Circ J 2005; **69:** 671–676

Angiotensin-Converting Enzyme Inhibitor Therapy Inhibits the Progression From Paroxysmal Atrial Fibrillation to Chronic Atrial Fibrillation

Yoshiyuki Hirayama, MD; Hirotsugu Atarashi, MD; Yoshinori Kobayashi, MD; Tsutomu Horie, MD; Yuuki Iwasaki, MD; Mitsunori Maruyama, MD; Yasushi Miyauchi, MD; Toshihiko Ohara, MD; Masaaki Yashima, MD; Teruo Takano, MD

Background Atrial fibrillation is a progressive disease, which in the paroxysmal form (PAF) becomes more frequent and finally becomes chronic (CAF). A retrospective analysis of patients with PAF was conducted to examine the hypothesis that angiotensin-converting enzyme inhibitors (ACEI) will prevent the progression to CAF.
Methods and Results On the basis of their treatment, 95 patients with PAF were divided into 2 groups: 42 patients treated with ACEI for hypertension throughout the period of treatment and follow-up (ACEI group) and 53 patients not given ACEI (non-ACEI group). Cardiac rhythms were assessed either from the medical records or the electrocardiograms recorded every 2–4 weeks at follow-up visits. The mean follow-up time was 8.3±3.5 years. There was no significant difference in the use of antiarrhythmic drugs, left atrial diameter or left ventricular ejection fraction between the 2 groups. The Kaplan-Meier curve for the time to occurrence of CAF showed a lower incidence of CAF in the ACEI group and demonstrated that the 5-year probability for persistence of PAF without progression to CAF was 88.3%, but 47.5% in the non-ACEI group.
Conclusions These results indicate that ACEI will prevent progression from PAF to CAF. (*Circ J* 2005; **69:** 671–676)

Key Words: Angiotensin-converting enzyme inhibitors; Antiarrhythmic therapy; Paroxysmal atrial fibrillation

Atrial fibrillation (AF) is a progressive disease, many of the clinical cases are characterized by paroxysmal episodes (PAF) that become more frequent and more prolonged over time, finally becoming chronic (CAF)[1] However, the optimal management of PAF is still unknown. The ACC/AHA/ESC practice guidelines[2] recommend the use of flecainide, propafenon or sotalol as initial antiarrhythmic therapy for patients with no, or minimal, structural heart disease, but many of these patients experience recurrent episodes of PAF and progression to CAF in the long-term despite these therapies. Large clinical trials such as the AFFIRM[3] and RACE[4] have shown that rhythm-control therapy does not offer any prognostic advantage over rate-control therapy in patients with persistent AF. However, we cannot apply this result to patients with PAF and normal cardiac function, because recently Komatsu et al[5] reported that antiarrhythmic therapy to maintain sinus rhythm improved the long-term prognosis of patients with PAF. In their report, they also showed that ischemic stroke occurred more frequently in patients with CAF than in patients with PAF[5] Thus, therapeutic efforts to prevent or delay the conversion from PAF to CAF are of clinical importance and contribute to improving prognosis in patients with PAF.

(Received December 24, 2004; revised manuscript received March 25, 2005; accepted April 5, 2005)
First Department of Internal Medicine, Nippon Medical School, Tokyo, Japan
Mailing address: Yoshiyuki Hirayama, MD, The First Department of Internal Medicine, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan. E-mail: Hirayama@nms.ac.jp

Electrical and structural remodeling of atrial muscle plays an important role in causing both the recurrent episodes of PAF and the progression to CAF. Recent studies of experimental congestive heart failure have reported that angiotensin-converting enzyme inhibitors (ACEI) prevent the atrial structural remodeling of the AF substrate by inhibiting further fibrous changes in the atria[6,7] Several clinical studies have also reported that ACEI reduced the incidence of AF in patients with left ventricular (LV) dysfunction[8,9] We therefore conducted a retrospective analysis of patients with PAF, but without overt heart disease, to investigate whether or not chronic ACEI therapy prevents the progression from PAF to CAF.

