Addition of Spironolactone in Patients With Resistant Arterial Hypertension (ASPIRANT)

A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract—There is currently limited data on which drug should be used to improve blood pressure (BP) control in patients with resistant hypertension. This study was designed to assess the effect of the addition of 25 mg of spironolactone on BP in patients with resistant arterial hypertension. Patients with office systolic BP >140 mm Hg or diastolic BP >90 mm Hg despite treatment with at least 3 antihypertensive drugs, including a diuretic, were enrolled in this double-blind, placebo-controlled, multicenter trial. One hundred seventeen patients were randomly assigned to receive spironolactone (n=59) or a placebo (n=58) as an add-on to their antihypertensive medication, by the method of simple randomization. Analyses were done with 111 patients (55 in the spironolactone and 56 in the placebo groups). At 8 weeks, the primary end points, a difference in mean fall of BP on daytime ambulatory BP monitoring (ABPM), between the groups was −5.4 mm Hg (95% CI −10.0; −0.8) for systolic BP (*P*=0.024) and −1.0 mm Hg (95% CI −4.0; 2.0) for diastolic BP (*P*=0.358). The APBM nighttime systolic, 24-hour ABPM systolic, and office systolic BP values were significantly decreased by spironolactone (difference of −8.6, −9.8, and −6.5 mm Hg; *P*=0.011, 0.004, and 0.011), whereas the fall of the respective diastolic BP values was not significant (−3.0, −1.0, and −2.5 mm Hg; *P*=0.079, 0.405, and 0.079). The adverse events in both groups were comparable. In conclusion, spironolactone is an effective drug for lowering systolic BP in patients with resistant arterial hypertension. (*Hypertension*. 2011;57:1069-1075.) ● Online Data Supplement

Key Words: resistant hypertension ■ spironolactone ■ clinical trials ■ blood pressure ■ ambulatory blood pressure monitoring

Resistant hypertension is a common clinical problem faced by both primary care clinicians and specialists worldwide. It is defined as blood pressure (BP) that remains above goal despite the concurrent use of 3 antihypertensive agents of different classes prescribed at optimal dosages; one of the 3 agents used should be a diuretic.[1]

The exact prevalence of resistant hypertension is not known, but it is estimated from large clinical trials to affect at least 10% to 15% of all hypertensive patients.[2,3] If no secondary cause of hypertension is found, the use of multidrug treatment regimens including 3, 4, or more antihypertensive drugs is usually necessary to lower BP and thus prevent future cardiovascular events.[4]

Spironolactone is a mineralocorticoid receptor antagonist that was shown to lower BP effectively in both general hypertensive patients and patients with primary aldosteronism.[5–7] A number of small, uncontrolled trials showed the positive effect of small doses of spironolactone in lowering BP in patients with resistant arterial hypertension.[8–11] In the nonrandomized post hoc analysis of the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm, the addition of spironolactone to a triple-drug treatment led, during an average of 1.3 years of follow-up, to a significant decrease of systolic BP of 21.9 mm Hg and diastolic BP of 9.5 mm Hg.[12] However, evidence from randomized trials was lacking, and it was necessary to provide definite proof for the efficacy of spironolactone as an add-on treatment in resistant hypertension.[12,13] Therefore, we designed a prospective randomized trial to evaluate the effect of adding spironolactone in patients with resistant arterial hypertension. We decided to administer a low dose of spironolactone (25 mg/day) in the trial, since the effect of this dose seemed to be substantial

according to data from previous trials, and we wanted to avoid possible side effects.

Methods

Study Design and Population

ASPIRANT (addition of spironolactone in patients with resistant arterial hypertension) was an investigator-led, prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. The design of the trial has been described previously.[14] We enrolled patients older than 18 years with resistant arterial hypertension. Resistant hypertension was defined as office systolic BP >140 mm Hg or diastolic BP >90 mm Hg despite being treated with at least 3 antihypertensive drugs, including a diuretic. Patients with diabetes or chronic kidney disease (defined as serum creatinine >133 μmol/L or proteinuria >300 mg/day) were enrolled if the office BP was >130/80 mm Hg.

