Efficacy and safety of two dosages of canrenone as add-on therapy in hypertensive patients taking ace-inhibitors or angiotensin II receptor blockers and hydrochlorothiazide at maximum dosage in a randomized clinical trial: The ESCAPE-IT trial

Giuseppe Derosa\textsuperscript{1,2,3} | Pamela Maffioli\textsuperscript{1,2,3} | Maria D’Avino\textsuperscript{4} | Carla Sala\textsuperscript{5} | Amedeo Mugellini\textsuperscript{1} | Vito Vulpis\textsuperscript{6} | Salvatore Felis\textsuperscript{7} | Luigina Guasti\textsuperscript{8} | Riccardo Sarzani\textsuperscript{9} | Alessandro Bestetti\textsuperscript{10} | Massimo Vanasia\textsuperscript{10} | Giovanni Gaudio\textsuperscript{11} | on behalf of the ESCAPE-IT Trial Investigators group

\textsuperscript{1}Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy
\textsuperscript{2}Diabetes and Metabolic Diseases Unit, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy
\textsuperscript{3}Centre for Prevention, Surveillance, Diagnosis and Treatment of Rare Diseases, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy
\textsuperscript{4}Unit for the treatment of Arterial Hypertension, Ospedale Cardarelli, Napoli, Italy
\textsuperscript{5}Unit of Cardiovascular Diseases, Fondazione Policlinico Milano, Milano, Italy
\textsuperscript{6}Unit for the Diagnosis and Treatment of Arterial Hypertension, Department of Internal Medicine, Policlinico di Bari, Bari, Italy
\textsuperscript{7}Cardiology Unit, Ospedale Garibaldi, Catania, Italy
\textsuperscript{8}Research Center on Dyslipidemia, Internal Medicine 1, University of Insubria, Varese, Italy
\textsuperscript{9}Center for the treatment of Hypertension and Cardiovascular Diseases, Ospedali Riuniti di Torrette, Ancona, Italy
\textsuperscript{10}THERABEL GiEnne Pharma, Milano, Italy
\textsuperscript{11}Internal Medicine Division, Ospedale Angelo Bellini, Somma Lombardo, Varese, Italy

Summary

\textbf{Aim:} To evaluate the effects of canrenone as add-on therapy in patients already treated with angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs) and hydrochlorothiazide at the maximum dosage (25 mg/d).

\textbf{Method:} In this randomized, open-label, controlled trial, we enrolled 175 Caucasian patients with essential hypertension not well controlled by concomitant ACE-I or ARBs and hydrochlorothiazide. At baseline, 87 patients (57 males and 30 females) were randomized to add canrenone 50 mg, and 88 (56 males and 32 females) patients to canrenone 100 mg, once a day, for 3 months. At baseline and after 3 months, we evaluated blood pressure (BP), pulse pressure (PP), heart rate (HR), fasting plasma glucose (FPG), homeostasis model assessment insulin (HOMA Index), lipid profile, electrolytes, uric acid, estimated glomerular filtration rate (eGFR), plasma urea, aldosterone, B-type natriuretic peptide (BNP), and galectin-3.
1 | INTRODUCTION

It has been reported that aldosterone blockade reduces the rate of death due to progressive heart failure and the rate of sudden death from cardiac causes, as well as the rate of hospitalizations for heart failure, among patients with severe heart failure due to systolic left ventricular dysfunction who are being treated with the angiotensin-converting enzyme inhibitors (ACE-I).\(^1\) Two generations of mineralocorticoid receptor antagonists are currently available: the first generation includes spironolactone and canrenone, and the second generation includes eplerenone, which is less potent but more selective, and has a shorter half-life.\(^2\) In the EPHEBUS and EMPHASIS-HF studies, eplerenone reduced morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure.\(^3,4\) Similarly, spironolactone was shown to reduce the risk of both morbidity and death among patients with severe heart failure.\(^5\) Finally, in the AREA CHF (Antiremodeling Effect of Canrenone in Patients With Mild Chronic Heart Failure Study) trial,\(^6\) canrenone was investigated in patients with or without metabolic syndrome and compensated heart failure with reduced ejection fraction on optimal therapy [including ACE-I or angiotensin II receptor blockers (ARBs), and β-blockers]. Canrenone stabilized heart failure with reduced ejection fraction, protected against deterioration of myocardial mechano-energetic efficiency, improved diastolic dysfunction, and maximized the decrease in B-type natriuretic peptide (BNP). In Italy, canrenone is licensed for the treatment of primary or secondary hyperaldosteronism, and for the treatment of hypertension in patients not adequately controlled by current therapy. However, although data about mineralocorticoid receptor antagonists are available in patients with chronic heart failure, multicentric clinical trial data for canrenone therapy in pure hypertensive patients are lacking.

