Spironolactone effect on the blood pressure of patients at risk of developing heart failure: an analysis from the HOMAGE trial

Short title: Spironolactone effect on blood pressure

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Abstract

Background: Uncontrolled blood pressure (BP) increases the risk of developing heart failure (HF). The effect of spironolactone on BP of patients at risk of developing HF is yet to be determined.

Aims: To evaluate the effect of spironolactone on the BP of patients at risk for HF and whether renin can predict spironolactone`s effect.

Methods: HOMAGE (Heart OMics in Aging) was a prospective multicenter randomized open-label blinded end-point (PROBE) trial including 527 patients at risk for developing HF randomly assigned to either spironolactone (25-50mg/day) or usual care alone for a maximum of 9 months. Sitting BP was assessed at baseline, month 1 and 9 (or last visit). Analysis of covariance (ANCOVA), mixed effects models, and structural modelling equations were used.

Results: The median (percentile$_{25-75}$) age was 73 (69-79) years, 26% were female, and >75% had history of hypertension. Overall, the baseline BP was 142/78mmHg. Patients with higher BP were older, more likely to have diabetes and less likely to have coronary artery disease, had greater left ventricular mass (LVM), and left atrial volume (LAV). Compared with usual care, by last visit, spironolactone changed SBP by -10.3 (-13.0 to -7.5)mmHg and DBP by -3.2 (-4.8 to -1.7)mmHg ($p<0.001$ for both). A higher proportion of patients on spironolactone had controlled BP <130/80mmHg (36 vs. 26%; $p=0.014$). Lower baseline renin levels predicted a greater response to spironolactone (interaction$_p$=0.041).

Conclusion: Spironolactone had a clinically important BP-lowering effect. Spironolactone should be considered for lowering blood pressure in patients who are at risk of developing HF.

Key-words: cardiovascular risk; hypertension; spironolactone; renin.

Introduction

Hypertension is the most prevalent cardiovascular condition worldwide and is a risk factor for developing heart failure (HF) [1, 2]. Prevention of new onset HF can be achieved with an optimal blood pressure (BP) control in patients with hypertension [3]. After the publication of SPRINT (Randomized Trial of Intensive versus Standard Blood-Pressure Control), showing a benefit of an intensive BP lowering strategy vs. a less intensive one in patients with high CV risk [4]; hypertension guidelines lowered the BP target to lower than 130/80 mmHg [5, 6].

In PATHWAY-2, spironolactone (compared to bisoprolol, doxazosin and placebo) was the most effective add-on BP-lowering treatment in patients with resistant hypertension [7]. However, the role of spironolactone for lowering and controlling BP in patients with a high risk of progressing towards HF, is not well established. HOMAGE (Heart OMics in Aging) was a prospective multicenter randomized open blinded end-point (PROBE) trial including people at risk for developing HF for assessing the effect of spironolactone on fibrosis and cardiac remodelling [8]. In HOMAGE, the effect of spironolactone in the BP of people with and without hypertension at baseline has not been reported yet [9]. Furthermore, there is a strong rationale supporting the hypothesis that spironolactone might have a more pronounced BP-lowering effect among people with lower renin levels, which can be a good surrogate of sodium retention [7].

In this prespecified secondary analysis, we investigated the effect of spironolactone on BP and its interaction with baseline renin levels, and whether BP could mediate the anti-fibrotic and anti-remodelling effects of spironolactone.

Methods

Trial design and population

The HOMAGE trial had a prospective, randomised, open-label, blinded-endpoint (PROBE), multicentre design, in which people at increased risk of developing HF were randomly assigned to receive either spironolactone or "control" - not receiving spironolactone or another mineralocorticoid receptor antagonist (MRA) (ClinicalTrials.gov Identifier: NCT02556450). The rationale, trial design and main results have been published[9]. The study was approved by all relevant ethics committees and regulatory bodies. All participants provided written informed consent prior to study-specific procedures. The main participating criteria included age of 65 or older (amended to 60 years during the course of the trial), cardiovascular risk defined by the presence of coronary artery disease or at least 2 of the following: diabetes, treated hypertension, microalbuminuria, abnormal ECG, and a NT-pro BNP between 125 and 1,000 ng/L (14.8 and 118.2 pmol/L) or BNP between 35 and 280 ng/L (4.1 and 33.1 pmol/L). The main exclusion criteria were glomerular filtration rate (eGFR) <30 mL/minute/1.73m2, serum potassium >5.0 mmol/L, left ventricular ejection fraction <45%, a diagnosis of HF or treatment with loop diuretics, and atrial fibrillation/flutter.

Endpoints, patients and follow-up

Participants were randomized to either spironolactone (25-50 mg/day; n =265) or control (n =262). The median (percentile$_{25\text{-}75}$) follow-up time was 8.9 (6.0-9.2) months. The primary endpoint was the interaction between the treatment and the baseline levels of galectin-3 for the change in serum concentrations of PIIINP from baseline to the end of follow-up ("9-month visit"). Secondary aims were to investigate the effects of spironolactone on the change (from baseline to the end of follow-up) of other markers of collagen metabolism PICP and collagen type I-C terminal telopeptide (CITP), NT-pro BNP, echocardiographic

measures of cardiac structure and function, and signs/symptoms. One-month changes were also assessed in exploratory analyses[8].

Blood pressure assessment

As specified in the protocol, at each main study visit (baseline, month 1, and month 9 [or last visit]), office BP was measured 3 times (with a 1-minute interval between measurements) with the participant in the sitting position after he/she had rested for at least 10 minutes. An electronic sphygmomanometer was used in the non-dominant arm and the mean of the 3 measurements was calculated. The devices and cuff sizes were used at the discretion of each participating centre. The BP measurements were performed in a quiet room where a study investigator could be present.

Renin measurement

Baseline plasma renin was determined using a proximity extension assay (PEA) technology (Olink Proseek® Multiplex), that provides Log2 normalized protein expression (NPX) data wherein a high protein value corresponds to a high protein concentration, but not an absolute quantification. A detailed description of the Olink® technology can be found on the website: https://www.olink.com/.

