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Prevention of Recurrent Lone Atrial Fibrillation by the Angiotensin-II Converting Enzyme Inhibitor Ramipril in Normotensive Patients

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Objectives The aim of the present study was to verify whether angiotensin-II converting enzyme (ACE) inhibition is also effective in preventing relapses of lone atrial fibrillation (LAF), that is, in the absence of hypertension and/or heart disease.

Background Several studies have shown that ACE inhibitors are effective in preventing atrial fibrillation (AF) relapses in patients with arterial hypertension or several forms of heart disease, that is, in the presence of clinical conditions that are recognized as causing a higher risk of atrial arrhythmias.

Methods Sixty-two patients admitted to the emergency department of our institution for a first-ever episode of LAF were enrolled in the study after excluding the presence of cardiac or extracardiac conditions known to be associated with an increased risk of AF, by medical history, physical examination, complete echocardiographic study, and the evaluation of blood pressure, thyroid function, urinary catecholamines, serum electrolytes, blood glucose, red blood cell count, and arterial blood gases. After cardioversion to sinus rhythm by intravenous propafenone, patients were randomized to either ramipril 5 mg/day ($n = 31$) or placebo ($n = 31$). Holter monitoring and clinical examination were performed every 3 months.

Results After a 3-year follow-up, AF relapses were observed in 3 patients treated with ramipril and in 10 patients allocated to placebo ($p < 0.03$, Kaplan-Meier, log-rank test). During follow-up, none of the patients developed arterial hypertension or other cardiac or extracardiac condition known to be associated with increased risk of AF, that is, in all patients the diagnosis of LAF was confirmed.

Conclusions Ramipril is effective in preventing relapses of LAF. (J Am Coll Cardiol 2009;53:24–9) © 2009 by the American College of Cardiology Foundation

Although angiotensin-II converting enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARBs) are not to be considered antiarrhythmic drugs, several studies have shown that they are associated with a lower incidence of ventricular arrhythmias in patients with ischemic heart disease and left ventricular (LV) dysfunction (1–4), possibly because of the adverse effects of angiotensin II on the cardiac remodeling process. More recently, attention has been focused in the evaluation of a potential role of these drugs in the prevention of atrial fibrillation (AF) associated with cardiovascular disease (3,5), and previous data from many different investigators, including our own experience (6), have already shown that these drugs are effective in preventing AF relapses in hypertensive patients (5–9). These data have been summarized in a recent meta-analysis (10). However, it must be recognized that in the presence of a cardiac disease-causing atrial overload and/or dysfunction, the effectiveness of ACE inhibitors and/or ARBs might be attributable either to a direct antiarrhythmic effect or to an effect on atrial structure and/or function likely able to favorably modify the arrhythmic substrate, such as the increase in left atrial (LA) dimensions that is frequently observed in patients with arterial hypertension and/or LV dysfunction.

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In contrast, to the best of our knowledge there are no data related to the prevention of AF recurrences with an ACE inhibitor in the absence of a well-defined cardiac or extracardiac cause, that is, in the setting of lone atrial fibrillation

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(LAF), as defined in 1954 by Evans and Swann (11), an effect that has been shown with the ARB irbesartan associated with amiodarone after electrical cardioversion (12).

The aim of the present study was therefore to investigate whether the ACE inhibitor ramipril is able to prevent LAF relapses, that is, to have an antiarrhythmic effect in the absence of clinically identifiable atrial structural alterations and of cardiac or extracardiac conditions known to be associated with AF.

Materials and Methods

Patient selection. The study was aimed at evaluating the role of chronic ramipril administration in preventing relapses of first-detected persistent LAF. To this aim, all patients admitted to the Department of Cardiology of our institution from January 2000 to December 2002 for a first-ever episode of AF with a duration <12 h (n = 469) underwent a thorough evaluation (as detailed later) to exclude cardiac or extracardiac conditions known to be associated with AF. After obtaining informed consent and cardioversion to sinus rhythm, which was confirmed via electrocardiographic (ECG) monitoring for at least 12 h, eligible patients were discharged and allocated to either ramipril treatment at the dose of 5 mg/day (n = 31) or placebo (n = 31), following an alternated double-blinded randomization protocol (i.e., successive patients were allocated to ramipril or placebo in an alternating fashion).