For these reasons, the ESCAPE-IT (Efficacy and Safety of Canrenone as Add-on in Patients with Essential Hypertension-Italy) trial was designed to evaluate the efficacy in terms of blood pressure reduction, safety, and tolerability of two different dosages of canrenone as add-on therapy in patients already treated with ACE-I or ARBs and hydrochlorothiazide at the maximum dosage.

2 | MATERIALS AND METHODS

2.1 | Study design

This multicenter, phase IV, randomized, controlled, open-label, parallel group trial was conducted in different Italian hospitals. (See Appendix for a complete description of the hospitals involved). The first patient was enrolled on April 07, 2011 and the last on April 10, 2015. The last patient completed the treatment on July 17, 2015.

The study protocol was conducted in accordance with the Declaration of Helsinki and its amendments, and the Good Clinical Practice Guidelines. The study protocol was approved by the local Ethical Committee at each site. Clinical Trial Registration: Eudract number: 2010-023606-13; ClinicalTrials.gov NCT02687178.

Suitable patients, identified from a review of case notes and/or computerized clinic registers, were contacted by the investigators in person or by telephone. All patients provided written informed consent to participate prior to entering the study.

2.2 | Patients

We enrolled 175 Caucasian patients affected by uncomplicated, essential hypertension, not well controlled (SBP>140 mm Hg and/or DBP>90 mm Hg) by concomitant administration of ACE-I or ARBs and hydrochlorothiazide at the maximum dosage (25 mg/d).
We excluded patients with severe hypertension identified by blood pressure \( \geq 180/110 \) mm Hg, patients taking diuretics different from hydrochlorothiazide or patients taking other antihypertensive drugs other than ACE-I or ARBs. Patients were also excluded if they had a history of active hepatitis or cirrhosis, impaired renal function (defined as serum creatinine level higher than 1.5 mg/dL or estimated glomerular filtration rate lower 45 mL/min/1.73 m\(^2\)), or hyperpotassemia or diabetes. Patients with cardiovascular disease (CVD), or patients with congestive heart failure or a history of myocardial infarction or stroke or cerebrovascular conditions within 12 months before study enrollment also were excluded. Patients with previous hypersensitivity to canrenone were also excluded. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded.

### 2.3 Treatments

Patients fulfilling the inclusion and exclusion criteria were randomized to canrenone 50 mg or canrenone 100 mg once a day, in addition to their current therapy, for 3 months (Figure 1). To obtain an optimal balance, the medication was randomized in a stratified way, that is, in blocks of four subjects. Each block contained two subject numbers for canrenone 50 mg and two subject numbers for canrenone 100 mg. Each investigational center enrolled subjects sequentially starting with the lowest subject number and completing a fully randomized block before starting with a new randomized block.

Treatment allocation was assessed according to a randomization list generated by the sponsor. The treatments were delivered to the centers accordingly to the rate of enrollment. Blinding was not applicable because the study was open label.

Medication compliance was assessed by counting the number of pills returned at the time of specified clinic visits. At baseline, we weighed participants and gave them a bottle containing a supply of the study medication for at least 100 days. Throughout the study, we instructed patients to take their first dose of new medication on the day after they were given the study medication. At the same time, all unused medication was retrieved for inventory. All medications were provided to the participants free of charge.

### 2.4 Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination, vital signs, and a 12-lead electrocardiogram. We evaluated at baseline and after 3 months the following parameters: height, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), HR: heart rate, fasting plasma glucose (FPG), fasting plasma insulin (FPI), HOMA Index, total cholesterol (TC), HDL-cholesterol (HDL-C), triglycerides (TG), LDL-cholesterol (LDL-C), sodium, potassium, calcium, magnesium, plasma urea, creatinine, estimated glomerular filtration rate, uric acid, aldosterone, BNP, and galectin-3.

All plasma parameters were determined after a 12-hour overnight fast. Venous blood samples were taken for all patients between 08.00 and 09.00. We used plasma obtained by addition of Na\(_2\)EDTA, 1 mg/mL, and centrifuged at 3000 \( \times \) g for 15 minutes at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at \(-80^\circ\)C for no more than 3 months. All measurements were performed in a central laboratory.