Methods

Study Population

We retrospectively examined the clinical characteristics and long-term outcome in patients with PAF who visited to the First Department of Internal Medicine at Nippon Medical School between January 1980 and July 2004. A total of 95 patients were included in this study. Electrocardiogram (ECG) and chest radiography of every patient were carried out at the first visit. A transthoracic echocardiogram was performed during sinus rhythm to examine the left atrial (LA) size, LV thickness and LV ejection fraction (LVEF). We reviewed the medical records or ECGs and assessed cardiac rhythm every 2–4 weeks during follow-up visits. We defined PAF as paroxysms of AF that terminated spontaneously within 7 days[2] and CAF as AF lasting >3 months for which cardioversion had failed or was

Table 1 Baseline Characteristics of Patients With Paroxysmal Atrial Fibrillation

	ACEI group	*Non-ACEI group*	*p value*
N	*42*	*53*	
Age (years)	*65.5±1.3*	*60.7±1.4*	*0.016*
Male (%)	*61.9*	*73.6*	*0.032*
Time interval from the first symptomatic episode to the clinic-visit day (day)	*32.9±7.0*	*20.3±3.6*	*0.093*
No. of symptomatic episodes (/week)	*1.77±0.29*	*2.53±0.58*	*0.294*
Duration of symptomatic episodes (h)	*3.34±0.97*	*2.24±0.61*	*0.320*
Use of antiarrhythmic drugs, n	*2.31±0.20*	*2.18±0.19*	*0.645*
CAF-free period (years)	*7.52±0.51*	*5.32±0.48*	*0.0225*
Hypertension (%)	*100*	*37.7*	*0.0004*
Hyperlipidemia (%)	*26.2*	*18.9*	*0.063*
Diabetes mellitus (%)	*9.5*	*11.3*	*0.122*
Left atrial diameter (mm)	*41.1±0.91*	*39.5±0.93*	*0.229*
Left ventricular ejection fraction (%)	*66.7±1.60*	*66.5±0.98*	*0.936*
Blood pressure after treatment (mmHg)	*132±8.6*	*129±7.3*	*0.787*
Medications			
Class I (%)	*85.7*	*84.9*	*0.129*
Class Ic (%)	*42.8*	*37.7*	*0.103*
β-blocker (%)	*9.5*	*9.4*	*0.130*
Class III (%)	*4.8*	*7.5*	*0.157*
Ca antagonist (%)	*59.5*	*49.1*	*0.053*
Digitalis (%)	*14.3*	*17.0*	*0.117*
Statin (%)	*26.2*	*18.9*	*0.063*

Values are mean±SE.
ACEI, angiotensin-converting enzyme inhibitor; CAF, chronic atrial fibrillation; Ca antagonist, calcium antagonist.

not attempted. We did not include patients with acute or old myocardial infarctions, congestive heart failure, cardiomyopathy, cardiac surgery within the past 6 months, hyperthyroidism or chronic obstructive pulmonary diseases.

Measurements

The 95 patients with PAF were divided into 2 groups on the basis of the treatment with ACEI: the ACEI group consisted of 42 patients, all of whom had hypertension for which they were taking ACEI; the non-ACEI group consisted of 53 patients, 20 of whom had hypertension and were taking a calcium antagonist or α- or β-blocker, but not ACEI. If all subsequent ECGs showed AF for longer than 3 months, PAF was considered to have progressed to CAF. For each patient, we examined the time to occurrence of CAF from the first visit to hospital by reviewing the medical records and ECGs. The mean follow-up time was 8.3±3.5 years, ranging from 5 to 17 years. We recorded standard 12-lead ECGs at the standard speed of 25 mm/s and sensitivity. All ECG tracings were calibrated to 1 cm = 10 mV. We measured the P-wave duration in lead II manually with a magnifying lens and examined its changes during follow-up. These measurements were performed with the investigators unaware of the medical treatments.

