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Prevention of Atrial Fibrillation After Atrial Flutter Ablation With *Ramipril* (from the PREFACE Study)

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The clinical efficacy of the inhibitors of the renin-angiotensin-aldosterone system (RAAS) as an upstream therapy for atrial fibrillation (AF) prevention is controversial. No study has itemized so far the role of RAAS inhibitors in AF prevention after atrial flutter (AFL) ablation. This trial aims to investigate the effect of ramipril compared with placebo on AF occurrence in patients hospitalized for AFL ablation without structural heart disease. The Prevention of Atrial Fibrillation by Inhibition Conversion Enzyme (ICE) After Radiofrequency Ablation of Atrial Flutter (PREFACE) trial was a prospective, multicenter, randomized, double-blind, double-dummy trial depicting the AF occurrence during a 12-month follow-up as the primary end point. A total of 198 patients hospitalized for AFL ablation were enrolled in the trial and randomized to placebo or ramipril 5 mg/day. Patients were followed up during 1 year after AFL ablation using 1-week Holter electrocardiogram at 3, 6, 9, and 12 months. The intention-to-treat population encompassed 97 patients in the ramipril group and 101 patients in the placebo group. The primary end point, such as AF occurrence during the 1-year follow-up, was not different between the 2 groups ($p = 0.96$). Secondary end points, including the occurrence of supraventricular arrhythmia ($p = 0.50$), heart failure, stroke, and death, were not different between the 2 groups. Safety outcome parameters, including serious adverse events leading to treatment disruption ($p = 0.10$), hypotension, impairment of renal function, and elevated serum potassium level, also were not different between the 2 groups. In conclusion, RAAS inhibition using ramipril does not reduce AF occurrence in patients facing AFL ablation during the 1-year follow-up.

Atrial fibrillation (AF) occurrence is very common in patients with a history of atrial flutter (AFL) ablation. Over 35% of these patients experience recorded AF after a 3-year follow-up.¹ The interrelation between AF and AFL seems to be explained by a common atrial substrate.² The persistence of atrial cardiomyopathy after AFL ablation could explain the high, long-term incidence of AF.³ The inhibitors of the renin-angiotensin-aldosterone system

(RAAS), such as angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers, seem to prevent atrial remodeling, in particular, by reducing atrial fibrosis.⁴ RAAS inhibition reduces AF occurrence in patients with structural heart disease and hypertension,⁵ but randomized clinical trials failed to prove a significant role of RAAS inhibitors on AF prevention in patients without structural heart disease.⁶ Recent guidelines suggest the use of RAAS inhibitors as an upstream therapy in patients with AF, but robust data are still lacking.⁷ In addition, no study has characterized so far the role of the inhibition of RAAS on AF occurrence after AFL ablation. This study aims to evaluate the role of ramipril, an angiotensin-converting enzyme inhibitor, on AF medium-term prevention after AFL ablation based on a randomized clinical trial.

The PREFACE study was a French, multicenter, prospective, randomized, double-blind, double-dummy, parallel-group, placebo-controlled trial comparing ramipril with placebo in patients with a first episode of AFL or recurrence of AFL. The trial was sponsored by the University Hospital of Saint-Étienne and was supported by a grant from the French Ministry of Health (PHRC Programme Hospitalier de Recherche Clinique National 2006). The trial was approved by the national authorities and ethics committee and was conducted in accordance with the Declaration of Helsinki. This study is registered with [ClinicalTrials.gov](https://www.clinicaltrials.gov) (NCT00736294).

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Consecutive patients aged 18 years or older who had an ablation of a cavotricuspid-dependent AFL within the previous 3 days (based on the radiofrequency of the cavotricuspid isthmus and the bidirectional line of the block) were eligible. Patients were excluded if they had any contraindication to ramipril, a serum potassium concentration >5 mmol/L, a severe chronic kidney disease (stage 4 and 5), a history of significant AF (i.e., AF with prescription of antiarrhythmic drug and/or antithrombotic agent), an indication for therapy with a RAAS inhibitor and no possibility of medication withdrawal, heart failure with left ventricular (LV) ejection fraction <40%, and were women who were pregnant or breast-feeding. All the participants provided written informed consent.

