

Original Article

Long-term Efficacy of Combination Therapy with Anti-arrhythmic Agents and Pravastatin in Patients with Paroxysmal Atrial Fibrillation

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Objective: To investigate the long-term effects of combination therapy with anti-arrhythmic agents and pravastatin (10 mg/day) in maintaining sinus rhythm in patients with paroxysmal atrial fibrillation (AF) and hyperlipidemia.

Method and Results: In all, 318 patients (mean age: 69 ± 12 years) with paroxysmal AF were divided into 2 groups, one receiving pravastatin for hyperlipidemia (pravastatin (+) group, N = 41) and the other not (pravastatin (-) group, N = 277). At 60 months, the survival rate for patients free from conversion to permanent AF was significantly greater in the pravastatin (+) group than in the pravastatin (-) group. The percentage of patients who eventually developed permanent AF despite anti-arrhythmic therapy was significantly lower in the pravastatin (+) group than in the pravastatin (-) group (9.8% vs. 25.3%). Left atrial dimensions were significantly increased in the pravastatin (-) group during the follow-up period (from 34.8 ± 6.6 mm to 37.6 ± 7.0 mm: $p < 0.01$). In contrast, in the pravastatin (+) group, left atrial dimensions remained unchanged between baseline and after treatment (34.4 ± 7.3 mm vs 35.5 ± 6.6 mm).

Conclusion: In patients with paroxysmal AF and hyperlipidemia, addition of pravastatin to anti-arrhythmic agents seems to enhance the efficacy of these agents in maintaining sinus rhythm and preventing the development of structural remodeling in the myocardium. (J Arrhythmia 2007; 23: 124–130)

Key words: Atrial fibrillation, Anti-arrhythmic agents, Cholesterol-lowering drugs, Prevention

Introduction

Atrial fibrillation (AF) is the most commonly encountered tachycardia in daily medical practice.

As the incidence of AF increases rapidly with age, the number of patients with AF is predicted to increase with the expanding elderly population in Japan,¹⁾ AF is an important disease from a health

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economics point of view. Furthermore, it not only causes severe complications such as thromboembolism and heart failure²⁾ but also worsens cardiovascular prognosis, especially in patients with cardiac dysfunction.³⁾ AF is recognized as a disease in which long-term treatment and follow-up is required.

Atrial biopsy of patients with lone AF reveals histopathological developments such as inflammatory cell infiltration, necrosis, and fibrosis.⁴⁾ Plasma concentrations of high-sensitivity C-reactive protein (hs-CRP), which reflect the degree of inflammation, are significantly elevated in these patients compared with those in normal sinus rhythm.^{5,6)} Combination therapy with statins and anti-arrhythmic agents has been shown to decrease the incidence of AF complicated with ischemic heart disease⁷⁾ and the recurrence of the persistent form of AF after cardioversion.⁸⁾ The pharmacological mechanism of statins in this setting is believed to involve an anti-inflammatory action.^{5,6)} It has been suggested that inflammation of atrial muscle provokes and prolongs AF. The inflammation of atrial muscle in patients with paroxysmal AF has been suggested to be lesser in degree than in those with permanent AF according to plasma concentrations of hs-CRP.^{5,6)} However, it remains unclear whether combination statin and anti-arrhythmic agent therapy elicits beneficial effects in patients with paroxysmal AF.

In the present study, we retrospectively examined the long-term effects of combination therapy with anti-arrhythmic agents and pravastatin in patients with paroxysmal AF.

Subjects and Method

Subjects

The study was performed from June 1993 to August 2004, with a mean follow-up period of 48.4 ± 31.0 months. Subjects were 318 patients with symptomatic paroxysmal AF (men: 221; women: 97; mean age: 69 ± 12 years) who visited our hospital to seek treatment for subjective symptoms such as palpitation which were interfering with their daily quality of life. All subjects were regular outpatients who visited our hospital every 2–4 weeks. All patients analyzed had undergone therapy to attempt maintenance of sinus rhythm for ≥ 12 months. Subjects were divided into 2 groups, one of which received pravastatin for hyperlipidemia (10 mg/day, pravastatin (+); N = 41) and the other not (pravastatin (-); N = 277).