Body mass index was calculated as weight in kilograms divided by the square of height in meters. Blood pressure measurements were obtained from each patient (using the right arm) in the seated position, using a standard mercury sphygmomanometer (Erkameter 3000, ERKA, Bad Tolz, Germany) (Korotkoff I and V) with a cuff of appropriate size. Blood pressure was measured by the same investigator at each visit, in the morning before daily drug intake and after the patient had rested for \( \geq 10 \) minutes in a quiet room. Three successive blood pressure readings were obtained at 1-minute intervals, and the mean of the three readings was calculated. Pulse pressure was calculated as the difference between the SBP and DBP.

Plasma glucose was assayed by glucose-oxidase method (GOD/PAP, Roche Diagnostics, Mannheim, Germany) with intra- and interassay coefficients of variability (CsV) of <2%. Plasma insulin was assayed with Phadiaseph insulin radioimmunoassay (RIA) (Pharmacia, Uppsala, Sweden) using a second antibody to separate the free and antibody-bound 125 I-insulin (intra- and interassay CsV: 4.6% and 7.3%, respectively).

The HOMA Index was calculated as the product of basal glucose (mmol/L) and insulin levels (\( \mu \)U/mL) divided by 22.5.

Total cholesterol and TG levels were determined using fully enzymatic techniques on a clinical chemistry analyzer (HITACHI 737; Hitachi, Tokyo, Japan); intra- and interassay CsV were 1.0 and 2.1 for TC measurement, and 0.9 and 2.4 for TG measurement, respectively. High-density lipoprotein cholesterol level was measured after precipitation of plasma apo B-containing lipoproteins with phosphotungstic acid; intra- and interassay CsV were 1.0 and 1.9, respectively, and LDL-C level was calculated by the Friedewald formula.

Estimated glomerular filtration rate was calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) equation.

Aldosterone was measured with a radioimmunoassay kit (Coat-A-Count, Diagnostic Products Corp., Los Angeles, CA, USA); intra- and interassay CsV were 5.3% and 8.4%, respectively.

Plasma galectin-3 levels were determined using a novel and optimized enzyme-linked immunosorbent assay kit (Galectin-3 Assay™, BG Medicine, Waltham, MA, USA) and were measured on a Bio-tekELx800 microplate reader (Biotek Instruments, Winooski, VT, USA). Calibration of the assay was performed according to the manufacturer’s recommendations, and values were normalized to a standard curve.
Plasma BNP was measured using the fully automated Access platform (Triage BNP reagents, Access Immunoassay Systems, REF 98200; Beckman Coulter, Inc., Fullerton, CA, USA). The intra- and interassay CsV for BNP were 4.2% and 6.3%, respectively.\textsuperscript{15}

2.5 | Statistical analysis

2.5.1 | Determination of sample size

The effect of canrenone administered as add-on therapy was clinically and statistically considered significant if the difference of the average of the clinic DBP between the value measured at baseline and that measured after 3 months of therapy was equal to or greater than 8 mm Hg. A sample of 32 subjects randomized in a ratio of 1:1, with a standard deviation of 8 mm Hg, would have allowed a 95% power to detect a significant difference with a two-tailed type I error (\(\alpha\)) equal to .05. Anticipating an incidence of dropout of about 20%, the sample size would have to be at least 178 subjects to have 148 evaluable subjects. The sample was rounded up to 180 patients.

2.5.2 | Statistics

Demographic data and all other clinically significant parameters were summarized and described to characterize the study population. Descriptive continuous variables were reported as mean, standard deviation, minimum, and maximum, while categorical descriptive variables were reported as absolute rates and percentages.

The analysis of the efficacy and safety variables for both canrenone 50 and 100 mg was carried out using the Student’s t test for paired data, comparing the values measured at the final visit with the values measured at the baseline visit. The Wilcoxon signed rank test was used in case of categorical data.

The analysis of the difference in efficacy and safety between doses of canrenone was carried out using the one-way analysis of variance (ANOVA) test, by comparing the reductions of the parameters (\(\Delta\)) between the baseline and the final visit produced by the two treatments. The Fisher’s exact test was used in case of categorical data. Statistical analysis of data was performed using the Statistical Package for Social

**FIGURE 2** CONSORT diagram showing the flow of patients through the study
3.1 | Study sample

One hundred and seventy-five patients were enrolled in this study: 88 were randomized to canrenone 50 mg and 87 to canrenone 100 mg. One hundred and fifty-nine patients completed the study. The flow of patients through the study is shown in Figure 2. Sixteen patients did not complete the study, and the reasons for premature withdrawal are explained in Figure 2. The characteristics of the enrolled patients are described in Table 1, together with antihypertensive treatment taken at the study start (ACE-I/ARBs), and concomitant medications.

