Long-Term Effects of Upstream Therapy on Paroxysmal Atrial Fibrillation in Patients Without Overt Heart Diseases

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SUMMARY

Most paroxysmal atrial fibrillation (PAF) ultimately becomes chronic atrial fibrillation (CAF), even in the presence of antiarrhythmic drugs. Upstream therapies such as calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI), or statins have attracted attention for treating AF patients. We have previously reported that ACEI inhibited the progression of PAF to CAF. CCB and statins were also reported to inhibit the development of AF, but the follow-up periods in several of the papers appeared to be too short to allow a clear verdict on the antiarrhythmic effects. We therefore conducted a retrospective analysis of the relationship between long-term treatment (over 5 years) with an ACEI, CCB, or statin and outcome in patients with PAF (n = 125).

The follow-up period was 7.7 ± 3.1 years. Class I antiarrhythmic drugs were prescribed for 76.6% of the patients, ACEI for 36.0%, CCB for 47.2%, and statins for 20.0%. We assessed the cardiac rhythm from the medical records or electrocardiograms and determined the time from the first visit to the development of CAF. Kaplan-Meier analysis showed that the use of an ACEI significantly decreased the cumulative probability of CAF, while class I antiarrhythmics, CCB, and statins did not inhibit progression to CAF. Multivariate analysis showed that only ACEI was related to a reduced progression to CAF (odds ratio, 0.112; 95% confidence interval, 0.034 to 0.374, P = 0.001). Class I antiarrhythmic drugs, CCBs, and statins showed no such association.

ACEI thus appear to be superior to CCB or statins with respect to upstream therapy. (Int Heart J 2009; 50: 141-151)

Key words: Atrial fibrillation, Angiotensin converting enzyme inhibitors, Calcium channel blockers, Statins, Upstream therapy

Atrial fibrillation (AF) is a common but clinically important arrhythmia...
because its prevalence is 2% to 4% in the population over 60 years of age, and this arrhythmia is associated with increased risk of ischemic stroke, congestive heart failure, and cardiac death.

Atrial fibrillation is a progressive disease because paroxysmal episodes of atrial fibrillation (PAF) often increase in frequency and length as time passes, ultimately becoming chronic atrial fibrillation (CAF). The transition rate is reported to be 18% of PAF patients without overt heart diseases. Since the incidence of ischemic stroke was more frequent in patients with CAF than in patients with PAF, therapeutic efforts to prevent or delay the progression from PAF to CAF tend to improve prognosis in PAF patients. However, in many cases the conventional antiarrhythmic drugs recommended by the ACC/AHA/ESC have shown limited effectiveness in preventing progression to CAF because the drugs have no inhibitory effects on electrical or structural remodeling, both of which play the important role of causing progression to CAF. Recent attention has been focused on upstream therapy with calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), because these drugs are expected to inhibit calcium overload and activation of the renin-angiotensin-aldosterone system or inflammation, both of which are responsible for remodeling of the atrium during AF.

We have previously reported that ACEI showed inhibitory effects on the progression of PAF to CAF. Upstream therapy with CCB or statins has also been reported to exhibit beneficial effects in inhibiting the development or recurrence of AF. However, the follow-up period in some of the reports was not even 1 year, which may well be too short to determine reliably the antiarrhythmic effects of these drugs. Therefore, to examine the long-term effects of upstream therapy for longer than 5 years on PAF, we conducted a retrospective analysis of the relationship between medical treatments including ACEI, CCB, or statins and outcomes in patients with PAF, but without overt heart diseases (n = 125). The endpoint of this study was progression of PAF to CAF.

**METHODS**

**Subjects:** We selected a total of 125 patients with symptomatic PAF who visited the Division of Cardiology in the Department of Internal Medicine at Nippon Medical School between January 1980 and December 2007. Patients followed-up for less than 5 years were excluded. Episodes of PAF were documented by Holter monitoring or electrocardiogram (ECG) in all patients. We retrospectively examined the clinical characteristics and long-term outcomes in these patients. Every patient underwent ECG and chest radiography at the first visit. Transtho-
Radic echocardiography was performed during the sinus rhythm to detect any organic heart diseases. Left ventricular ejection fraction (LVEF), left ventricular thickness, and left atrial (LA) diameter were obtained by transthoracic echocardiography. We excluded patients with organic heart diseases such as myocardial infarction, cardiomyopathy, congestive heart failure, chronic obstructive pulmonary diseases, or hyperthyroidism. The medical records or ECGs were reviewed in order to evaluate the cardiac rhythm every 2-6 weeks during follow-up visits.