On admission, after a 12-lead ECG had confirmed the diagnosis of AF, a careful history was taken that aimed at excluding any clinical evidence of cardiac disease (ischemic, valvular, or congenital heart disease; dilated, hypertrophic, or restrictive cardiomyopathy; pericardial disease; intracardiac masses; conduction system abnormalities; previous cardiac surgery) or extracardiac conditions known to be associated with AF, such as arterial hypertension (i.e., blood pressure ≥140/90 mm Hg, in agreement with both the 2007 European Society of Hypertension/European Society of Cardiology [ESH/ESC] guidelines [13] and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC-7] [14]), diabetes mellitus, recent surgery, thyroid dysfunction, pheochromocytoma, hypokalemia, toxic abuse (alcohol, caffeine, illicit drugs), acute anemia, gastroenteric conditions (gallbladder stones, hiatal hernia), cancer, fever or systemic diseases, pleural disease (effusion, neoplasia, inflammation), chronic obstructive lung disease, pneumonia, current or previous pulmonary embolism, or intravenous fluid overload.

To be included in the study, the patients should be able to time the onset of palpitations or of an arrhythmic pulse as occurring in the 12 h before hospital admission. Patients in whom the onset of AF was associated with syncope or dizziness were excluded. An arterial blood pressure <140/90 mm Hg in the absence of any antihypertensive medication and a normal standard 2-view plain chest radiograph were also required as inclusion criteria. Venous and arterial blood samples were drawn to obtain complete blood count, gas analysis, serum electrolytes, renal function, hepatic function, myocardial enzymes, and thyroid hormones. Only patients with normal findings were enrolled in the study.

Abbreviations and Acronyms

ACE = angiotensin-II converting enzyme

AF = atrial fibrillation

ARB = angiotensin-II receptor blocker

ECG = electrocardiogram/electrocardiograph

ESH/ESC = European Society of Hypertension/European Society of Cardiology

LA = left atrial/atrium

LAF = lone atrial fibrillation

LV = left ventricular

A complete echocardiographic study was performed with a 2.5- to 3.5-MHz probe, and images were obtained in parasternal (transverse long axis), apical (4- and 2-chamber), and subcostal views, excluding patients with a suboptimal echocardiographic window from further analyses. Patients with alterations in regional systolic function (on a 16-segment LV analysis), LV ejection fraction <55% (by the length-area method in the 4-chamber apical view), LV chamber dilation (end-diastolic diameter >56 mm), interventricular septum and/or free wall thickness >10 mm, valvular heart disease, or a mitral regurgitation grade higher than 0/4 (paraphysiological) were excluded from the study. The LA was evaluated in telesystole in the 4-chamber apical view. Care was taken to measure the longitudinal supero-inferior diameter (from the mitral valvular plane to the posterior wall), the mediolateral transverse diameter (from the interatrial septum to the lateral wall), as well as LA area by planimetry. Patients with atrial diameters and/or atrial area above mean reference value + 1 SD were excluded from the study. The following reference values were used (mean ± SD): superoinferior: 4.3 ± 0.6 cm, mediolateral: 3.6 ± 0.4 cm, and LA area: 14.7 ± 2.2 cm^2. An additional exclusion criteria was an abnormal early-to-late peak velocity ratio (E/A <1) by conventional pulsed Doppler transmitral flow velocimetry after conversion to sinus rhythm. Echocardiographic images were evaluated in real time and concomitantly recorded on videotape for a further off-line analysis, and for comparison with a second ultrasound evaluation at the end of the study.

Sinus rhythm cardioversion. Pharmacological cardioversion was obtained in all of the enrolled patients within 6 h with intravenous propafenone (2 mg/kg in a 10-min bolus followed by 0.007-mg/kg/min infusion). After 12-h ECG monitoring had confirmed the persistence of a stable sinus rhythm, patients were administered either ramipril 5 mg/day or placebo, following the above-described randomization procedure (alternated randomization protocol).

Follow-up. All patients were given a questionnaire investigating the presence of palpitations, symptomatic hypotension, and/or dizziness; regular assumption of the study drug; and side effects. Patients were re-evaluated every 3 months for the first year and every 6 months thereafter (clinical assessment, 12-lead ECG, 24-h Holter monitor-

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ing, and questionnaire collection). Moreover, patients were prompted to perform a 12-lead ECG should they experience palpitations. After a 3-year follow-up, an echocardiogram was performed by an operator who was blinded to the patient's allocation, and a complete blood sample was withdrawn for comparison with the baseline results.

Statistics. Data are expressed as mean values ± SD. Statistical analyses were performed using the MedCalc software package (version 9.4.2.0, MedCalc Software, Mariakerke, Belgium). Continuous variables were examined for statistical significance by paired or unpaired Student *t* tests, as appropriate. The time to first AF recurrence was analyzed using the Kaplan-Meier method and compared using the log-rank test. A p value of <0.05 was considered significant.

