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Effect of Valsartan and Ramipril on Atrial Fibrillation Recurrence and P-wave dispersion in Hypertensive Patients With Recurrent Symptomatic Lone Atrial Fibrillation

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BACKGROUND

This study compared the effect of antihypertensive treatment with valsartan or ramipril on atrial fibrillation (AF) recurrence, on P-wave dispersion, (PWD) and on serum procollagen type I carboxy terminal peptide (PIP).

METHODS

A total of 369 mild hypertensive (systolic blood pressure (SBP) >140 and/or 90 < diastolic blood pressure (DBP) < 110 mm Hg) outpatients in sinus rhythm but with at least two episodes of AF in the previous 6 months were randomized to valsartan ($n = 122$), ramipril ($n = 124$), or amlodipine ($n = 123$) for 1 year. Clinic blood pressure (BP) and a 24-h electrocardiogram (ECG) were evaluated monthly. Patients were asked to report any episode of symptomatic AF and to perform an ECG as early as possible. PWD and serum PIP levels were evaluated before and after each treatment period.

RESULTS

SBP and DBP were significantly reduced by the three treatments ($P < 0.001$). A total of 46 (47.4%) patients treated with amlodipine had a recurrence of AF as did 26 (27.9%) patients treated with ramipril ($P < 0.01$ vs. amlodipine) and 16 (16.1%) patients treated with valsartan ($P < 0.01$ vs. amlodipine and $P < 0.05$ vs. ramipril). The Kaplan–Meyer analysis showed a significant reduction of AF episodes in the valsartan group ($P = 0.005$ log-rank test) as well as in the ramipril group ($P = 0.021$), even if at a lesser degree. PWD values were significantly reduced by ramipril (–4.2 ms, $P < 0.05$) and even more by valsartan (–11.2 ms, $P < 0.01$), the difference being significant ($P < 0.01$). Serum PIP levels were reduced by ramipril (–49.7 µg, $P < 0.001$) and valsartan (–49.3 µg, $P < 0.001$).

CONCLUSIONS

Despite similar BP lowering, valsartan and ramipril were more effective than amlodipine in preventing new episodes of AF, but the effect of valsartan was greater than that of ramipril. This could be related to the greater PWD reduction observed with valsartan.

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Atrial fibrillation (AF) is the most common arrhythmia affecting the general population[1] and is associated with a three- to fivefold risk for stroke and a 1.5- to 1.9-fold risk of total mortality.[2,3] In patients with arterial hypertension, the risk of developing AF is increased as much as 42%, and the addition of AF to hypertension contributes to increased rates of cardiovascular morbidity and mortality in these patients.[4] Hence the clinical and prognostic importance of restoring and remaining in sinus rhythm. Unfortunately, restoring sinus rhythm by direct current conversion and/or antiarrhythmic drugs is hampered by a high percentage of recurrence, which has roused an interest in developing novel approaches to AF therapy.

AF is known to produce atrial electrical and structural remodeling, characterized by shortening, maladaptation, and increased dispersion of atrial effective refractory period, depression of atrial conduction and atrial fibrosis.[5,6] Atrial remodeling might be one important mechanism contributing to the recurrence and the maintenance of AF.[7,8]

In various animal models, angiotensin II (Ang II) has been suggested to play a pivotal role in atrial remodeling through its effects on ionic currents, fibroblast activity, and modulation of sympathetic tone.[9–12] There is evidence that the expression of angiotensin-converting enzyme (ACE) is increased threefold in patients with chronic AF,[13] and an upregulation of AT1 receptors, which occurs in the left atrium of patients with AF, has been related to the remodeling process and stabilization of AF.[14] Inhibition of Ang II has been demonstrated to produce beneficial effects on AF development in animal models.[15,16]