Statistical considerations

The characteristics of patients at baseline were compared between categories of SBP (<120, 120-139, 140-159, and ≥160 mmHg) and SBP ≥130 or DBP ≥80 mmHg (vs. <130/80 mmHg), using comparison of proportions, means or medians as appropriate. The BP change from baseline to month 1 and last visit was studied using analysis of covariance (ANCOVA), where a linear regression model was fitted, with the BP change as outcome variable, the binary variable to indicate the treatment group (control/spironolactone) as explanatory variable, and age, sex, eGFR plus the baseline BP value as adjustment variables. Residual analysis was

used to examine the fit of the model. No data transformation was required to meet the assumptions of linear regression. Treatment-by-covariate interaction terms were fitted in regression models using the BP changes from baseline to the last visit as outcome variable. The baseline covariates tested as interaction terms were age, sex, eGFR, galectin-3, body mass index (BMI), waist circumference (WC), use of angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), thiazides, and plasma renin levels. These variables were chosen due to their clinical importance (age, sex, renal function, obesity and use of background anti-HT therapy), galectin-3 was the prespecified interaction term in the HOMAGE trial[8], and renin was found to predict the response to spironolactone in the PATHWAY-2 trial[7]. The effect of spironolactone on BP was also assessed in baseline BP subgroups, ≥130/80 and <130/80 mmHg. Multilevel mixed effect models were used to assess the BP changes over time, using age, sex, eGFR and the baseline BP as fixed effects, plus an interaction between treatment and visit time (in months), and random effects fitted at the patient level. To assess whether the spironolactone effect on variables of interest previously found to be modified by the treatment (NT-pro BNP, PICP, body surface area indexed left ventricular mass [LVMi] and left atrial volume [LAVi][8]) was mediated by the change in SBP, structure equations modelling were used with the aforementioned variables of interest as dependent variables, the treatment (spironolactone or control) as the independent variable, and SBP change as the mediator variable. The direct, indirect and total effects were estimated. No data imputation was performed. No correction for multiplicity of tests was applied due to the exploratory nature of the study. The hypothesis that renin levels might interact with the effect of spironolactone on BP was prespecified because of the results of PATHWAY-2. All analyses were performed using Stata® (version 16, StataCorp LP).

Results

Baseline characteristics by blood pressure values

The median (percentile$_{25\text{-}75}$) age was 73 (69-79) years, 26% were female, and >75% had a history of hypertension. The mean baseline BP was 142/78 mmHg and 70% of the participants had a BP ≥130 or 80 mmHg. Patients with higher SBP were older, had a lower prevalence of coronary artery disease, and a greater prevalence of diabetes. They were more likely to use thiazide-type diuretics, and had greater LVMi and LAVi. The biomarker levels were not significantly different between groups. **Table 1**. The characteristics of the patients with a SBP ≥130 or a DBP ≥90 mmHg vs. those with a SBP <130 or DBP <80 mmHg is presented in the **Supplemental Table 1**. The proportion of patients with presumed "resistant hypertension" defined as a BP ≥130/80 mmHg plus the use of 3 or more anti-hypertensive drugs including a diuretic was low (2.8%; n =15).

Spironolactone effect on blood pressure

Spironolactone treatment changed SBP by -6.3 (-8.9 to -3.8) mmHg at month 1 and -10.1 (-12.8 to -7.4) at the last visit; the corresponding changes for DBP were -2.5 (-4.1 to -1.0) and -3.2 (-4.8 to -1.7) mmHg. **Table 2**. Patients whose baseline BP was ≥130/80 mmHg had a greater BP reduction with spironolactone treatment at last visit. **Table 3**. In the control group, patients with higher BP regressed towards a lower BP throughout follow-up, whereas patients with lower BP regressed towards a higher BP. Beyond lowering BP, spironolactone also avoided the BP increase in patients with lower baseline BP and more patients achieved an adequate BP control on the spironolactone group. **Figures 1** & **2**. The BP-lowering effect of spironolactone was not modified by age, sex, eGFR, diabetes, galectin-3, BMI, WC, ACEi, ARB or thiazide-diuretic use. **Figure 3**. However, the effect was modified by plasma renin

levels, where patients with lower renin had a greater BP reduction with spironolactone than patients with higher renin (p for interaction =0.041). **Figure 4**. Patients with higher renin (above the median) were older, more likely to be male, and to have diabetes and hypertension, they were more often treated with thiazides, had higher BMI, lower eGFR, hemoglobin, and PICP, and higher galectin-3 levels. Patients with lower renin levels had higher systolic and diastolic BP. Baseline renin levels were not significantly different between treatment groups. **Supplemental Table 2**.

Mediation analysis

The effect of spironolactone on LAVi could be partly (≈19%) mediated by the change in SBP (p =0.048). The effect on NT-pro BNP, PICP, and LVMi were less influenced by the SBP change. **Supplemental Table 3**. It should also be noted that the direct effect of spironolactone on LVMi was of small magnitude and did not reach statistical significance. The correlations between the change in SBP and LAVi, NT-pro BNP, PICP, and LVMi were weak (Spearman Rho <0.2 for all) and are presented in the **Supplemental Table 4**.

Discussion

Several clinically relevant observations are reported in this study. The BP-lowering effect of spironolactone in a population with high CV risk (and without resistant hypertension) was clinically important, with SBP reductions (vs. control) greater than 10 mmHg at 9 months. Lower plasma renin levels could identify patients in whom spironolactone was more effective in lowering BP; findings that are similar to those of the PATHWAY-2 study, where the BP-lowering effects of spironolactone were more marked among people with lower baseline renin [7]. Together, these findings support the "salt retention hypothesis" and suggest that, despite the neurohormonal activation, plasma renin can be suppressed by

sodium retention, and spironolactone may be more effective in patients with greater sodium retention and/or higher expression of the mineralocorticoid receptor, as supported by prior studies [10]. Moreover, in HOMAGE patients with lower baseline renin had higher systolic and diastolic BP, similar to the findings of other cohorts [11-15]. Therefore, spironolactone targeting the low renin physiology, can improve BP control [11].