Results

Because of the above mentioned exclusion criteria, of 469 consecutive patients admitted for a first-ever episode of AF with a duration <12 h, LAF was diagnosed in 62 subjects who were all randomized to either ramipril or placebo after giving informed consent. As shown in Table 1, which includes the main demographic features and blood test results, no difference was observed between the 2 groups in baseline data, which according to the study protocol had to be within the normal range. The same also held true at the end of the study, with no significant difference between the 2 groups, with the exception of an increase in serum potassium levels in patients allocated to ramipril treatment (Table 1). Regarding the blood pressure values, there was a nonsignificant trend to a minor increase (from 133 ± 6/75 ± 8 mm Hg to 134 ± 7/78 ± 6 mm Hg; p = NS) in the placebo group (Fig. 1). Indeed, according to both the 2007 ESC/ESH guidelines (13) and the JNC-7 report (14), at the final follow-up visit 1 placebo-treated patient was diagnosed as grade 1 isolated systolic hypertension, his blood pressure values being 140/82 mm Hg. In contrast, ramipril treatment was associated with blood pressure reduction from 136 ± 4/78 ± 4 mm Hg to 128 ± 4/70 ± 4 mm Hg ($p < 0.05$) (Fig. 1).

Table 1 Clinical and Ematochemical Parameters at Baseline and at the Final Follow-Up Visit in Ramipril-Treated Patients and in the Control Group

	Ramipril Baseline (n = 31)	Placebo Baseline (n = 31)	Ramipril Follow-Up (n = 31)	Placebo Follow-Up (n = 31)
Age (yrs)	60 ± 4	59 ± 7	—	—
Women (n)	16	15	—	—
Men (n)	13	18	—	—
Serum potassium levels (MEq/l)	4.1 ± 0.5	4.2 ± 0.5	4.5 ± 0.4*	4.3 ± 0.5
Glucose plasma levels (mg/dl)	93 ± 18	96 ± 15	89 ± 10	90 ± 12
Thyroid-stimulating hormone (mU/ml)	2.6 ± 0.7	2.7 ± 1.1	2.8 ± 0.9	2.5 ± 1.1
Hemoglobin (g/dl)	15.1 ± 1.4	14.7 ± 1.3	15.6 ± 1.9	15.0 ± 1.6
Urinary catecholamines (μg/24 h)	67 ± 26	58 ± 36	62 ± 22	61 ± 18

*$p < 0.05$ follow-up versus respective baseline.

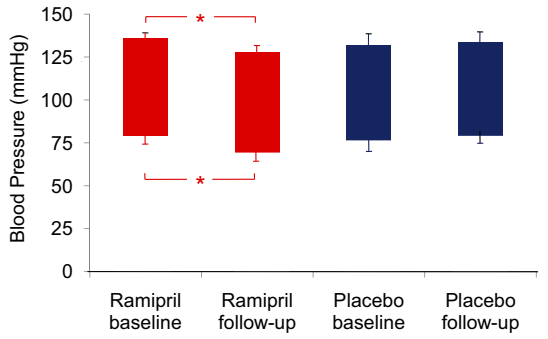

Figure 1 Blood Pressure Value at Baseline and at the Final Follow-Up Visit in Ramipril-Treated Patients and in the Control Group

*$p < 0.05$ ramipril follow-up versus baseline.

The echocardiographic data were superimposable both at baseline and at follow-up, in terms of LV wall motion, chamber dimensions, wall thicknesses, and systolic and diastolic function (Table 2). Although remaining in the normal range, placebo treatment was associated with an increase in LA diameters and areas. In contrast, no change in LA anatomy was observed in patients allocated to ramipril treatment.

According to the questionnaires, treatment was very well tolerated (no patient complained of side effects), and it was maintained by all of the enrolled patients. At the end of the study, AF relapses were observed in 3 ramipril-treated patients and in 10 control patients ($p < 0.03$) (Fig. 2). Twelve of 13 patients experiencing a relapse did come back to the emergency department, whereas 1 refused the referral to the hospital after an ECG-proven diagnosis made by her general practitioner at home. Moreover, sporadic episodes of palpitations were reported by 8 control group patients, 6 of whom had an ECG-proven AF relapse. Spontaneous cardioversion to sinus rhythm was reported in 3 patients

Table 2 Echocardiographic Data at Baseline and at the Final Follow-Up Visit in Ramipril-Treated Patients and in the Control Group

