Effect of ramipril/hydrochlorothiazide and ramipril/canrenone combination on atrial fibrillation recurrence in hypertensive type 2 diabetic patients with and without cardiac autonomic neuropathy

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Abstract

Introduction: The aim of this study was to compare the effect of ramipril/canrenone versus ramipril/hydrochlorothiazide (HCTZ) combination on atrial fibrillation (AF) recurrence in type 2 diabetic hypertensives with and without cardiac autonomic neuropathy (CAN).
Material and methods: A total of 289 hypertensive type 2 diabetic patients, 95 with CAN, in sinus rhythm but with at least two episodes of AF in the previous 6 months were randomized to ramipril 5 mg plus canrenone 50 mg (titrated to 10/100 mg) or to ramipril 5 mg plus HCTZ 12.5 mg (titrated to 10/25 mg) or to amlodipine 5 mg (titrated to 10 mg) for 1 year. Clinic blood pressure (BP) and a 24-h ECG were evaluated monthly. Patients were asked to report any episode of symptomatic AF and to perform an ECG as early as possible. Serum procollagen type I carboxy-terminal peptide (PIP) and carboxy-terminal telopeptide of collagen type I (CITP) were evaluated before and after each treatment period.
Results: Blood pressure was similarly and significantly reduced by all treatments. A total of 51% of patients with amlodipine had a recurrence of AF, as did 31% of patients with ramipril/HCTZ ($p < 0.05$ vs. amlodipine) and 13% of patients with ramipril/canrenone ($p < 0.01$ vs. amlodipine and $p < 0.05$ vs. ramipril/HCTZ). A similar trend was found in diabetic patients with CAN. Both combinations reduced PIP and increased CITP, but the effects of ramipril/canrenone were significantly more marked.
Conclusions: These findings suggest that in type 2 diabetic hypertensives, ramipril/canrenone treatment was more effective than ramipril/HCTZ in reducing AF recurrence. This could be related to the greater improvement in cardiac fibrosis.

Key words: diabetes mellitus, atrial fibrillation, antihypertensive treatment, canrenone, cardiac autonomic neuropathy.

Introduction

Atrial fibrillation (AF) is frequently observed in diabetic patients [1–3]. Subjects with diabetes frequently suffer from cardiac autonomic neu-

ropathy (CAN) [4, 5], which may contribute to creation of electrical instability leading to AF [2]. The renin-angiotensin-aldosterone system (RAAS) is well known to play a major role in the pathophysiology of AF, being involved in myocardial fibrosis, oxidative stress, inflammation and electrical abnormalities, which all contribute to the atrial remodeling underlying the occurrence of this arrhythmia [6]. As a consequence, RAAS blockade has been shown to be effective in preventing new onset as well as recurrence of AF in a variety of clinical settings [7].

Lately the role of aldosterone in AF pathophysiology has been recognized with special focus on the effects on AF-induced structural and electrical atrial remodeling [8]. Accordingly, a positive role of aldosterone and mineralocorticoid receptor (MR) antagonism in "upstream" treatment of AF has been suggested, although no definite clinical data exist in this regard [9, 10]. There is evidence that MR antagonism may reduce the incidence of AF in patients with heart failure [10, 11], whereas some studies suggested that it may be useful to add an aldosterone/MR antagonist to ACE-I or ARBs in patients with AF [12].

Given that treatment of hypertensive patients with diabetes almost always requires combination of two or more drugs [13], the aim of the present study was to evaluate the effect of the ACE-I ramipril plus the aldosterone antagonist canrenone as compared to ramipril/hydrochlorothiazide (HCTZ) combination in preventing the recurrence of AF in hypertensive patients with diabetes mellitus and a history of a recent AF episode. The effects on P-wave dispersion (PWD), assessed as a marker of inhomogeneous atrial propagation of sinus impulses [14], were also evaluated, as were the effects on serum procollagen type 1 carboxy-terminal peptide (PIP) levels, used as a marker of extracellular collagen type 1 synthesis and myocardial fibrosis [15] and on carboxy-terminal telopeptide of collagen type 1 (CITP), used as marker of extracellular collagen type 1 degradation [12, 13]. Due to the role of CAN in AF pathophysiology, the effects of study medications were evaluated in patients with and without CAN.