The study was done in accordance with the principles of the Helsinki declaration. The study protocol was approved by the ethical review committees at all six participating secondary or tertiary care centers and by the State Institute for Drug Control of the Czech Republic. Written informed consent was obtained from all patients before enrollment. This study was registered at clinicaltrials.gov as NCT00524615, and the EudraCT number of the trial was 2007-003558-27.

For safety reasons, we excluded all patients with severe hypertension (systolic BP >180 mm Hg or diastolic BP >110 mm Hg) who needed an immediate adjustment of treatment, renal insufficiency with serum creatinine >180 μmol/L or glomerular filtration rate <40 mL/min calculated by the Modification of Diet in Renal Disease formula,[15] hyperkalemia >5.4 mmol/L, hyponatremia <130 mmol/L, and porphyria; pregnant or lactating women or women of fertile age not using effective contraception; and patients with known prior hypersensitivity to the drug Verospiron (spironolactone; Richter Gedeon Ltd) or who are currently using any aldosterone antagonist (spironolactone, eplerenone or canreonate).

Procedures

Patients were randomly assigned in a 1:1 ratio to receive either spironolactone at a dose of 25 mg once daily or a placebo once daily in the morning, as an add-on to their current antihypertensive therapy, by the method of simple randomization without stratification. Patients received color-marked, blinded study therapy in a random manner. The individual who prepared the blinded color-marked containers of drugs was not otherwise connected to the study, and all the investigators and patients were blinded to treatment during the entire study period from September 25, 2007 until October 5, 2010, when the randomization codes were opened. All the study investigators deemed the blinding throughout the study as adequate and sufficient.

After randomization, visits were scheduled at 4 and 8 weeks. In patients with diabetes, patients older than 75 years, and patients with serum creatinine >133 μmol/L, an additional safety visit was performed 2 weeks after randomization. During every visit, office BP was recorded by a calibrated mercury sphygmomanometer in seated patients with their arm supported. The value was recorded as the average of the second and third measurements with a minimum delay of 3 minutes between the measurements. At baseline and 8 weeks, 24-hour ambulatory BP monitoring (ABPM) was performed using validated devices.[16,17] Average daytime BP was calculated from values measured between 9:00 AM and 9:00 PM, average nighttime BP was calculated from values measured between 1:00 and 6:00 AM, and average 24-hour BP was calculated from all the values recorded by ABPM.[18]

Serum sodium, potassium, chlorides, urea and creatinine, body weight, and pulse were measured during every visit. Plasma renin activity (PRA), plasma aldosterone and aldosterone/renin ratio (ARR), microalbuminuria, and proteinuria in a 24-hour urine sample were measured at baseline and at 8 weeks. The blood samples for PRA and aldosterone were collected in the morning, after the patients have been seated for 5 to 15 minutes, without discontinua-

tion of the medications.[19] Antihypertensive medications and all other medications were recorded at baseline, and patients did not change doses or the number of their antihypertensive medication throughout the trial. At every visit, patients were asked about the occurrence of any adverse effects of the medication. Compliance of patients was assessed by the calculation of returned tablets.

According to study protocol, the administration of randomized medication was to be terminated at any time in case of symptomatic hypotension <100/60 mm Hg, increase of serum potassium >6.0 mmol/L, increase of serum creatinine >25% compared to baseline and exceeding the upper reference limit of 104 μmol/L, if the patient did not tolerate the study medication because of side effects or any other reason, or if the patient withdrew informed consent.

Our primary end points were to show a statistically significant difference between the fall of average daytime systolic and diastolic pressure on ABPM between the spironolactone and placebo groups after 8 weeks of treatment. The secondary end points were to show a statistically significant difference in the fall of average 24-hour systolic and diastolic BP and a difference in the fall of office BP between spironolactone and a placebo during 8 weeks of treatments. Further secondary end points were to compare the changes of serum levels of sodium, potassium, serum creatinine, and body weight between treatment groups and to evaluate the response to spironolactone treatment based on the baseline aldosterone level and baseline ARR.