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Also clinical trials in human subjects have shown that inhibition of the renin–angiotensin system with both ACE inhibitors (ACE-Is)[17–19] and angiotensin receptor blockers (ARBs)[20–23] may decrease the incidence of AF. Besides, adding an ARB to amiodarone has been shown to be more effective in maintaining sinus rhythm compared with treatment with amiodarone alone.[23,24] Most of these studies, however, were conducted in patients with heart failure and/or left ventricular dysfunction, and it remains unclear whether the beneficial effects observed with ACE-I and ARB are due to actual antiarrhythmic properties on atrial remodeling of these drugs or to their positive effects on hemodynamics and left ventricular function. Furthermore, there are no data about the comparative effects of ACE-I and ARB on AF recurrence.

With this background, the present study was undertaken to evaluate the effect of antihypertensive treatment with the ARB valsartan as compared to the ACE-I ramipril and the calcium-channel blocker amlodipine in preventing the recurrence of AF in hypertensive patients with a history of recent AF episode. The effects on P-wave dispersion (PWD), used as a marker of inhomogeneous atrial propagation of sinus impulses,[25,26] and on serum procollagen type I carboxy terminal peptide (PIP) levels, used as a marker of increased collagen type I synthesis and myocardial fibrosis,[27,28] were also evaluated.

METHODS

This was a double-blind, randomized, parallel-group, study. Between September 01, 2004 and August 30, 2007 the study population was selected according to the following inclusion criteria: outpatients of either sex, with mild essential hypertension (140 systolic blood pressure (SBP) < 160 mm Hg and/or 90 < diastolic blood pressure (DBP) < 100 mm Hg), in sinus rhythm but with at least two electrocardiogram (ECG)-documented episodes of symptomatic AF in the previous 6 months, and without any antiarrythmic treatment. Previous AF episodes could be self-terminating or terminated after pharmacological and/or electrical cardioversion; cardioversion, however, had to be performed between a maximum of 6 months and a minimum of 8 weeks before enrollment and no patient underwent cardioversion in the last 8 weeks. Exclusion criteria were the following: in treatment with AT1R blockers, ACE-Is, or antiarrythmic agents, cardioversion within the last 8 weeks, secondary hypertension, myocardial infarction or stroke in the preceding 6 months, congestive heart failure, coronary heart disease, valvular disease, diabetes mellitus, a left atrium size >45 mm, need to continue the use of digitalis, cardiac surgery during the pervious 6 months, significant thyroid, pulmonary, renal, or hepatic disease, pregnancy or fertile female, known hypersensitivity or contraindications to the study medications. The study protocol was approved by the local Ethical Committees and informed consent was obtained from each participant at the time of enrolment. After an initial 2-week antihypertensive placebo period, patients fulfilling the inclusion criteria were randomly assigned to receive amlodipine 5 mg once daily (o.d.) or ramipril 5 mg o.d. or valsartan 160 mg o.d. To maintain blindness, the study medications were provided in capsules of identical appearance (same size, taste, and color) stored in coded bottles. Patients were required to take trial medications in the morning between 8:00 and 10:00 AM. In nonresponder patients (blood pressure (BP) >140/90 mm Hg), the study drugs were titrated after 4 weeks (amlodipine 7.5 mg, ramipril 7.5 mg, and valsartan 240 mg) and 8 weeks (amlodipine 10 mg, ramipril 10 mg, and valsartan 320 mg) of treatment to achieve a target BP of <140/90 mm Hg. Those patients who did not achieve the target BP after 12 weeks were considered to have finished the follow-up. Patients were checked every 4 weeks for 1 year. Clinical examination included clinic BP evaluation, a resting 12-lead surface ECG, and a 24-h ECG registration. BP measurements were obtained from each patient in the seated position using a standard mercury sphygmomanometer (Korotkoff I and V). Measurements were taken in the morning before daily drug intake (i.e., 24 h after dosing) and after the subject had rested 10 min in a quiet room. Three successive BP readings were taken at 1-min intervals and averaged. To identify asymptomatic AF episodes, 24-h ambulatory ECG monitoring was performed every 4 weeks using a Syneflash Holter recorder (Ela Medical, Paris, France). Recordings were always started after drug intake and were performed throughout a full 24-h period, during which subjects were allowed to follow their normal daily routine, after they left the laboratory. Patients were also asked to report any episode of palpitations, to take their pulse and, in presence of arrhythmia, to perform an ECG as early as possible. Only AF episodes confirmed with an ECG were considered as recurrences. Palpitations alone were not taken into consideration nor were patients' subjective appraisals.