Statistical Analysis

The baseline characteristics of patients were compared with Student's t-test and the chi-square tests. Data are presented as mean±SEM. A value of $p<0.05$ was considered statistically significant. We analyzed the time to the occurrence of CAF during the follow-up period by the Kaplan-Meier method and used Cox proportional-hazard models for each variable during ACEI treatment.

Results

Baseline Characteristics of the Patients

The baseline characteristics of the 2 groups are summarized in Table 1. The mean age was higher in the ACEI group than in the non-ACEI group (p=0.016). There were fewer men in the ACEI group than in the non-ACEI group (p=0.032). There was no significant difference in the time interval from the first symptomatic episode to the clinic-visit day between the 2 groups. The duration or number of symptomatic episodes per week before treatment and the number of antiarrhythmic drugs used during the follow-up period did not differ between the 2 groups. The percentage of patients with hypertension was higher in the ACEI group than in the non-ACEI group (p=0.0004). There was no significant difference in LA diameter or LVEF between the 2 groups. There was no statistically significant difference in blood pressure between the 2 groups after the treatment. The percentage of patients with diabetes mellitus did not differ between the 2 groups. Of the 42 patients taking ACEI, 8 were taking enalapril 5–10 mg; 8, lisinopril 10–20 mg; 4, captopril 37.5 mg; 6, 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; and 2, perindopril 2–4 mg. The dose of each drug was within the upper permitted limit for prescription, and has been demonstrated as effective in Japan. All patients in the ACEI group continued to take ACEI during the follow-up period. The most common antiarrhythmic drugs prescribed by the attending physician were class Ia, but the percentage of class I, class Ic, β-blocker, class III and digitalis was not different between the 2 groups (Table 1). The use of calcium antagonists or statins seemed to be more frequent in the ACEI group, but was not statistically significant.

Progression From PAF to CAF

There was no significant difference in mean follow-up time between the 2 groups, but PAF progressed to CAF in 12 patients (28.7%) of the ACEI group and in 38 patients (71.6%) of the non-ACEI group during the follow-up. In the remaining 30 patients of the ACEI group and 15 patients of the non-ACEI group, PAF continued without change during the observation period. We defined the CAF-free period as the longest time that a patient remained

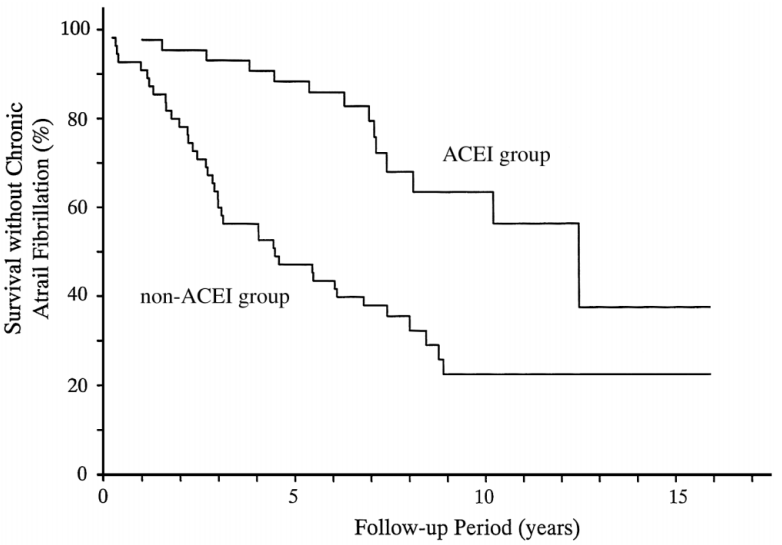

Fig 1. Kaplan-Meier curve for survival without occurrence of CAF. ACEI, angiotensin-converting enzyme inhibitor; CAF, chronic atrial fibrillation.