Material and methods

This was a prospective, randomized, double-blind, parallel-arm trial. The study population was selected according to the following inclusion criteria: outpatients of either sex with essential hypertension (systolic blood pressure (SBP) ≥ 140 and < 160 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 and < 100 mm Hg at the end of a 2-week wash-out period) and well-controlled diabetes mellitus (glycated haemoglobin (HbA_{1c}) < 7%) in sinus rhythm but with at least 2 ECG-documented episodes of symptomatic AF in the previous 6 months. Previous AF episodes could be self-terminating or terminated after pharmacological and/or electrical cardioversion. Exclusion criteria were: secondary hypertension, cardioversion within the last 8 weeks, in current treatment with angiotensin converting enzyme-inhibitors (ACE-I), angiotensin II receptor blockers (ARBs) or β-blockers, antiarrhythmic agents, myocardial infarction or stroke in the previous 6 months, congestive heart failure, left atrium size > 45 mm, need to continue the use of digitalis, cardiac surgery during the preceding 6 months, significant thyroid, renal or hepatic disease, pregnancy, and known contraindications to the study medications. The study protocol was approved by the local Ethical Committee, and informed consent was obtained from each participant.

The patients were evaluated for CAN using 4 different clinical tests: 1) heart rate variability: the standard deviation of 150 consecutive R-R intervals recorded while the subjects lay quietly breathing when ≤ 2 mms was considered abnormal; 2) resting heart rate (HR): a resting HR of more than 100 beats per minute was considered abnormal; 3) orthostatic hypotension: BP was first measured in a supine position and then after 2 min of standing; a fall in SBP of > 20 mm Hg and/or in DBP > 10 mm Hg was considered abnormal; 4) ECG recording – QTc interval > 440 ms was considered abnormal. If two or more of the above tests were abnormal, the patient was diagnosed as positive for CAN. We choose to use the above described tests for CAN detection instead of the widely used Ewing tests [16] because two of the latter, i.e. the Valsalva maneuver and handgrip test, require full cooperation of the patient, which would have been difficult to obtain in elderly patients such as those enrolled in the present study.

After an initial 2-week antihypertensive wash-out period on placebo, patients were randomly assigned to receive ramipril 5 mg plus 50 mg of canrenone or ramipril 5 mg plus 12.5 mg of HCTZ or 5 mg of amlodipine once daily (od). In non-responder patients (BP > 135/85 mm Hg), the study drugs were titrated after 4 weeks (ramipril/canrenone 5/100 mg, ramipril HCTZ 5/25 mg and amlodipine 7.5 mg) and 8 weeks (ramipril/canrenone 10/100 mg, ramipril HCTZ 10/25 mm Hg and amlodipine 10 mg) to achieve a target BP of less than 135/85 mm Hg (Figure 1). Those patients who did not achieve the target BP after 12 weeks were excluded. Patients were checked every 4 weeks for 1 year. Clinical examination included BP evaluation, a resting ECG and a 24-h ECG registration (using a Syneflah Holter recorder, Ela Medical, Paris, France) [17]. 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.

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

P-wave analysis measurements were calculated in 12-lead surface ECG recordings obtained at a paper speed of 50 mm/s and were transferred into a computer and opened with a high-performance graphic program. Measurements of P duration were performed by two cardiologists blinded to the patients' clinical data. Four cycles were measured for each lead. The difference between maximum and minimum P duration was defined as PWD [18]. Blood samples for PIP and CITP evaluation were taken in the morning after an overnight fast. Serum PIP was determined by a rapid equilibrium radioimmunoassay according to the method of Meikko *et al.* [19] using commercial antisera specifically directed against the terminal carboxy terminal peptide. Serum CITP was also determined by a specific radioimmunoassay using specific antisera (Orion Diagnostica, Espoo, Finland), according to the method of Risteli *et al.* [16].

The primary end-point of the study was to assess the efficacy of ramipril/canrenone combination as compared to ramipril/HCTZ combination and amlodipine with regard to the cumulative number of patients relapsing into documented atrial fibrillation. Secondary end points were time to a first ECG-confirmed recurrence of AF, the changes in PWD and the changes in PIP and CITP serum levels.