Patients with an AF history were enrolled in the trial only in case of paroxysmal AF, with rare and brief episodes of AF without any prescription of antiarrhythmic drugs.

Patients were centrally randomized in a 1:1 ratio to receive either ramipril 5 mg/day or placebo for 12 months using a central computerized Internet-based system (Clin-Info SA Lyon, France). Using a computer algorithm, a statistician from the Clinical Investigation Center of Saint-Étienne (CIC 1408) generated the assignment list in randomly permuted blocks of 2, 3, 4, or 6. Randomization was stratified according to the center and the presence or absence of an AF history before AFL ablation. The selection of patients was made after hospitalization for AFL ablation 3 days before randomization. After written informed consent had been obtained, patients were randomly assigned to receive 1 tablet of ramipril 5 mg/day or an identical-looking placebo. All patients were followed up for 12 months. Face-to-face visits were scheduled at 3, 6, 9, and 12 months after randomization. During the follow-up visits, the adherence of patients to treatment and their tolerance were assessed. Systematic clinical, biologic, and electrophysiologic examination was managed as follows: systematic clinical examination, blood pressure measurement, assessment of a 7-day electrocardiogram (ECG) Holter recording, creatinine clearance, and potassium serum concentration. According to clinical and biologic tolerance related to the treatment administration, the dosage was appropriately adjusted, either reduced/terminated or increased to 10 mg/day. In case of severe hypotension defined by systolic blood pressure lower than 95 mm Hg, symptomatic hypotension, angioedema, serum potassium concentration more than 5 mmol/L, and a severe chronic kidney disease, study medication was stopped. All the patients were followed up as planned in the protocol, that is, until the follow-up visit at 12 months, even if the treatment was stopped before the end of the study.

The primary outcome of the trial was the diagnosis of an episode of AF of more than 1 minute assessed by either ECG or 7-day ECG Holter up to 12 months. Secondary outcomes were supraventricular tachyarrhythmia excluding AF (i.e., atrial tachycardia, atypical AFL, or recurrence of cavotricuspid isthmus-dependent AFL), major cardiovascular event (death or thromboembolic event or hospitalization for heart failure), and adverse events caused by ramipril administration and leading to discontinuation of the treatment (symptomatic or severe hypotension, worsening of renal function defined by chronic kidney disease stage 3 and 4,

elevated serum potassium more than 5 mmol/L, angioedema, and cough).

Based on previous studies,⁸⁻¹¹ we assumed with placebo a rate of 30% of AF at 1 year after AFL ablation. Assuming a reduction by 40% of AF at 1 year with ramipril administration,¹² a sample size of 195 patients per group had an 80% power to detect a difference between the groups (two-sided 5% level of significance). Because of the lack of recruitment, the study was prematurely stopped after the inclusion of 198 patients. All analyses were performed using the intention-to-treat population, that is, all randomized patients. Patients who were lost to follow-up were censored at the time of their last follow-up assessment. Time-to-event outcomes were estimated by the Kaplan-Meier method, and between-groups comparisons were performed using the log-rank test. The hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated. If any baseline characteristics was differently distributed between the 2 groups (differences being evaluated in clinical terms), the comparisons were adjusted on the variables concerned using a Cox proportional hazards regression model. Regarding the safety outcome, that is, serious or nonserious adverse event, the differences between the 2 groups of treatment were evaluated by the Fisher's exact test. The relative risks (RRs) and corresponding 95% CIs were calculated. Statistical analyses were performed using the SAS software, version 9.4 SAS Institute Inc., Cary, USA.

