Long-Term Efficacy of Upstream Therapy Using Angiotensin-Converting Enzyme Inhibitors and Statins in Combination With Antiarrhythmic Agents for the Treatment of Paroxysmal Atrial Fibrillation

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Summary

The long-term efficacy of upstream therapy to prevent occurrence of paroxysmal atrial fibrillation (AF) in Japanese patients remains unclear. We retrospectively assessed the long-term efficacy of combination therapy with pravastatin (10 mg/day) and enalapril (5 mg/day) in addition to antiarrhythmic drugs (AAD) for maintaining sinus rhythm in patients with AF. This study included 319 patients (221 men, 98 women, mean age, 68 ± 10 years, mean follow-up period, 50 ± 34 months) who were divided into 4 groups: group I (n = 191) without combination therapy - namely pravastatin(-) and enalapril(-); group II (n = 81) with combination therapy - pravastatin (-) and enalapril (+) (n = 81); group III (n = 29) with combination therapy - pravastatin (+) and enalapril (-); and group IV (n = 18) with combination therapy - pravastatin (+) and enalapril (+). The percentages of patients free from conversion to permanent AF at 12, 36, 60, 90, and 120 months were as follows: group I 88, 83, 78, 75, and 73%, respectively; group II (n = 81) with combination therapy - pravastatin (-) and enalapril (+) (n = 81); group III (n = 29) with combination therapy - pravastatin (+) and enalapril (-); and group IV (n = 18) with combination therapy - pravastatin (+) and enalapril (+). The percentages of patients free from conversion to permanent AF at 12, 36, 60, 90, and 120 months were as follows: group I 88, 83, 78, 75, and 73%, respectively; group II 96, 88, 79, 77, and 75%, respectively; group III 100, 97, 91, 91, and 86%, respectively; group IV 100, 100, 100, 94, and 94%, respectively. The actuarial rate free from conversion to permanent AF at 120 months was significantly higher in group IV than in group I (P < 0.05). The results suggest that in patients with paroxysmal AF, the addition of both pravastatin and enalapril to AAD was more effective for maintaining sinus rhythm in terms of an upstream therapy. (Int Heart J 2009; 50: 465-476)

Key words: Atrial fibrillation, Enalapril, Pravastatin, Antiarrhythmic drug

Atrial fibrillation (AF) is the form of supraventricular tachycardia en-
countered most commonly in daily medical practice. In Europe and the United States, it is estimated that at least 0.5% of the general population suffer from this condition. Patients in the 68-85 age group account for about 7.0% of that number.\textsuperscript{1,2} Given our rapidly aging population, the morbidity associated with AF is almost as high in Japan as in Western countries.\textsuperscript{3} AF is therefore regarded as an independent risk factor for cardiovascular disease.\textsuperscript{4} However, antiarrhythmic drug therapy whose aim is the maintenance of sinus rhythm has prognostic limitations.\textsuperscript{5} Recently, in order to correct arrhythmogenic structural remodeling of the atrial muscle, an etiological factor for AF, upstream therapy combining angiotensin-converting enzyme inhibitors (ACEI) and statins with antiarrhythmic agents, has drawn attention. The long-term efficacy of ACEI and statins to prevent the occurrence of paroxysmal AF in Japanese patients remains unclear.

In this study, we determined retrospectively the long-term prophylactic efficacy of upstream therapy using ACEI and statins in combination with antiarrhythmic drugs in Japanese patients with paroxysmal AF.

**Methods**

**Subjects:** The study subjects included 319 patients (221 men, 98 women, mean age, 68 ± 10 years) who had subjective symptoms such as palpitations and in whom AF was confirmed from ECG findings consistent with their symptoms. All of these patients visited our outpatient clinic every 2 - 4 weeks and were followed-up for at least one year. These patients were classified into 4 groups based on concomitant use of ACEI (enalapril 5 mg/day) and statins (pravastatin 10 mg/day) as follows: Group I \( (n = 191) \) without concomitant therapy - pravastatin (-) and enalapril (-); Group II \( (n = 81) \) with concomitant use of ACEI(+) and statins (-); Group III \( (n = 29) \) with concomitant use of ACEI (-) and statins (+); and Group IV \( (n = 18) \) with concomitant use of both ACEI (+) and statins (+). Enalapril was administered to 99 patients (63 men and 36 women) for hypertension and heart failure and pravastatin to 47 patients (23 men and 24 women) for dyslipidemia.