At the end of the placebo period and of each treatment period, PWD was evaluated and serum PIP level was determined.

P-wave analyses. P-wave analyses measurements were calculated in 12-lead surface ECG recordings obtained at a paper speed of 50 mm/s and a signal size of 10 mm/mV. ECG recordings were transferred into a computer and opened with a high-performance graphic program. Manual measurements of P duration were performed with digital calipers on a high-resolution computer screen by two cardiologists blinded to the patients' clinical data. Four cycles were measured for each lead. The P-wave onset was defined as the first atrial deflection from the isoelectric line and the offset was the return of the atrial signal to baseline. Mean P duration was calculated as the mean value in each lead. The difference between maximum and minimum P duration was defined as PWD. Intra- and inter-observer variability were 3.3 and 3.8%, respectively, for P-wave duration and 2.9 and 3.6%, respectively, for PWD.

PIP determination. Serum PIP was determined by a rapid equilibrium radioimmunoassay according to the method of Meikko *et al.*[29] using commercial antisera specifically directed against the terminal carboxy terminal peptide. The sensitivity (lower detection limit) was 1.1 μg of PIP/l. The intra- and interassay coefficients of variation were 4 and 7%, respectively.

End points of study. The present study compared valsartan to ramipril and amlodipine to assess the efficacy of valsartan with regard to the cumulative number of patients relapsing into documented atrial fibrillation. Secondary end points were the time to a first electrocardiographically confirmed recurrence of atrial fibrillation, the changes in PWD, and the changes in PIP serum levels.

Statistical analysis. The sample size calculations are based on an estimated efficacy at 1 year of 50% for amlodipine, 65% for ramipril, and 80% for valsartan. With an α level of 0.05 and a test power of 0.80, the resulting sample size was 91 patients for each treatment group. A risk of loss of patients to follow-up of 10–15% was assumed. Data are expressed as means ± s.d. for continuous variables, and frequencies were measured for categorical variables. Baseline characteristics were examined for statistical significance for continuous variables using a Student's *t*-test. The Fisher exact test was used for categorical variables. The end points were analyzed on an intention-to-treat basis. The time to first atrial fibrillation recurrence was analyzed using the Kaplan–Meier method and compared with the log-rank test. The number of days to AF recurrence (median and range) was compared among the treatment groups by the non-parametric Wilcoxon test.

RESULTS

Baseline characteristics

A total of 450 consecutive hypertensive patients, 201 untreated and 149 previously treated for hypertension, were referred to our hypertension center with a history of paroxysmal atrial fibrillation. Of them, 369 were finally randomized to participate in this study (**Figure 1**). Fifty-nine patients were excluded from this protocol because they did not meet the inclusion/exclusion criteria. Twenty-two patients refused to participate. The baseline demographic and clinical characteristics of each group are shown in **Table 1**. The three treatment groups were well matched and similar with regard to all pretreatment characteristics. Twenty-four patients in the amlodipine group, 31 patients in the ramipril group, and 27 patients in the valsartan group underwent electrical cardioversion before entering the study whereas pharmacological cardioversion was performed in 64 patients in the amlodipine group, 59 patients in the ramipril group, and 61 patients in the valsartan group.