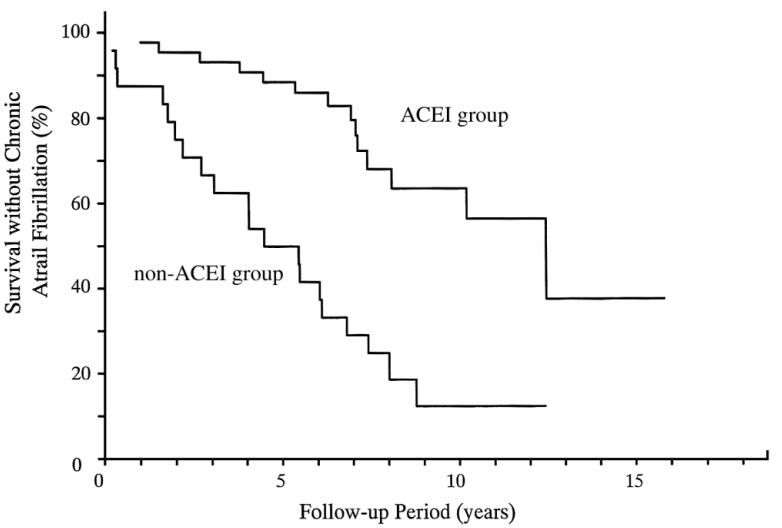

Fig 2. Kaplan-Meier curve for survival without occurrence of CAF among patients with hypertension. ACEI, angiotensin-converting enzyme inhibitor; CAF, chronic atrial fibrillation.

in PAF without a transition to CAF during the follow-up and it was significantly longer in the ACEI group than in the non-ACEI group (7.52±0.51 years vs 5.32±0.48 years, p=0.022) (Table 1). The Kaplan-Meier curve for survival without the occurrence of CAF (Fig 1) showed that the ACEI group had a higher incidence of patients remaining in PAF without developing CAF. This analysis demonstrated a 5-year probability of 88.3% for remaining in PAF in patients who received ACEI, compared with 47.5% in patients who did not (p=0.002). Because of the higher blood pressure and/or higher serum cholesterol, there was greater use of calcium antagonists and/or statins in the ACEI group than in the non-ACEI group (Table 1), but the use of ACEI was the only significant variable related to inhibition of the progression to CAF because the Cox proportional hazard model showed that, after correction for those variables that could influence the result, the hazard ratio was 0.343 and 0.408 for the use of a calcium antagonist and a statin, respectively.

All patients in the ACEI group (n=42) and 20 patients in the non-ACEI group had hypertension, and of these patients PAF progressed to CAF in 8 patients (40%) in the non-ACEI group during the follow-up. The CAF-free period was significantly longer in the ACEI group than in the patients with hypertension in the non-ACEI group (7.52±0.51 years vs 5.18±0.36 years, p=0.019). The Kaplan-Meier curve for survival without the occurrence of CAF (Fig 2) showed that the ACEI group had a higher incidence of patients remaining in PAF without developing CAF (p=0.0015).

There was no significant difference between patients with (n=50) and without (n=45) a transition to CAF in the duration of the symptomatic episodes (2.55±0.63 h vs 2.88±0.91 h, p=0.759) or in the number of symptomatic episodes per week (1.78±0.27 vs 2.69±0.70, p=0.211) before the treatment. The comparison of the time interval from the symptomatic episode to the first clinic-visit day was not significant between patients with and without a transition to CAF (23.3±4.9 days vs 29.2±5.7 days, p=0.438).