Patients at risk for HF enrolled in HOMAGE share common characteristics with patients with HF and preserved ejection fraction (HFpEF) and with resistant hypertension [9]. In patients with HFpEF enrolled in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, spironolactone reduced SBP by -3.7 ± 0.9 mmHg [16, 17]. The difference was greater in TOPCAT patients with presumed resistant hypertension in whom spironolactone decreased SBP by −6.1 (−8.9 to −3.3) mmHg during the first 8 months of follow-up [18]. In the PATHWAY-2 trial, the difference in SBP with spironolactone vs. placebo was of -12.8 (-13.8 to -11.8) mmHg [7]. In HOMAGE the difference in SBP with spironolactone vs. control was of -10.1 (-12.8 to -7.4) mmHg and -11.9 (-15.2 to -8.7) mmHg among patients with baseline BP $\geq$130/80 mmHg, which is a similar effect to that observed in patients with resistant hypertension enrolled in PATHWAY-2 and greater than the effect observed in patients with HFpEF enrolled in TOPCAT. This difference may be explained by the differences in the characteristics of the patients and by the lower spironolactone doses used in TOPCAT where patients were started at 15 mg/day and the achieved doses were on average inferior to 25 mg/day [19].

The mediation analysis suggests that the effect of spironolactone on PICP change was not mediated by the BP drop, which may indicate a direct anti-fibrotic effect of spironolactone; an hypothesis that has also been supported by animal models [20]. Furthermore, when assessing the effect of spironolactone in multiple circulating protein

markers, the effect on the markers of collagen synthesis is the strongest [21], independently of BP [22]. The spironolactone effect on LAVi could have been partly mediated by the reduction in BP. The LAV may change in consequence of hemodynamic alterations, which supports our findings [23].

These findings can be applied to spironolactone doses commonly used in clinical practice (25-50 mg/day), as the dose of spironolactone used in the HOMAGE trial was similar to the dose used in PATHWAY-2 (25-50 mg/day) and in HF trials (25 mg/day up-titrated to 50, if tolerated.

Limitations

Blood pressure was measured in the clinics during the trial visits, which could have increased the BP values compared to home- or 24h ambulatory BP values [24]. However, due to consistency of the effects in subgroups and the replication of similar results in other settings and populations, these findings may be regarded as robust.

Conclusion

Spironolactone had a clinically important BP-lowering effect and should be considered for lowering blood pressure in patients who are at risk of developing HF.

Funding

HOMAGE was funded by a grant from the European Union 7th Framework Programme for Research and Technological Development (HEALTH-F7-305507 HOMAGE (EU FP7 305507 http://www.homage-hf.eu).

JPF, PR, NG, FZ are supported by the RHU Fight-HF, a public grant overseen by the French National Research Agency (ANR) as part of the second “Investissements d’Avenir” program

(reference: ANR-15-RHUS-0004), by the French PIA project “Lorraine Université d’Excellence” (reference: ANR-15-IDEX-04-LUE), Contrat de Plan Etat Lorraine IT2MP and FEDER Lorraine.

Disclosures

The authors report having no conflicts of interest with regards to the content of this manuscript.

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Table 1. Patients` characteristics by groups of baseline systolic blood pressure (in mmHg)

Characteristic	<120	120-139	140-159	≥160	p-value
N.	64	185	179	90	
Age, yr	71.5 ± 7.2	72.8 ± 6.3	74.0 ± 6.7	75.4 ± 5.9	0.001
Female	14 (21.9%)	40 (21.6%)	48 (26.8%)	30 (33.3%)	0.17
Smoker	7 (10.9%)	20 (10.8%)	12 (6.7%)	5 (5.6%)	0.36
CAD	54 (84.4%)	137 (74.1%)	125 (69.8%)	55 (61.1%)	0.013
MI	38 (70.4%)	85 (61.6%)	65 (52.0%)	23 (41.8%)	0.009
PCI	45 (83.3%)	96 (69.6%)	80 (64.0%)	37 (67.3%)	0.080
CABG	14 (25.9%)	40 (29.0%)	60 (48.0%)	22 (40.0%)	0.004
Diabetes	15 (23.4%)	82 (44.3%)	78 (43.6%)	40 (44.4%)	0.020
Hypertension	31 (48.4%)	147 (79.5%)	147 (82.1%)	82 (91.1%)	<0.001
Stroke/TIA	1 (1.6%)	10 (5.4%)	8 (4.5%)	9 (10.0%)	0.12
COPD	5 (7.8%)	10 (5.4%)	15 (8.4%)	2 (2.2%)	0.22
Antiplatelet agent	53 (82.8%)	149 (80.5%)	137 (76.5%)	67 (74.4%)	0.49
Beta-blocker	52 (81.3%)	127 (68.6%)	124 (69.3%)	56 (62.2%)	0.092
ACEi	30 (46.9%)	108 (58.4%)	89 (49.7%)	45 (50.0%)	0.25
ARB	17 (26.6%)	47 (25.4%)	45 (25.1%)	34 (37.8%)	0.13
CCB	6 (9.4%)	40 (21.6%)	43 (24.0%)	19 (21.1%)	0.099
Thiazide	5 (7.8%)	26 (14.1%)	31 (17.3%)	24 (26.7%)	0.011
Statin	54 (84.4%)	155 (83.8%)	150 (83.8%)	67 (74.4%)	0.21
BMI, Kg/m^2	28.0 ± 4.7	29.0 ± 5.3	28.8 ± 5.0	29.3 ± 4.9	0.48
SBP, mmHg	111.8 ± 5.8	130.5 ± 6.0	149.0 ± 6.1	174.0 ± 11.5	<0.001
DBP, mmHg	70.2 ± 8.8	76.6 ± 9.6	80.2 ± 10.0	84.5 ± 10.8	<0.001
Heart rate, bpm	60.1 ± 8.8	61.7 ± 9.6	62.7 ± 9.4	61.7 ± 10.1	0.32
LVEF, %	61.3 ± 6.3	61.9 ± 7.2	61.5 ± 6.3	64.0 ± 6.5	0.065
LVMi, g/m^2	92.5 ± 28.7	96.4 ± 24.9	99.2 ± 25.8	105.6 ± 27.9	0.018
LAVi, ml/m^2	29.6 ± 9.2	30.5 ± 7.8	32.9 ± 9.9	32.2 ± 9.0	0.045
E/E` ratio	9.3 ± 3.5	9.5 ± 3.3	10.1 ± 3.1	10.8 ± 3.5	0.016
E/A ratio	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.34
TAPSE, mm	20.9 ± 6.0	22.4 ± 6.7	21.4 ± 6.4	23.0 ± 6.4	0.16
MAPSE, mm	14.8 ± 3.2	15.6 ± 3.1	15.5 ± 3.3	15.6 ± 2.8	0.38
eGFR, ml/min	72.3 ± 18.5	74.3 ± 19.7	74.0 ± 18.6	71.7 ± 18.6	0.68
eGFR <60	17 (26.6%)	39 (21.1%)	37 (20.7%)	23 (25.6%)	0.65
Hemoglobin, g/dl	13.9 ± 1.6	14.1 ± 1.3	13.9 ± 1.4	14.0 ± 1.4	0.76
Sodium, mmol/l	138.9 ± 3.1	139.3 ± 2.9	139.5 ± 2.7	139.4 ± 2.7	0.63
Potassium, mmol/l	4.3 ± 0.4	4.3 ± 0.3	4.3 ± 0.4	4.3 ± 0.4	0.67
Urea, mmol/l	6.5 (5.5, 14.5)	9.0 (6.0, 15.0)	8.6 (5.6, 14.3)	9.5 (5.8, 13.6)	0.36
NT-pro BNP, ng/l	221 (137, 430)	191 (121, 299)	215 (143, 342)	247 (159, 369)	0.063
Galectin-3, ng/ml	17.9 ± 5.6	16.8 ± 5.0	17.0 ± 4.9	17.9 ± 6.1	0.24
PICP, ng/ml	84.1 ± 25.7	84.6 ± 26.4	83.8 ± 29.2	86.6 ± 26.1	0.88
PIIINP, ng/ml	7.7 ± 2.5	7.7 ± 2.5	7.7 ± 2.7	7.8 ± 2.7	0.99
CITP, ug/l	4.2 ± 2.1	4.2 ± 2.1	4.3 ± 2.5	4.2 ± 2.0	0.92
PICP/CITP ratio	23.8 ± 12.6	23.6 ± 12.1	22.4 ± 9.5	23.3 ± 9.4	0.71
Renin (NPX)	7.2 ± 0.7	7.1 ± 0.9	7.0 ± 0.9	6.8 ± 1.0	0.15

