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Anti-remodelling effect of canrenone in patients with mild chronic heart failure (AREA IN-CHF study): final results

Alessandro Boccanelli[1], Gian Francesco Mureddu[1], Giuseppe Cacciatore[1], Francesco Clemenza[2], Andrea Di Lenarda[3], Antonello Gavazzi[4], Maurizio Porcu[5], Roberto Latini[6], Donata Lucci[7], Aldo Pietro Maggioni[7]*, Serge Masson[6], Massimo Vanasia[8], and Giovanni de Simone[9] on behalf of AREA IN-CHF Investigators†

[1]Department of Cardiovascular Diseases, San Giovanni-Addolorata Hospital, Roma, Italy; [2]Heart Failure Unit, ISMETT, Palermo, Italy; [3]Cardiovascular Department, Azienda Ospedali Riuniti, Trieste, Italy; [4]Department of Cardiology, Azienda Ospedali Riuniti, Bergamo, Italy; [5]Department of Cardiology, Azienda G. Brotzu—S. Michele, Cagliari, Italy; [6]Department of Cardiovascular Research, Istituto Mario Negri, Milan, Italy; [7]ANMCO Research Center, Via A. La Marmora 34, 50121 Florence, Italy; [8]Therabel GiEnne Pharma SpA, Milan, Italy; and [9]Department of Clinical and Experimental Medicine, Federico II University Hospital, Napoli, Italy

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Aims To test whether canrenone, an aldosterone receptor antagonist, improves left ventricular (LV) remodelling in NYHA class II heart failure (HF). Aldosterone receptor antagonists improve outcome in severe HF, but no information is available in NYHA class II.

Methods and results AREA IN-CHF is a randomized, double-blind, placebo-controlled study testing canrenone on top of optimal treatment in NYHA class II HF with low ejection fraction (EF) to assess 12-month changes in LV end-diastolic volume (LVEDV). Brain natriuretic peptide (BNP) was also measured. Information was available for 188 subjects on canrenone and 194 on placebo. Left ventricular end-diastolic volume was similarly reduced (−18%) in both arms, but EF increased more ($P = 0.04$) in the canrenone (from 40% to 45%) than in the placebo arm (from 40–43%). Brain natriuretic peptide ($n = 331$) decreased more in the canrenone (−37%) than in the placebo arm (−8%; $P < 0.0001$), paralleling a significant reduction in left atrial dimensions (−4% vs. 0.2%; $P = 0.02$). The composite endpoint of cardiac death and hospitalization was significantly lower in the canrenone arm (8% vs. 15%; $P = 0.02$).

Conclusion Canrenone on top of optimal treatment for HF did not have additional effects on LVEDV, but it increased EF, and reduced left atrial size and circulating BNP, with potential beneficial effects on outcome. A large-scale randomized study should be implemented to confirm benefits on cardiovascular outcomes in patients with HF in NYHA class II.

Keywords Brain natriuretic peptide • Aldosterone receptor antagonists • Heart failure • Ejection fraction • Diastolic function

Introduction

The renin-angiotensin-aldosterone system (RAAS) plays a central role in the maintenance of the neurohormonal imbalance that promotes progression of heart failure (HF).[1–6] Chronic neurohormonal activation acts, over time, to modify cardiac structure and function, inducing both left ventricular (LV) hypertrophy and collagen network remodelling,[7] all changes that increase cardiovascular morbidity and mortality.[8,9]

Although drugs interfering with the RAAS attenuate or even reverse LV remodelling and improve prognosis,[9–12] aldosterone levels often remain elevated or even increase in these patients,

* Corresponding author. Tel: +39 055 5101361, Fax: +39 055 5101310, Email: centrostudi@anmco.it, maggioni@anmco.it
†See Appendix for a complete list.

due to the well-known 'escape' phenomenon.[13,14] In addition to the other components of the RAAS, aldosterone directly promotes LV overload, hypertrophy, tissue-mediated responses (increase in cytokines, adhesion molecules, and endothelial dysfunction), and myocardial fibrosis.[15]

The pathophysiological rationale for aldosterone blockade in the treatment of HF is supported by large-scale randomized clinical trials demonstrating that anti-aldosterone agents, when added to optimal therapy, consistently reduce cardiovascular morbidity and mortality both in patients with advanced HF[16] (NYHA class III and IV) and in those with systolic dysfunction and HF following acute myocardial infarction.[17] As a consequence, current guidelines recommend using aldosterone receptor antagonists (ARAs) in advanced HF on the top of optimal therapy, including β-blockers and ACE-inhibitors (ACE-I).[18] Whether ARAs should also be maintained or recommended in patients with a milder degree of HF (NYHA class II) has not been clarified.