Patients with the following conditions were excluded: 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, and pregnancy. Those concomitantly receiving β -blocker and/or T-type calcium antagonist or having other serious complications were also excluded.

Method

According to the American Heart Association (AHA) guidelines,⁹⁾ pharmacological or electrical cardioversion under intravenous anesthesia with thiopental was performed immediately for patients in whom the duration of AF was < 48 hrs. Before the AHA guidelines were recommended, cardioversion was performed with subsequent warfarin anti-coagulation therapy after confirmation that neither 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 anti-coagulation 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 between 1.6 and 2.6.

After sinus rhythm was restored following pharmacological or electrical cardioversion, one of the following class Ia or Ib anti-arrhythmic agents (disopyramide 300 mg/day, aprindine 60 mg/day, or cibenzoline 300 mg/day) was randomly selected by an envelope method as the first-line agent and administered orally. Individual subjects were then monitored carefully for recurrence of paroxysmal AF. When paroxysmal AF recurred during the follow-up period, cardioversion was immediately performed and one of the class Ic anti-arrhythmic agents (flecainide 150 mg/day, pilsicanide 150 mg/day), or bepridil 150 mg/day was randomly selected by an envelope method as the second-line agent. Patients in whom paroxysmal AF recurred after receiving the second agent were given either a class I anti-arrhythmic agent that had not been used before or amiodarone. The selection of the third-line agent was left to the decision of the physician. At 2–4 weeks after administration of the anti-arrhythmic agent, 12-lead electrocardiogram and ambulatory 24-h electrocardiogram were recorded in all subjects and it was confirmed that sinus rhythm was maintained at each hospital visit. Once sinus rhythm was being maintained without recurrence of paroxysmal AF after administration of the anti-arrhythmic agent, venous blood was collected from an upper extremity with the subject in a resting recumbent position to assay plasma concentrations of atrial natriuretic

Table 1 Clinical characteristics of patients.

	Pravastatin (+) group (N = 41)	Pravastatin (-) group (N = 277)	P-value
Age (yr)	69.7 ± 8.9	68.7 ± 12.0	N.S.
Male:female	18:23	203:74	P < 0.01
Smoking	9 (22.0%)	85 (30.7%)	N.S.
Hypertension	16 (34.0%)	123 (44.4%)	N.S.
Diabetes mellitus	3 (7.3%)	39 (14.1%)	N.S.
Hyperuricemia	4 (9.8%)	17 (6.1%)	N.S.
Alcohol	9 (22.0%)	139 (50.2%)	P < 0.01
Organic heart disease	12 (29.3%)	91 (32.9%)	N.S.
Organic pulmonary disease	4 (9.8%)	24 (8.7%)	N.S.
Thromboembolism	9 (22.0%)	55 (19.9%)	N.S.
ACE-inhibitor	8 (19.5%)	73 (26.4%)	N.S.
Observed period (months)	50.9 ± 37.4	48.0 ± 30.0	N.S.
Suffering period (months)	16.0 ± 22.5	17.0 ± 28.1	N.S.
LVDd (mm)	46.1 ± 5.3	45.9 ± 5.9	N.S.
LAD (mm)	34.6 ± 6.8	34.2 ± 6.3	N.S.
LVEF (%)	70.5 ± 10.0	68.3 ± 11.3	N.S.
ANP during SR (pg/ml)	36.7 ± 36.3	42.2 ± 40.7	N.S.
CRP (mg/dl)	0.17 ± 0.21	0.17 ± 0.19	N.S.
Cholesterol (mg/dl)	193.6 ± 42.7	198.3 ± 26.5	N.S.
Triglyceride (mg/dl)	163.5 ± 41.5	144.7 ± 42.9	N.S.
Onset of Paroxysmal AF; Diurnal:nocturnal:mixed	9:15:17	46:91:140	N.S.

Continuous values are mean ± SD. Values in parentheses are %.

Abbreviations: ACE, angiotensin converting enzyme; LVDd, left ventricular end-diastolic dimension; LAD, left atrial dimension; LVEF, left ventricular ejection fraction; ANP, atrial natriuretic peptide; SR, sinus rhythm; CRP, C-reactive protein.

peptide (ANP) and C-reactive protein (CRP) during sinus rhythm.