Statistical Analysis

Standard descriptive statistics were applied in the analysis. Continuous variables were described using mean and SD when the prerequisite of normality was fulfilled and using the median and 5th and 95th percentile range in case of non-normal distribution. Categorical variables were described by the number of cases and the percentages of categories. The statistical significance of differences between study groups was analyzed using the Mann-Whitney U test for continuous variables and the Fisher exact test for categorical variables. Statistical analysis was computed using SPSS 18.0.2 (IBM Corporation).

Power calculations were originally based on an expected average difference of systolic BP fall between spironolactone and the placebo of 10 mm Hg (SD 18.0 mm Hg) and a diastolic BP fall difference of 5 mm Hg (SD 10.7 mm Hg).[12] We needed a total of 102 patients to have 90% power for systolic BP and 146 patients for diastolic BP at $P<0.05$. We expected about 90% randomized patients to complete the trial and therefore decided to recruit 160 patients.

Role of the Funding Source

The study sponsors only provided financial support; they were not involved in the study design; had no role in the collection, analysis, or interpretation of the data; and were not involved in decisions about its publication. J.V. had full access to all data and had final responsibility for the decision to submit this paper for publication.

Results

The trial profile is shown in Figure 1. Patients were recruited from September 2007 to June 2010, with follow-up during the 2 following months. Of the 168 screened patients, 117 (69.6%) were eligible for enrollment, and 51 (30.4%) were not included for reasons specified in Figure 1. The trial was stopped prematurely in accordance with the protocol after the first interim analysis of the complete data of the 117 enrolled patients in September 2010 showed a significant decrease of systolic BP in one of the treatment arms, together with a much lower than expected decrease of diastolic BP. An updated power analysis with actual study data of diastolic BP showed that we would need a total of 282 patients in both arms finishing the trial to reach $P<0.05$ for daytime ABPM diastolic BP.

Baseline characteristics were well matched between the treatment groups in baseline demographic characteristics,
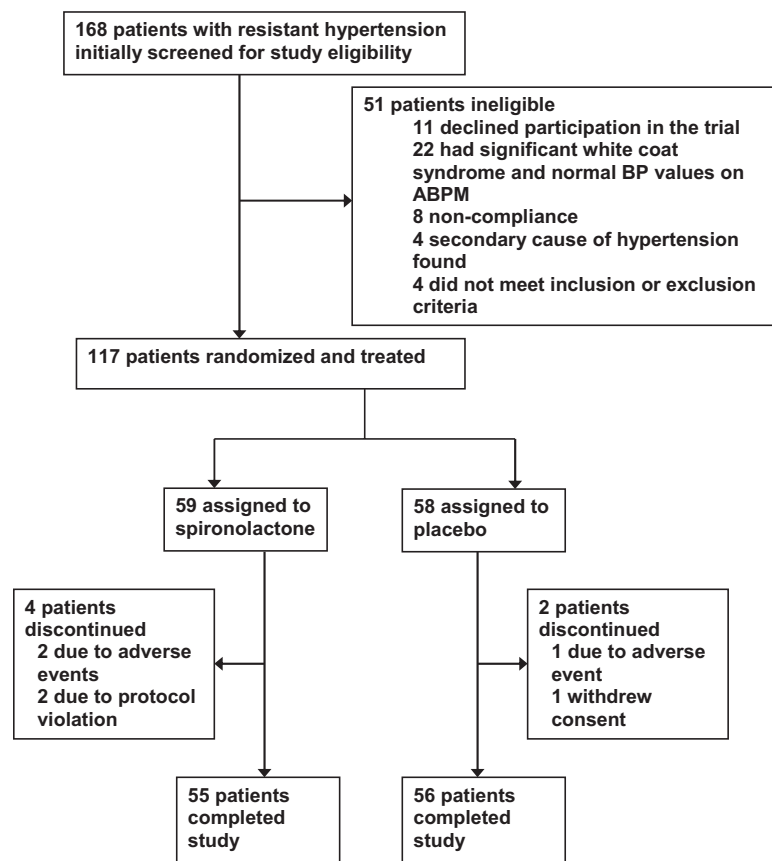
Figure 1. Trial profile.