From July 8, 2008 to January 21, 2014, a total of 198 patients underwent randomization at 7 centers in France. A total of 97 patients were randomly assigned to receive ramipril and 101 to receive placebo (Figure 1). Of these, 75 of 97 patients (77.3%) in the ramipril group and 70 of 101 patients (69.3%) in the placebo group attended the 12-month visit. In both groups, the most common reason for dropping out was the refusal of patients to continue the follow-up process. Baseline characteristics were well balanced between the 2 groups except that more patients with a history of coronary artery disease were assigned to receive ramipril (Table 1). Briefly, randomized patients were 67 years old, mainly men (79.8%), overweight (26.7%), had a history of hypertension (45.5%) or AF (24.7%), and had a normal renal function (creatinine clearance \geq 90 mL/min, 34.0%). Regarding cardiac function, the studied population did not face LV dysfunction and had a mild left atrial dilation. Patients were included during hospitalization for a persistent (78.3%) or counterclockwise (91.4%) AFL ablation, and 8.1% of the patients were included because of a recurrent AFL.

The median (interquartile range) duration of trial-drug administration was 11.9 months (2.9 to 12.3). The trial drug was prematurely discontinued in 45 patients overall, including 25 patients in the ramipril group and 20 patients in the placebo group. The median (interquartile range) duration of trial-drug administration in patients who prematurely discontinued the study treatment was 3.1 months (1.0 to 6.7). During the study, 103 patients overall had at least 1 dose adjustment, 58 patients in the ramipril group and 45 patients in the placebo group. The median follow-up was 12 months (interquartile range, 11.6 to 12.3) in the ramipril group and 12 months (interquartile range, 8.5 to 12.2) in the placebo group.

During the 12-month treatment period, AF occurred in 22 patients (29.7%) in the ramipril group and in 20 patients