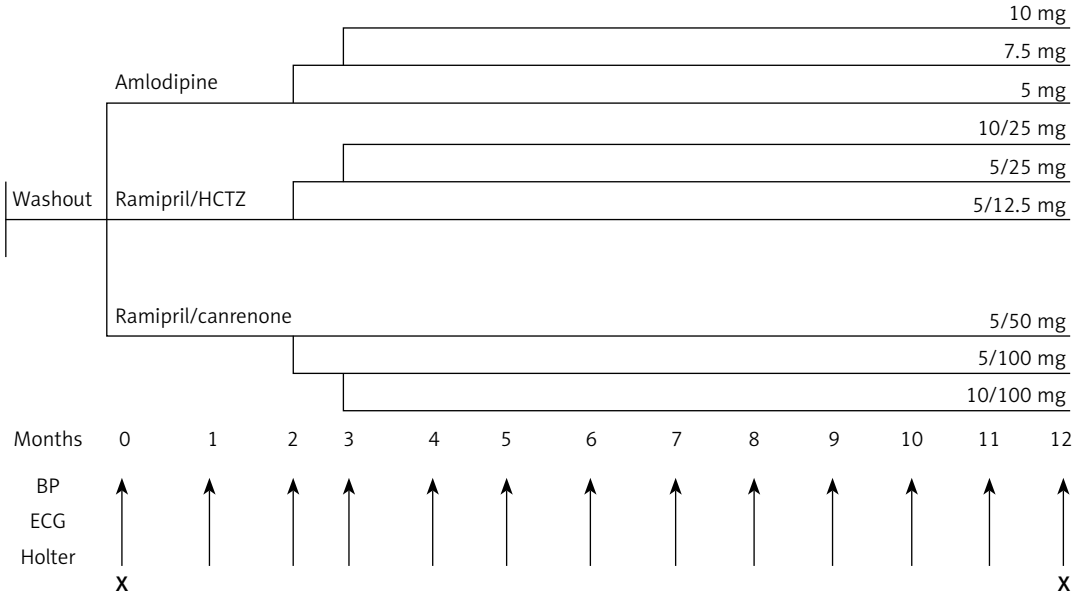
Statistical analysis

The sample size calculations are based on an estimated efficacy at 1 year of 75% for ramipril/canrenone, 80% for ramipril/HCTZ and 60% for amlodipine. With a level of 0.05 and a test power of 0.80, the resulting sample size was 87 patients for each treatment group. Data are expressed as means ± SD for continuous variables, and frequencies were measured for categorical variables. Baseline characteristics were examined for statistical significance for continuous variables using 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 number of days to AF recurrence (median and range) was compared among the treatment groups by the non-parametric Wilcoxon test.

Results

A total of 342 consecutive hypertensive patients with type 2 diabetes were referred to our hypertension center with a history of paroxysmal AF. Of them 289 were finally randomized to participate in this study (Figure 2). Ninety-five (32.8%) patients were found to have CAN. Forty-two patients were excluded from this protocol according to the inclusion/exclusion criteria. Twelve patients refused to participate. The baseline demographic and clinical characteristics of each treatment group are shown in Table I. Patients in the 3 groups were well matched and similar with regard to all pre-treatment characteristics.

A total of 98 patients were allocated for treatment with ramipril/canrenone combination, 97 for



X procollagen C propeptide type I and carboxy-terminal telopeptide

Patients were asked to report any episode of symptomatic AF and to perform an ECG and an evaluation of plasma cardiac troponin-I as early as possible.