3.2 | Blood pressure and heart rate

We recorded a decrease in SBP and DBP with both dosages of canrenone compared to baseline (P<.001 vs baseline), although the 100 mg dose was more effective than canrenone 50 mg in reducing blood pressure compared to baseline (Table 2). Regarding PP, both dosages were equally effective in reducing it compared to baseline (each P<.001), without differences between the two dosages. About 70% of patients treated with canrenone 50 mg and 83% of patients treated with canrenone 100 mg reached a reduction in DBP ≥8 mm Hg.

3.3 | Glyco-metabolic control

We did not observe any differences regarding FPG, FPI, or HOMA Index during treatment, both compared to baseline or between the two groups. Regarding lipid profile, TC, HDL-C, and LDL-C did not change, while Tg increased compared to baseline with canrenone 50 mg (P<.01), but not with canrenone 100 mg, although, in group-to-group comparison, no differences were recorded (Table 3).

3.4 | Electrolytes

Sodium, calcium, magnesium levels did not change, while potassium increased compared to baseline with both canrenone 50 mg, and with canrenone 100 mg (P<.01 vs baseline for both), without statistically significant differences between groups (Table 3).

### Table 1: Baseline characteristics (all randomized patients)

| Parameters                   | Canrenone 50 mg (n=87) | Canrenone 100 mg (n=88) |
|------------------------------|-------------------------|-------------------------|
| N                            | 87                      | 88                      |
| Sex (M/F)                    | 57/30                   | 56/32                   |
| Age (y)                      | 57.15±8.91              | 57.75±9.18              |
| Duration of hypertension (y) | 6.24±2.72               | 6.93±3.19               |
| Height (cm)                  | 169.84±9.79             | 169.94±9.39             |
| Weight (kg)                  | 78.90±12.36             | 79.59±14.79             |
| BMI (kg/m²)                  | 27.50±3.47              | 27.43±3.62              |

### Table 2: Variations in hemodynamic parameters over time

| Parameters                  | Canrenone 50 mg | Canrenone 100 mg | Δ 3 Months-baseline |
|-----------------------------|-----------------|-------------------|---------------------|
| SBP (mm Hg)                 | 153.97±8.95     | 133.71±12.53*     | −20.26±12.12        |
| DBP (mm Hg)                 | 92.95±8.49      | 82.37±9.24*       | −10.58±9.03         |
| PP (mm Hg)                  | 61.01±12.31     | 51.34±10.72*      | −9.67±10.87         |
| HR (beats/min)              | 72.72±7.49      | 70.71±8.34        | −2.01±7.68          |

*P<.001 vs baseline, **P<.05 vs canrenone 50 mg.

DBP, diastolic blood pressure; HR, heart rate; PP pulse pressure; SBP, systolic blood pressure.

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**Table 1:** Baseline characteristics (all randomized patients)

**Table 2:** Variations in hemodynamic parameters over time

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Data are mean±standard deviation (SD) or no. (%).
TABLE 3 Variations in metabolic parameters over time