mean baseline BPs, baseline serum and urinary laboratory characteristics, and antihypertensive medication (Table 1). Baseline mean serum aldosterone and ARR tended to be nonsignificantly higher in the placebo group (122 ng/L and 32.3) compared to the spironolactone group (94 ng/L and 15.2) (P=0.075 for aldosterone and P=0.406 for ARR).

The mean age of patients was approximately 61 years, heart rate was 69 bpm, and body mass index was 32.3 kg/m². Mean office BP was 154/92 mm Hg, daytime ABPM BP was 142/82 mm Hg, and 24-hour ABPM BP was 141/80 mm Hg. Isolated systolic hypertension (office systolic BP >140 mm Hg and diastolic BP <90 mm Hg) was present in 36.4% of patients in the spironolactone group and in 39.3% of patients in the placebo group. Patients were using a mean of 4.6 antihypertensive drugs in the spironolactone group and 4.5 in the placebo group; the median was 4 antihypertensive drugs in each group. Most patients used either hydrochlorothiazide or indapamide. A small number of patients used a combination of more diuretics, such as a fixed combination of hydrochlorothiazide with amiloride (<22% in each group, mean dose of amiloride of 3.75 mg/day), and a few used a combination of hydrochlorothizide with furosemide or indapamide with furosemide.

The change of BP values after 8 weeks of treatment compared to baseline is shown in Table 2. The difference between the fall of mean ABPM daytime systolic BP between the spironolactone and placebo groups was −5.4 mm Hg (95% CI −10.0; −0.8) (P=0.024). The difference between the groups in the fall of ABPM daytime diastolic BP was not significant −1.0 mm Hg (−4.0; 2.0) (P=0.358).

A significantly greater reduction of systolic BP was observed in all measured systolic BP parameters, whereas the difference of diastolic BP reduction was not significant between the spironolactone and placebo groups (Table 2). Spironolactone significantly reduced pulse pressure in all of the ABPM measurements (Table 2). When a stratification analysis according to diastolic BP at entry was applied, the reduction of BP was not significantly different between the study groups in patients with isolated systolic hypertension, systolic-diastolic hypertension, or with ABPM daytime diastolic BP above or below 85 mm Hg (see online supplemental Table S1 at http://hyper.ahajournals.org).

A small comparable weight gain was observed in both study groups (Table 2). Also, serum sodium did not change significantly between groups. Serum potassium increased by a median 0.3 mmol/L and serum creatinine by a median 7 μmol/L in the spironolactone group. The mean serum potassium increased during the 8 weeks of spironolactone treatment from 4.15 to 4.52 mmol/L, and the highest serum potassium value reached at 8 weeks was 5.53 mmol/L. No patient was excluded from the study because of severe hyperkalemia, progression of renal insufficiency, or inadequate drug compliance.

The goal office systolic BP <140 mm Hg at 8 weeks was reached in 30 (54.5%) patients using spironolactone and in 24 (42.9%) patients using the placebo (P=0.257). The respective office diastolic BP goal <90 mm Hg was reached in 38 (69.1%) patients using spironolactone and 36 patients using the placebo (64.3%) (P=0.688).