In all patients, the investigations performed included a clinical history, chest radiography, and noninvasive examinations such as exercise ECG testing and transthoracic echocardiography. In cases where the attending physicians deemed it necessary, pulmonary function testing, chest computed tomography (CT), and intracardiac catheter testing were also performed. Exclusion criteria included serious bradyarrhythmia (sick sinus syndrome, atrioventricular block, intraventricular conduction disturbance), laboratory test abnormalities showing hepatic or renal impairment, women of child-bearing age, and patients receiving a β-blocker and type T calcium antagonist concomitantly. This study was
conducted from June 1996 to August 2007. The mean follow-up period (for all patients) was 50.4 ± 34.1 months.

Protocols for cardioversion and antiarrhythmic drug therapy: In accordance with AHA guidelines, patients with atrial fibrillation of 48 hours or less were treated immediately with cardioversion either pharmacologically or electrically under anesthesia with intravenous administration of thiopental. Prior to publication of the AHA guidelines, patients in whom atrial fibrillation persisted for 48 hours or more underwent cardioversion after the absence of thrombi in the left atrium or spontaneous echo contrast was confirmed by transesophageal echocardiography. Anticoagulant therapy using warfarin was then added. In contrast, in cases occurring after establishment of the AHA guidelines, electrical cardioversion was performed together with anticoagulant therapy using warfarin for 3 weeks precardioversion and 4 weeks postcardioversion. The protocols for prevention of AF recurrence using antiarrhythmics were as follows: in patients whose left ventricular ejection fraction (LVEF) was at least 40% as demonstrated by trans-thoracic echocardiography, pharmacological or electrical cardioversion was performed to restore sinus rhythm. After conversion to sinus rhythm, these patients were given either class Ia (disopyramide 300 mg/day or cibenzoline 300 mg/day) or Ib drugs (apridine 60 mg/day), assigned at random by the envelope method, as the first- and second-choice drugs, followed by close observation for development of AF recurrence. If AF recurrence occurred with either drug during the observation period, cardioversion was performed again. Following this, the second choice drug, either a class Ic drug (flecainide 150 mg/day or pilsica-nide 150 mg/day) or bepridil 150 mg/day, chosen at random was administered, followed by close observation for manifestation of AF recurrence in a similar manner. When further recurrence of AF was observed after administration of the second choice drug, amiodarone was administered to patients who gave consent. For patients whose LVEF was less than 40% as confirmed by trans-thoracic echocardiography, electrical cardioversion was performed to restore sinus rhythm. After conversion to sinus rhythm, these patients were given either aprindine 60 mg/day or bepridil 150 mg/day as the first-choice or second-choice drugs. If AF relapsed under treatment with one of these two drugs, amiodarone was administered to patients who consented. Amiodarone was administered orally at 400 mg/day for 2 weeks. After the initial loading phase, a maintenance dose of 200 mg/day was given. Prior to the initiation of treatment with amiodar-one, we explained the need for the use of an antiarrhythmic drug and possible adverse drug reactions before obtaining oral or written informed consent from each subject. Under this treatment, patients were observed closely for the presence or absence of AF recurrence.

In all cases, at 2 to 4 weeks after the start or switch of any oral antiarrhyth-
mic drug chosen for an individual patient, standard 12-lead ECG and ambula-
tory 24-hour monitoring were performed. In addition, at every visit the mainte-
nance or otherwise of sinus rhythm was confirmed with a portable ECG monitor
(IEC-1101 ‘Heart Mate’, Nihon Kohden Corp, Japan). Together with these
examinations, in patients not reporting palpitation attack and sinus rhythm con-
firmed by ECG during an outpatient clinic visit, blood samples were taken from
an upper limb vein with the patient resting in a supine position for measurement
of atrial natriuretic peptide (ANP) under sinus rhythm. In patients reporting pal-
pitations on the basis of subjective symptoms, an ambulatory ECG was taken at
the discretion of the attending physician to confirm the recurrence of AF.

**Definitions:** Paroxysmal AF was defined as AF terminating spontaneously
within one week after onset as confirmed by subjective symptoms or ambulatory
ECG findings. Permanent AF was defined when the condition was refractory to
treatment (sinus rhythm was never observed continuously for 6 months, despite
administration of multiple antiarrhythmic drugs). Cerebral thromboembolism
was diagnosed on the basis of clinical manifestation of symptoms and confirma-
tion of an infarct lesion larger than 3 mm on CT or magnetic resonance imag-
ing. Hypertension was defined as blood pressure, measured at any time, with a
systolic pressure higher than 140 mmHg and diastolic pressure higher than 90
mmHg. Dyslipidemia was established when fasting serum cholesterol levels
were greater than 220 mg/dL and triglycerides were higher than 150 mg/dL.
The time of onset of paroxysmal AF was defined as the time of onset of equiva-
 lent symptoms in patients in whom AF had already been observed in recorded
findings by a cardiac monitor or ambulatory ECG, or during consultation. Par-
oxysmal and persistent AF were classified into diurnal type (07:00 to 17:00),
nocturnal type (17:00 to 07:00 next morning), and mixed type (symptoms ap-
pearing at any time). Recurrence of AF was defined as the time AF was first
confirmed on ECG after initiation of treatment with oral antiarrhythmic drugs.