Definition and Statistical Analysis

Paroxysmal AF was defined as AF terminating spontaneously within 7 days of onset. The history of AF was the period from the initial episode of paroxysmal AF to the time of the initiation of anti-arrhythmic 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 symptoms and the development of a new low-density lesion greater than 3 mm on CT or MRI images of the head. Hypertension was defined as a casual blood pressure greater than 140 mmHg at systole or 90 mmHg at diastole.¹⁰ Hyperlipidemia was defined as a fasting cholesterol concentration greater than 220 mg/dl and a fasting plasma concentration of acylglycerol greater than 150 mg/dl.¹¹ Paroxysmal AF was divided into three groups; diurnal type (7:00AM to 5:00PM), nocturnal type (5:00PM to 7:00AM), and mixed type (symptoms

appearing at any time) based on the time of equivalent symptom onset on ECG recording.¹²

All data are shown as mean ± S.D. Clinical characteristics and the numbers of recurrences of AF in individual patients were compared between the 2 groups by unpaired t-test for continuous variables and by the chi-square test for categorical variables. The parameters determined by echocardiography were compared by paired t-test for continuous variables. In all tests, a p-values of <0.05 was considered a significant difference.

Results

Clinical Characteristics of Patients

As shown in **Table 1**, no significant differences were found in age, percentage of the patients who smoke, or those who have hypertension, diabetes mellitus, hyperuricemia, organic heart disease, organic pulmonary disease or thromboembolism. The percentage of patients treated with angiotensin converting-enzyme inhibitor or angiotensin receptor antagonist did not differ between the 2 groups. The percentage of women was greater in the pravastatin

(+) group than in the pravastatin (-) group, while the percentage of patients with an alcohol habits was significantly greater in the pravastatin (-) group than in the pravastatin (+) group (both $P < 0.01$). There were no significant differences between the 2 groups in the observation period, history of AF, left ventricular end-diastolic dimension (LVDD), left atrial dimension (LAD) or LVEF determined by echocardiography, ANP during sinus rhythm (SR), plasma concentrations of C-reactive protein (CRP), cholesterol, or triglyceride, or onset of paroxysmal AF. Plasma cholesterol concentration in the pravastatin (+) group was 243.5 ± 23.9 mg/dl at baseline with a significant ($P < 0.01$) reduction to 193.6 ± 42.7 mg/dl after therapy. As anti-thrombotic therapy, warfarin was administered in 148 patients and aspirin (81–100 mg/day) in 101 patients.

Recurrence of AF after Therapy with Anti-arrhythmic Agent

The rate of recurrence of AF in the individual patients during the follow-up period was 1.4 ± 1.8 in the pravastatin (+) group, and 1.5 ± 2.0 in the pravastatin (-) group. There was no significant difference between the 2 groups.

Rate of Sinus Rhythm Maintenance

The actuarial rates for the maintenance of sinus

rhythm in the 2 groups are shown in **Figure 1**. At 60 months, the survival rate of patients who did not have permanent AF was 93% in the pravastatin (+) group, and 79% in the pravastatin (-) group. There was a statistically significant difference between the 2 groups ($P = 0.0348$). Relative risk reduction of conversion to permanent AF was 3.43 (95% confidence limits: 3.32–3.54). in the pravastatin (+) group. Seventy patients (25.3%) (men: 50, women: 20) in the pravastatin (-) group, and only 4 patients (9.8%) (men: 3, women: 1) in the pravastatin (+) group eventually developed permanent AF during the follow-up period. There was a significant difference in the rate between the 2 groups ($P = 0.029$, **Figure 2**).

Transthoracic Echocardiographic Findings at Baseline and after Therapy

Echocardiography was performed at baseline and after therapy in 31 cases in the pravastatin (+) group. The mean follow-up period was 39.4 ± 23.2 months. There was no significant difference in LVDD, LAD, and LVEF determined by echocardiography between baseline and after therapy in the pravastatin (+) group (**Figure 3**).