Accordingly, the AREA IN-CHF study (Anti-remodelling Effect of Canrenone in Patients with Mild Chronic Heart Failure) was designed to test the hypothesis that administration of ARAs on the top of optimal treatment also improves LV remodelling and function in patients with mild HF. The ARA used in the present study, canrenone, is an active metabolite of spironolactone.

Methods

Study population and inclusion criteria

From September 2002 to July 2005, patients aged 18–80 years, with NYHA class II HF, were enrolled in the study at 46 cardiology centres in Italy (see Appendix). The protocol and the consent form were approved by the local Institutional Review Board at each participating hospital.

Criteria for inclusion into the study, which have been reported previously, are summarized as follows.[19] Established evidence of NYHA class II HF, stable, optimized therapy according to European Society of Cardiology criteria,[20] and an LV ejection fraction (EF) $\leq$45%, as measured locally up to 6 months before enrolment. Exclusion criteria were: creatinine $>$2.5 mg/dL; K^+ $>$5.0 mEq/L; valvular heart disease amenable to surgical treatment; congenital heart disease; unstable angina or acute myocardial infarction or coronary revascularization procedure within 3 months before enrolment; intravenous therapy with inotropic drugs within 3 months before enrolment; treatment with lithium salts, K^+-sparing diuretics, TNF-α antagonists, or ARA during the last 3 months; history of resuscitated ventricular arrhythmias (unless this occurred within 24 h of a previous acute myocardial infarction or in subjects with an implantable cardioverter defibrillator); other clinical or general conditions contraindicating participation in a clinical trial.

Baseline characteristics of the participating population have also been reported previously in detail.[21]

Study design

AREA IN-CHF is a multicentre, randomized, double-blind, parallel group comparison of the ARA canrenone, vs. placebo, over 12 months.[19,21] Follow-up visits and laboratory examinations were performed every month for the first 3 months and thereafter every 3 months until the end of the study. Echocardiograms were performed at baseline and repeated after 6 and 12 months. Brain natriuretic peptide (BNP) and procollagen type III amino-terminal peptide (PIIINP) were measured at baseline and after 6-month therapy.

The dose of 25 mg/o.d. of canrenone at randomization was increased to 50 mg/o.d. after the first month, if serum K^+ was $\leq$5 mEq/L, and in the absence of deterioration in renal function. During follow-up, if serum K^+ increased up to 5 mEq/L and/or creatinine increased up to 2.5 mg/dL, the dosage of canrenone was reduced to 25 mg/o.d. Subjects requiring down-titration of study medications were asked to return to the outpatient clinic within 2 weeks for a supplemental visit to evaluate the effectiveness of this change in therapy. If serum K^+ remained $>$5.5 mEq/L, or if creatinine was $\geq$3 mg/dL or had increased by over 1 mg/dL, the study medication was discontinued and the patient managed with conventional treatment only.

The pre-specified primary endpoint was the change in echocardiographic LV end-diastolic volume (LVEDV) over 12 months, measured centrally at the Echocardiographic Reading Centre. Secondary endpoints included changes in EF, estimated diastolic filling pressure, NYHA class, BNP, cardiac mortality, hospitalization for cardiac causes, and the combination of cardiac mortality and hospitalization for cardiac causes.

Concomitant therapy

Prior to enrolment, ACE-I or angiotensin receptor blockers (ARBs), and β-blockers were recommended, with the condition that treatment was initiated at least 3 months before randomization. In a few patients not already receiving a β-blocker, eligibility was confirmed only if the local investigator had determined that the patient was not likely to receive a β-blocker within the following 12 months. Aspirin, diuretics, digoxin, nitrates, antiarrhythmic agents, oral anticoagulants, and any other therapy were allowed when indicated by the local investigators. Oral K^+ supplementation was not recommended.

Echocardiography

Standard, transthoracic M-mode and 2D-echocardiograms were performed locally and recorded onto S-VHS video-tapes. A CD-ROM was used to train personnel at each of the participating centres to standardize the sequence of acquisitions. All video-tapes were sent to the Echocardiographic Reading Centre and were read at the end of the study by one experienced independent observer (G.F.M.) who was blinded to all clinical data and treatment allocation.[22] The videos were read using a digital work-station (MediMatic 7.1; Genova, Italy).

Linear measurements of cardiac structures were obtained from the 2D parasternal long-axis view, according to standardized methods,[23] when M-mode was not available. Left ventricular mass was calculated using the adjusted-ASE formula.[24] Left ventricular geometry was evaluated as relative wall thickness (ratio between posterior wall thickness and LV end-diastolic radius).[25] Left ventricular end-diastolic and end-systolic volumes were obtained using Simpson's rule in apical 4-chamber and 2-chamber views[26] and used to generate EF.

