groups III and IV, on the other hand, LAD was significantly greater after therapy compared to the baseline value (34.5 ± 6.3 mm at baseline, 38.0 ± 4.3 mm after therapy in group III, and 35.7 ± 6.4 mm at baseline, 41.5 ± 7.4 mm after therapy in group IV; both, \( P < 0.05 \)).

6. Changes from baseline in the concentration of human atrial natriuretic peptide during sinus rhythm (Figure 5): No significant changes between baseline and after therapy were seen in plasma concentrations of human atrial natriuretic peptide during sinus rhythm in either group.
7. Adverse effects of amiodarone: Adverse drug reactions to amiodarone that required discontinuation of treatment in this study included interstitial pneumonia in 2 subjects (3.4%) and eruption in 1 subject (1.7%). No death caused by amiodarone was observed.

**DISCUSSION**

Our research has demonstrated that concomitant therapy with amiodarone and enalapril (ACEI) prevents not only recurrence of AF but also the development of structural atrial remodeling.

1. **Pharmacological actions of amiodarone:** The pharmacological action of amiodarone on the ionic current of single myocardial cells during the chronic stage AF is the inhibition of the Ito, Iks, Ik1, and Ikach channels as well as the Ikur channel specific to atrial muscle cells, which results in the prolongation of the atrial refractory period.\textsuperscript{13-15} The current density of the Ito and Iks channels varies depending on the site within the myocardial tissue, which contributes to nonuniformity of action potential duration over the myocardium. Due to its inhibitory effect on all of these channels, amiodarone has been suggested to reduce the non-uniformity of the atrial refractory period.

2. **Therapeutic effects of amiodarone on heart failure:** Amiodarone is thought to have not only a potent antiarrhythmic effect but also beneficial effects on heart
failure. Amiodarone has $\alpha$- and $\beta$-sympathetic blocking actions,\textsuperscript{16-17} an inhibitory effect on the production of cytokines such as TNF-$\alpha$ and IL-6,\textsuperscript{18} antioxidant action to inhibit production of active oxygen,\textsuperscript{19} and cardiotonic action via an increase in the intracellular concentration of Ca associated with its Na-K pump inhibitory effect.\textsuperscript{20} During sinus rhythm, in this research, no significant change in plasma ANP level from baseline to after the administration of amiodarone was observed in either the presence or absence of enalapril and imidapril (ACEI). This suggests that the therapeutic effect of amiodarone on heart failure improves cardiovascular dynamics by reducing the increase in atrial pressure and/or extension of the atrial wall,\textsuperscript{21-22} resulting in the prevention of AF recurrence.

3. Efficacy of RAAS inhibitors for the prevention of AF: Nattel, \textit{et al} reported that enalapril inhibited atrial muscle fibrosis in a laboratory model of atrial muscle fibrosis induced by high-frequency pacing.\textsuperscript{23} Kumagai, \textit{et al} also reported that an angiotensin II receptor blocker inhibited conduction delay and fibrosis of atrial muscle.\textsuperscript{11} Further, Kalman, \textit{et al} reported that the refractory period of atrial muscle was not shortened in a pressure-overloaded model induced by angiotensin II and proposed a mechanism of induction of AF through conduction delay.\textsuperscript{24} On the other hand, a meta-analysis of large-scale comparison studies has demonstrated that concomitant therapy using RAAS inhibitors is effective in the treatment of AF in patients with a medical history of heart failure and those with cardiac dysfunction.\textsuperscript{25} Previous reports have demonstrated that the pharmacological actions of RAAS inhibitors are involved in suppressing apoptosis in experimental congestive heart failure induced by rapid atrial pacing\textsuperscript{26} and anti-inflammatory effects in AF patients with essential hypertension.\textsuperscript{27}

In our study, the preventive effect of RAAS inhibitors on AF recurrence and structural remodeling was superior in group A, which showed a significantly lower left ventricular ejection fraction than group B. Our findings thus support the results of the above meta-analysis\textsuperscript{25} and suggest a close correlation between the effects of RAAS inhibitors and improvement in cardiovascular dynamics or reduction of wall stress in the left atrium and ventricle.\textsuperscript{28}

4. Reversal of remodeling by amiodarone: Shinakawa, \textit{et al} reported that amiodarone experimentally administered prior to high-frequency pacing inhibited the shortening of atrial refractory period induced by high-frequency atrial pacing for 7 days and shortened the duration of AF.\textsuperscript{10} These findings suggest that amiodarone may improve the electrophysiological properties of atrial muscle that has already undergone remodeling.\textsuperscript{29} Madrid, \textit{et al} reported that concomitant therapy using irbesartan and amiodarone significantly prevented the recurrence of persistent AF in patients compared with amiodarone alone.\textsuperscript{30} However, there have been few reports that suggest concomitant therapy with amiodarone and RAAS inhibitor (s) inhibits the progression of structural atrial remodeling in AF patients, as
demonstrated in this research. Our study suggests an improvement in remodeling, ie, reverse remodeling, by concomitant therapy using amiodarone and ACEI in patients with a pre-existing substrate of AF.

Ueng, *et al* demonstrated that an independent predictor for the maintenance of sinus rhythm in patients with long-standing persistent AF was left atrial dimension > 40 mm prior to electrical cardioversion. Our study has shown that LAD at baseline is significantly greater in group A than in group B, whereas, the survival rate free from AF recurrence is significantly higher in group A than in group B. Our outcome was similar to that previous report, and these findings may suggest the potential reversibility of structural remodeling as a therapeutic benefit of ACEI to reduce recurrence of AF.

**Limitations:** Our study has some limitations. First, since this was not a prospective study, there was some bias in subject selection. However, according to guidelines prepared by the Japanese Circulation Society, amiodarone is recommended as the third-choice drug in patients with cardiac dysfunction to prevent recurrence of AF. This means there are limitations in conducting a prospective study of amiodarone in Japan. Second, the sample size was relatively small. It was relatively difficult to enroll a large number of eligible patients because of the limited indication of amiodarone for AF accompanying hypertrophic cardiomyopathy in Japan and the regimen recommended in the above guidelines. Third, Page, *et al* suggested that asymptomatic AF occurs more frequently than symptomatic AF in patients with paroxysmal AF. In the current study, we diagnosed AF recurrence on the basis of ECG findings or symptoms recorded during outpatient visits once or twice monthly. Therefore, the possibility of asymptomatic AF during the study period could not be entirely ruled out. On the other hand, a study using Cardiophone in patients with paroxysmal AF reported that 30-70% of patients developed sinus tachycardia or supraventricular extrasystole when they complained of palpitations. Detection methods based on symptoms and ECG findings have their methodological limitations in accurately detecting AF recurrence.

**Conclusions:** Our study suggests that combination therapy using amiodarone and ACEI prevents not only recurrence of atrial fibrillation but also structural remodeling of atrial muscle in patients with paroxysmal and persistent atrial fibrillation.

**REFERENCES**