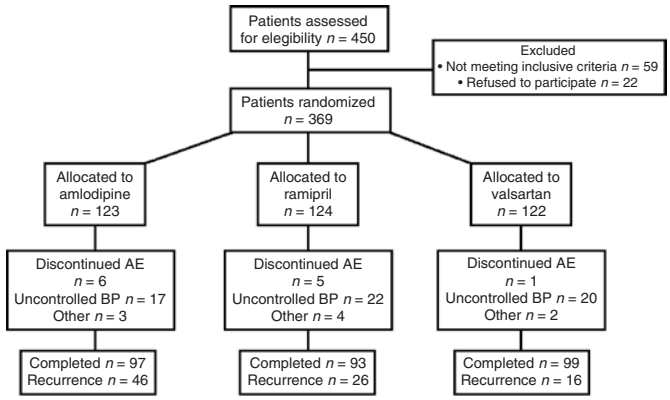

Figure 1 | Flow diagram of the study.

Table 1 | Main demographic and clinical characteristics of patients in the three treatment groups

	Amlodipine (*n* = 123)	Ramipril (*n* = 124)	Valsartan (*n* = 122)	*P*
Age (years)	65 ± 7	64 ± 7	66 ± 8	0.64
Sex (male/female)	55/68	57/67	57/65	0.34/0.38
Weight (kg)	73 ± 9	74 ± 10	73 ± 10	0.49
Smoking (%)	14	15	16	0.31
SBP (mm Hg)	154 ± 8	152 ± 7	153 ± 7	0.55
DBP (mm Hg)	95 ± 3	95 ± 2	95 ± 3	0.76
HR (beats/min)	74 ± 11	75 ± 10	76 ± 11	0.38
Echocardiogram				
EDLV dimension (mm)	51.1 ± 0.8	50.6 ± 0.6	49.9 ± 0.7	0.28
Ejection fraction (%)	60.4 ± 8.2	62.1 ± 8.4	61.2 ± 9.1	0.26
LA inferosuperior dimension (mm)	40.4 ± 2.2	40.1 ± 1.9	40.6 ± 2.4	0.22
Septal thickness (mm)	10.8 ± 0.26	10.9 ± 0.31	10.7 ± 0.27	0.28
Patients with LVH (%)	17 (13.8)	14 (11.3)	16 (13.1)	0.19
Previous AF episodes (*N*)	2.2 ± 0.9	2.4 ± 1.1	2.3 ± 1.0	0.22

AF, atrial fibrillation; DBP, diastolic blood pressure; EDLV, end-diastolic left ventricular; HR, heart rate; LA, left atrial; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.

Therapy

A total of 123 patients were allocated for treatment with amlodipine, 124 for treatment with ramipril, and 122 for treatment with valsartan.

There were substantial reductions in SBP and DBP values in the three treatment groups. At the end of follow-up, SBP was reduced by 15.7 mm Hg ($P < 0.001$ vs. baseline) in the valsartan group, by 15.8 mm Hg in the ramipril group ($P < 0.001$ vs. baseline), and by 16.9 mm Hg in the amlodipine group ($P < 0.001$ vs. baseline), with no significant difference among treatments. Corresponding changes for DBP were 12.1, 12.2, and 12.9 mm Hg ($P < 0.001$ vs. baseline), respectively, again without any significant difference among treatments. Heart rate did not show any significant change from baseline in any treatment group.

Recurrence of AF

The main results of the study are shown in **Table 2**. At the 12-week follow-up visit (end of titration period), 33 patients had a recurrence of atrial fibrillation: by intention-to-treat analysis, the occurrence rate was significantly lower in the valsartan group (five patients) than in the amlodipine group (17 patients). Kaplan–Meier analysis demonstrated a 12-week probability of 95% for maintaining sinus rhythm in patients who received valsartan compared with a 91% in patients who received ramipril and a 85% in patients who received amlodipine ($P = 0.02$).