Echocardiography was performed in 153 cases in the pravastatin (-) group. The mean follow-up period was 38.3 ± 23.6 months. There was no

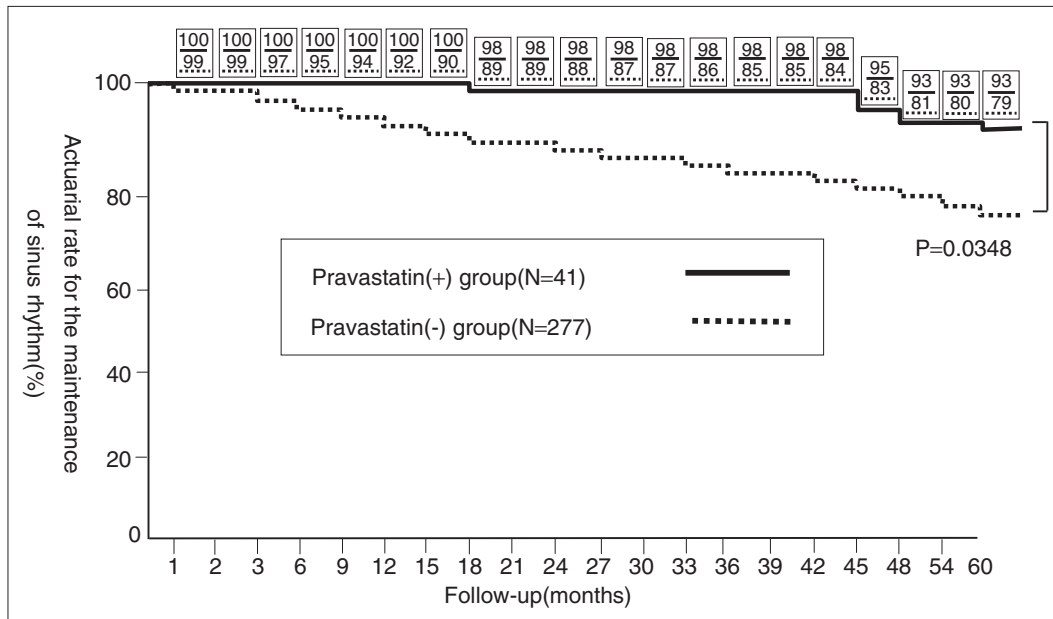


Figure 1 Event free rate for the onset of permanent AF in all patients with paroxysmal atrial fibrillation. Abscissa: follow-up period (months). Ordinate: rate of patients maintaining sinus rhythm (%). Straight line and dotted line indicate changes in the rate of patients maintaining sinus rhythm in pravastatin (+) group and pravastatin (-) group, respectively. Note that the rate of patients maintaining sinus rhythm in the pravastatin group was significantly greater than that in the pravastatin (-) group ($p < 0.05$; χ^2 -test).

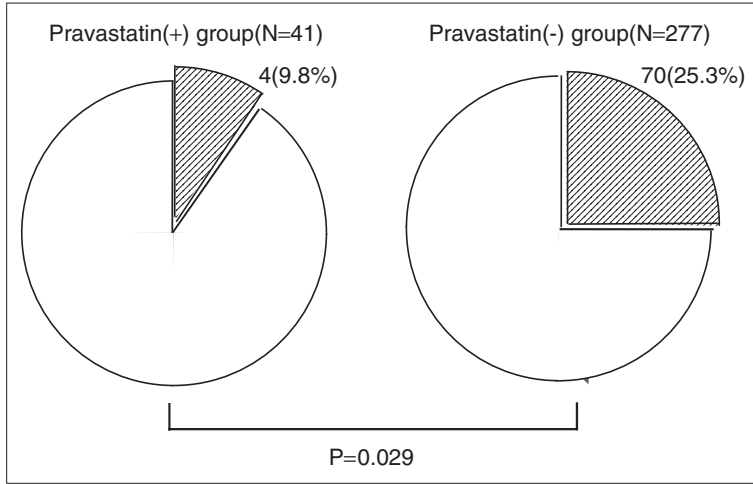


Figure 2 Comparison of patients with paroxysmal AF who developed permanent AF despite therapy at 60 weeks in the pravastatin (+) and pravastatin (-) groups. Note that the rate of patients converting to permanent AF in the pravastatin (+) group was significantly lower than in the pravastatin (-) group ($p < 0.05$; χ^2 -test).