Figure 1. Study design

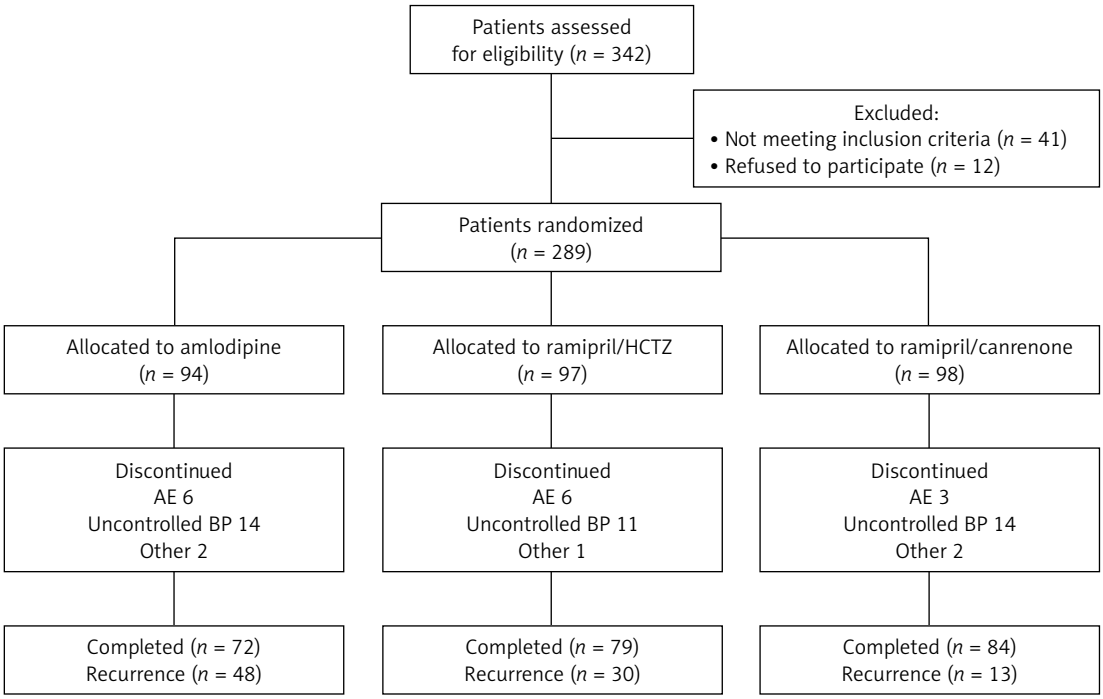


Figure 2. Flow diagram of the study

treatment with ramipril/HCTZ combination and 94 for treatment with amlodipine. There were substantial reductions in SBP and DBP values in all treatment groups. At the end of follow-up SBP was reduced by 18.9 mm Hg ($p < 0.001$) with ramipril/canrenone, by 19.3 mm Hg ($p < 0.001$) with ramipril/HCTZ and by 17.2 mm Hg ($p < 0.001$) with amlodipine, with no significant difference among treatments. Corresponding changes for DBP were 14.5, 14.9 and 13.6 mm Hg ($p < 0.001$ vs. baseline),

Table I. Main demographic and clinic characteristics of patients in the three treatment groups

Parameter	Amlodipine (*n* = 94)	Ramipril/HCTZ (*n* = 97)	Ramipril/canrenone (*n* = 98)	*P*-value
Age [years]	68 ±7.5	67 ±7.1	68 ±8.2	NS
Sex (M/F)	45/49	46/51	48/50	NS
Weight [kg]	75.4 ±10.1	75.7 ±10.5	76.2 ±10.6	NS
SBP [mm Hg]	148.8 ±7.3	148.2 ±7.5	149.1 ±7.8	NS
DBP [mm Hg]	92.3 ±3.7	92.7 ±3.5	93.1 ±3.9	NS
Heart rate [bpm]	76.1 ±9.9	75.9 ±10.8	75.5 ±11.2	NS
FPG [mg/dl]	126.1 ±19.3	123.4 ±20.2	125.3 ±18.6	NS
HbA_{1c} (%)	6.8 ±0.3	6.6 ±0.5	6.7 ±0.4	NS
Serum potassium [mEq/l]	4.49 ±0.39	4.43 ±0.36	4.52 ±0.35	NS
eGFR [ml/min/1.73 m^2]	86.6 ±5.9	88.1 ±6.2	83.7 ±5.7	NS
Echocardiogram:				NS
LV end-diastolic dimension [mm]	50.8 ±0.7	51.5 ±0.6	50.4 ±0.5	NS
Ejection fraction (%)	61.2 ±8.1	62.1 ±8.3	60.7 ±8.9	NS
LA inferosuperior dimension [mm]	42.8 ±2.3	42.6 ±2.1	42.9 ±2.2	NS
Septal thickness [mm]	11.3 ±0.29	11.1 ±0.33	11.4 ±0.27	NS
AF episodes (number)	2.6 ±0.8	2.8 ±0.9	2.7 ±0.8	NS

Data are expressed as mean ± SD. SBP – systolic blood pressure, DBP – diastolic blood pressure, FPG – fasting plasma glucose, HbA_{1c} – glycated hemoglobin, eGFR – estimated glomerular filtration rate, LV – left ventricular, LA – left atrial, AF – atrial fibrillation.

respectively, again without any significant difference among treatments. Heart rate did not show any significant change from baseline.