Legend: CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary-artery bypass grafting; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; LVMi, body surface indexed left ventricular mass; LAVi, body surface indexed left atrial volume; TAPSE, tricuspid annular plane systolic excursion; MAPSE, mitral annular plane systolic excursion; eGFR, estimated glomerular filtration rate; PICP, procollagen type I carboxy-terminal propeptide; PIIINP, procollagen type III N-terminal peptide; CITP, collagen type I carboxy-terminal telopeptide.

Table 2. Blood pressure effect of spironolactone in the trial population

	SBP change			
	Control	Spironolactone	Difference (95%CI)*	P-value
Month 1 (n=498)	-3.4 (16.1)	-9.5 (16.7)	-6.3 (-8.9 to -3.8)	<0.001
Month 9 (n=481)	-3.3 (19.5)	-13.2 (17.5)	-10.1 (-12.8 to -7.4)	<0.001
	DBP change			
	Control	Spironolactone	Difference (95%CI)*	P-value
Month 1 (n=498)	-0.1 (11.1)	-2.5 (8.4)	-2.5 (-4.1 to -1.0)	0.003
Month 9 (n=481)	-1.3 (10.0)	-4.4 (9.1)	-3.2 (-4.8 to -1.7)	<0.001

Legend: SBP, systolic blood pressure; DBP, diastolic blood pressure.

*No significant interaction was found between the spironolactone effect on the change of SBP or DBP and (baseline) age, sex, estimated glomerular filtration rate, galectin-3 levels body mass index, waist circumference, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, thiazides, and diabetes.

Table 3. Blood pressure effect of spironolactone by baseline blood pressure subgroups

BP≥130/80 mmHg				
	SBP change			
n=373	Control	Spironolactone	Difference (95%CI)*	P-value
From bsl to last visit	-5.3 (20.4)	-16.9 (17.1)	-11.9 (-15.2 to -8.7)	<0.001
	DBP change			
n=372	Control	Spironolactone	Difference (95%CI)*	P-value
From bsl to last visit	-2.1 (10.4)	-6.0 (9.0)	-3.8 (-5.6 to -2.0)	<0.001
BP<130/80 mmHg				
	SBP change			
n=108	Control	Spironolactone	Difference (95%CI)*	P-value
From bsl to last visit	3.6 (14.1)	0.1 (11.7)	-4.7 (-9.3 to -0.1)	0.045
	DBP change			
n=108	Control	Spironolactone	Difference (95%CI)*	P-value
From bsl to last visit	1.5 (8.0)	1.1 (7.3)	-0.7 (-3.5 to 2.1)	0.61

Legend: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*The BP lowering effect of spironolactone was greater in patients with higher baseline SBP (≥130/80 mmHg), p for interaction =0.015.

Figure 1. Treatment effect on blood pressure by baseline values

Legend: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure. BP $\geq$130/80mmHg SBP change N. =373 and DBP change N. =372. BP <130/80mmHg SBP change N. =108 and DBP change N. =108. See also the Table 3.

Baseline renin levels were similar between spironolactone and control groups: mean±SD =7.0±0.9 NPX in both groups, p =0.61.

Figure 2. Proportion of patients with controlled blood pressure over time

Legend: BP, blood pressure.

Spironolactone N. =265; Control N. =262.

Figure 3. Blood pressure lowering across age and renal function stratified by sex

Legend: SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate.

The effect was consistent across age, eGFR and sex (no interaction was observed; p for interaction >0.1 for all comparisons).

Spironolactone treatment & Male N. =205; Control & Male N. =187; Spironolactone treatment & Female N. =60; Control & Female N. =75.

Figure 4. Treatment effect across the baseline circulating renin levels

Caption: Change in systolic blood pressure from baseline to the last visit by treatment groups (spironolactone or control) with an interaction term by the baseline renin levels. The effect of spironolactone was of higher magnitude at lower baseline levels of renin.

Legend: SBP, systolic blood pressure; NPX, concentration in log2 normalized Olink® values. Baseline renin levels were similar between spironolactone and control groups: mean±SD =7.0±0.9 NPX in both groups, p =0.61.

See the methods section for more details.