Myocardial after-load was estimated by circumferential end-systolic wall stress, based on a cylindrical model.[27] Myocardial pre-load was computed as LV end-diastolic wall stress, according to a validated geometric model,[28] obtained in a subgroup of patients with available pulmonary vein flow interrogation. The duration of pulmonary vein reverse flow at atrial contraction (PVa) and the duration of transmitral late forward flow velocity (A)[29] were used to generate an estimate of LV end-diastolic pressure (LVEDP), using Appleton's formula.[30]

Laboratory analyses and biohumoral assays

Standard laboratory tests were performed locally. Two additional blood samples were collected, at randomization and after 6 months,

the morning after an overnight fast and following 30 min of supine rest. These two plasma samples were sent to a central laboratory for measurement of circulating biomarkers (BNP and PIIINP), as published previously.[21,31] The intra- and inter-assay coefficients of variability for BNP (IRMA Shionogi) were 4.2% and 6.3%, respectively. Corresponding values for PIIINP (RIA, Orion Diagnostica) were 5.3% and 9.6%.

Glomerular filtration rate (GFR) was estimated by the Cockcroft–Gault equation.[32]

Statistics

Based on pre-analyses obtained in 100 consecutive patients meeting the study inclusion criteria,[19] it was estimated that 250 patients had to be enrolled in each arm to detect with $\geq$90% power and a 0.05 α level a 10% change in LVEDV. Incidence of side effects and adverse events, as well as laboratory abnormalities during treatment or up to 14 days after discontinuation of therapy has been tabulated as frequency distribution by treatment group.

Statistical analysis was based on the intention to treat. Categorical data, reported as per cent, were compared using χ^2 statistics and continuous variables, expressed as mean $\pm$ SD, using the Mann–Whitney *U*-test. Variables deviating from normality were also log transformed for parametric statistics and presented as median and inter-quartile range for descriptive statistics.

The echocardiographic measures done at the entry visit were compared with those at study end (i.e. 12 months or, in case of permanent discontinuation, 6 months). Differences in echocardiographic and laboratory measurements between groups (treatment effect) and overall changes over time within each group (time effect), as well as any interaction (different trend over time between groups), were assessed by repeated-measures analysis of variance.

Least squares linear correlation was used to study bivariate relations and, when needed, partial correlation was used to adjust for potential confounders. All analyses were conducted using SAS, version 8.2 (SAS Institute Inc., Cary, NC, USA). The null hypothesis was rejected for two-tailed α value <0.05.

Results

Five hundred and five patients were initially randomized. However, data from 38 patients at one site were disqualified after randomization, before unblinding, because the adequacy of the informed consent process and quality of data could not be ensured. Of the remaining 467 participants, 231 were assigned to canrenone and 236 to placebo. Reliable measures of LVEDV were available in 431 patients at baseline and in 382 patients at study end for the intention-to-treat analysis (188 on canrenone and 194 on placebo).

Table 1 shows the baseline characteristics of both the randomized and the echo-population by treatment. There was no between-treatment difference in demographics or the distribution of cardiovascular risk factors, with the exception of heart rate which was significantly higher in patients assigned to canrenone than in those on placebo ($P = 0.04$). The type of prevalent cardiovascular disease, possibly causing HF, and prior hospitalization for HF were not different between the groups.

Similarly, concomitant pharmacological therapy did not differ between the groups (*Table 2*) except for the greater use of ACE-I in the treatment arm that was counterbalanced by a more frequent use of ARBs in the placebo arm. Overall, an ACE-I or

Table 1 Baseline demographic characteristics of the study population divided according to the two treatment arms at entry

	As randomized (467 pts)			Echo available (382 pts)		
	Canrenone (231 pts)	Placebo (236 pts)	*P*	Canrenone (188 pts)	Placebo (194 pts)	*P*
Age (years), mean $\pm$ SD	62.3 $\pm$ 9.5	62.7 $\pm$ 9.5	0.59	62.4 $\pm$ 9.5	62.0 $\pm$ 9.6	0.69
>70 years (%)	22.1	21.6	0.90	22.9	19.6	0.43
Females (%)	18.2	14.8	0.33	16.5	15.0	0.68
Body mass index (kg/m^2), mean $\pm$ SD	26.7 $\pm$ 3.5	26.9 $\pm$ 3.6	0.98	26.4 $\pm$ 3.3	26.8 $\pm$ 3.6	0.47
Systolic blood pressure (mmHg), mean $\pm$ SD	127.9 $\pm$ 16.2	128.0 $\pm$ 17.2	0.92	127.8 $\pm$ 16.5	128.6 $\pm$ 17.6	0.59
Heart rate (b.p.m.), mean $\pm$ SD	68.0 $\pm$ 11.8	65.7 $\pm$ 10.7	0.04	67.3 $\pm$ 11.5	64.7 $\pm$ 9.8	0.04
Hypertension (%)	48.5	42.4	0.18	46.3	43.8	0.63
Diabetes (%)	20.9	19.9	0.80	21.4	18.6	0.49
Ischaemic aetiology (%)	51.1	52.1	0.82	51.1	49.0	0.68
Diagnosis of HF >12 months (%)	73.2	76.7	0.61	73.4	77.3	0.58
Prior hospitalization for HF (%)	44.6	49.2	0.32	42.6	46.4	0.45
Prior stroke (%)	1.7	3.0	0.38	2.1	3.6	0.39
Prior revascularization (%)	36.4	35.2	0.79	35.1	30.9	0.39
Implantable cardiac defibrillator (%)	6.1	5.1	0.65	4.8	5.2	0.87
Peripheral vascular disease (%)	3.0	3.4	0.83	2.7	3.1	0.80
Chronic atrial fibrillation (%)	7.4	8.5	0.66	6.9	8.3	0.62
Left bundle branch block (%)	28.1	28.8	0.87	25.5	30.4	0.29