**Definitions and statistical analysis:** We considered that PAF had progressed to CAF if all subsequent ECGs at the clinical visits showed AF for longer than 3 months. For each patient, we examined the time from the first visit to our hospital to the occurrence of CAF by reviewing the medical records and ECGs. The mean follow-up time was 7.7 ± 3.1 years, ranging from 5 to 19 years.

We compared the baseline characteristics of patients using the unpaired Student’s *t*-test. Data are presented as the mean ± SD. Survival without occurrence of CAF was calculated using the Kaplan-Meier method and difference was calculated with a log-rank test. A *P* value of < 0.05 was considered statistically significant. A univariate logistic regression model was used to analyze the association between the development of CAF at 5 years and clinical factors. Significant variables associated with the development of CAF were entered into multivariate analysis. Variables showing a *P* value < 0.05 were included in univariate analysis. The association between the variables and the development of CAF was evaluated by calculating the odds ratio and 95% confidence intervals. Data were analyzed using SPSS version 14.0 (SPSS Inc., Chicago, IL).

**Results**

**Baseline characteristics of the patients:** The baseline characteristics are summarized in Table I. The mean age was 62.7 ± 10.0 years old. The time interval from the first symptomatic episode to the clinic-visit day was 36 ± 16 days. The mean number of symptomatic episodes per week before treatment was 1.9 ± 2.7 and the mean duration was 3.0 ± 6.0 hours. Seventy-five of the 125 patients (60.0%) had hypertension and 25 of the 125 patients (20.0%) had hyperlipidemia. Left ventricular ejection fraction (LVEF) was normal and blood pressure after treatment was 128 ± 12 mmHg. During follow-up, 36.0% of the patients were prescribed ACEI; 47.2%, CCB; and 20.0%, statins. Class I antiarrhythmic drugs were prescribed in 76.6% of the patients. The most common antiarrhythmic drugs prescribed by the attending physician were class Ia, and the percentages of class I, class Ic, β-blocker, and class III drugs were 76.6%, 41.9%, 34.7%, and 10.5%, respectively. We used ACEI for the treatment of hypertension. Of the 45 patients taking an ACEI, 8 were taking enalapril 5-10 mg; 8, lisinopril
10-20 mg; 7, captopril 37.5 mg; 4, alacepril 25-50 mg; 4, imidapril 5-10 mg; 3, quinapril 10 mg; 3, cilazapril 1 mg; 2, temocapril 2 mg; 2, benazepril 5-10 mg; 2, alacepril 25-50 mg; and 2, perindopril 2-4 mg. Of the 59 patients taking a CCB, 22 were taking amlodipine 2.5-5 mg; 11, diltiazem 60-90 mg; 11, verapamil 80-160 mg; 8, nifedipine 10-20 mg; 3, benidipine 4-8 mg; 2, manidipine 10-20 mg; and 2, nisoldipine 5-10 mg. Of the 25 patients taking a statin, 15 were taking pravastatin 10-20 mg; 5, simvastatin 5-20 mg; 4, fluvastatin 20-30 mg; and 1, atorvastatin 10-20 mg. The dose of each drug was within the upper permitted limit for prescription, and was demonstrated to be effective in Japan.