Spironolactone effect on the blood pressure of patients at risk of developing heart failure: an analysis from the HOMAGE trial

Short title: Spironolactone effect on blood pressure

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Abstract

Background: Uncontrolled blood pressure (BP) increases the risk of developing heart failure (HF). The effect of spironolactone on BP of patients at risk of developing HF is yet to be determined.

Aims: To evaluate the effect of spironolactone on the BP of patients at risk for HF and whether renin can predict spironolactone`s effect.

Methods: HOMAGE (Heart OMics in Aging) was a prospective multicenter randomized open-label blinded end-point (PROBE) trial including 527 patients at risk for developing HF randomly assigned to either spironolactone (25-50mg/day) or usual care alone for a maximum of 9 months. Sitting BP was assessed at baseline, month 1 and 9 (or last visit). Analysis of covariance (ANCOVA), mixed effects models, and structural modelling equations were used.

Results: The median (percentile$_{25-75}$) age was 73 (69-79) years, 26% were female, and >75% had history of hypertension. Overall, the baseline BP was 142/78mmHg. Patients with higher BP were older, more likely to have diabetes and less likely to have coronary artery disease, had greater left ventricular mass (LVM), and left atrial volume (LAV). Compared with usual care, by last visit, spironolactone changed SBP by -10.3 (-13.0 to -7.5)mmHg and DBP by -3.2 (-4.8 to -1.7)mmHg ($p<0.001$ for both). A higher proportion of patients on spironolactone had controlled BP <130/80mmHg (36 vs. 26%; $p=0.014$). Lower baseline renin levels predicted a greater response to spironolactone (interaction$_p$=0.041).

Conclusion: Spironolactone had a clinically important BP-lowering effect. Spironolactone should be considered for lowering blood pressure in patients who are at risk of developing HF.

Key-words: cardiovascular risk; hypertension; spironolactone; renin.

Introduction

Hypertension is the most prevalent cardiovascular condition worldwide and is a risk factor for developing heart failure (HF) [1, 2]. Prevention of new onset HF can be achieved with an optimal blood pressure (BP) control in patients with hypertension [3]. After the publication of SPRINT (Randomized Trial of Intensive versus Standard Blood-Pressure Control), showing a benefit of an intensive BP lowering strategy vs. a less intensive one in patients with high CV risk [4]; hypertension guidelines lowered the BP target to lower than 130/80 mmHg [5, 6].

In PATHWAY-2, spironolactone (compared to bisoprolol, doxazosin and placebo) was the most effective add-on BP-lowering treatment in patients with resistant hypertension [7]. However, the role of spironolactone for lowering and controlling BP in patients with a high risk of progressing towards HF, is not well established. HOMAGE (Heart OMics in Aging) was a prospective multicenter randomized open blinded end-point (PROBE) trial including people at risk for developing HF for assessing the effect of spironolactone on fibrosis and cardiac remodelling [8]. In HOMAGE, the effect of spironolactone in the BP of people with and without hypertension at baseline has not been reported yet [9]. Furthermore, there is a strong rationale supporting the hypothesis that spironolactone might have a more pronounced BP-lowering effect among people with lower renin levels, which can be a good surrogate of sodium retention [7].

In this prespecified secondary analysis, we investigated the effect of spironolactone on BP and its interaction with baseline renin levels, and whether BP could mediate the anti-fibrotic and anti-remodelling effects of spironolactone.

Methods

Trial design and population

The HOMAGE trial had a prospective, randomised, open-label, blinded-endpoint (PROBE), multicentre design, in which people at increased risk of developing HF were randomly assigned to receive either spironolactone or "control" - not receiving spironolactone or another mineralocorticoid receptor antagonist (MRA) (ClinicalTrials.gov Identifier: NCT02556450). The rationale, trial design and main results have been published[9]. The study was approved by all relevant ethics committees and regulatory bodies. All participants provided written informed consent prior to study-specific procedures. The main participating criteria included age of 65 or older (amended to 60 years during the course of the trial), cardiovascular risk defined by the presence of coronary artery disease or at least 2 of the following: diabetes, treated hypertension, microalbuminuria, abnormal ECG, and a NT-pro BNP between 125 and 1,000 ng/L (14.8 and 118.2 pmol/L) or BNP between 35 and 280 ng/L (4.1 and 33.1 pmol/L). The main exclusion criteria were glomerular filtration rate (eGFR) <30 mL/minute/1.73m2, serum potassium >5.0 mmol/L, left ventricular ejection fraction <45%, a diagnosis of HF or treatment with loop diuretics, and atrial fibrillation/flutter.

Endpoints, patients and follow-up

Participants were randomized to either spironolactone (25-50 mg/day; n =265) or control (n =262). The median (percentile$_{25\text{-}75}$) follow-up time was 8.9 (6.0-9.2) months. The primary endpoint was the interaction between the treatment and the baseline levels of galectin-3 for the change in serum concentrations of PIIINP from baseline to the end of follow-up ("9-month visit"). Secondary aims were to investigate the effects of spironolactone on the change (from baseline to the end of follow-up) of other markers of collagen metabolism PICP and collagen type I-C terminal telopeptide (CITP), NT-pro BNP, echocardiographic

measures of cardiac structure and function, and signs/symptoms. One-month changes were also assessed in exploratory analyses[8].

Blood pressure assessment

As specified in the protocol, at each main study visit (baseline, month 1, and month 9 [or last visit]), office BP was measured 3 times (with a 1-minute interval between measurements) with the participant in the sitting position after he/she had rested for at least 10 minutes. An electronic sphygmomanometer was used in the non-dominant arm and the mean of the 3 measurements was calculated. The devices and cuff sizes were used at the discretion of each participating centre. The BP measurements were performed in a quiet room where a study investigator could be present.

Renin measurement

Baseline plasma renin was determined using a proximity extension assay (PEA) technology (Olink Proseek® Multiplex), that provides Log2 normalized protein expression (NPX) data wherein a high protein value corresponds to a high protein concentration, but not an absolute quantification. A detailed description of the Olink® technology can be found on the website: https://www.olink.com/.