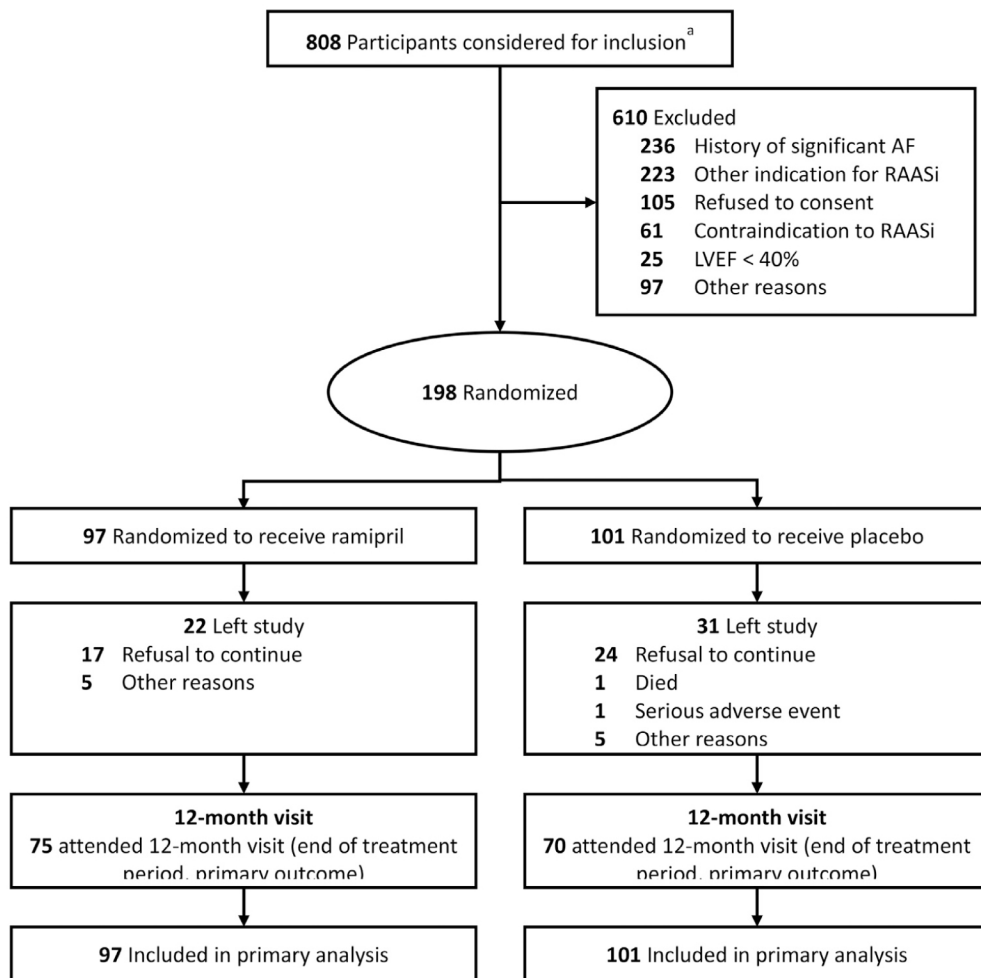


Figure 1. Flow chart of the trial. Patients were stratified by the center of inclusion and AF history before randomization. LVEF = left ventricular ejection fraction; RAASi = inhibitors of renin-angiotensin-aldosterone system.

(25.1%) in the placebo group (HR 1.04; 95% CI 0.57 to 1.90; $p=0.90$) (Figure 2, Table 2). When adjusting the results on the history of coronary artery disease, the results are the same (HR 1.02; 95% CI 0.55 to 1.88, $p=0.96$; data not shown). In a post hoc analysis, the incidence of AF was analyzed according to the status of AF history (Figure 3). Of the 149 patients without AF history, AF was diagnosed in 13 patients (23.6%) in the ramipril group versus 14 patients (22.1%) in the placebo group (HR 0.91; 95% CI 0.43 to 1.95; $p=0.81$). Of the 49 patients with AF history, AF was diagnosed in 9 patients (47.2%) in the ramipril group versus 6 patients (36.9%) in the placebo group (HR 1.12; 95% CI 0.40 to 3.15; $p=0.84$).

At 12 months, 33 patients presented a supraventricular tachyarrhythmia, 15 patients (19.2%) in the ramipril group and 18 patients (25.7%) in the placebo group (HR 0.79; 95% CI 0.40 to 1.57; $p=0.50$) (Figure 4, Table 2). Overall, 36 patients were presented with major cardiovascular events during the 12-month follow-up, 18 in each group (22.3% vs 25.7% in the ramipril and placebo group, respectively; HR 0.96, 95% CI 0.50 to 1.84) (Table 2). The incidence of stroke, hospitalization for heart failure, or death was low and did not differ between the 2 groups (Table 2).

The frequency of adverse events leading to treatment discontinuation did not differ significantly between the

ramipril and the placebo group; such events occurred in 11 of 76 patients (14.5%) in the ramipril group and in 4 of 70 patients (5.7%) in the placebo group ($p=0.10$) (Table 3). Ramipril treatment was discontinued because of severe hypotension and impairment of renal function in 2 patients and because of cough in 6 patients or other reasons in 3 patients. In the placebo group, treatment was discontinued because of cough (1 patient) or other reasons in 4 patients. No angioedema was diagnosed during the 12-month follow-up in both groups. Serious adverse events occurred in 23 of 77 patients (29.9%) in the ramipril group and in 26 of 73 patients (35.6%) in the placebo group (RR 0.84; 95% CI 0.53 to 1.33, $p=0.45$). Elevated serum potassium level more than 5 mmol/L was diagnosed in 14 of 72 patients (19.4%) in the ramipril group and in 15 of 70 patients (21.4%) in the placebo group (RR 0.91; 95% CI 0.47 to 1.74, $p=0.77$). Elevated serum potassium concentration more than 5.5 mmol/L was detected in 3 patients, 2 of 69 patients (2.9%) in the ramipril group and 1 of 68 patients (1.5%) in the placebo group (RR 1.97; 95% CI 0.18 to 21.2, $p=0.57$). During the 12-month follow-up, no variation of arterial blood pressure, renal function, and potassium serum level was observed in both ramipril and placebo groups (Figure 5).