**Progression from PAF to CAF:** PAF progressed to CAF in 76 of the 125 patients (60.8%, 6.4% of patients per year) during follow-up. In the remaining 49 patients, PAF continued without progression to CAF during the observation period. The Kaplan-Meier curve for the cumulative probability of CAF was constructed for each drug (Figure). Patients receiving an ACEI showed a significantly lower incidence of developing CAF than those without an ACEI ($P < 0.001$). This analysis demonstrated a 5-year probability of 15.7% for progression to CAF in patients who received an ACEI, compared with 46.2% in those who did not. With the other drugs, there was no significant difference in the cumulative probability of CAF between those who received drug treatment and those who did not. In order to adjust for various factors, such as background characteristics and

**Table I. Baseline Characteristics of Patients With Paroxysmal Atrial Fibrillation**

<table>
<thead>
<tr>
<th>n</th>
<th>125</th>
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<tr>
<td>Age (years)</td>
<td>62.7 ± 10.0</td>
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<tr>
<td>Men (%)</td>
<td>69.6</td>
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<tr>
<td>Interval in days from first episode to clinic visit</td>
<td>36 ± 16</td>
</tr>
<tr>
<td>Number of symptomatic episodes (/week)</td>
<td>1.9 ± 2.7</td>
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<tr>
<td>Duration of symptomatic episodes (hours)</td>
<td>3.0 ± 6.0</td>
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<tr>
<td>CAF-free period (years)</td>
<td>6.8 ± 4.1</td>
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<tr>
<td>Hypertension (%)</td>
<td>60.0</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>6.4</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>40.0 ± 6.3</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>66.6 ± 8.0</td>
</tr>
<tr>
<td>Blood pressure after treatment (mmHg)</td>
<td>128 ± 12</td>
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**Medications**
- **Class I (%):** 76.6
- **Class Ic (%):** 41.9
- **β-Blocker (%):** 34.7
- **Class III (%):** 10.5
- **ACEI (%):** 36.0
- **Calcium channel blocker (%):** 47.2
- **Statin (%):** 20.0
- **Digitalis (%):** 16.3

Values are mean ± S.D.
ACEI indicates angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; and CAF, chronic atrial fibrillation.
medications, we examined the association between baseline characteristics and progression to CAF at 5 years (Table II). Univariate analysis showed that treatment with an ACEI and that with a CCB were significantly associated with inhibition of the progression to CAF. In multivariate analysis, however, only treatment with an ACEI was associated with such inhibition (odds ratio, 0.112; 95% confidence interval (CI), 0.034 to 0.373, \( P = 0.001 \)). Treatment with a Class I antiarrhythmic drug or statin did not benefit patients with PAF by inhibiting progression to CAF.

There was no significant difference between patients with \( (n = 76) \) and without a transition to CAF \( (n = 49) \) in the duration of the symptomatic episodes \( (2.3 \pm 4.7 \) hours versus \( 3.5 \pm 6.7 \) hours) or in the number of symptomatic

**Figure.** Cumulative probability of chronic atrial fibrillation. CAF indicates chronic atrial fibrillation; Class I, Class I antiarrhythmic drugs; ACEI, angiotensin-converting enzyme inhibitor; and CCB, calcium channel blocker. Note that ACEI significantly inhibited the cumulative probability of CAF \( (P < 0.001, \) log-rank test).
episodes per week (1.5 ± 1.7 versus 2.1 ± 3.1) before the treatment. A comparison of the time intervals from the symptomatic episode to the first clinic-visit day showed no significant difference between patients with and without a transition to CAF (32.4 ± 16.6 days versus 35.9 ± 18.9 days).

**DISCUSSION**

The major findings of the present study were: (1) that treatment with an ACEI inhibits the progression of PAF to CAF, and (2) that Class I antiarrhythmic drugs, CCB and statins did not show this beneficial effect. ACEI were more effective than CCB or statins with respect to the upstream therapy for patients with PAF.