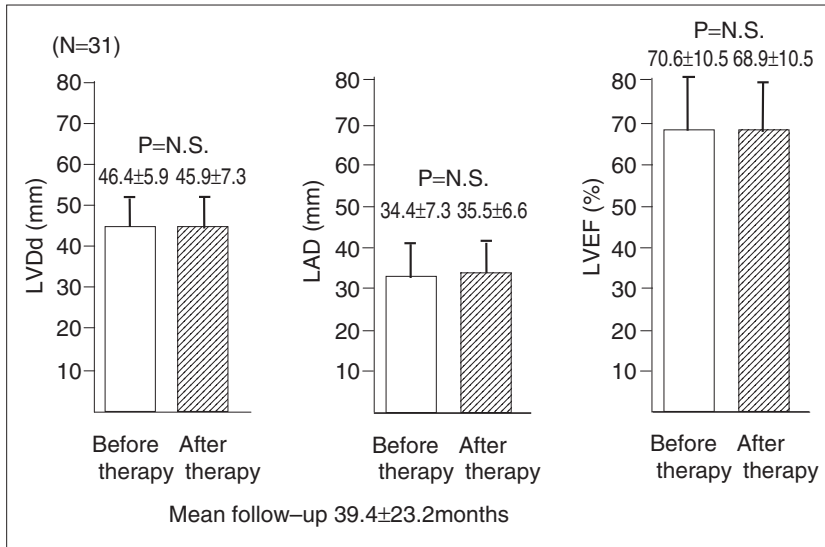


Figure 3 Changes in left ventricular end-diastolic dimension (LVDd), left atrial dimension (LAD), and left ventricular ejection fraction (LVEF) in 31 patients with paroxysmal AF determined by echocardiography at baseline and after therapy treated with pravastatin therapy. Average follow-up period: 39.4 ± 23.2 months. Note that all markers determined were unaltered in the pravastatin (+) group.

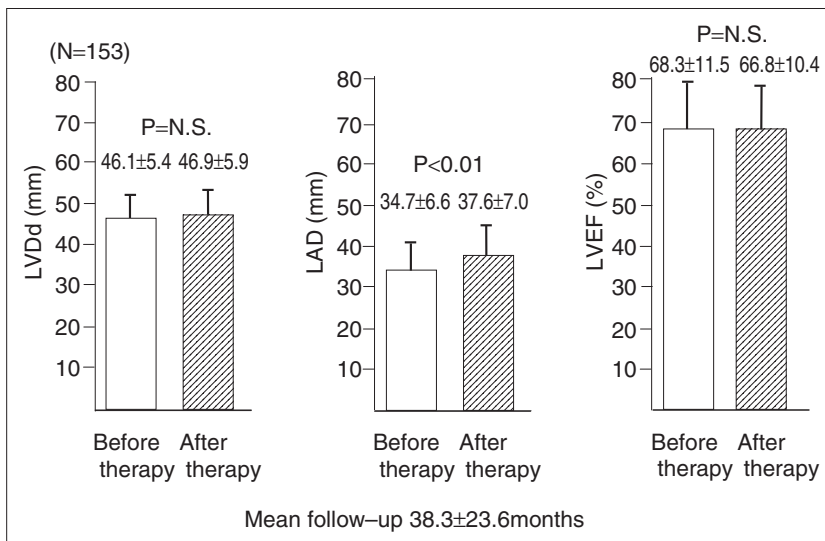


Figure 4 Changes in left ventricular end-diastolic dimension (LVDd), left atrial dimension (LAD), and left ventricular ejection fraction (LVEF) in 153 patients with paroxysmal AF determined by echocardiography at baseline and after treatment with antiarrhythmic agents alone. Average follow-up period: 38.3 ± 23.6 months. Note that LAD after therapy was significantly increased in the pravastatin (-) group compared to baseline.

significant difference in LVDD and LVEF between baseline and post-therapy in this group, whereas, LAD was significantly greater post-therapy than at baseline ($P < 0.01$, **Figure 4**).