To evaluate the BP response to treatment, both the spironolactone and placebo groups were divided into tertiles. As

Table 1. Patient Demographics and Baseline Characteristics (Completed Study Set)

Patient Characteristics	Spironolactone Group (n=55)	Placebo Group (n=56)
Demographic characteristics		
Age, years	61.4 (±9.6)	60.1 (±9.4)
Sex (female)	18 (32.7%)	24 (42.9%)
Height, cm	173.1 (±8.9)	170.7 (±8.3)
Weight, kg	96.9 (±17.1)	94.1 (±17.3)
BMI, kg/m^2	32.3 (±5.1)	32.3 (±5.3)
Heart rate, bpm	67.8 (±10.4)	70.0 (±9.2)
Mean baseline BP		
Office systolic BP, mm Hg*	154.9 (±10.4)	153.5 (±12.0)
Office diastolic BP, mm Hg*	92.6 (±10.7)	90.6 (±10.9)
ABPM systolic daytime BP, mm Hg	144.7 (±14.8)	140.1 (±16.2)
ABPM diastolic daytime BP, mm Hg	83.6 (±11.1)	80.9 (±10.4)
ABPM systolic nighttime BP, mm Hg	136.4 (±19.0)	134.4 (±20.4)
ABPM diastolic nighttime BP, mm Hg	76.7 (±13.4)	74.1 (±11.8)
24-h ABPM systolic BP, mm Hg	143.1 (±13.5)	139.8 (±16.4)
24-h ABPM diastolic BP, mm Hg	81.1 (±10.2)	79.3 (±10.2)
Baseline serum laboratory characteristics		
Na, mmol/L	140.4 (±2.8)	140.9 (±3.0)
K, mmol/L	4.2 (±0.5)	4.2 (±0.5)
Cl, mmol/L	104.0 (±3.8)	103.8 (±3.2)
Urea, mmol/L	6.2 (3.8; 10.4)	5.8 (4.0; 10.0)
Creatinine, μmol/L	81.0 (56.0; 128.0)	83.0 (55.0; 128.0)
Glycemia, mmol/L	6.0 (4.6; 17.3)	6.5 (4.5; 12.5)
PRA, ng/ml/h	0.4 (0.1; 5.8)	0.3 (0.1; 8.2)
Aldosteronem ng/L	94 (23; 297)	122 (34; 430)
ARR†	15.2 (1.6; 235.0)	32.3 (0.9; 322.0)
Metanephrine, ng/L	30.0 (15.0; 95.8)	30.0 (15.0; 61.2)
Normetanephrine, ng/L	60.0 (30.0; 147.7)	60.0 (30.0; 184.3)
TSH, mIU/L	1.7 (0.3; 5.0)	1.7 (0.4; 7.4)
Cortisol, nmol/L	458 (273; 767)	475 (266; 822)
Baseline urinary laboratory characteristics		
Total urinary cortisol (nmol/day)	250.0 (38.4; 750.0)	234.0 (50.9; 559.0)
Free urinary cortisol, nmol/day	69.7 (0.0; 1 036.0)	52.4 (27.9; 810.6)
Microalbuminuria, mg/day	12.8 (0.0; 347.0)	15.0 (2.5; 221.0)
Proteinuria, g/day	0.1 (0.0; 2.8)	0.2 (0.0; 4.4)
		(Continued)

Table 1.   Continued

Patient Characteristics	Spironolactone Group (n=55)	Placebo Group (n=56)
Medication at randomization		
Angiotensin-converting enzyme inhibitor	42 (76.4%)	43 (76.8%)
β-blocker	41 (74.5%)	47 (83.9%)
Calcium channel blocker	49 (89.1%)	43 (76.8%)
Diuretics	55 (100.0%)	56 (100.0%)
Angiotensin II receptor blocker	25 (45.5%)	27 (48.2%)
α-blocker	8 (14.5%)	5 (8.9%)
Centrally acting antihypertensives	32 (58.2%)	31 (55.4%)
Other antihypertensives	2 (3.6%)	0 (0.0%)
Median no. of antihypertensives	4 (3; 6)	4 (3; 6)

Data are mean (SD) when normally distributed and median (5th and 95th percentile range) when they have non-normal distributions. Categorical variables are number (percentage). None of the baseline parameters is statistically significantly different between the groups.