HF, heart failure.

Table 2 Concomitant pharmacological therapy in the two treatment arms at entry

	As randomized (467 pts)			Echo available (382 pts)		
	Canrenone (231 pts)	Placebo (236 pts)	*P*	Canrenone (188 pts)	Placebo (194 pts)	*P*
Diuretics (%)	67.8	72.0	0.37	68.1	68.0	0.99
Beta-blockers (%)	81.3	77.5	0.36	80.9	77.8	0.47
ACE-I (%)	84.9	74.6	0.01	86.7	72.7	<0.01
ARBs (%)	12.1	24.2	<0.01	12.2	26.8	<0.01
ACE-I/ARBs (%)	96.1	95.8	0.59	97.3	96.4	0.60
Digitalis (%)	24.4	27.2	0.78	23.9	25.8	0.68
Nitrates (%)	26.1	27.1	0.58	25.5	22.7	0.51
Amiodarone (%)	18.3	17.4	0.35	17.7	15.5	0.51
Calcium channel blockers (%)	6.1	7.6	0.48	6.4	7.7	0.61
Statins (%)	44.4	45.7	0.82	43.1	44.3	0.81
Antiplatelets (%)	57.0	57.1	0.62	57.5	54.2	0.52
Other anticoagulants (%)	23.7	24.8	0.86	22.6	24.7	0.62
Bronchodilators (%)	4.0	3.4	0.96	4.8	2.6	0.52

ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

Table 3 Biochemical analyses and bio-humoral assays in the two treatment arms at entry

	As randomized (467 pts)			Echo available (382 pts)		
	Canrenone (231 pts)	Placebo (236 pts)	*P*	Canrenone (188 pts)	Placebo (194 pts)	*P*
Hb <12.0 (g/dL), %	6.5	6.5	0.14	6.9	5.2	0.30
WBC >9000 (mm^3), %	9.2	8.2	0.50	9.7	6.8	0.55
Serum creatinine (mg/dL), mean ± SD	1.1 ± 0.3	1.1 ± 0.2	0.11	1.1 ± 0.3	1.1 ± 0.2	0.42
Serum potassium (mEq/L), mean ± SD	4.3 ± 0.4	4.4 ± 0.4	0.62	4.3 ± 0.4	4.4 ± 0.4	0.50
BNP (pg/mL), median [Q1–Q3]	90 [39–198]	87 [34–172]	0.55	78 [38–188]	77 [32–148]	0.19
PIIINP (μg/L), median [Q1–Q3]	5.3 [3.9–6.9]	5.4 [4.0–7.4]	0.76	5.3 [3.9–7.2]	5.3 [4.0–6.8]	0.72

Hb, haemoglobin; WBC, white blood cells; BNP, brain natriuretic peptide; PIIINP, procollagen type III amino-terminal peptide.

an ARB was prescribed in a similar proportion of patients (*Table 2*). Baseline laboratory tests, including BNP and PIIINP, were not statistically different between treatment groups (*Table 3*).

The mean dose of canrenone was 43.8 ± 11.5 mg/day. The maximal dosage over follow-up was reached in 90.5% of patients and maintained in 65%.

Cardiac geometry and function

Left ventricular end-diastolic volume was similarly reduced in both arms (interaction time*treatment: $P = 0.72$, *Table 4*), but EF was significantly more increased with canrenone than with placebo (interaction time*treatment: $P = 0.04$), end-systolic stress showed a trend towards a greater reduction in the canrenone arm with respect to the placebo arm, although it did not reach statistical significance (interaction time*treatment: $P = 0.11$).

Left ventricular mass was more markedly reduced by canrenone than by placebo (interaction time*treatment: $P = 0.02$), whereas no between-treatment difference was found for the significant increase in relative wall thickness during treatment. Left atrial dimension was also significantly more reduced by canrenone than placebo (interaction time*treatment: $P = 0.02$). Derived variables of LV filling pressure, (LVEDP and LV end-diastolic stress) showed a trend towards a more pronounced reduction in the canrenone group (*Table 4*), without achieving conventional statistical significance.