| Parameters, mean±SD | Canrenone 50 mg | 3 mo | Δ 3 Months-baseline |
|---------------------|----------------|------|--------------------|
| Sodium (mEq/L)      | 141.41±2.58    | 141.05±3.23 | −0.36±2.96 |
| Calcium (mg/dL)     | 9.48±0.37      | 9.50±0.36  | 0.02±0.38 |
| Magnesium (mg/dL)   | 2.08±0.23      | 2.08±0.21  | 0.001±0.17 |
| Potassium (mEq/L)   | 4.25±0.43      | 4.50±0.45* | 0.25±0.50 |
| Creatinine (mg/dL)  | 0.93±0.19      | 0.95±0.20  | 0.02±0.15 |
| eGFR (mL/min/1.73 m²) | 83.10±16.67    | 81.45±18.35 | −1.65±12.43 |
| Plasma urea (mg/dL) | 38.87±9.15     | 42.01±12.18* | 3.14±11.33 |
| Uric acid (mg/dL)   | 5.86±1.61      | 5.67±1.58  | −0.19±1.37 |
| Aldosterone (pg/dL) | 58.64±54.67    | 77.76±72.14* | 19.12±74.61 |
| Galectine-3 (ng/mL) | 13.67±5.85     | 13.59±4.74  | −0.08±2.87 |
| BNP (pg/mL)         | 82.32±129.38   | 76.22±161.62 | −6.10±73.56 |
| FPG (mg/dL)         | 94.14±12.42    | 96.31±23.27 | 2.17±12.20 |
| FPI (μU/mL)         | 11.35±6.17     | 12.87±4.40  | 1.52±1.77 |
| HOMA Index          | 2.64±1.97      | 3.06±2.04  | 0.42±1.63 |
| TC (mg/dL)          | 196.06±37.37   | 195.63±37.02 | −0.43±28.09 |
| HDL-C (mg/dL)       | 51.31±11.68    | 52.82±16.75 | 1.51±13.23 |
| LDL-C (mg/dL)       | 127.19±37.53   | 123.78±96.32 | −3.41±30.62 |
| Tg (mg/dL)          | 124.37±53.50   | 138.13±58.38* | 13.76±46.14 |

| Parameters, mean±SD | Canrenone 100 mg | 3 mo | Δ 3 Months-baseline |
|---------------------|-----------------|------|--------------------|
| Sodium (mEq/L)      | 141.51±2.70     | 141.01±3.73 | −0.50±3.60 |
| Calcium (mg/dL)     | 9.44±0.47       | 9.54±0.64  | 0.10±0.64 |
| Magnesium (mg/dL)   | 2.10±0.20       | 2.07±0.22  | −0.03±0.19 |
| Potassium (mEq/L)   | 4.32±0.72       | 4.65±0.40* | 0.34±0.80 |
| Creatinine (mg/dL)  | 0.87±0.18       | 0.92±0.22* | 0.05±0.11 |
| eGFR (mL/min/1.73 m²) | 83.79±17.75    | 81.58±16.80 | −2.21±12.42 |
| Plasma urea (mg/dL) | 36.89±7.74      | 41.86±11.12* | 4.97±10.38 |
| Uric acid (mg/dL)   | 5.40±1.65       | 5.64±1.58  | 0.14±0.88 |
| Aldosterone (pg/dL) | 68.77±63.19     | 68.50±66.01 | −0.27±69.38** |
| Galectine-3 (ng/mL) | 14.18±4.71      | 13.74±4.74  | −0.44±3.54 |
| BNP (pg/mL)         | 87.00±130.43    | 74.17±113.31 | −12.83±56.47 |
| FPG (mg/dL)         | 94.44±15.23     | 97.74±18.05 | 3.30±10.94 |
| FPI (μU/mL)         | 11.24±6.03      | 11.56±6.27 | 0.32±0.24 |
| HOMA Index          | 2.62±1.96       | 2.79±1.97  | 0.17±1.74 |
| TC (mg/dL)          | 198.44±37.91    | 200.63±41.10 | 2.19±35.52 |
| HDL-C (mg/dL)       | 56.20±27.79     | 53.38±14.63 | −2.82±18.98 |
| LDL-C (mg/dL)       | 125.43±35.26    | 127.35±36.81 | 1.92±28.30 |
| Tg (mg/dL)          | 118.81±49.03    | 128.42±51.11 | 9.61±39.68 |

*P<.01 vs baseline; **P<.05 vs canrenone 50 mg.
eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HOMA, homeostasis model assessment; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation; Tg, triglycerides.
3.5 | Renal function

Plasma urea increased with both canrenone 50 mg and canrenone 100 mg (P<.01 compared to baseline for both), without differences between the two dosages. Regarding creatinine levels, they slightly increased with canrenone 100 mg (P<.01 vs baseline), although no variations of eGFR were observed in either groups. Uric acid levels did not change during the study (Table 3).

3.6 | Aldosterone, BNP, Galectin-3

There was an increase in aldosterone levels compared to baseline with canrenone 50 mg (P<.01 vs baseline), but not with canrenone 100 mg. No changes in BNP or galectin-3 were recorded (Table 3).

3.7 | Correlations

We found a significant inverse correlation between potassium levels and eGFR with both canrenone 50 mg (r=−.28; P<.05) and canrenone 100 mg (r=−.332; P<.01). We did not observe any correlation between SBP and eGFR with canrenone 50 mg (r=.108; P=.402), while there was a high significant correlation between SBP and eGFR with canrenone 100 mg (r=.334; P<.01). Furthermore, we found a significant correlation between DBP and eGFR, with both canrenone 50 mg (r=.362; P<.01) and canrenone 100 mg (r=.370; P<.01).