Results regarding AF recurrence are shown in Tables II and III. At the 4-month follow-up visit (end of titration period), 37 patients had a recurrence of AF by intention-to-treat analysis; the occurrence rate was lower in the ramipril/canrenone group (9 patients) than in the ramipril/HCTZ group (11 patients) and the amlodipine group (17 patients), the difference of ramipril/canrenone vs amlodipine being statistically significant ($p < 0.05$).

At the end of the follow-up, 48 (51%) patients undergoing treatment with amlodipine had a recurrence of AF, as did 30 patients (31%) undergoing treatment with ramipril plus HCTZ ($p < 0.05$ vs. amlodipine) and 13 (13%) patients undergoing treatment with ramipril plus canrenone ($p < 0.01$ vs. amlodipine and $p < 0.05$ vs. ramipril/HCTZ). The time to a first ECG-confirmed recurrence of AF was of 69 ±31 days (median ± SD) in the amlodipine group, of 139 ±73 days in the ramipril/HCTZ group ($p < 0.05$ vs. amlodipine) and of 175 ±91 days in the ramipril/canrenone group ($p < 0.01$ vs. amlodipine and $p < 0.05$ vs. ramipril/HCTZ).

Table III shows the main results according to an intention-to treat analysis in the subgroup of patients with CAN at baseline. At the end of follow-up the number of patients who had a recurrence of AF was lower in the ramipril/canrenone group (5) than in the ramipril/HCTZ group (12) and the amlodipine group (17). Similarly, the number of days to AF recurrence was higher in the ramipril canrenone group (116 ±69) than in the ramipril/HCTZ group (91 ±49) and the amlodipine group (58 ±25), but the differences among treatments were not statistically significant.

The percentage of patients with CAN who had an AF recurrence was not different from that of the total population in all the 3 treatment groups: 54.8% vs. 51.1% with amlodipine, 35.2% vs. 31.% with ramipril/HCTZ and 16.6 vs. 13.3% with ramipril/canrenone.

The PWD values did not show any significant change in the amlodipine treated patients, whereas a significant reduction was observed in both the ramipril/HCTZ ($p < 0.05$ vs. baseline) and the ramipril/canrenone group ($p < 0.01$ vs. baseline). Such a reduction was significantly greater in the ramipril/canrenone than in the ramipril/HCTZ treated patients ($p < 0.01$) (Table IV).

Serum PIP levels were not affected by amlodipine treatment, whereas they were reduced by both ramipril plus HCTZ ($p < 0.01$ vs. baseline and $p < 0.05$ vs. amlodipine) and ramipril plus canrenone ($p < 0.01$ vs. baseline and vs. amlodipine). The reduction was significantly greater in the ramipril/canrenone than in the ramipril/HCTZ group ($p < 0.01$) (Table IV).

Serum CITP levels were not affected by amlodipine treatment, whereas they were increased by both ramipril plus HCTZ ($p < 0.05$ vs. baseline) and ramipril plus canrenone ($p < 0.01$ vs. baseline and vs amlodipine). Again the increase was significantly greater in the ramipril plus canrenone than in the ramipril/HCTZ treated patients ($p < 0.05$).

No significant change in fasting plasma glucose values was observed in the 3 treatment groups (Table V). Similarly, no significant change was ob-

Table II. Main results of the study according to an intention-to-treat analysis

Variable	Amlodipine	Ramipril/HCTZ	Ramipril/canrenone
Patients randomized	94	97	98
AF recurrence at 4 months after randomization (end of titration)	17	11	9[a]
AF recurrence at 1 year after randomization (end of follow-up)	48	30[a]	13[b,c]
Days to recurrence, median ± SD (range)	69 ±31 (28–329)	139 ±73[a] (39–336)	175 ±91[a] (48–349)

[a]p < 0.05 vs. amlodipine, [b]p < 0.01 vs. amlodipine, [c]p < 0.05 vs. ramipril/HCTZ, AF – atrial fibrillation.