Biohumoral assays

Figure 1 shows the difference over time in the concentrations of BNP and PIIINP.

At the 6-month follow-up, BNP ($n = 331$ patients with baseline and 6-month values) was significantly more decreased with canrenone (−37%) than with placebo (−8%; interaction time*treatment: $P < 0.0001$). At baseline, in pooled groups, BNP ($n = 420$) was linearly related to left atrial dimension ($n = 363$, $r = 0.28$, $P < 0.001$), LVEDV ($n = 431$, $r = 0.39$, $P < 0.0001$), estimated end-diastolic pressure ($n = 248$, $r = 0.39$, $P < 0.0001$), and end-diastolic stress ($n = 228$, $r = 0.47$, $P < 0.0001$). Similar relations were found in the subgroup of patients with available estimation

Table 4 Echocardiographic variables at baseline and at study end in the two treatment arms

Variables	Canrenone ($n = 188$)		Placebo ($n = 193$)		P*
	Baseline	Study end	Baseline	Study end	
End-diastolic volume (Simpson, mL)	156.8 ± 54.5	128.2 ± 44.6	164.0 ± 62.8	133.9 ± 49.1	0.72
Ejection fraction (Simpson, %)	39.9 ± 8.6	45.1 ± 9.6	39.7 ± 8.6	42.9 ± 9.7	0.04
End-systolic stress (kdynes/cm^2)	231.6 ± 57.9	191.2 ± 48.0	229.7 ± 54.0	200.4 ± 52.6	0.11
Left ventricular mass (g)	264.0 ± 72.5	238.0 ± 67.6	264.8 ± 74.6	249.5 ± 75.8	0.02
Relative wall thickness	0.33 ± 0.06	0.34 ± 0.06	0.33 ± 0.06	0.34 ± 0.06	0.20
Left atrial diameter (cm)	4.24 ± 0.76	4.07 ± 0.77	4.12 ± 0.59	4.13 ± 0.67	0.02
End-diastolic pressure (mmHg)	14.7 ± 8.2	11.4 ± 7.0	14.4 ± 7.7	12.3 ± 7.5	0.30
End-diastolic wall stress (kdynes/cm^2)	50.4 ± 32.5	33.5 ± 25.5	47.2 ± 28.7	37.4 ± 30.3	0.17

Intention-to-treat analysis. Data are expressed as mean ± SD.
*Interaction time*treatment.

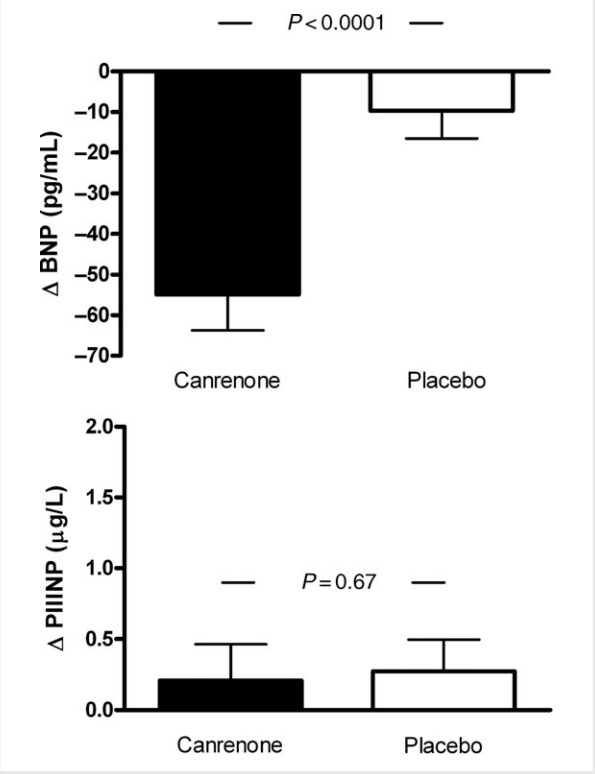

Figure 1 Absolute changes from randomization to 6 months in the plasma concentration of BNP and PIIINP in patients randomized to placebo ($n = 166$) or canrenone ($n = 165$). Data are presented as mean ± SEM. BNP, brain natriuretic peptide; PIIINP, procollagen type III amino-terminal peptide. Per cent relative changes of BNP and PIIINP have been reported in the text.

of LVEDP at the 6-month control ($n = 125$): BNP was correlated with left atrial dimension ($r = 0.29$) LVEDV ($r = 0.31$), LVEDP ($r = 0.39$, all $P < 0.0001$), and end-diastolic stress ($r = 0.48$). There was no significant difference in the changes over time of PIIINP in the canrenone (+3.7%) and placebo arms (+5.0%, interaction time*-treatment: $P = 0.8487$).