Statistical considerations

The characteristics of patients at baseline were compared between categories of SBP (<120, 120-139, 140-159, and ≥160 mmHg) and SBP ≥130 or DBP ≥80 mmHg (vs. <130/80 mmHg), using comparison of proportions, means or medians as appropriate. The BP change from baseline to month 1 and last visit was studied using analysis of covariance (ANCOVA), where a linear regression model was fitted, with the BP change as outcome variable, the binary variable to indicate the treatment group (control/spironolactone) as explanatory variable, and age, sex, eGFR plus the baseline BP value as adjustment variables. Residual analysis was

used to examine the fit of the model. No data transformation was required to meet the assumptions of linear regression. Treatment-by-covariate interaction terms were fitted in regression models using the BP changes from baseline to the last visit as outcome variable. The baseline covariates tested as interaction terms were age, sex, eGFR, galectin-3, body mass index (BMI), waist circumference (WC), use of angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), thiazides, and plasma renin levels. These variables were chosen due to their clinical importance (age, sex, renal function, obesity and use of background anti-HT therapy), galectin-3 was the prespecified interaction term in the HOMAGE trial[8], and renin was found to predict the response to spironolactone in the PATHWAY-2 trial[7]. The effect of spironolactone on BP was also assessed in baseline BP subgroups, ≥130/80 and <130/80 mmHg. Multilevel mixed effect models were used to assess the BP changes over time, using age, sex, eGFR and the baseline BP as fixed effects, plus an interaction between treatment and visit time (in months), and random effects fitted at the patient level. To assess whether the spironolactone effect on variables of interest previously found to be modified by the treatment (NT-pro BNP, PICP, body surface area indexed left ventricular mass [LVMi] and left atrial volume [LAVi][8]) was mediated by the change in SBP, structure equations modelling were used with the aforementioned variables of interest as dependent variables, the treatment (spironolactone or control) as the independent variable, and SBP change as the mediator variable. The direct, indirect and total effects were estimated. No data imputation was performed. No correction for multiplicity of tests was applied due to the exploratory nature of the study. The hypothesis that renin levels might interact with the effect of spironolactone on BP was prespecified because of the results of PATHWAY-2. All analyses were performed using Stata® (version 16, StataCorp LP).

Results

Baseline characteristics by blood pressure values

The median (percentile$_{25\text{-}75}$) age was 73 (69-79) years, 26% were female, and >75% had a history of hypertension. The mean baseline BP was 142/78 mmHg and 70% of the participants had a BP ≥130 or 80 mmHg. Patients with higher SBP were older, had a lower prevalence of coronary artery disease, and a greater prevalence of diabetes. They were more likely to use thiazide-type diuretics, and had greater LVMi and LAVi. The biomarker levels were not significantly different between groups. **Table 1**. The characteristics of the patients with a SBP ≥130 or a DBP ≥90 mmHg vs. those with a SBP <130 or DBP <80 mmHg is presented in the **Supplemental Table 1**. The proportion of patients with presumed "resistant hypertension" defined as a BP ≥130/80 mmHg plus the use of 3 or more anti-hypertensive drugs including a diuretic was low (2.8%; n =15).

Spironolactone effect on blood pressure

Spironolactone treatment changed SBP by -6.3 (-8.9 to -3.8) mmHg at month 1 and -10.1 (-12.8 to -7.4) at the last visit; the corresponding changes for DBP were -2.5 (-4.1 to -1.0) and -3.2 (-4.8 to -1.7) mmHg. **Table 2**. Patients whose baseline BP was ≥130/80 mmHg had a greater BP reduction with spironolactone treatment at last visit. **Table 3**. In the control group, patients with higher BP regressed towards a lower BP throughout follow-up, whereas patients with lower BP regressed towards a higher BP. Beyond lowering BP, spironolactone also avoided the BP increase in patients with lower baseline BP and more patients achieved an adequate BP control on the spironolactone group. **Figures 1** & **2**. The BP-lowering effect of spironolactone was not modified by age, sex, eGFR, diabetes, galectin-3, BMI, WC, ACEi, ARB or thiazide-diuretic use. **Figure 3**. However, the effect was modified by plasma renin

levels, where patients with lower renin had a greater BP reduction with spironolactone than patients with higher renin (p for interaction =0.041). **Figure 4**. Patients with higher renin (above the median) were older, more likely to be male, and to have diabetes and hypertension, they were more often treated with thiazides, had higher BMI, lower eGFR, hemoglobin, and PICP, and higher galectin-3 levels. Patients with lower renin levels had higher systolic and diastolic BP. Baseline renin levels were not significantly different between treatment groups. **Supplemental Table 2**.

Mediation analysis

The effect of spironolactone on LAVi could be partly (≈19%) mediated by the change in SBP (p =0.048). The effect on NT-pro BNP, PICP, and LVMi were less influenced by the SBP change. **Supplemental Table 3**. It should also be noted that the direct effect of spironolactone on LVMi was of small magnitude and did not reach statistical significance. The correlations between the change in SBP and LAVi, NT-pro BNP, PICP, and LVMi were weak (Spearman Rho <0.2 for all) and are presented in the **Supplemental Table 4**.

Discussion

Several clinically relevant observations are reported in this study. The BP-lowering effect of spironolactone in a population with high CV risk (and without resistant hypertension) was clinically important, with SBP reductions (vs. control) greater than 10 mmHg at 9 months. Lower plasma renin levels could identify patients in whom spironolactone was more effective in lowering BP; findings that are similar to those of the PATHWAY-2 study, where the BP-lowering effects of spironolactone were more marked among people with lower baseline renin [7]. Together, these findings support the "salt retention hypothesis" and suggest that, despite the neurohormonal activation, plasma renin can be suppressed by

sodium retention, and spironolactone may be more effective in patients with greater sodium retention and/or higher expression of the mineralocorticoid receptor, as supported by prior studies [10]. Moreover, in HOMAGE patients with lower baseline renin had higher systolic and diastolic BP, similar to the findings of other cohorts [11-15]. Therefore, spironolactone targeting the low renin physiology, can improve BP control [11].