**Statistical analysis:** The values for patient background factors and actual number
of AF recurrences are expressed as the mean ± standard deviation (SD). For
statistical comparisons among the 4 groups, one-way ANOVA was used for
continuous variables and the $\chi^2$-test for categorical variables. For comparison of
actual recurrence-free rates, a log-rank test (Mantel-Cox) was used, and differ-
ences were regarded as significant at $P < 0.05$.

**Results**

**Comparison of patient clinical characteristics:** The mean age was significantly
higher for group II than for groups I and III. The proportion of male patients was
significantly higher for group I than for group III. Patients with hypertension
Table I. Comparison of Characteristics of Patients With Paroxysmal Atrial Fibrillation Among the 4 Groups

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n = 191 )</td>
<td>( n = 81 )</td>
<td>( n = 29 )</td>
<td>( n = 18 )</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.0 ± 13.1</td>
<td>70.4 ± 8.1</td>
<td>66.8 ± 9.8</td>
</tr>
<tr>
<td>Smoking</td>
<td>61 (31.9%)</td>
<td>24 (29.6%)</td>
<td>6 (20.7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>62 (32.5%)</td>
<td>60 (74.1%)</td>
<td>7 (24.1%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 (11.5%)</td>
<td>17 (21.0%)</td>
<td>2 (6.9%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>29 (100%)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>10 (5.2%)</td>
<td>8 (9.9%)</td>
<td>3 (10.3%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>92 (48.2%)</td>
<td>32 (39.5%)</td>
<td>6 (20.7%)</td>
</tr>
<tr>
<td>Organic heart disease</td>
<td>54 (28.3%)</td>
<td>33 (40.7%)</td>
<td>7 (24.1%)</td>
</tr>
<tr>
<td>Organic pulmonary disease</td>
<td>13 (6.8%)</td>
<td>11 (13.6%)</td>
<td>2 (6.9%)</td>
</tr>
</tbody>
</table>

*P < 0.05.

Table II. Comparison of Characteristics of Patients With Paroxysmal Atrial Fibrillation Among the 4 Groups

<table>
<thead>
<tr>
<th>Group I</th>
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<th>Group IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n = 191 )</td>
<td>( n = 81 )</td>
<td>( n = 29 )</td>
<td>( n = 18 )</td>
</tr>
<tr>
<td>Observed period (months)</td>
<td>47.8 ± 29.6</td>
<td>46.5 ± 28.7</td>
<td>54.1 ± 41.1</td>
</tr>
<tr>
<td>Suffering period (months)</td>
<td>19.9 ± 32.3</td>
<td>17.3 ± 36.2</td>
<td>19.8 ± 30.5</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>45.0 ± 5.7</td>
<td>48.1 ± 5.3</td>
<td>45.7 ± 5.7</td>
</tr>
<tr>
<td>LAD (mm)</td>
<td>33.5 ± 6.2</td>
<td>36.0 ± 6.3</td>
<td>34.5 ± 6.7</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>69.8 ± 10.2</td>
<td>65.1 ± 12.2</td>
<td>70.6 ± 9.4</td>
</tr>
<tr>
<td>ANP during SR (pg/mL)</td>
<td>40.5 ± 41.9</td>
<td>46.1 ± 39.3</td>
<td>31.7 ± 19.8</td>
</tr>
<tr>
<td>Amiodarone administration</td>
<td>26 (13.6%)</td>
<td>18 (22.2%)</td>
<td>7 (24.1%)</td>
</tr>
</tbody>
</table>

*P < 0.05.

AF indicates atrial fibrillation; LVDd, left ventricular diastolic dimension; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; HANP, human atrial natriuretic peptide, and SNR, sinus nodal rhythm.
accounted for a significantly higher proportion in groups II and IV compared to groups I and III. The proportion of patients with dyslipidemia was significantly higher for groups III and IV than for groups I and II \((P < 0.05, \text{Table I})\).

Left ventricular end-diastolic diameter (LVEDD) as measured by transthoracic echocardiography was significantly higher in group II than in groups I and III. Left atrial diameter (LAD) was significantly higher in group I than in group II. Left ventricular ejection fraction (LVEF) was significantly higher in groups I and III than in group II \((P < 0.05, \text{Table II})\).