	Ramipril Baseline (n = 31)	Placebo Baseline (n = 31)	Ramipril Follow-Up (n = 31)	Placebo Follow-Up (n = 31)
Left atrium SI (cm)	4.1 ± 0.3	4.3 ± 0.4	4.0 ± 0.3	4.5 ± 0.4*
Left atrium ML (cm)	3.4 ± 0.4	3.6 ± 0.3	3.3 ± 0.3	4.2 ± 0.5*†
Left atrium area (cm^2)	14.0 ± 2.1	14.9 ± 2.1	13.2 ± 2.0	16.8 ± 1.9*†
LVEF (%)	66 ± 7	65 ± 7	67 ± 6	63 ± 7
LVEDV (ml)	44 ± 5	47 ± 5	43 ± 5	46 ± 7

*Placebo versus respective ramipril. †$p < 0.05$ follow-up versus respective baseline.
LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; ML = mediolateral atrial diameter; SI = superoinferior atrial diameter.

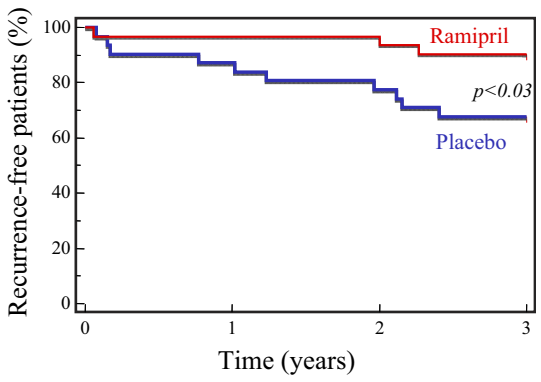

Figure 2 **Kaplan-Meier Curves Illustrating New-Onset ECG-Verified AF During the 3-Year Follow-Up in Ramipril-Treated Patients and in the Control Group**

Log-rank test, $p < 0.03$ ramipril versus placebo.
AF = atrial fibrillation; ECG = electrocardiogram.

experiencing an ECG-proven AF episode (1 ramipril-treated patient and 2 control group patients). In the ramipril-treated patient the AF episode occurred 7 days after enrollment, whereas in the other 2 control patients the AF relapse took place at least 2 years after randomization. In only 1 patient with a prolonged episode, pharmacological cardioversion was repeated with propafenone (according to the above-described protocol). All patients with an AF relapse continued on the treatment assigned at the beginning of the study.

Discussion

The results of the present study show that ramipril is effective in preventing AF relapses in LAF patients, independent of any sizeable effect on cardiac echocardiographic anatomy when compared with baseline data.

Atrial fibrillation is the most common chronic cardiac arrhythmia, being a major cause of morbidity and mortality, with increased risk for death (15,16), congestive heart failure (17), and embolic phenomena, including stroke (15,17). Normally, AF occurs in the presence of structural heart disease and/or clinical conditions such as hypertension, diabetes, hyperthyroidism, acute infections, recent cardiothoracic or abdominal surgery, and systemic inflammatory diseases. However, AF may also occur in the absence of clinical and echocardiographic evidence of cardiovascular, pulmonary, or endocrine disease, a condition that is currently defined as LAF, a term that was introduced by Evans and Swann (11) in 1953. By the current guidelines' definition, the term LAF applies to individuals younger than age 60 years without clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension (18). Although LAF is associated with a lower risk of subsequent events when compared with other forms of AF, the long-term prognosis is still debated (19–23). Indeed, any AF episode is disturbing for the patient, prompts seeking medical assistance, carries a sizeable risk of thromboembolism, and increases the possibility of further future episodes. After successful sinus rhythm restoration, any decision on prophylactic antiplatelet or anticoagulant therapy will impact not only the subsequent thromboembolic risk but also the patient's quality of life, at least in terms of possible adverse drug reactions, bleeding complications, and collateral effects. The clinical management of any patient experiencing an episode of AF should rely on these considerations, which cannot be overlooked in the setting of LAF, although this clinical condition carries an undoubtedly benign prognosis.

Although the protocol of the present study did not include a formal quality-of-life assessment, the high number of hospital readmissions caused by LAF relapses (12 of 13 patients experienced a new documented AF episode) cannot be overlooked. In this respect, it must be noted that aside from preventing new AF episodes, ramipril treatment also was associated with a marked reduction in emergency department visits (2 vs. 10; $p < 0.02$). During the 3-year follow-up, none of the patients was diagnosed as having a thromboembolic event.