At the end of the follow-up (median 258 days (range 29–360)), 46 (47.4%) patients undergoing treatment with

amlodipine had a recurrence of atrial fibrillation, as did 26 (27.9%) patients undergoing treatment with ramipril ($P < 0.01$ vs. amlodipine) and 16 (16.1%) patients undergoing treatment with valsartan ($P < 0.01$ vs. amlodipine and $P < 0.05$ vs. ramipril). Figure 2 shows the Kaplan–Meyer AF recurrence-free survival analysis which demonstrated a significant reduction in AF recurrence in the valsartan group ($P = 0.005$ log-rank test) as well as in the ramipril group ($P = 0.021$ log-rank test) when compared to the amlopidine group, but also in the valsartan group ($P = 0.045$ log-rank test) when compared to the ramipril group.

P-wave duration and dispersion

No significant change in P-minimum values was observed with any treatment. P-maximum values were not significantly modified by amlodipine, whereas they were significantly reduced by ramipril (−3.2 ms, $P < 0.05$) and even more by valsartan (−10.7 ms, $P < 0.01$), the difference between the ACE-I and the ARB being statistically significant ($P = 0.009$) (Table 3).

The PWD values did not show any significant change in the amlodipine group and a significant reduction in the ramipril ($P < 0.05$) as well as in the valsartan group ($P < 0.01$). Again the reduction was significantly greater in the valsartan group when compared with the ramipril group ($P < 0.01$) (Figure 3).

Table 2 | Results: Intention-to-treat analysis

	Amlodipine	Ramipril	Valsartan
Recurrence of atrial fibrillation at 12 weeks after randomization	17	11	5*
Recurrences of atrial fibrillation at 1 year after randomization	46	26*	16**,***
Days to recurrence, median ± s.d. (range)	61 ± 55 (36–340)	126 ± 79* (44–344)	160 ± 94* (69–350)

*$P < 0.05$ vs. amlodipine; **$P < 0.01$ vs. amlodipine; ***$P < 0.05$ vs. ramipril.

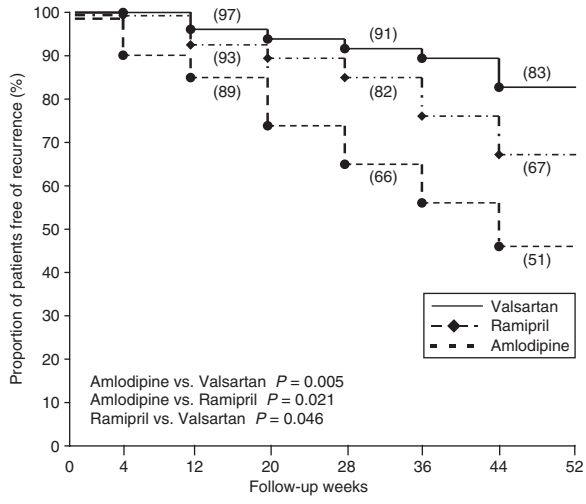

Figure 2 | Recurrence of atrial fibrillation in the three study groups.

Serum PIP concentration

Serum PIP concentration was significantly reduced ($P < 0.001$) after 12 months of treatment both in the ramipril and the valsartan group without any difference between the two groups. No change has been observed in the amlodipine group (Table 3).

Adverse events

Total adverse events requiring the discontinuation of treatment occurred in six patients in the amlodipine group, five patients in the ramipril group, and one patient in the valsartan group. In the amlodipine group, one patient had an atrial flutter and underwent radiofrequency ablation, one complained of rash and skin eruptions that disappeared after treatment cessation, and four did not tolerate ankle edema. In the ramipril group, one patient had an atrial flutter and underwent radiofrequency ablation and four patients discontinued because of an intolerable and unproductive cough. In the valsartan group, one patient discontinued because of hypotension.