Changes in P Wave Duration During the Follow-up Period

We examined the changes in P wave duration 5 years after the initial diagnosis of PAF. We obtained paired ECGs recorded during sinus rhythm at baseline and after 5 years from 26 patients in the ACEI group and from 30 patients in the non-ACEI group. In these patients, PAF did not progress to CAF for 5 years during the follow-up period. The mean value of the P wave duration increased significantly

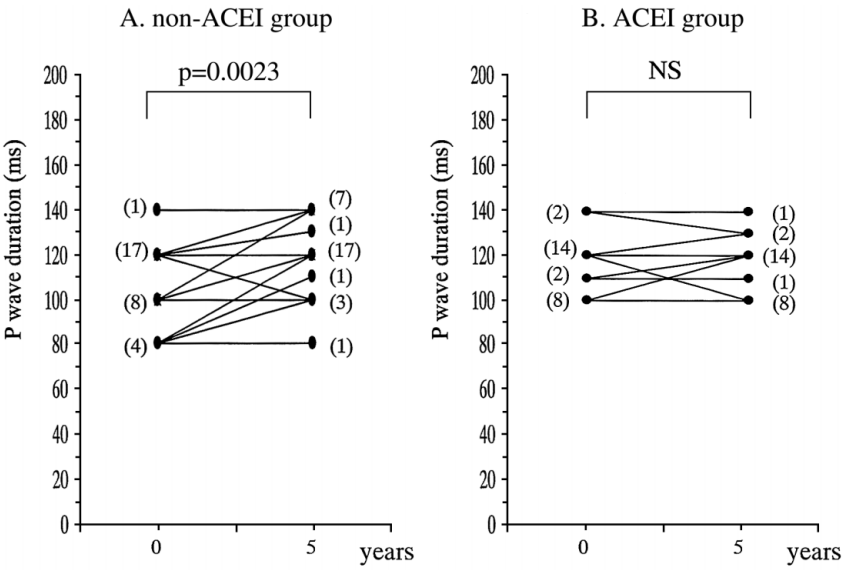

Fig 3. Comparison of the changes in the P wave duration in limb lead II during 5 years between ACEI group and non-ACEI group. ACEI, angiotensin-converting enzyme inhibitor.

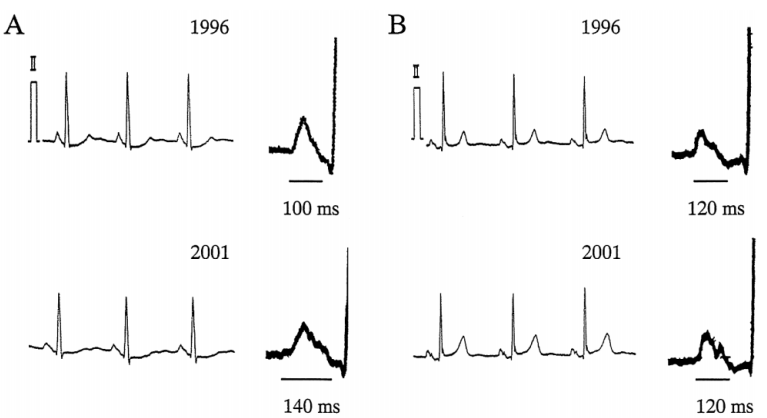

Fig 4. Electrocardiograms in limb lead II recorded in 1996 and 2001 from the same patient during sinus rhythm. (A) Flecainide (200 mg) was prescribed for the treatment of paroxysmal atrial fibrillation (PAF). The P wave duration increased from 100 ms to 140 ms in 5 years. (B) Disopyramide (300 mg) and enalapril (10 mg) were prescribed for the treatment of PAF and hypertension, respectively. The P wave duration did not change during the follow-up period.

from 110.0±2.8 ms to 121.3±2.6 ms in 5 years in the patients not treated with an ACEI (p=0.0023) (Fig 3), but did not change significantly in the patients treated with an ACEI. There was no significant difference in the mean value of the P wave duration at baseline between the non-ACEI group and ACEI group (110.0±2.8 vs 114.6±2.3, p=0.198).