*Average of second and third office BP measurement.

†Calculated as serum aldosterone (ng/L)/[10 × PRA (ng/ml/h)].

expected, in the placebo group, the changes of BP from baseline to 8 weeks between tertiles of baseline serum potassium, baseline aldosterone, ARR, and PRA were insignificant. The only baseline parameter that significantly predicted both systolic and diastolic BP response to spironolactone treatment after 8 weeks was the baseline ARR; mean change of systolic/diastolic BP in the first tertile (ARR <7) was −4.0/0.0 mm Hg, in the second tertile (ARR 7 to 45) was −13.0/−5.0 mm Hg, and in the third tertile (ARR >45) was −15.0/−7.0 mm Hg ($P=0.019$ for systolic and $P=0.049$ for diastolic 24-hour ABPM BP) (Table 3). Baseline PRA significantly predicted systolic 24-hour BP response (with the greatest BP response in the lowest tertile of baseline PRA, $P=0.006$), but not diastolic BP response ($P=0.107$) (Table 3). The baseline aldosterone value did not significantly predict BP response to spironolactone treatment.

In 28 patients (24%) enrolled into the trial, the secondary cause of hypertension was found during subsequent evaluation after trial completion with comparable distribution in both study arms: primary aldosteronism (8 in the spironolactone and 9 in the placebo groups), renovascular hypertension (3 and 3), obstructive sleep apnea (1 and 2), and nephrogenic hypertension (1 and 1).

The frequency of adverse events was comparable in both study arms (see online supplemental Table S2). Serious adverse events leading to study medication discontinuation occurred in 2 patients using spironolactone and in 1 patient using the placebo ($P=0.618$). The total number of adverse events was 24 in the spironolactone group and 26 in the placebo group.

Discussion

This randomized trial showed that the addition of spironolactone in patients with resistant arterial hypertension using a

Table 2.   Change of Patient Characteristics at 8 Weeks Compared to Baseline

Patient Characteristics	Spironolactone (n=55)	Placebo (n=56)	Between-Group Difference*	P†
Systolic BP				
ABPM daytime systolic BP, mm Hg	−9.3 (±12.6)	−3.9 (±12.1)	−5.4 (−10.0; −0.8)	0.024
ABPM nighttime systolic BP, mm Hg	−11.2 (±17.6)	−2.6 (±17.7)	−8.6 (−15.2; −2.0)	0.011
24-h ABPM systolic BP, mm Hg	−13.8 (±11.8)	−4.0 (±12.7)	−9.8 (−14.4; −5.2)	0.004
Office systolic BP, mm Hg‡	−14.6 (±15.6)	−8.1 (±14.8)	−6.5 (−12.2; −0.8)	0.011
Diastolic BP				
ABPM daytime diastolic BP, mm Hg	−4.2 (±8.0)	−3.2 (±8.2)	−1.0 (−4.0; 2.0)	0.358
ABPM nighttime diastolic BP, mm Hg	−5.6 (±10.5)	−2.6 (±11.0)	−3.0 (−7.0; 1.0)	0.079
24-h ABPM diastolic BP, mm Hg	−4.2 (±7.0)	−3.2 (±7.7)	−1.0 (−3.7; 1.7)	0.405
Office diastolic BP, mm Hg‡	−6.6 (±9.6)	−4.1 (±8.6)	−2.5 (−5.9; 0.9)	0.079
Pulse Pressure§				
ABPM daytime pulse pressure, mm Hg	−5.1 (±8.4)	−0.7 (±8.3)	−4.4 (−7.5; −1.3)	0.007
ABPM nighttime pulse pressure, mm Hg	−5.6 (±12.9)	0.0 (±10.4)	−5.6 (−10.0; −1.2)	0.005
24-h ABPM pulse pressure, mm Hg	−6.5 (±7.2)	−0.8 (±7.6)	−5.7 (−8.5; −2.9)	<0.001
Office pulse pressure, mm Hg‡	−8.0 (±11.2)	−4.0 (±11.8)	−4.0 (−8.3; 0.3)	0.056
Other Characteristics				
Weight, kg	0.3 (±1.6)	0.5 (±2.6)	−0.2 (−1.0; 0.6)	0.772
Serum Na, mmol/L	−1 (−6; 3)	−1 (−5; 4)	0.0	0.135
Serum K, mmol/L	0.3 (−0.5; 1.5)	0.0 (−0.8; 0.6)	0.3	<0.001
Serum creatinine, μmol/L	7 (−11; 22)	0 (−11; 18)	7.0	<0.001
Microalbuminuria, mg/day	−4.4 (−257.0; 11.0)	0.0 (−87.0; 98.0)	−4.4	0.023
Proteinuria, g/day	0.0 (−0.5; 0.1)	0.0 (−0.3; 1.7)	0.0	0.221