Table III. Main results according to an intention-to-treat analysis in the subgroup of patients with CAN at baseline

Variable	Amlodipine	Ramipril/HCTZ	Ramipril/canrenone
Patients	31	34	30
AF recurrence at 4 months after randomization (end of titration)	6	4	3
AF recurrence at 1 year after randomization (end of follow-up)	17	12	5*
Days to recurrence, median ± SD (range)	58 ±25 (21–211)	91 ±49 (32–229)	106 ±69 (39–244)

**p < 0.05 vs. amlodipine. AF – atrial fibrillation.*

Table IV. P-wave dispersion and serum PIP and CITP values before and after treatment in patients who completed the study without any AF recurrence

Parameter	Amlodipine (*n* = 24)	Ramipril/HCTZ (*n* = 49)	Ramipril/canrenone (*n* = 71)
PWD [ms]:			
Placebo	39.3 ±10.8	40.2 ±8.7	39.8 ±9.2
Treatment	40.1 ±11.9	34.5 ±9.1[a]	27.1 ±7.9[b,d,e]
Serum PIP [µg/l]:			
Placebo	148.5 ±35.2	147.2 ±34.6	149.8 ±36.7
Treatment	138.1 ±32.7	101.8 ±24.7[b,c]	84.2 ±18.3[b,d,e]
Serum CITP [µg/l]:			
Placebo	2.44 ±1.23	2.48 ±1.26	2.49 ±1.25
Treatment	2.49 ±1.28	2.68 ±1.28[a]	3.11 ±1.29[b,d,e]

Data are expressed as mean ± SD. [a]p < 0.05 vs. placebo, [b]p < 0.01 vs. placebo, [c]p < 0.05 vs. amlodipine, [d]p < 0.01 vs. amlodipine, [e]p < 0.05 vs. ramipril/HCTZ. PWD – P-wave dispersion, PIP – propeptide of procollagen type I, CITP – carboxy-terminal telopeptide of collagen type I.

Table V. Adverse events and biochemical parameters at the end of the follow-up

Parameter	Amlodipine (*n* = 94)	Ramipril/HCTZ (*n* = 97)	Ramipril/canrenone (*n* = 98)	*P*-value
Adverse events	10	9	8	NS
FPG [mg/dl]	125.2 ±17.3	126.6 ±19.4	124.9 ±18.8	NS
Serum potassium [mEq/l]	4.51 ±0.41	4.29 ±0.34	4.67 ±0.39	NS
eGFR [ml/min/1.73 m^2]	85.8 ±5.7	87.4 ±6.3	84.5 ±5.4	NS

Data are expressed as mean ± SD. FPG – fasting plasma glucose, eGFR – estimated glomerular filtration rate.

served in serum potassium levels or glomerular filtration rate (GFR) (Table V).

Adverse events requiring the discontinuation of treatment occurred in 3 patients in the ramipril/canrenone group, 6 patients in the ramipril/HCTZ group and in 6 patients in the amlodipine group, with no significant difference among the 3 treatment groups.

Discussion

The results of this study showed that in hypertensive patients with type 2 diabetes and a history of AF episodes antihypertensive treatment with both ramipril/canrenone and ramipril/HCTZ combination was more effective than amlodipine monotherapy in reducing new episodes of AF, but the preventive effect of ramipril plus canrenone on AF relapse was significantly greater than that of ramipril plus HCTZ despite a similar BP reduction. These results were already evident after 3 months of therapy and persisted after 1 year, when the difference between the two combinations was more marked.

These findings on one hand confirm that ACE inhibition per se may be effective in preventing AF recurrence, which is in agreement with previous observations [20–22]. Such a preventive effect has been related to several mechanisms, including inhibition of angiotensin II-induced myocardial fibrosis, interference with ion channel function, in particular K^+ channel subunits and Ca^{++} ion currents, modulation of refractoriness, reduced atrial stretch, improved left ventricular hemodynamics and modulation of sympathetic nerve activity [23, 24]. On the other hand, the findings of this study indicate that adding an antialdosteronic drug such as canrenone to an ACE-I may provide a greater AF-preventing effect, possibly related to the positive impact of aldosterone inhibition on the atrial electrical and structural remodeling documented by the effects on PWD as well as on PIP and CITP levels.

Inhomogeneous atrial propagation of sinus impulses, marked by PWD, has been demonstrated to be an independent predictor for AF [14, 25]. In the present study, both combinations significantly reduced PWD, but the reducing effect of the latter was more marked. Aldosterone, whose levels are elevated in patients with AF [26], has been demonstrated to affect atrial electrophysiology via modulation of both K^+ and Ca^{++} channels [27]. It increases L-type calcium currents and prolongs action potential duration, which may result in early afterdepolarizations [28]. It also alters repolarizing potassium currents [27]. Additionally, aldosterone enhances potassium and magnesium excretion, decreases myocardial reuptake of catecholamines, attenuates baroreceptor activity, increases baroreceptor sensitivity to catecholamines and re-

duces sinus rhythm variability, mechanisms that all contribute to the arrhythmogenic potential of aldosterone. Therefore inhibition of aldosterone actions by canrenone might result in an AF-preventing effect at least in part through amelioration of atrial electrical remodeling.