Fig 4A shows an example of the changes in P wave duration in lead II during sinus rhythm in a patient with PAF in the non-ACEI group. The P wave duration was 100 ms at the first medical examination in 1996, and this patient was prescribed flecainide 200 mg for 5 years. The morphology of the P wave became irregular and the duration increased to 140 ms in 2001. Fig 4B is a representative ECG in lead II from a patient in ACEI group. The P wave duration did not change during the follow-up period and this patient was prescribed enalapril 10 mg and disopyramide 300 mg for 5 years. These results indicate that ACEI therapy is effective at inhibiting prolongation of the P wave in patients with PAF.

Discussion

The major findings of the present study are: (1) treatment with ACEI inhibits the progression of PAF to CAF and (2) ACEI inhibit the prolongation of the P wave recorded during sinus rhythm in patients with PAF.

There are several reports stating that ACEI exert antiarrhythmic effects that prevent the occurrence of AF. Pedersen et al reported that treatment with trandolapril reduced the risk of developing AF by 55% in patients with LV dysfunction caused by acute myocardial infarction[8] A retrospective analysis of patients from the Montreal Heart Institute enrolled in the Studies Of Left Ventricular Dysfunction showed that enalapril brought about a 78% risk reduction of developing AF in patients with LV dysfunction[9] The addition of enalapril[10] or irbesartan[11] to amiodarone decreased the recurrence of AF and facilitated long-term maintenance of sinus rhythm in patients with AF after cardioversion. Possible mechanisms of the efficacy of ACEI treatment have been reported, although the underlying mechanisms by which ACEI exerts its antiarrhythmic effects are not clear. Pedersen et al speculated that ACEI treatment attenuated the susceptibility to AF by lowering atrial pressure and reducing LA enlargement[8] because ACEI can decrease atrial pressure[12] We did not measure atrial pressure in this study. Lowering blood pressure with ACEI can contribute to the mechanism of benefit, but there was no statistical difference in blood pressure between the present 2 groups after the treatment (Table 1). Therefore, it is unlikely that lowering blood pressure played an important role in the outcome of our study. ACEI seems to exhibit antiarrhythmic effects by other mechanisms[10] Recent studies have demonstrated that a train of repetitive rapid

discharges originating from the pulmonary veins could initiate PAF[13] and that radiofrequency catheter ablation can effectively eliminate these focal areas.[13–16] Chen SA et al examined the electrophysiological characteristics of these ectopic beats and found that a β-blocker could suppress the abnormal automaticity originating from the pulmonary veins.[14] Because ACEI causes sympatho-inhibitory effects by reducing the plasma norepinephrine concentrations[17] or by augmenting both the arterial and cardiopulmonary reflexes that tonically inhibit sympathetic outflow,[18] treatment with ACEI might be effective in suppressing the abnormal repetitive discharges and reducing the frequency or duration of PAF. It is well known that AF can induce the shortening of the atrial refractory period. This electrical remodeling is characterized by a gradual worsening with time and causes the perpetuation of AF.[19] Thus, a reduction in the frequency or duration of abnormal repetitive discharges by ACEI may effectively suppress the electrical remodeling and inhibit the progression into CAF. Actually Nakashima et al have reported that atrial electrical remodeling in the canine heart models during rapid atrial pacing was prevented by captopril.[20]

Atrial fibrosis produces electrophysiological inhomogeneity of the atria, and this mechanism of atrial structural remodeling involves the activation of angiotensin-converting enzyme and angiotensin-converting enzyme dependent kinases in the atrium. Li et al have reported that in a canine heart failure model atrial fibrosis caused the heterogeneity in atrial conduction and increased the inducibility of prolonged episodes of AF.[21] The development of atrial fibrosis in their model was associated with an increase in atrial angiotensin II concentrations.[22,23] Shi et al have reported that a congestive heart failure model induced by rapid ventricular stimulation produced atrial structural remodeling including atrial dilatation and fibrosis, which favors the inducibility of AF. They showed that enalapril could cause this arrhythmogenic atrial structural remodeling to regress and reduce the incidence of AF. But these results from experimental models of heart failure may not apply to our results because all patients in our study had normal LV function.