4 | DISCUSSION

The ESCAPE-IT trial confirmed that canrenone has a beneficial effect on blood pressure control, in line with what already reported in the literature by Fogari et al.,18 and which is similar to that reported with spironolactone.19,20 As expected, canrenone 100 mg was more effective than canrenone 50 mg in decreasing blood pressure. This greater efficacy was obtained without producing a greater increase in potassium levels compared to the lower dose. Both doses, in fact, gave a slight, similar increase in potassium, statistically significant, but not clinically relevant. In fact, the laboratory value for clinical significance for potassium was >5 mEq/L. Of course this applies to patients involved in this study, but it is possible that some patients who may start with a higher potassium level or may have a greater increase in potassium with canrenone may develop significant hyperkalaemia; to test this, a longer follow-up would be required and it is actually ongoing. Compared to data already published in the literature,21,22 in this study we recorded a neutral effect of canrenone on metabolic parameters; canrenone did not influence glycemia or HOMA Index or lipid profile, with just a slight increase in Tg levels, even if not clinically significant. This is in contrast with that already reported in the literature. In two randomized clinical trials, Derosa et al. reported that canrenone gave a significant decrease in FPI and HOMA Index, and an increase in M value, an index of insulin sensitivity, both compared to baseline and to placebo.21,22 In the studies by Derosa et al., canrenone also decreased Tg and glycemia and improved some inflammatory cytokines such as high sensitivity C-reactive protein and tumor necrosis factor-α.21,22 These contrasting results may be due to the longer period of administration of canrenone in these two studies, (6 months vs 3 months of the ESCAPE-IT trial). In addition, the characteristics of the study population involved were different; patients with metabolic syndrome in the studies by Derosa et al., and hypertensive patients in the ESCAPE-IT trial. Given that patients with metabolic syndrome have higher levels of glyceremia and a worse glycemic profile, this may be another reason for improvement of their glyco-metabolic control, compared to a neutral effect in the ESCAPE-IT trial.

Galexine-3 is a pleiotropic lectin with an important role in cell proliferation, adhesion, differentiation, angiogenesis, and apoptosis. Galexine-3 activates many profibrotic factors, promotes fibroblast proliferation and transformation, and mediates collagen production.23,24 Higher levels of galexine-3 have been associated with a worse prognosis in patients with acute respiratory distress syndrome.25 In our study, canrenone did not increase galexine-3 levels, suggesting that fibrosis did not increase, even if an echocardiographic examination was not performed to confirm this.

In contrast to previously published studies conducted with canrenone21,22 or with spironolactone in patients with resistant hypertension26, we did not observe a variation of aldosterone levels, which may be due to the short duration of the study or to the fact that canrenone was used in combination with ACE-I or ARB therapy, which can induce aldosterone escape, a phenomenon characterized by the inability of ACE-I or ARBs to reliably suppress aldosterone release.

The main limitation of our study is the lacking of a placebo group, but this is due to the fact that the aim of the study was not verifying whether canrenone lowers blood pressure, but to verify whether a higher dose of canrenone can give a greater decrease in blood pressure compared to a lower dose, without increasing adverse events. Another limitation is the brief period of observation; however, a follow-up of this study is currently ongoing. Moreover, this is the first study to report the effect of canrenone on blood pressure and metabolic parameters in hypertensive patients already taking ACE-I or ARBs and diuretic at the maximum dosage.

5 | CONCLUSION

Both canrenone dosages decreased blood pressure, with canrenone 100 mg more effective than the lower dose, with only a slight increase in potassium and creatinine levels, which were not clinically relevant. Neither treatments resulted in any increase in adverse events. Canrenone should be recommended in hypertensive patients already taking ACE-I or ARBs and diuretic at the maximum dosage.

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ETHICS

The study was performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments and the Good Clinical Practice Guidelines. The protocol was approved by the local Ethical Committee at each site. Informed consent was obtained from all individual participants included in the study.

CONFLICT OF INTEREST

Andrea Bestetti and Massimo Vanasia are employed by THERABEL GiEnne Pharma, Milano, Italy. The other authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors meet ICMJE authorship criteria. All authors approved the final version of the manuscript before submission.

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SUPPORTING INFORMATION

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