Table 3 | Comparison of P-wave duration and serum PIP values among groups before and after treatment

	Amlodipine	Ramipril	Valsartan
P maximum (ms)			
Placebo	107.4 ± 10.6	105.8 ± 9.7	106.6 ± 10.1
Treatment	105.9 ± 8.1	102.6 ± 7.8*,***	95.0 ± 7.2*,**,***
P minimum (ms)			
Placebo	65.9 ± 12.8	64.6 ± 11.8	65.1 ± 12.3
Treatment	65.8 ± 12.5	64.9 ± 12.9	65.3 ± 12.2
PWD (ms)			
Placebo	41.3 ± 8.9	41.5 ± 9.1	41.6 ± 9.2
Treatment	39.9 ± 9.3	37.3 ± 9.5*,***	30.4 ± 9.3*,**,***
Serum PIP (μg/l)			
Placebo	142.4 ± 33.1	144.1 ± 34.2	139.5 ± 32.3
Treatment	138.9 ± 32.5	94.4 ± 22.5*,***	90.2 ± 20.1*,***

*$P < 0.001$ vs. placebo; **$P < 0.01$ vs. ramipril; ***$P < 0.01$ vs. amlodipine.

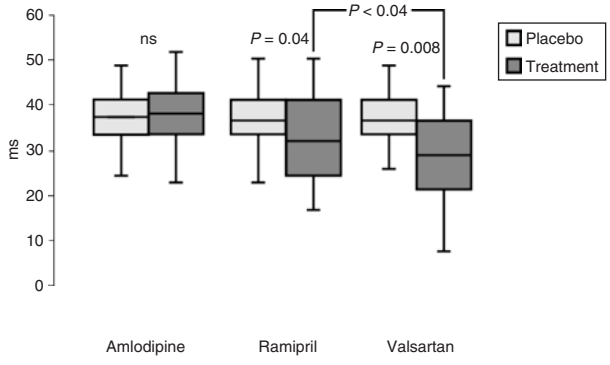

Figure 3 | P-wave dispersion values in the three study groups before and after treatment.

DISCUSSION

The results of this study showed that in hypertensive patients with a history of recent recurrent lone AF antihypertensive treatment with both the ARB valsartan and the ACE-I ramipril was more effective than amlodipine treatment in reducing new episodes of AF, but the preventive effect of valsartan on AF relapse was greater than that of ramipril. Unlike previous studies[17,23–24] that suggested an additive effect of ARB or ACE-I over that obtained from standard antiarrhythmic therapy in the prevention of AF recurrence in hypertensive patients, in the present study the choice to exclude patients on antiarrhythmic drug therapy allowed us to assess the AF-preventing effect of these drugs *per se*.

Although the lowering of BP could be an important part of the mechanism of benefit observed with both inhibitors of the renin–angiotensin system, there was no statistically significant difference in our study in BP among the three treatment groups. This suggests that both ARB and ACE-I may exert an antiarrhythmic action beyond their BP lowering effect. Multiple mechanisms other than BP reduction have been proposed to explain antiarrhythmic actions of ACE-I and ARB in AF including interference with ion-channel function and modulation of refractoriness, inhibition of Ang II–induced fibrosis, reduced atrial stretch, improved left ventricular hemodynamics, and modulation of sympathetic nerve activity.[15,30–34]