In addition to electrical remodeling, AF itself can produce atrial structural remodeling mediated by interstitial fibrosis even in the absence of structural heart disease. Goette et al have reported a potential vicious circle involving the stretch-activated atrial angiotensin–aldosterone system.[22] They have proposed that myocardial stretching enhanced by atrial volume or filling pressure during AF is a potent stimulus that increases local angiotensin II concentrations via the angiotensin-converting enzyme system. Angiotensin II induces proliferation of fibroblasts and accumulation of interstitial fibrosis through the activation of mitogen-activated protein kinases (MAP kinases) in cardiac fibroblasts. Actually, they have shown increased atrial expression of angiotensin-converting enzyme and an angiotensin-converting enzyme dependent increase in the amounts of activated Erk1 and Erk2, which belong to subfamilies of the MAP kinases, in patients with PAF.[24] The levels of activated Erk1 and Erk2 became lower during treatment with ACEI.[24] Therefore, treatment with ACEI seemed to have beneficial effects on the clinical course in patients with PAF by inhibiting structural remodeling of the atria and suppressing the formation of an arrhythmogenic substrate that leads to CAF. Our study showed that P wave duration increased over 5 years in patients without ACEI, but treatment with ACEI prevented this prolongation. Our result lends support to the idea that ACEI can prevent atrial structural remodeling by inhibiting atrial fibrosis, because there is a correlation between P wave duration with atrial fibrosis and increased P wave duration as atrial fibrosis increases.[25,26]

Study Limitations

There is a potential misclassification that may influence this study because our definition of PAF was based on electrocardiographic documentation of AF at prescribed intervals and it is possible that several patients who were classified as CAF may have had sinus rhythm between visits. This study was retrospective and treatment with ACEI was not randomized. We enrolled only 95 patients and used different ACEI. The study excluded patients with congestive heart failure, valvular heart disease, old myocardial infarction and cardiomyopathy and so a randomized prospective mass study is needed to extend our conclusions to such patients and to clarify the clinical importance of ACEI in the management of PAF.

Acknowledgments

We thank Ms Nobuko Yoshida and Mr CWP Reynolds for their assistance.

References

1. Kato T, Yamashita T, Sagara K, Iinuma H, Fu LT. Progression nature of paroxysmal atrial fibrillation: Observations from a 14-year follow-up study. *Circ J* 2004; **68:** 568–572.
2. Fuster V, Ryden LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for practice guidelines and policy conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation). *Circulation* 2001; **104:** 2118–2150.
3. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002; **347:** 1825–1833.
4. Gelder ICV, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002; **347:** 1834–1840.
5. Komatsu T, Nakamura S, Suzuki O, Horiuchi D, Yomogida K, Okumura K. Long-term prognosis of patients with paroxysmal atrial fibrillation depends on their response to antiarrhythmic therapy. *Circ J* 2004; **68:** 729–733.
6. Li D, Shinagawa K, Pang L, Leung TK, Cardin S, Wang Z, et al. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. *Circulation* 2001; **104:** 2608–2614.
7. Shi Y, Li D, Tardif JC, Nattel S. Enalapril effects on atrial remodeling and atrial fibrillation in experimental congestive heart failure. *Cardiovasc Res* 2002; **54:** 456–461.
8. Pedersen OD, Bagger H, Kober L, Pedersen CT. Trandolapril reduces the incidence of atrial fibrillation after acute myocardial infarction in patients with left ventricular dysfunction. *Circulation* 1999; **100:** 376–380.
9. Vermes E, Tardif JC, Bourassa MG, Racine N, Levesque S, White M, et al. Enalapril decreases the incidence of atrial fibrillation in patients with left ventricular dysfunction: Insight from the studies of left ventricular dysfunction (SOLVD) trials. *Circulation* 2003; **107:** 2926–2931.
10. Ueng KC, Tsai TP, Yu WC, Tsai CF, Lin MC, Chan KC, et al. Use of enalapril to fcilitate sinus rhythm maintenance after external cardioversion of long-standing persistent atrial fibrillation: Results of a prospective and controlled study. *Eur Heart J* 2003; **24:** 2090–2098.
11. Madrid AH, Bueno MG, Rebollo JMG, Marin I, Pena G, Bernal E, et al. Use of Irbesartan to maintain sinus rhythm in patients with long-