Table 5 Patients with clinical events

Variables	Canrenone	Placebo	P
All cause mortality, *n* (%)	6/215 (2.8)	12/223 (5.4)	0.17
Cardiac, *n* (%)	5 (2.3)	8 (3.6)	—
Vascular, *n* (%)	0	1 (0.4)	—
Non-cardiovascular, *n* (%)	1 (0.5)	3 (1)	—
Hospital admission, *n* (%)*	37/218 (17)	43/227 (18.9)	0.59
Cardiac, *n* (%)	13 (6)	29 (12.9)	0.01
Worsening heart failure, *n* (%)	6 (2.8)	17 (7.6)	0.02
Vascular, *n* (%)	1 (0.5)	0	—
Renal, *n* (%)	1 (0.5)	0	—
Stroke, *n* (%)	1 (0.5)	0	—
Other non-cardiovascular causes, *n* (%)	19 (8.8)	15 (6.7)	—
Cardiac death or hospital admission for cardiac cause, *n* (%)	17/216 (7.9)	34/225 (15.1)	0.02

*Patients could be admitted to hospital for more than one reason.

Clinical endpoints

Clinical outcomes in the canrenone and placebo groups are shown in *Table 5*. Survival status at 12 months was available in 438 patients (94%). Deaths occurred in 12 of 223 individuals in the placebo arm and in 6 of 215 patients in the canrenone arm ($P = 0.17$).

Information on hospitalizations was available in 445 patients (95%): the number of patients with hospitalization for cardiac cause and for worsening HF were significantly reduced in the canrenone arm ($P = 0.01$ and $P = 0.02$, respectively). The composite endpoint of cardiac death or hospital admission for cardiac cause was also significantly lower in the canrenone (7.9%) than in the placebo arm (15.1%; $P = 0.02$) (*Table 5*).

Finally, only 0.9% of the canrenone group progressed from NYHA class II to class III and IV compared with 3.8% of the placebo arm ($P = 0.06$), while at the end of the study, 22.4% in the active treatment arm were in NYHA class I vs. 13.2% in the

placebo group ($P = 0.01$). Sudden death occurred in 11 cases: in 4 patients taking the active treatment and in 7 receiving placebo.

Safety

Treatment discontinuation was more frequent in the canrenone arm (11.7%) than in the placebo arm (6.5%, $P = 0.05$). Patient's decision and increasing creatinine or/and K^+ were the most frequent causes of discontinuation. Discontinuation due to increased K^+ occurred in 13 patients taking canrenone and in three on placebo ($P = 0.06$); whereas discontinuation due to an increase in creatinine occurred in only one patient in both groups.

Hyperkalaemia (defined as $K^+ > 5.5$ mEq/L) occurred in 31 patients, 23 in the canrenone arm (10.1%) and 8 in the placebo arm (3.5%; $P < 0.01$). Only three patients in the canrenone arm and two patients in the placebo arm had a $K^+ \geq 6.0$ mEq/L ($P = 0.65$). One patient in the canrenone arm with a K^+ value of 6.4 mEq/L was hospitalized for monitoring of potassium levels. Among the patients with increased K^+, only one death occurred, this was in the canrenone group but was not attributable to hyperkalaemia. Moreover, no episodes of cardiac arrest or hyperkalaemia-related cardiac deaths were observed.

A creatinine level of >2.5 mg/dL was observed in six patients, five in the canrenone arm (2.2%) and one in the control arm (0.4%; $P = 0.01$). All patients underwent strict control of biochemical analyses with supplementary blood sample collections. All of them exhibited at least partial regression of serum creatinine levels in the follow-up. At 1 year, only two patients showed a serum creatinine >2.5 mg/dL and none of them showed a progression towards end-stage renal disease. Finally, no cases of gynaecomastia were reported during the study.

Discussion

Nearly all patients enrolled in the AREA IN-CHF study received optimized therapy including an ACE-I or an ARB and a β-blocker, according to clinical indications[33] and guidelines.[20] Since AREA IN-CHF was conceived to extend the RALES indications from patients in NYHA class III and IV to those in NYHA class II, patients were recruited on the basis of functional status. Being in NYHA class II, additional therapy with anti-aldosterone medications was, therefore, not required. As previously reported, the ARA used in the present study, canrenone, which is widely employed in Italy, is an active metabolite of spironolactone with a long half-life and is derived from the rapid conversion *in vivo* of the salt potassium canrenoate,[34] which has shown important anti-remodelling effects in post-infarction LV remodelling processes.[35,36] We demonstrate that adding canrenone to optimal therapy in patients in NYHA class II significantly improves LV systolic function and reduces LV mass and left atrial size, all recognized independent markers of adverse outcomes.[7–9,37,38] However, canrenone did not improve LV diastolic volume beyond that already achieved by optimal therapy and strict monitoring of clinical conditions.[39]