Among the several other aspects that should be taken into consideration in the follow-up of patients presenting with LAF, special attention should be given to the possible development of arterial hypertension (24) and/or cardiac abnormalities, such as atrial enlargement, that should prompt a change in the diagnosis. Indeed, in these settings AF cannot be defined any longer as LAF (18). In the present study, none of the patients allocated to ramipril treatment developed arterial hypertension or LA enlargement. In contrast, blood pressure tended to increase in the placebo group, with 1 patient having at the last follow-up visit blood pressure values equal to 140/82 mm Hg, that is, developing grade 1 (13) (or stage 1 [14]) isolated systolic hypertension according to the current guidelines' definitions (13,14). Placebo treatment was also associated with an increase in LA chamber dimensions, although remaining within the normal range. Opposite trends were observed in patients treated with ramipril. In general, these data further confirm the diagnosis of LAF in our series, at least over a 3-year follow-up, with the exception of a single placebo-treated patient developing grade 1 (13) (or stage 1 [14]) isolated systolic hypertension. To put these data into perspective, it is important to consider that in the setting of LAF, Katritsis et al. (24) showed an increase in LA diameter (from 3.5 ± 0.3 cm to 3.8 ± 0.4 cm) over a 3-year follow-up in patients becoming hypertensive, whereas a 7.5% incidence of hypertension was reported by Rostagno et al. (25) during a 7-year period. Moreover, Osranek et al. (26) showed that patients with increased LA dimension either at baseline or during follow-up have a higher risk of events and of persistent AF. These data underscore the relation among AF, blood pressure values, and LA dimensions. Moreover, a collateral clinically relevant aspect that cannot be overlooked is the fundamental role of echocardiography in the early evaluation of patients presenting a first

episode of AF, aimed at clarifying the initial diagnosis and the subsequent optimization of the therapeutic strategy.

The present study shows that in patients with blood pressure in the 130 to 139 mm Hg range, that is, without a current indication to treat with an antihypertensive drug (13), ramipril and placebo had opposite effects on blood pressure and LA dimensions, the ACE inhibitor being also associated with a lower incidence of LAF relapses. This new finding could suggest the rationale of considering the occurrence of LAF as a marker of subclinical organ damage in subjects with blood pressure values in the 130 to 139 mm Hg range, that is, in the pre-hypertension classification according to the JNC-7 report (14), and of high normal blood pressure levels according to the 2007 ESC/ESH guidelines (13).

The association between ramipril treatment and a lower incidence of relapses of LAF after the first-documented episode in normotensive patients extends previous observations on the efficacy of ACE inhibition in preventing AF incidence in patients with post–acute myocardial infarction LV dysfunction (3), congestive heart failure (27), and hypertension (28,29). In considering the possible mechanism(s) of these effects, it must be recognized that several alterations in atrial histological structure have been described in LAF patients, such as myocarditis-like alterations, noninflammatory localized cardiomyopathy, and patchy fibrosis (30,31). Angiotensin II has been shown to modify the electrical properties of pulmonary vein cardiomyocytes (32), and it has been shown that ACE inhibition prevents the shortening of the atrial refractory period during rapid atrial pacing that is observed under angiotensin II exposure (33). Moreover, among the several recent studies suggesting a possible genetic background contributing to the etiology of LAF (34–36), a permissive role has been attributed to the ACE D allele (37).

Therefore, in line with the observations in other (and more common) forms of AF, the protective effect of ACE inhibition on the electrical and structural remodeling of the atria is very likely caused by the combination of their actions on atrial distension/stretch (38), sympathetic tone, local renin-angiotensin system, a stabilizing effect on electrolyte concentration, and last but not least, a minor reduction in blood pressure, and therefore in cardiac loading conditions (33,39,40). Unfortunately, one limitation of the present study is the lack of data related to the effects of ramipril and placebo on time-varying blood pressure values, which are independent predictors of new-onset AF. However, data from several studies indicate that AF prevention is also dependent on the mechanism of blood pressure reduction, inasmuch as antihypertensive drugs interfering with the renin-angiotensin system may be more effective (5–10). For example, the LIFE (Losartan Intervention For End Point Reduction in Hypertension) study (7) showed that despite superimposable blood pressure reduction the angiotensin receptor antagonist losartan was more effective than the beta-blocker atenolol in reducing new-onset AF and in maintaining sinus rhythm in hypertensive patients with ECG LV hypertrophy (7).

Conclusions

The present study shows the efficacy of the ACE inhibitor ramipril in preventing relapses of LAF in normotensive patients. When added to the several previous findings in hypertensive patients and in patients with LV hypertrophy, these data indicate that the antiarrhythmic effect of the interference with the renin-angiotensin system is also present in the setting of a normal heart in normotensive patients, that is, in LAF.

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