Table 1
Demographic and baseline characteristics of the patients

Variable	Ramipril (N = 97)	Placebo (N = 101)
Median age (interquartile range)- (years)	67 (61-74)	67 (60-73)
Men	73 (75.3%)	85 (84.2%)
Median body mass index (IQR)-(kg/m ²)	27.1 (24.2-31.0)	26.4 (23.7-29.0)
≥30	30 (31.3%)	22 (22.2%)
Medical conditions		
Diabetes mellitus	13 (13.4%)	23 (22.8%)
Arterial hypertension	44 (45.4%)	46 (45.5%)
Smoker	48 (53.9%)	52 (59.1%)
Valvular heart disease	11 (11.3%)	8 (7.9%)
History of coronary artery disease	16 (16.5%)	7 (6.9%)
History of atrial fibrillation	25 (25.8%)	24 (23.8%)
History of heart failure	14 (14.4%)	13 (12.9%)
Characteristics of the AFL		
Counterclockwise	91 (93.8%)	90 (89.1%)
Persistent	71 (73.2%)	84 (83.2%)
Paroxysmal	26 (26.8%)	17 (16.8%)
Recurrent AFL	7 (7.2%)	9 (8.9%)
Laboratory tests		
Median systolic blood pressure (IQR)-(mm Hg)	127 (120-140)	130 (120-138)
Median diastolic blood pressure (IQR)-(mm Hg)	76 (67-83)	77 (70-82)
Creatinine clearance (ml/min)		
<30	1 (1.0%)	1 (1.0%)
30 to 60	18 (18.8%)	22 (22.4%)
60 to 90	46 (47.9%)	40 (40.8%)
≥90	31 (32.3%)	35 (35.7%)
Median serum potassium level (IQR)-(mmol/L)	4.2 (4.0-4.5%)	4.3 (4.0-4.5%)
Echocardiographic features		
Significant mitral regurgitation [†]	19 (44.2%)	16 (31.4%)
Median left ventricular ejection fraction (IQR)-(%)	60 (50-65)	60 (55-65)
Median left atrial diameter (IQR)-(mm)	41 (36-46)	40 (35-48)

*Cockcroft-Gault formula.

[†] Mitral regurgitation of stage II or more.

AFL = atrial flutter; IQR = interquartile range; No. (%) = number of patients (percentages).

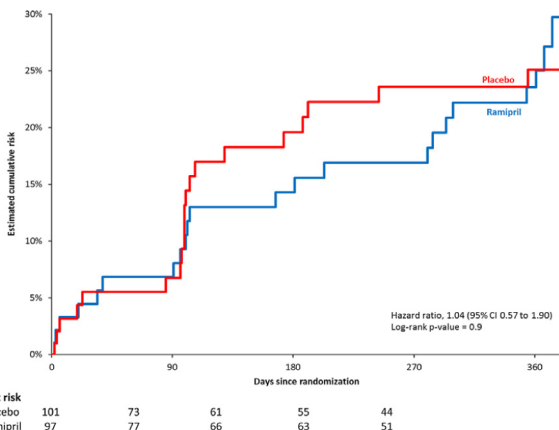


Figure 2. Kaplan-Meier analysis of atrial fibrillation within the 12-month study period. No difference between the treatment groups was observed. No. = number of patients.

Table 2
Primary and secondary outcomes within the 12-month study period

Outcomes	No. (%) of patients with events*		Hazard Ratio (95% CI)	p Value
	Ramipril (N = 97)	Placebo (N = 101)		
Primary outcome				
Atrial fibrillation	22 (29.7%)	20 (25.1%)	1.04 (0.57-1.90)	0.90
Secondary outcomes				
Supraventricular tachyarrhythmia	15 (19.2%)	18 (25.7%)	0.79 (0.40-1.57)	0.50
Heart failure	3 (5.2%)	1 (1.3%)		
Stroke	1 (1.0%)	1 (1.3%)		
Death	0 (0.0%)	1 (1.3%)		

* Percentages are Kaplan-Meier estimates.