Discussion

Atrial biopsy in patients with lone AF which is refractory to anti-arrhythmic agents for maintenance of sinus rhythm reveals pathological changes such as infiltration of inflammatory cells, necrosis, and fibrosis.^{4,13,14} Chronic inflammation of atrial myocardium is thus implicated in the pathogenesis of AF. According to studies using sterile pericarditis in experimental animal models, electrophysiological properties of AF such as a shortened refractory period and reduction of conduction velocity in which AF can easily be induced and prolonged are developed by inflammation of the atrium. Namely, inflammation contributes strongly to the formation of an arrhythmogenic substrate providing a reentry circuit in AF. Statins have been shown to prolong a shortened refractory period, to improve a delays in intra-atrial conduction, and to prevent fibrosis of atrial myocardium,¹⁵ possibly due to their anti-inflammatory effects. According to epidemiological investigations performed in Europe and the USA, the elevation of plasma concentrations of CRP, a marker of inflammatory responses, is considered a high risk factor for myocardial infarction and cerebral thromboembolism.^{16,17} CRP, which is elevated by vascular inflammation, is therefore considered to promote tissue factor expression and to lead to a thrombosis-prone state.¹⁸ Furthermore, the pharmacological action of statins act on cell membranes composed of phospholipid rather than intracellular structures believed to modulate conduction velocity in sodium channels and/or calcium channels located on membrane surfaces,¹⁹ and to exert an anti-arrhythmic action by suppression of reperfusion arrhythmias following release of coronary artery ligation.²⁰ In an epidemiological study of cardiovascular prognosis in patients with AF, thromboembolism occurred in approximately 30% of all patients at least once during their lives.²¹ If the long-term efficacy of combination therapy with anti-arrhythmic drugs and statins that have an anti-thrombotic action is superior to conservative treatment, this strategy may reduce the incidence of thromboembolism associated with AF.

According to studies attempted in Europe and the USA, high-dose pravastatin (40 mg/day) exerted an anti-inflammatory action that reduced plasma concentrations of CRP to an average of 17%.²² Furthermore, another large clinical trial has shown

that statins significantly reduced recurrence of ventricular tachycardia in patients with severe ventricular dysfunction.²³ In the present study, pravastatin at the standard dose recommended in Japan (10 mg/day), enhanced the effect of anti-arrhythmic agents preventing conversion to permanent AF, although recurrence of AF was not remarkably ameliorated remarkably. Since underlying heart diseases enhance the development of structural remodeling in atrial myocardium, we analyzed the effect of combination therapy with anti-arrhythmic agent and pravastatin in patients with lone paroxysmal AF only. Furthermore, according to the follow-up observation for approximately 3 years by echocardiography, LAD in the pravastatin (+) group did not change after combination therapy, whereas LAD after combination therapy in the pravastatin (–) group was significantly greater than that at baseline. These findings suggests that the development of structural remodeling in atrial myocardium can be prevented with combination therapy.²⁴

Plasma concentrations of high-sensitivity CRP at baseline and after combination therapy were not measured in the present study, and the standard dose of pravastatin in Japan was relatively low at approximately 1/4 of the dose administered in Europe and the USA.²³ It therefore remains unclear whether the anti-inflammatory action of pravastatin described above affected the prevention of recurrence of AF and development of structural remodeling in atrial myocardium in the present study. In addition, pravastatin is shown to have pleiotropic effects such as anti-oxidant activity, protective activity against endothelial cells, and stabilizing activity in cellular membranes.²⁵ The etiology of these pleiotropic effects of statins remains unclear in the present study.

Age, underlying heart diseases, LAD, and duration of disease, which have been reported as risk factors for recurrence of paroxysmal AF, did not differ statistically between the 2 groups in this study. However, as all patients in the pravastatin (+) group had hyperlipidemia, some bias existed in the selection of subjects. Also, the total number of patients was relatively small. This places a limitation on our evaluation of the effects of combination therapy for prevention of recurrence of AF and development of structural remodeling in atrial myocardium. Further investigation through prospective and multi-center studies will be required to assess the therapeutic efficacy of combination therapy with anti-arrhythmic agents and pravastatin in patients with paroxysmal AF.

Conclusion

The addition of pravastatin to anti-arrhythmic agents appears to enhance the effects of anti-arrhythmic agents in maintaining sinus rhythm and preventing the development of structural remodeling in atrial myocardium.

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