In this study valsartan and ramipril, but not amlodipine, significantly lowered PWD and P_{max}. This finding, which is in agreement with some previous observations,[35] can be important in the prevention of AF recurrence by these drugs. Prolongation of intraatrial and interatrial conduction times and the inhomogeneous propagation of sinus impulses are well-known electrophysiological characteristics of the atrium prone to fibrillate.[25,26] Patients with more prolonged atrial conduction time (marked by P_{max}) and more nonuniform inhomogeneous atrial conduction (marked by PWD) have been demonstrated to carry a higher risk for recurrence of AF attacks and to have a higher incidence of AF episodes after cardioversion.[36] Therefore, drugs that reduce PWD are expected to decrease the incidence of AF. We found that PWD and P_{max} values in the valsartan-treated patients were significantly lower than those in the ramipril-treated ones. Reasons for such a difference are unclear. One possible explanation might be related to the different effect on the non-ACE-dependent Ang II–forming activity caused by chimase, which seems to be higher in the left atrium than in other chambers.[15,35] Although ARB is effective on both non-ACE and ACE-dependent Ang II pathways, ACE-I is not able to inhibit Ang II activity caused by chimase in the left atrium. Because increased chimase activity may play an important role in nonhomogeneous atrial conduction, ARBs may have a greater effect on atrial electrophysiological properties than ACE-I and result in lower PWD values. Because in this study the chimase pathway has not been measured, we can only hypothesize such a mechanism. Another factor that might explain the greater response to valsartan as compared with ramipril is that the latter is a competitor inhibitor of ACE that can be overcome by the reactive rise in renin that occurs during treatment. Unfortunately, we did not measure renin activity and, due to this study limitation, renin response could not be evaluated.

It is of interest that the greatest difference in AF recurrence between valsartan and ramipril was observed in the first 12 weeks of treatment (5 vs. 11 cases, respectively), whereas the difference was less marked on the rest of the 1-year period (11 vs. 15 cases). Reasons for this earlier beneficial effect of valsartan on AF recurrence rate in comparison to ramipril remain unclear. A more precocious effect of valsartan on PWD can be hypothesized, but we have no specific data in this regard.

Fibrosis in atrial muscles is a critical factor responsible for AF mainly through decrease in the atrial conduction velocity.[8,14] Blockade of Ang II type 1 receptors has been shown to reduce the synthesis of collagen type I fibers and to stimulate the degradation of collagen type I fibers.[37,38] Thus losartan was able to decrease myocardial collagen content, assessed using echoreflectivity and serum collagen markers, in patients with left ventricular hypertrophy[33] as well in patients with AF[38] and reduced fibrosis in hypertensive patients with biopsy-proven myocardial fibrosis, independently of its antihypertensive effect.[37] Positive effects on myocardial fibrosis have been described also with ACE-I.[16,39] In this study both valsartan and ramipril significantly decreased the serum concentrations of PIP, which have been proposed as a marker of the tissue synthesis of collagen type I.[27,28] Although this parameter provides only indirect information on myocardial fibrosis and no cardiac biopsies were performed in this study, the significant decrease in PIP levels allows us to hypothesize that the positive effect of both valsartan and ramipril on AF recurrence might be at least partly related to reduction in atrial fibrosis.

In the recently published ONTARGET study,[40] the incidence of new onset AF did not significantly differ between the ACE-I ramipril (6.9%) and the ARB telmisartan (6.7%). Possible reasons for this difference between our results and those of ONTARGET may be that: (i) regarding the incidence of AF, ONTARGET was a primary prevention study, whereas our trial was a secondary prevention study; (ii) the ARBs studied were different: telmisartan in ONTARGET, valsartan in our study; (iii) in ONTARGET, ramipril was always used at the dosage of 10 mg o.d. in all patients, whereas in our study ramipril was used at dosages ranging from 5 to 10 mg o.d. according to the pressor response of the patients.

CONCLUSIONS

This study showed that renin–angiotensin system inhibition with both the ARB valsartan and the ACE-I ramipril was more effective than amlodipine treatment in preventing new episodes of AF in hypertensive patients with a history of lone AF, but the effect of valsartan was greater than that of ramipril. This advantage of valsartan in preventing relapses of AF might be related at least partly to its greater lowering effect on PWD, which in turn might reflect a more positive effect of the ARB on atrial electrical remodeling. The decrease in PIP levels observed with both valsartan and ramipril suggested a reduction in cardiac fibrosis as one possible mechanism for AF prevention by these drugs.

Disclosure: The authors declared no conflict of interest.

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