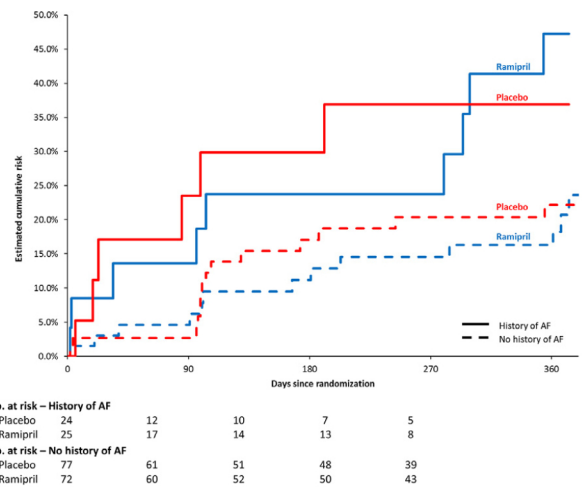


Figure 3. Kaplan-Meier analysis of atrial fibrillation within the 12-month study period according to AF history status. No difference between the treatment groups was observed, whether in patients with AF history or not. No. = number of patients.

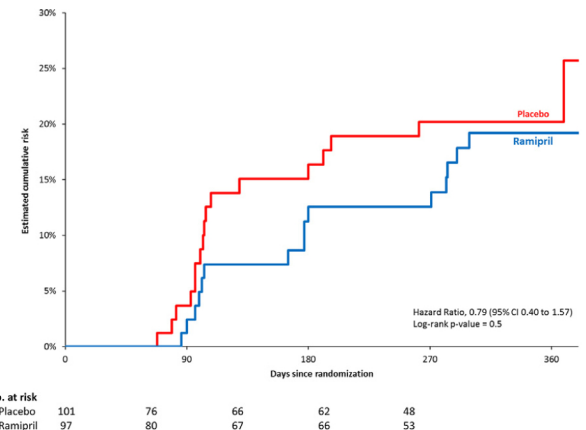


Figure 4. Kaplan-Meier analysis of supraventricular arrhythmia within the 12-month study period. No difference between the treatment groups was observed. No. = number of patients.

Table 3
Safety outcomes within the 12-month study period

Safety outcomes	<i>No. (%) of patients with events</i>		Relative Risk (95% CI)	P value
	Ramipril (n = 97)	Placebo (n = 101)		
Serious adverse events leading to treatment discontinuation	11/76 (14.5%)	4/70 (5.7%)	2.53 (0.85-7.59)	0.10
Cough	6	1		
Angioedema	0	0		
Symptomatic hypotension and/or systolic blood pressure <95 mm Hg	1	0		
Impairment of renal function	1	0		
Other*	3	4		
Serious adverse events[†]	23/77 (29.9%)	26/73 (35.6%)	0.84 (0.83-1.33)	0.45
Surgical and medical procedures	4 (5.2%)	7 (9.6%)		
Injury, poisoning, and procedural complications	2 (2.6%)	2 (2.7%)		
Cardiac disorders [‡]	13 (16.9%)	7 (9.6%)		
Vascular disorders	5 (6.5%)	4 (5.5%)		
Respiratory, thoracic, and mediastinal disorders	3 (3.9%)	2 (2.7%)		
General disorders and administration site conditions	0	4 (5.5%)		
Gastrointestinal disorders	1 (1.3%)	1 (1.4%)		
Infections and infestations	0	1 (1.4%)		
Nervous system disorders	0	1 (1.4%)		
Investigations	0	1 (1.4%)		
Neoplasms benign, malignant, and unspecified	0	1 (1.4%)		
Hepatobiliary disorders	1 (1.3%)	0		
Serum potassium (mmol/L)				
>5	14/72 (19.4%)	15/70 (21.4%)	0.91 (0.47-1.74)	0.77
>5.5	2/69 (2.9%)	1/68 (1.5%)	1.97 (0.18-21.2)	0.57

* In ramipril group: fatigue (1 patient), nausea (1 patient), and vomiting and dizziness (1 patient); in placebo group: trembling and dizziness (1 patient), nausea, dizziness, and diarrhea (1 patient), dyspnea (1 patient), and palpitation (1 patient).