Fibrosis in atrial muscles is another critical factor responsible for AF, mainly through decrease in the atrial conduction velocity and heterogeneity of the conduction tissue [29, 30]. Increased interstitial fibrosis can physically separate myocytes, decreasing myocyte electrical coupling and creating a barrier to impulse propagation. Since the use of cardiac biopsies for documenting and measuring myocardial fibrosis is an invasive methodology not useful for wide-scale application, serological markers of collagen turnover have been introduced for non-invasive monitoring of myocardial fibrosis in clinical practice. In particular, serum concentrations of PIP and CITP may be useful for assessing the synthesis and degradation, respectively, of collagen type I fibers and provide indirect information on both the extent of myocardial fibrosis and the ability of antihypertensive agents to reduce myocardial fibrosis [15, 16]. In this study, both ramipril plus HCTZ and ramipril plus canrenone significantly decreased the serum concentration of PIP and increased CITP levels, thus confirming the ability of ACE-I inhibition to reduce the synthesis and to stimulate the degradation of collagen type I fibers with consequent reduction of myocardial fibrosis [31]. These effects, however, were significantly more marked in the ramipril/canrenone treated patients, which again indicates the relevant role of aldosterone inhibition. Several studies have shown that aldosterone promotes fibrotic atrial remodeling [32, 33]. It stimulates collagen I and III synthesis and fibroblasts by activating mineralocorticoid receptors, which promote gene transcription of fibrotic and hypertrophic proteins [8]. By blocking aldosterone at its receptor, canrenone would mitigate these effects, thereby reducing myocardial fibrosis, which in turn may result in prevention of AF recurrence.

Since an increase in aldosterone levels may occur during treatment with ACE-I due to the well-known phenomenon of aldosterone escape, caused by non-ACE-dependent Ang II forming activity mediated by chymase [34, 35], add-on therapy with an aldosterone antagonist such as canrenone may be more effective in reducing AF recurrence than HCTZ addition, which is devoid of anti-aldosteronic action. As a corollary of this observation, we can hypothesize that the better AF preventive effect found in various studies with ARBs [21, 22, 36, 37] might be related to the more complete blockade of the unfavorable actions of Ang II, including aldosterone production. Indeed, ARBs are effective on both ACE and non-ACE dependent Ang II/aldosterone formation.

Although the decrease in BP could be an important part of the mechanism of benefit observed with both ramipril/canrenone and ramipril/HCTZ combination, our study revealed no statistical difference in BP. This suggests that the greater preventive effect of ramipril plus canrenone was independent from its BP-lowering effect.

Similarly, since glycemic control was stable throughout the study period in all treatment groups, the observed difference in AF recurrence did not seem to be related to the difference in glycemic status.

In the subgroup of patients with CAN, no significant difference was observed with respect to the total population with any treatment. Reasons for these inconsistent findings are unclear, but we hypothesize that a greater sample size could perhaps have resulted in different data.

During the entire study period, the enrolled patients were given only the drugs included in the study protocol. This represents an advantage and a limitation at the same time. The advantage was the possibility of detecting exclusively the effects of the study medications. The limitation was that it was not possible to ascertain whether the observed effects would be the same or less evident in case of concomitant treatment with first-line drugs for AF such as β-blockers.

In conclusion, this study showed that antihypertensive treatment with both ramipril/canrenone and ramipril/HCTZ combination was more effective than amlodipine monotherapy in preventing AF relapse in diabetic patients with a history of AF episodes, but the effect of ramipril/canrenone was greater than that of ramipril/HCTZ. The advantage of ramipril/canrenone in preventing new episodes of AF might be related to the canrenone-mediated greater lowering effect on PWD and PIP levels and greater increasing effect on CITP levels. This in turn might reflect a more positive impact of this combination of an ACE-I with an antialdosteronic drug on atrial electrical and structural remodeling due to a more complete inhibition of the RAAS.

Conflict of interest

The authors declare no conflict of interest.

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