Data are mean (SD) when normally distributed and median (5th and 95th percentile range) when they have non-normal distributions.

*Difference between spironolactone and placebo group is expressed as difference in their means supplemented by 95% confidence interval or as difference in medians when they have non-normal distributions.

†Statistical significance was tested by the Mann-Whitney *U* test.

‡Average of second and third office BP measurements.

§Calculated as systolic BP minus diastolic BP in all measured parameters.

mean of 4.5 antihypertensive drugs, led to a significant decrease of systolic BP both in the office and on ABPM after 8 weeks of treatment. Spironolactone, compared to the placebo, did not significantly influence the diastolic BP, although a trend toward a decrease was observed for the ABPM nighttime and office diastolic BP. Spironolactone led to small but significant increases of serum potassium and creatinine without adverse clinical consequences and was

Table 3.   Mean BP Differences of 24-Hour ABPM Systolic and Diastolic BP after 8 Weeks of Spironolactone Treatment in Relation to Baseline Laboratory Parameters

Baseline Parameter	First Tertile*	Second Tertile*	Third Tertile*	P†
Potassium, mmol/L	≤3.9	3.9–4.37	>4.37	
Systolic BP	−13.6 (−31.0; 2.1)	−10.5 (−29.0; 13.0)	−6.5 (−36.0; 13.0)	0.066
Diastolic BP	−7.0 (−17.6; 5.9)	−5.0 (−14.6; 7.0)	0.0 (−25.0; 11.0)	0.183
Serum aldosterone, ng/L	≤74	74–123	>123	
Systolic BP	−13.0 (−36.0; 13.0)	−9.0 (−29.0; 13.0)	−8.0 (−28.0; 6.6)	0.615
Diastolic BP	−3.0 (−25.0; 8.0)	−6.0 (−17.6; 11.0)	−2.1 (−14.6; 7.6)	0.524
ARR	≤7	7–45	>45	
Systolic BP	−4.0 (−36.0; 13.0)	−13.0 (−31.0; 13.0)	−15.0 (−28.0; 2.1)	0.019
Diastolic BP	0.0 (−25.0; 11.0)	−5.0 (−14.0; 8.0)	−7.0 (−17.6; 5.9)	0.049
PRA, ng/ml/h	≤0.12	0.13–1.34	>1.34	
Systolic BP	−19.0 (−31.0; 2.1)	−12.0 (−29.0; 13.0)	−4.0 (−36.0; 13.0)	0.006
Diastolic BP	−6.0 (−17.6; 5.9)	−5.0 (−14.6; 8.0)	0.0 (−25.0; 11.0)	0.107

*Twenty-four–hour systolic and diastolic ABPM was described by the median and 5–95% percentile range.

†Statistical significance was evaluated by the Kruskal-Wallis test.

well tolerated, and the number of side effects was comparable to the placebo.