[†] Serious adverse event coded in MedDRA.

[‡] Including decompensated heart failure, myocardial infarction, supraventricular and ventricular tachyarrhythmia, and bradycardia.

After the 12-month follow-up, this randomized clinical trial showed a cumulative AF incidence of 24.7% after AFL ablation and a cumulative incidence of overall supraventricular tachyarrhythmia of 22.3%. No effect of ramipril was found in the prevention of

medium-term AF incidence after typical AFL ablation, regardless of the status of AF history. Lastly, this study confirmed an appropriate safety profile of RAAS inhibitors in a general population facing supraventricular tachyarrhythmia.

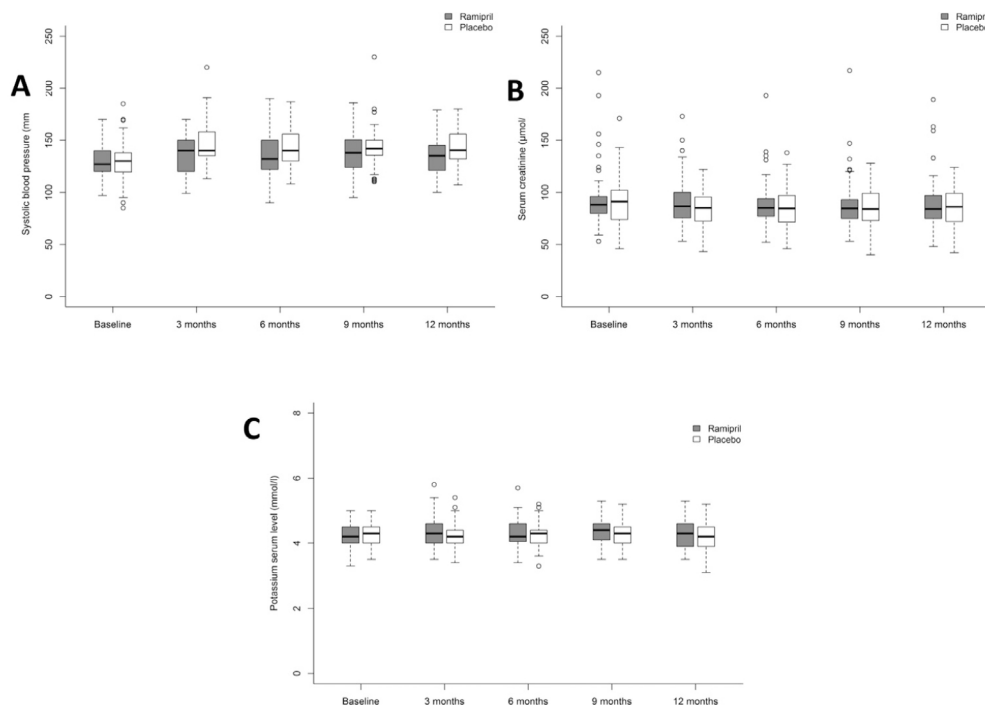


Figure 5. Evolution of (A) systolic blood pressure, (B) serum creatinine, and (C) potassium serum level during the 12-month study period.