Paralleling the reduction in LV mass and improvement in EF, BNP, a very potent marker of LV load, was also substantially reduced after 6 months of canrenone treatment, suggesting that addition of canrenone on the top of optimal therapy also ameliorates LV loading conditions. The close relation between decreased BNP and canrenone-related LV unloading was also confirmed by the relation with critical haemodynamic parameters, including LVEDV and LVEDP, as well as LV end-diastolic wall stress, consistent with the notion that myocardial stretch modulates BNP expression in human overload hypertrophy or failure.[38,40] Left atrial dimension was also reduced by canrenone, a recognized sign of improved cardiac distensibility.[41,42] The slightly more frequent use of ACE-I in the canrenone arm was balanced by the more frequent use of ARBs in the placebo group, making the overall rate of use of ACE-I/ARBs similar in the two treatment groups. It is therefore unlikely that these slight differences could have influenced aldosterone breakthrough to potentially affect our results.

The haemodynamic improvement obtained by addition of canrenone on top of optimal therapy was also confirmed clinically by both the favourable change in NYHA class and the significant improvement in incident 1 year combined hard endpoints (cardiac death and hospitalization), which is especially relevant if the initial, mild functional class is considered.

The results of the present study could extend the RALES indications, by demonstrating that ARAs might also be beneficial in patients in NYHA class II, adding some benefits in terms of cardiac geometry (mass, atrium) and function, but also potentially reducing relevant clinical events (cardiac deaths and hospitalizations due to cardiac causes). Although no conclusion can be drawn, due to the relatively small number of events and the short time of follow-up, the potential improvement in prognosis might be relevant, considering that almost 80% of our participants were on β-blockers, compared with only 11% of patients enrolled in the RALES study.

In contrast with the RALES trial, β-blockers were used extensively in the more recent EPHESUS study.[17] In EPHESUS, addition of eplerenone on top of optimal therapy significantly reduced cardiovascular risk in patients with post-ischaemic HF, including also a lower rate of sudden cardiac death within 30 days from randomization.[43] In our study, the aetiology of HF was previous coronary artery disease in 50% of cases, suggesting that the strategy of continuing anti-aldosterone therapy may be adopted for all types of HF, including ischaemic HF.

Other studies that have focused on changes in LV remodelling have given, conflicting results over time.[15,44] Tsutamoto *et al.*[15] showed that in patients on stabilized HF treatment, spironolactone could reduce LV volume, in addition to increasing LV EF and decreasing BNP, however, the sample size was small (37 patients) and background therapy was not optimized, because β-blockers were not used in all patients. In a study by Cicoira *et al.*,[44] spironolactone also improved both LV volumes and function in 52 chronic HF patients taking ACE-I, but none of them was on an ARB and 28% were not taking β-blockers. In addition, the patients also exhibited higher mean LV volumes and lower EF at baseline when compared with the AREA IN-CHF patients, accounting for a more evident effect of ARAs on LV remodelling. In contrast to these positive findings, a number of studies have failed to show an additional effect of ARAs on LV volumes, when administered on the top of near-optimal therapy, including drugs to reduce the activity of the RAAS.[45–47]

Substantial changes in LV volume should not be expected in a near-maximally treated population in which the degree of remodelling was either heterogeneous (different HF aetiology) or already established over time. The improvement in cardiac conditions observed in the current study is likely associated with improved diastolic properties (due to possible structural changes in the collagen network), as suggested by the reduction of left atrial volume[41,42] that paralleled the reduction in LV end-diastolic wall stress, LVEDP, and the favourable changes in the neurohormonal pattern.

Finally, in the present study, canrenone did not show a significant reduction in PIIINP an aspecific marker of connective tissue remodelling, over time. However, at the stabilized level of HF studied in AREA IN-CHF, the cardiac contribution to modifying the level of the circulating component of the collagen turnover (PIIINP) is probably too low to be detectable.

Overall, canrenone therapy was well tolerated: no cases of gynaecomastia were reported during the study. The rate of discontinuation of treatment, hyperkalaemia, or worsening of renal function was not different from that expected on the basis of the current literature on ARAs. In this context, canrenone was also shown to produce a lower incidence of side effects than the parent compound.[48]

Study limitations

This study was initially powered for 250 patients in each arm. However, only 382 of the originally recruited patients were evaluable. This relative reduction in the required sample size could have increased the chance of a type II error. However, the mean and SD of the primary endpoint, LVEDV, suggests that even with the calculated sample size the result would not change substantially. In addition, the scenario represented by the cardiac changes and BNP is consistent and pathophysiologically plausible. The positive relationships between BNP and the reduction in both left atrial size and LVEDP reinforce the notion of the overall favourable effect of canrenone on cardiac geometry. Canrenone can only partly explain the effects of spironolactone, since another metabolite of spironolactone (7-α-thiomethyl-spironolactone) has also been shown to be present in the plasma[49] and to possess antimineralocorticoid properties. However, at present, no clinical data are available on its therapeutic activity.