**AF recurrence after treatment with antiarrhythmic drugs:** The rate of AF recurrence in each group during the follow-up period was 1.6 ± 2.0 in group I, 2.4 ± 1.9 in group II, 1.4 ± 1.8 in group III, and 0.6 ± 0.9 in group IV, with the group IV rate being significantly lower than that in groups I, II, and III \((P < 0.05, \text{Figure 1})\).

**Efficacy for preventing conversion to permanent AF after treatment with antiarrhythmic drugs:** When the rate for preventing conversion to permanent AF in patients with paroxysmal and persistent AF was calculated by counting cases which did not meet the criteria for permanent AF at the time of last examination, the percentages of patients free from conversion to permanent AF at 12, 36, 60, 90, and 120 months were 88, 83, 78, 75, and 73% in group I, 96, 88, 79, 77, and 75% in group II, 100, 97, 91, 91, and 86% in group III, and 100, 100, 100, 94, and 94% in group IV. The actuarial rate for preventing progression to the per-

**Figure 1.** Incidence of AF recurrence after combination therapy with pravastatin and enalapril in addition to antiarrhythmic drug therapy in individual patients with paroxysmal atrial fibrillation. ACEI indicates angiotensin converting enzyme inhibitor.
permanent form in patients with paroxysmal and persistent AF at 120 months was significantly higher in group IV than in group I ($P < 0.05$, Figure 2).

In a Cox model adjusted for differences in baseline age and sex, the combination therapy with pravastatin and enalapril was associated with the rate for preventing conversion to permanent form in patients with paroxysmal AF (hazard ratio 0.23, 95% CI 0.04-0.61, $P < 0.05$).

Adverse events requiring discontinuation of oral treatment with ACEI and statins: In the present study, enalapril was used in 105 cases, 6 (5.7%) of whom developed an unproductive cough requiring discontinuation of the drug. Similarly, pravastatin was administered to 49 cases, 2 (4.1%) of whom discontinued the drug due to myalgia and elevation in CPK levels ($\geq 500$ IU/L) due to rhabdomyolysis. However, no fatal adverse event developed with either of these drugs.

**Discussion**

**Main findings:** The findings of this study indicate that upstream therapy for paroxysmal and persistent AF with concomitant use of ACEI and statins is effective not only for preventing conversion to permanent AF but also for prophylaxis against AF recurrence. Moreover, no serious adverse events were seen with either of these concomitantly used drugs. We have thus demonstrated that upstream therapy using ACEI and statins is effective as a rhythm control therapy.
aimed at maintaining sinus rhythm in patients with paroxysmal and persistent AF. To the best of our knowledge, there have been no studies assessing the long-term prophylactic efficacy of upstream therapy using ACEI and statins as concomitant drugs in Japanese patients with paroxysmal AF.

**Role of renin-angiotensin-aldosterone system (RAAS) inhibitors in electrical and structural remodeling:** In an experimental model, it has been found that frequent application of pacing for one week persistently causes shortening of the atrial effective refractory period, with a gradual delay in intra-atrial conduction from 5 weeks onwards. Easy development and persistence of AF may then be seen.\(^{12}\) Due to atrial high frequency excitation, down-regulation of type-L Ca channels occurs because of intracellular Ca hyper-load,\(^ {13}\) leading to shortening of the effective refractory period of the atrium. Furthermore, persistence of tachycardia causes down-regulation of the sodium channel, with delay in intra-atrial conduction.\(^ {14}\) As a result, the excitation wavelength, a product of the refractory period and conduction rate, is shortened.\(^ {15}\) With increased nonuniformity in the intra-atrial refractory period, structural changes occur which favor the development of AF. These changes in electrical remodeling progress to degeneration and fibrosis of myocardial cells through persistence of tachycardia, and develop to structural remodeling such as irreversible dilation of the atrium.

On the other hand, in a study using an experimental model of frequent pacing, an increase in the blood level of angiotension II was observed in the presence of persistent tachyrdia.\(^ {16}\) It has been reported that the expression of ErK1/ErK2 of intracellular adjusting kinase and ACE was increased in patients with AF.\(^ {17}\) Elevation in left atrial pressure (LAP) associated with an increase in angiotensin II activates the stretch activated channel,\(^ {18}\) shortens the effective refractory period in the atrial muscle, and increases the nonuniformity of the refractory period,\(^ {19}\) resulting in easy induction of AF. With respect to ANP, an increase in stretch of atrial pressure activates the Erk cascade via angiotensin II receptors, accelerating degeneration or fibrosing changes in myocardial cells.\(^ {17}\) RAAS inhibitors have been reported to reduce atrial pressure and mural stretch as suggested previously,\(^ {20}\) in addition to controlling sympathetic nerves,\(^ {21}\) stabilizing electrolyte balance, and inhibiting activation of K-channels.\(^ {22}\) Moreover, mechanisms to prevent new onset of myocardial damage such as inhibition of apoptosis,\(^ {23}\) and anti-inflammatory effects have also been reported.\(^ {24}\) Clinically, it has also been reported that combined use of RAAS inhibitors showed favorable efficacy for the maintenance of sinus rhythm and prevention of paroxysmal and persistent AF.\(^ {25,26}\)