PAF gradually progressed to CAF with an overall annual ratio of 6.4%. Kato, et al have reported that this ratio was 5.5%. The higher ratio in the present study could be partially related to the older population (mean, 62.7 ± 10.0 years at entry) than in their study (58.3 ± 11.8 years at PAF onset), because aging is an important factor that increases the development ratio of CAF. The pathophysiology of the progression of PAF to CAF consists mainly of two processes; electrical and structural remodeling of atrium. Because conventional antiarrhythmic drugs may have limited effectiveness in inhibiting this atrial remodeling, they cannot prevent the progression from PAF to CAF completely in the long-term in many clinical cases. Accordingly, upstream therapies to inhibit or to reverse electrical and structural remodeling have become the focus for treating AF patients. Electrical remodeling is a functional change that is characterized by the shortening of the atrial refractory period, by prolonging atrial
conductivity, and by the loss of rate adaptation of the atrial refractory period. Electrical remodeling of these changes gradually worsens with time during AF and promotes the perpetuation of AF. Rapid irregular depolarization increases the intracellular Ca\(^{2+}\) concentration in cardiac myocytes, resulting in shortening of the action potential duration by activating Ca\(^{2+}\)-dependent outward currents. Shortening of the atrial refractory period contributes to the maintenance of multiple reentrant circuits occurring during AF. Experimental animal studies have shown that electrical remodeling of the atrium was significantly attenuated by verapamil. In clinical studies, conflicting results have been reported. Tieleman, et al have shown that CCB lowered the recurrence rate of AF after successful electrical cardioversion. However, Bertaglia, et al have reported that verapamil could not reduce the recurrence rate of AF after cardioversion.

Recently, Patten, et al have reported that the combination of verapamil and quinidine was as effective as sotalol in the prevention of symptomatic episodes of PAF. But it was not clear from their study whether verapamil can prevent the asymptomatic episodes of PAF, because asymptomatic AF occurs far more often than symptomatic AF in patients with PAF. We did not find any beneficial inhibitory effects of CCB on the progression of PAF to CAF. There are several possible explanations for this. One possibility is that the doses of CCB used in our study were not high enough to inhibit the electrical remodeling. These doses were within the upper permitted limit for prescription in Japan, but they may not have been high enough to inhibit atrial remodeling. The second is that CCB could not inhibit the structural remodeling of the atrium in spite of the inhibition of electrical remodeling. Finally, the third possibility is that the decreases in the gene expression of intracellular Ca\(^{2+}\) regulatory proteins such as ryanodine receptor and Ca\(^{2+}\)-ATPase might occur after frequent episodes of PAF and that this might cause an intracellular Ca\(^{2+}\) overload in a manner that could not be inhibited by CCB.

Structural remodeling occurs in parallel with electrical remodeling during AF. Structural remodeling is characterized by a progressive increase in interstitial fibrosis which causes atrial dilatation. Deposition of connective tissue between individual atrial cells produces separation of atrial cells from each other and subsequent atrial conduction delays, which initiates the maintenance of AF. Recently Goette, et al have reported that the expression of extracellular signal-regulated kinase (ERK1/ERK2) and ACE is increased in patients with AF. Angiotensin II, which is secreted locally or systematically, plays a critical role in the progression of PAF to CAF by promoting structural remodeling of the atrium during AF, because it can produce cellular hypertrophy, apoptosis, and fibrosis, which result in an increase in conduction heterogeneity and conduction delay. These structural changes cause arrhythmogenic substrate and pro-
mote perpetuation of AF. Experimental studies have shown that atrial structural remodeling is reversible and is attenuated by ACEI or ARB.\cite{11,21} This effect is particularly convincing in the earlier stages of structural remodeling. In clinical studies, ACEI or ARB have been reported to inhibit the new onset or the recurrence of AF by inhibiting the structural remodeling of the atrium. Pedersen, et al reported that trandolapril reduced the incidence of AF by 55\% in patients with acute myocardial infarction.\cite{22} The Studies Of Left Ventricular Dysfunction (SOLVD) reported that enalapril brought about a 78\% risk reduction of AF development in patients with LV dysfunction.\cite{23} Our study showed that ACEI inhibited the progression of PAF to CAF in patients without overt heart diseases, suggesting that the beneficial effects observed with ACEI were not due to the improvement of hemodynamics or left ventricular function, but rather to actual antiarrhythmic effects on atrial structural remodeling. We have previously reported that the P wave duration increased over 5 years in patients without ACEI, but treatment with ACEI inhibited the prolongation of the P wave duration.\cite{6} This result supports the idea that ACEI can prevent atrial structural remodeling by inhibiting further fibrous changes and by suppressing the development of the arrhythmogenic substrate which leads to CAF.