An upregulation of RAAS occurs in patients with AF, leading to an increase in angiotensin II serum concentration.¹³ Although angiotensin II induces atrial fibrosis and atrial remodeling, the role of RAAS inhibitors as antiremodeling agents in AF is still unclear. Preclinical studies highlighted the potential action of RAAS inhibitors on the development of atrial structural remodeling, but clinical data are inconsistent. RAAS inhibitors seem to prevent AF in patients with hypertension, heart failure, and LV hypertrophy, but data regarding the effect of RAAS blockage in the general AF population are controversial. The use of olmesartan, an angiotensin-II receptor blocker, in patients facing paroxysmal AF does not reduce the AF burden.¹⁴ After electrical cardioversion for persistent AF, prospective trials show the lack of efficiency of RAAS inhibitors regarding AF recurrence,⁶ and a prospective study confirms the futility of RAAS inhibition after pulmonary vein isolation to prevent AF recurrence.¹⁵ Our study corroborates the previous data, suggesting the lack of ramipril efficacy in AF prevention after AFL ablation.

The emerging concept of atrial cardiomyopathy grows in importance concerning AF management this last decade.¹⁶ The current strategy regarding AF management is to focus on AF itself and atrial remodeling as well.⁷ Therefore, the first research axis focuses on the evaluation of antiremodeling pharmacologic agents as an upstream therapy, such as statins and omega-3 fatty acids, β blockers, and RAAS inhibitors.⁶ There is a lack of proof based on randomized clinical trials concerning the benefit of these drugs as antiremodeling agents. The second axis itemizes the role of the management of AF risk factors on atrial remodeling. Pathak et al^{17,18} attest to the role of the integrated management of AF risk factors in patients with paroxysmal AF to decrease the AF burden before¹⁷ and after AF ablation.¹⁸ These data highlight 2 potential clinical features explaining the lack of efficacy of ramipril. First, the prevention of atrial remodeling seems to be effective if managed early in supraventricular arrhythmia natural history. Second, a set of arguments suggests the role of the integrated management of AF risk factors. Hence, the global management of atrial remodeling risk factors seems to be essential considering AF prevention.

The evidence for an epidemiologic interrelation between AF and AFL is robust. In a meta-analysis collecting observational studies, Maskoun et al¹ highlight an AF incidence of 19% during a 2-year follow-up after AFL ablation using 7-day ECG Holter recordings. These data are consistent with the data in our study showing a cumulative incidence of 24.7%. These results support the need for an intensive AF screening after AFL ablation. Pathophysiologic characteristics of AFL could explain the lack of effect of ramipril regarding AF occurrence after AFL ablation. Different works managed by Waldo et al³ highlight the crucial role of AF in the genesis of AFL. Therefore, the atrial remodeling leading to AF onset and perpetuation is likely already fixed when AFL is diagnosed and ablated. The possibility of atrial reverse remodeling is a matter of some debate.¹⁹ Recent data confirm that AFL itself does not lead to structural atrial remodeling through an inflammatory and fibrotic process, unlike AF.² So, prevention of the onset of the atrial remodeling preceding AFL diagnosis seems to be crucial.

Despite the multicenter, randomized, controlled, double-blind, and double-dummy design, this trial faces several limitations. First, the number of patients included in this trial does not reach the target threshold of 390 patients. The rate of recruitment in the 7 centers was lower than expected, potentially inducing a lack of statistical power regarding the analysis of the primary outcome. However, no trends toward the superiority of ramipril versus placebo were observed regarding primary and secondary end points. Second, a significant number of patients discontinued the follow-up. This is because of the recurrent AF screening, including the 1-week Holter ECG every 3 months during 1 year. This kind of screening was crucial to avoid undersensing of AF occurrence but led to an increased rate of follow-up disruption. Therefore, an intention-to-treat analysis was managed regarding the primary and secondary end points to take into account the patients lost to follow-up. Third, a long-term effect of ramipril cannot be excluded as a result of the relatively short-term (1 year) follow-up managed in the trial.

In conclusion, RAAS inhibition using ramipril does not reduce AF occurrence in patients facing AFL ablation during the 1-year follow-up.

Disclosures

The authors have no conflicts of interest to disclose.

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