**Role of statins in electric and structural remodeling:** Since a relatively high incidence of AF (about 25 - 40%) has been reported to occur after cardiac surgery, the relationship between AF and postoperative inflammation has come under at-
tention. Moreover, myocardial biopsy findings have shown that the site of local inflammation formed the basis for arrhythmia in AF;\(^{27,28}\) an experimental model of AF could be formed by causing pericarditis;\(^{29}\) and among cases of isolated AF, blood levels of high sensitivity C-reactive protein were higher in cases of persistent AF than in paroxysmal AF.\(^{30}\) All of these findings indicate that inflammation of the atrial muscle is deeply involved in the manifestation or persistence of AF.

Statins are drugs which exert a pleiotropic action (anti-inflammatory, antioxidizing, antithrombotic, vascular endothelium protecting or cell membrane stabilizing effect). Recently, in experimental models of AF induced by high frequency stimulation of the atrium\(^{31}\) and in human atrial muscle after cardiac surgery,\(^{32}\) oxidizing stress has been observed, indicating its involvement in atrial muscle remodeling. After administration of statins, effective suppression of production of reactive oxygen species as well as control of proliferation of fibroblasts were reported in a study using an experimental model.\(^{33}\) A large clinical study performed in Western countries reported that recurrence of arrhythmia was significantly reduced in patients with serious ventricular tachyardia.\(^{34}\) Clinically, the inhibition of new onset of AF by combined use of statins and antiarrhythmic drugs was observed in AF patients complicated with ischemic cardiopathy.\(^{35}\) In cases of persistent AF, recurrence after cardioversion could be prevented.\(^{36,37}\) It has been reported sporadically that pretreatment with statins reduced the incidence of new manifestation of postoperative AF, which was associated with a shortened hospital stay. However, since the doses used in the studies in Western countries mentioned above were about 2 - 3 times higher than the standard dose used in Japan, it remains unknown whether statins at the standard Japanese dose could also be effective for the prevention of progression of AF into structural remodeling as well as recurrence of AF. It has recently been reported that in the treatment of paroxysmal and persistent AF, combination therapy using antiarrhythmic drugs and statins even at standard Japanese doses was effective for the maintenance of sinus rhythm, and that combination therapy was able to prevent structural remodeling such as dilation of the left atrium.\(^{38}\)

**Study limitations:** Firstly, this was a retrospective observational study, so there would have been some bias in the patient characteristics among the groups. Concomitant use of ACEI was decided on the basis of whether hypertension or heart failure was present or not, and use of statins by whether dyslipidemia was present or not. Secondly, many antiarrhythmic drugs were used by the envelope method in this study. From comparisons made using the standard dose in Japan as the base, it has been suggested that the efficacy for preventing recurrence of AF varies between drugs.\(^{39}\) A third limitation arises from the use of subjective symptoms or ECG findings to determine the exact time of manifestation
of recurrence. A study using ambulatory ECG revealed that even patients with paroxysmal AF who had clear subjective symptoms were not aware of more than half of their tachycardia attacks. On the other hand, an analysis using a portable cardiophone in cases of symptomatic AF demonstrated that 30-70% of patients complaining of palpitations had sinus tachycardia or atrial extrasystole. Therefore, there is a methodological limitation to determining the time of relapse, even if we utilize both subjective symptoms and ECG findings. Lastly, although the efficacy of upstream therapy for paroxysmal AF has been shown by the present study, the pharmacological mechanism by which ACEI or statins achieve this efficacy has yet to be elucidated.

In future also, the therapeutic results obtained from combination therapy using RAAS inhibitors and statins in paroxysmal and persistent AF should be re-evaluated in a prospective multicenter comparative study in a Japanese population.

**Conclusion:** The findings of the present study indicate that combination therapy using both ACEI and statins in addition to antiarrhythmic drugs has possible efficacy as a pharmacological upstream therapy, and can be effective for the prevention of permanent AF, thus providing a promising therapeutic strategy.

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**REFERENCES**