ACEI were more effective than CCB with respect to upstream therapy. This result was compatible with those of previous reports.\cite{24} Fogari, et al have reported that ramipril was more effective than amlodipine in inhibiting new episodes of AF in hypertensive patients.\cite{25} Schmieder, et al have reported that valsartane reduced the new-onset of AF in hypertensive patients with a high risk of cardiovascular risk factors compared with amlodipine.\cite{26} Both our present results and the recent studies by others suggest that ACEI or ARB offer greater benefits than CCB with respect to upstream therapy. These results suggest that structural remodeling of the atrium plays a more important role than electrical remodeling in bringing about the progression of PAF to CAF.

The importance of inflammation in the pathogenesis of AF has recently been reported in several papers. Bruins, et al showed that the peak incidence of AF occurrence coincided with the peak elevation of CRP levels after cardiac surgery.\cite{27} Frustaci, et al performed atrial biopsies from patients with paroxysmal lone AF and presented histological evidence of active inflammation in the atrium.\cite{28} Mihm, et al have demonstrated significant oxidative damage in the atrium of AF patients undergoing the Maze operation.\cite{29} These results suggest that inflammation may be an initiator of the development of AF rather than a consequence of AF.\cite{14} Statins have pleiotropic effects including anti-inflammatory or antioxidant actions that are expected to favorably affect arrhythmogenic activity.\cite{30} Siu, et al expanded this idea in relation to patients with AF. They have reported that statins decrease the risk of AF recurrence after successful cardio-
version in patients with persistent AF.\textsuperscript{31)}

Recently, Liu, \textit{et al} conducted a systematic review and meta-analysis of randomized clinical trials and observational studies.\textsuperscript{32)} Their results suggested the usefulness of statins in preventing AF, but they concluded that the data were insufficient to recommend the widespread use of statins for AF prevention. Fauchier, \textit{et al} performed another systematic meta-analysis of randomized controlled human trials, including 6 studies with a total of 3557 patients, and concluded that the use of statins significantly decreased the incidence or recurrence of AF.\textsuperscript{33)} In this meta-analysis, 3 studies were conducted in patients with persistent AF after undergoing electrical cardioversion and the other 3 studies in patients with acute coronary syndrome or after cardiac surgery. Several possible explanations can be proposed for the conflicting effects of statins on AF. The duration of the follow-up of our study was longer than 5 years and other studies included in Fauchier’s meta-analysis varied in length from 3 to 26 weeks. The progression of PAF to CAF may occur over the long-term, even in the presence of statins. We did not include patients with overt heart disease or those undergoing cardiac surgery or electrical cardioversion. The mechanism of AF occurrence may vary from patient to patient, from an inflammatory to oxidative process. These differences may cause the different results for statin use. 

\textbf{Limitations:} Our analysis is based on observational study that may include some biases.\textsuperscript{6)} Our definitions of PAF and CAF were based on electrocardiographic documentation of AF at clinic visits and the duration of the clinic visits varied. It is possible that some patients who were classified as CAF had a sinus rhythm after the diagnosis. This potential misclassification may have influenced the results of our study. Our study was retrospective and treatment with ACEI, CCB or statins was not randomized. We enrolled 125 patients and used different types of ACEI, CCB and statins depending on the attending physicians. A randomized prospective study is needed to clarify the significance of the difference between ACEI and CCB or statins in the management of PAF. We excluded patients with overt heart diseases such as congestive heart diseases, myocardial infarction, valvular heart diseases, and cardiomyopathy. We did not include patients who had had electrical cardioversion. A large multicenter trial including these patients is required to extend our conclusions to patients with overt heart diseases or after electrical cardioversion.

\textbf{Clinical implication:} Despite these limitations, the present study suggests that treatment with ACEI is a valid strategy for hypertensive patients with PAF to improve their prognosis.

\textbf{Conclusions:} Our findings suggest that ACEI are superior to CCB or statins with respect to upstream therapy for inhibiting the progression of PAF to CAF in patients without overt heart disease.
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