lasting persistent arial fibrillation: A prospective and randomized study. *Circulation* 2002; **106:** 331–336.
12. Webster MWI, Fitzpatrick A, Nicholls G, Ikram H, Wells JE. Effect of enalapril on ventricular arrhythmias in congestive heart failure. *Am J Cardiol* 1985; **56:** 566–569.
13. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998; **339:** 659–666.
14. Chen SA, Hsieh MH, Tai CT, Tsai CF, Prakash VS, Yu WC, et al. Initiation of atrial fibrillation by ectopic beats originating from the pulmonary veins: Electrophysiological characteristics, pharmacological responses, and effects of radiofrequency ablation. *Circulation* 1999; **100:** 1879–1886.
15. Tsai CF, Tai CT, Hsieh MH, Lin WS, Yu WC, Ueng KC, et al. Initiation of atrial fibrillation by ectopic beats originating from the superior vena cava: Electrophysiological characteristics and results of radiofrequency ablation. *Circulation* 2000; **102:** 67–74.
16. Tada H, Naito S, Kurosaki K, Ueda M, Ito S, Shinbo G, et al. Segmental pulmonary vein isolation for paroxysmal atrial fibrillation improves quality of life and clinical outcomes. *Circ J* 2003; **67:** 861–865.
17. Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A, et al. Plasma norepinephrine, plasma rennin activity, and congestive heart failure: Relation to survival and the effects of therapy in V-HeFT II. *Circulation* 1993; **87**(Suppl VI)**:** VI-40–VI-48.
18. Dibner-Dunlap ME, Smith ML, Kinugawa T, Thames MD. Enalaprilat augments arterial and cardiopulmonary baroreflex control of sympathetic nerve activity in patients with heart failure. *J Am Coll Cardiol* 1996; **27:** 358–364.
19. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: A study in awake chronically instrumented goats. *Circulation* 1995; **92:** 1954–1968.
20. Nakashima H, Kumagai K, Urata H, Gondo N, Ideishi M, Arakawa K. Angiotensin II antagonist prevents electrical remodeling in atrial fibrillation. *Circulation* 2000; **101:** 2612–2617.
21. Li D, Fareh S, Leung TK, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: Atrial remodeling of a different sort. *Circulation* 1999; **100:** 87–95.
22. Goette A, Lendeckel U, Klein HU. Signal transduction systems and atrial fibrillation. *Cardiovasc Res* 2002; **54:** 247–258.
23. Li D, Cardin S, Han H, Wang Z, Nattel S. Signal transduction underlying arrhythmogenic atrial remodeling due to congestive heart failure (abstract). *Circulation* 2000; **102**(Suppl II)**:** 736.
24. Goette A, Staack T, Röcken C, Arndt M, Geller JC, Huth C, et al. Increased expression of extracellular signal-regulated kinase and angiotensin-converting enzyme in human atria during atrial fibrillation. *J Am Coll Cardiol* 2000; **35:** 1669–1677.
25. Scott CC, Leier CV, Kilman JW, Vasko JS, Unverferth DV. The effect of left atrial histology and dimension on P wave morphology. *J Electrocardiol* 1983; **16:** 363–366.
26. Goette A, Juenemann G, Peter B, Klein HU, Roessner A, Huth C, et al. Determinants and consequences of atrial fibrosis in patients undergoing open heart surgery. *Cardiovasc Res* 2002; **54:** 390–396.