Patients at risk for HF enrolled in HOMAGE share common characteristics with patients with HF and preserved ejection fraction (HFpEF) and with resistant hypertension [9]. In patients with HFpEF enrolled in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, spironolactone reduced SBP by -3.7 ± 0.9 mmHg [16, 17]. The difference was greater in TOPCAT patients with presumed resistant hypertension in whom spironolactone decreased SBP by −6.1 (−8.9 to −3.3) mmHg during the first 8 months of follow-up [18]. In the PATHWAY-2 trial, the difference in SBP with spironolactone vs. placebo was of -12.8 (-13.8 to -11.8) mmHg [7]. In HOMAGE the difference in SBP with spironolactone vs. control was of -10.1 (-12.8 to -7.4) mmHg and -11.9 (-15.2 to -8.7) mmHg among patients with baseline BP $\geq$130/80 mmHg, which is a similar effect to that observed in patients with resistant hypertension enrolled in PATHWAY-2 and greater than the effect observed in patients with HFpEF enrolled in TOPCAT. This difference may be explained by the differences in the characteristics of the patients and by the lower spironolactone doses used in TOPCAT where patients were started at 15 mg/day and the achieved doses were on average inferior to 25 mg/day [19].

The mediation analysis suggests that the effect of spironolactone on PICP change was not mediated by the BP drop, which may indicate a direct anti-fibrotic effect of spironolactone; an hypothesis that has also been supported by animal models [20]. Furthermore, when assessing the effect of spironolactone in multiple circulating protein

markers, the effect on the markers of collagen synthesis is the strongest [21], independently of BP [22]. The spironolactone effect on LAVi could have been partly mediated by the reduction in BP. The LAV may change in consequence of hemodynamic alterations, which supports our findings [23].

These findings can be applied to spironolactone doses commonly used in clinical practice (25-50 mg/day), as the dose of spironolactone used in the HOMAGE trial was similar to the dose used in PATHWAY-2 (25-50 mg/day) and in HF trials (25 mg/day up-titrated to 50, if tolerated.

Limitations

Blood pressure was measured in the clinics during the trial visits, which could have increased the BP values compared to home- or 24h ambulatory BP values [24]. However, due to consistency of the effects in subgroups and the replication of similar results in other settings and populations, these findings may be regarded as robust.

Conclusion

Spironolactone had a clinically important BP-lowering effect and should be considered for lowering blood pressure in patients who are at risk of developing HF.

Funding

HOMAGE was funded by a grant from the European Union 7th Framework Programme for Research and Technological Development (HEALTH-F7-305507 HOMAGE (EU FP7 305507 http://www.homage-hf.eu).

JPF, PR, NG, FZ are supported by the RHU Fight-HF, a public grant overseen by the French National Research Agency (ANR) as part of the second “Investissements d’Avenir” program

(reference: ANR-15-RHUS-0004), by the French PIA project “Lorraine Université d’Excellence” (reference: ANR-15-IDEX-04-LUE), Contrat de Plan Etat Lorraine IT2MP and FEDER Lorraine.

Disclosures

The authors report having no conflicts of interest with regards to the content of this manuscript.

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Table 1. Patients` characteristics by groups of baseline systolic blood pressure (in mmHg)

Characteristic	<120	120-139	140-159	≥160	p-value
N.	64	185	179	90	
Age, yr	71.5 ± 7.2	72.8 ± 6.3	74.0 ± 6.7	75.4 ± 5.9	0.001
Female	14 (21.9%)	40 (21.6%)	48 (26.8%)	30 (33.3%)	0.17
Smoker	7 (10.9%)	20 (10.8%)	12 (6.7%)	5 (5.6%)	0.36
CAD	54 (84.4%)	137 (74.1%)	125 (69.8%)	55 (61.1%)	0.013
MI	38 (70.4%)	85 (61.6%)	65 (52.0%)	23 (41.8%)	0.009
PCI	45 (83.3%)	96 (69.6%)	80 (64.0%)	37 (67.3%)	0.080
CABG	14 (25.9%)	40 (29.0%)	60 (48.0%)	22 (40.0%)	0.004
Diabetes	15 (23.4%)	82 (44.3%)	78 (43.6%)	40 (44.4%)	0.020
Hypertension	31 (48.4%)	147 (79.5%)	147 (82.1%)	82 (91.1%)	<0.001
Stroke/TIA	1 (1.6%)	10 (5.4%)	8 (4.5%)	9 (10.0%)	0.12
COPD	5 (7.8%)	10 (5.4%)	15 (8.4%)	2 (2.2%)	0.22
Antiplatelet agent	53 (82.8%)	149 (80.5%)	137 (76.5%)	67 (74.4%)	0.49
Beta-blocker	52 (81.3%)	127 (68.6%)	124 (69.3%)	56 (62.2%)	0.092
ACEi	30 (46.9%)	108 (58.4%)	89 (49.7%)	45 (50.0%)	0.25
ARB	17 (26.6%)	47 (25.4%)	45 (25.1%)	34 (37.8%)	0.13
CCB	6 (9.4%)	40 (21.6%)	43 (24.0%)	19 (21.1%)	0.099
Thiazide	5 (7.8%)	26 (14.1%)	31 (17.3%)	24 (26.7%)	0.011
Statin	54 (84.4%)	155 (83.8%)	150 (83.8%)	67 (74.4%)	0.21
BMI, Kg/m^2	28.0 ± 4.7	29.0 ± 5.3	28.8 ± 5.0	29.3 ± 4.9	0.48
SBP, mmHg	111.8 ± 5.8	130.5 ± 6.0	149.0 ± 6.1	174.0 ± 11.5	<0.001
DBP, mmHg	70.2 ± 8.8	76.6 ± 9.6	80.2 ± 10.0	84.5 ± 10.8	<0.001
Heart rate, bpm	60.1 ± 8.8	61.7 ± 9.6	62.7 ± 9.4	61.7 ± 10.1	0.32
LVEF, %	61.3 ± 6.3	61.9 ± 7.2	61.5 ± 6.3	64.0 ± 6.5	0.065
LVMi, g/m^2	92.5 ± 28.7	96.4 ± 24.9	99.2 ± 25.8	105.6 ± 27.9	0.018
LAVi, ml/m^2	29.6 ± 9.2	30.5 ± 7.8	32.9 ± 9.9	32.2 ± 9.0	0.045
E/E` ratio	9.3 ± 3.5	9.5 ± 3.3	10.1 ± 3.1	10.8 ± 3.5	0.016
E/A ratio	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.34
TAPSE, mm	20.9 ± 6.0	22.4 ± 6.7	21.4 ± 6.4	23.0 ± 6.4	0.16
MAPSE, mm	14.8 ± 3.2	15.6 ± 3.1	15.5 ± 3.3	15.6 ± 2.8	0.38
eGFR, ml/min	72.3 ± 18.5	74.3 ± 19.7	74.0 ± 18.6	71.7 ± 18.6	0.68
eGFR <60	17 (26.6%)	39 (21.1%)	37 (20.7%)	23 (25.6%)	0.65
Hemoglobin, g/dl	13.9 ± 1.6	14.1 ± 1.3	13.9 ± 1.4	14.0 ± 1.4	0.76
Sodium, mmol/l	138.9 ± 3.1	139.3 ± 2.9	139.5 ± 2.7	139.4 ± 2.7	0.63
Potassium, mmol/l	4.3 ± 0.4	4.3 ± 0.3	4.3 ± 0.4	4.3 ± 0.4	0.67
Urea, mmol/l	6.5 (5.5, 14.5)	9.0 (6.0, 15.0)	8.6 (5.6, 14.3)	9.5 (5.8, 13.6)	0.36
NT-pro BNP, ng/l	221 (137, 430)	191 (121, 299)	215 (143, 342)	247 (159, 369)	0.063
Galectin-3, ng/ml	17.9 ± 5.6	16.8 ± 5.0	17.0 ± 4.9	17.9 ± 6.1	0.24
PICP, ng/ml	84.1 ± 25.7	84.6 ± 26.4	83.8 ± 29.2	86.6 ± 26.1	0.88
PIIINP, ng/ml	7.7 ± 2.5	7.7 ± 2.5	7.7 ± 2.7	7.8 ± 2.7	0.99
CITP, ug/l	4.2 ± 2.1	4.2 ± 2.1	4.3 ± 2.5	4.2 ± 2.0	0.92
PICP/CITP ratio	23.8 ± 12.6	23.6 ± 12.1	22.4 ± 9.5	23.3 ± 9.4	0.71
Renin (NPX)	7.2 ± 0.7	7.1 ± 0.9	7.0 ± 0.9	6.8 ± 1.0	0.15