Clinical outcomes were a secondary endpoint and the study was not adequately powered to test the hypothesis of a clinical benefit of canrenone in terms of mortality or hospitalizations. Given the relatively small number of events, a large-scale randomized study might be necessary to establish the clinical efficacy of this strategy to reduce mortality in NYHA class II patients, and to confirm the recently hypothesized role of ARAs in reducing sudden deaths in patients with HF.[50]

Conclusion

In patients with stabilized HF, in NYHA class II, addition of canrenone on the top of optimal treatment improved LV function, haemodynamic conditions, plasma BNP, clinical symptoms, and outcome, but did not further reduce LVEDV beyond that achieved by optimal therapy.

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Appendix

Steering Committee: A.B. (Chairman), G.C., A.G., A.D.L., M.P., F.C., G. de S., G.F.M.

Executive Committee: A.B., A.P.M., M.V.

Trial Management and Secretary: Marco Gorini, Laura Sarti, Verusca Canu.

Statistical analysis: D.L., Lucio Gonzini.

Echocardiography Core Lab: G.F.M.

Biomarker Core Lab: S.M., R.L., Monica Salio.

Clinical Monitoring: Martina Ceseri, Ilaria Cangioli, Iacopo Cangioli, Francesca Bianchini, Chiara Serio, Arianna Tafi, Marco Gianfriddo, Vittoriana Canu.

Participating Centres and Investigators (by geographic region).

Piemonte Ivrea (M. Dalmasso, G. Ronzani); *Lombardia* Bergamo (A.G., M. Gori); Milano Osp. FBF (S. Gramenzi, B. Brusoni); Passirana-Rho (C. Schweiger, F. Rusconi); Pavia IRCCS San Matteo (L. Tavazzi, C. Campana); Saronno (D. Nassiacos, S. Meloni); Sesto San Giovanni Multimedica (F. Donatelli, R. Mattioli); Varese (J. Salerno Uriarte, F. Morandi); *P.A.Bolzano* Bolzano (W. Pitscheider); *Veneto* Feltre (M. Guarnerio, F. De Cian); San Bonifacio (R. Rossi, E. Carbonieri); Venezia (G. Risica, P.L. Tenderini); *Friuli Venezia Giulia* Trieste (G. Sinagra, A.D.L.); *Liguria* Genova A.O.U. San Martino (S. Chierchia, P. Sartori); Sarzana (D. Bertoli, R. Petacchi); *Emilia-Romagna* Modena Hesperia Hospital (F. Zacà, A. Schipani); Modena Policlinico (M.G. Modena, L. Reggianini); Rimini (G. Piovaccari, F. Bologna); *Toscana* Empoli (A. Zipoli, F. Venturi); Pescia (G. Italiani, S. Di Marco)*****; Pisa Azienda Creas (A. L'Abbate, M.A. Morales); Pontedera (G. Tartarini, S. Viani); *Umbria* Perugia (G. Ambrosio, G. Alunni); *Marche* Ancona Lancisi (G. Perna, D. Gabrielli); *Lazio* Roma Osp. S. Camillo Cardiologia I (E. Giovannini, G. Pulignano); Roma Osp. S. Camillo Cardiologia III (P. Tanzi, F. Pozzar); Roma Osp. S. Giovanni (A.B., G.C.); Roma Osp. S. Andrea (M. Volpe, L. De Biase); Roma Osp. S. Spirito (V. Ceci, N. Aspromonte); Roma Policlinico di Liegro (A. Salustri, E. Cerquetani); *Campania* Avellino (G. Rosato, G. Stanco); Aversa (G. De Marco, T. Chiacchio); Caserta (A. Palermo, P. Golino); Napoli Fond. Betania (N. Esposito, A. Alfieri); Salerno (F. Silvestri, A. Pipolo); Telese Terme (G. Furgi, A. Nicolino); Vallo Della Lucania (G. Gregorio, R. Citro); *Puglia* Barletta (M. Russo, G. Saggese); Francavilla Fontana (V. Gallone, F. Cocco); San Giovanni Rotondo (R. Fanelli,

A. Maggi); Tricase (A. Galati, P. Morciano); *Sicilia* Cefalù (T. Cipolla, G. Ferrara); Palermo Osp. Cervello (F. Enia, M. Floresta); Ragusa (V. Spadola, G. Iabichella); *Sardegna* Cagliari A.O. Brotzu (S. Salis, P. Orrù); Sassari (P. Terrosu, F. Uras).

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