Legend: CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary-artery bypass grafting; TIA, transient ischemic attack; COPD, chronic obstructive pulmonary disease; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; LVMi, body surface indexed left ventricular mass; LAVi, body surface indexed left atrial volume; TAPSE, tricuspid annular plane systolic excursion; MAPSE, mitral annular plane systolic excursion; eGFR, estimated glomerular filtration rate; PICP, procollagen type I carboxy-terminal propeptide; PIIINP, procollagen type III N-terminal peptide; CITP, collagen type I carboxy-terminal telopeptide.

Table 2. Blood pressure effect of spironolactone in the trial population

	SBP change			
	Control	Spironolactone	Difference (95%CI)*	P-value
Month 1 (n=498)	-3.4 (16.1)	-9.5 (16.7)	-6.3 (-8.9 to -3.8)	<0.001
Month 9 (n=481)	-3.3 (19.5)	-13.2 (17.5)	-10.1 (-12.8 to -7.4)	<0.001
	DBP change			
	Control	Spironolactone	Difference (95%CI)*	P-value
Month 1 (n=498)	-0.1 (11.1)	-2.5 (8.4)	-2.5 (-4.1 to -1.0)	0.003
Month 9 (n=481)	-1.3 (10.0)	-4.4 (9.1)	-3.2 (-4.8 to -1.7)	<0.001

Legend: SBP, systolic blood pressure; DBP, diastolic blood pressure.

*No significant interaction was found between the spironolactone effect on the change of SBP or DBP and (baseline) age, sex, estimated glomerular filtration rate, galectin-3 levels body mass index, waist circumference, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, thiazides, and diabetes.

Table 3. Blood pressure effect of spironolactone by baseline blood pressure subgroups

BP≥130/80 mmHg				
	SBP change			
n=373	Control	Spironolactone	Difference (95%CI)*	P-value
From bsl to last visit	-5.3 (20.4)	-16.9 (17.1)	-11.9 (-15.2 to -8.7)	<0.001
	DBP change			
n=372	Control	Spironolactone	Difference (95%CI)*	P-value
From bsl to last visit	-2.1 (10.4)	-6.0 (9.0)	-3.8 (-5.6 to -2.0)	<0.001
BP<130/80 mmHg				
	SBP change			
n=108	Control	Spironolactone	Difference (95%CI)*	P-value
From bsl to last visit	3.6 (14.1)	0.1 (11.7)	-4.7 (-9.3 to -0.1)	0.045
	DBP change			
n=108	Control	Spironolactone	Difference (95%CI)*	P-value
From bsl to last visit	1.5 (8.0)	1.1 (7.3)	-0.7 (-3.5 to 2.1)	0.61

Legend: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

*The BP lowering effect of spironolactone was greater in patients with higher baseline SBP (≥130/80 mmHg), p for interaction =0.015.

Figure 1. Treatment effect on blood pressure by baseline values

Legend: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure. BP $\geq$130/80mmHg SBP change N. =373 and DBP change N. =372. BP <130/80mmHg SBP change N. =108 and DBP change N. =108. See also the Table 3.

Baseline renin levels were similar between spironolactone and control groups: mean±SD =7.0±0.9 NPX in both groups, p =0.61.

Figure 2. Proportion of patients with controlled blood pressure over time

Legend: BP, blood pressure.

Spironolactone N. =265; Control N. =262.

Figure 3. Blood pressure lowering across age and renal function stratified by sex

Legend: SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate.

The effect was consistent across age, eGFR and sex (no interaction was observed; p for interaction >0.1 for all comparisons).

Spironolactone treatment & Male N. =205; Control & Male N. =187; Spironolactone treatment & Female N. =60; Control & Female N. =75.

Figure 4. Treatment effect across the baseline circulating renin levels

Caption: Change in systolic blood pressure from baseline to the last visit by treatment groups (spironolactone or control) with an interaction term by the baseline renin levels. The effect of spironolactone was of higher magnitude at lower baseline levels of renin.

Legend: SBP, systolic blood pressure; NPX, concentration in log2 normalized Olink® values. Baseline renin levels were similar between spironolactone and control groups: mean±SD =7.0±0.9 NPX in both groups, p =0.61.

See the methods section for more details.