To our knowledge, this is the first randomized trial to assess the antihypertensive effects of low-dose spironolactone in patients with truly drug-resistant hypertension. Previous uncontrolled observational trials showed a substantial BP reduction after the addition of spironolactone (ranging from 21.7 to 25 mm Hg systolic and 8.5 to 12.5 mm Hg diastolic office BP) in patients treated with at least 2 or 3 antihypertensive drugs.[8–12] However, various confounding factors could significantly influence the results, and with the absence of a control group, the cause-and-effect relationship as well as safety could not be established.[13,20]

Compared to the previous observational trials, the magnitude of average fall of BP in the spironolactone group compared to the placebo was smaller. In a similar randomized trial with black patients, using a diuretic and calcium channel blocker, the addition of 25 mg of spironolactone led to a mean BP decrease of 4.6/1.8 mm Hg after 9 weeks, and the reduction of diastolic BP also did not reach statistical significance.[21]

The lesser than expected effect of spironolactone on diastolic BP in our trial may be partially explained by the relatively low baseline diastolic BP (mean office diastolic BP 92 mm Hg, mean daytime ABPM diastolic BP 82 mm Hg), with a significant proportion of patients (38%) having isolated systolic hypertension. Recently, spironolactone has been shown to reduce pulse pressure to a greater extent when compared to dual blockade of the renin-angiotensin-aldosterone system, which resulted in unchanged office diastolic BP after 12 weeks.[22] Besides the diuretic effect of spironolactone, its reduction of vascular stiffness probably plays a major role in patients with resistant hypertension, contributing to systolic BP reduction and decrease of pulse-wave velocity and augmentation index,[23,24] and could explain the more profound effect of spironolactone on systolic BP rather than diastolic BP. As pulse pressure is an independent cardiovascular risk factor and predictor of coronary artery disease mortality in persons over the age of 50,[25–27] our observation of the positive effect of spironolactone on pulse pressure could be of great importance for future treatment of older patients with isolated systolic hypertension.

The appropriate dosing range for spironolactone has not been well defined in resistant hypertension.[20] According to recent meta-analysis, there may be a dose response effect with spironolactone up to 50 mg/day in patients with hypertension, and higher doses >50 mg/day do not produce further reductions of BP.[5] It is possible that the increase of the spironolactone dose to 50 mg/day could have led to a more substantial decrease of BP.

The maximal hypotensive effect of spironolactone requires 3 to 4 weeks to be fully expressed in patients with mild hypertension[28] and 7 weeks in patients with resistant hypertension.[21] Therefore, we feel that the designed length of our trial, 8 weeks, was sufficient for the full effect of spironolactone to show.

The mild increase of serum potassium and creatinine with spironolactone was expected. It needs to be stressed that the majority of recruited patients had normal renal functions with only 20% of patients exceeding the baseline creatinine upper

reference limit 104 μmol/L. The risk of hyperkalemia and worsening of renal functions would be higher if spironolactone was used in patients with chronic kidney disease, especially with a glomerular filtration rate <45 mL/min and serum potassium >4.5 mmol/L.[29]

Previous trials reported conflicting data about whether the BP response to spironolactone can be predicted by baseline aldosterone, ARR, or baseline potassium.[10, 21, 23, 30,31] In our trial, the BP response to spironolactone treatment in patients with baseline ARR ≤7 and PRA >1.34 ng/mL per hour was significantly worse than the BP response of patients with ARR >7 and PRA ≤1.34 ng/mL per hour. This could possibly help to identify the patients for which treatment with spironolactone is most effective.

Antihypertensive drugs were not discontinued before blood sampling in accordance with current guidelines,[19] which might have affected the measured values of ARR and may be a limitation of this study, but we believe that this approach is more easily generalizable and practical to adopt in everyday practice.

Further limitation of our study is the relatively small sample size. We calculated, based on our data, that we would need to recruit almost 300 patients to reach statistical significance for diastolic BP reduction, which would require broader clinical settings and additional funding.

Perspective

This randomized, double-blind, placebo-controlled trial shows that spironolactone is an effective drug to lower systolic BP in patients with resistant arterial hypertension. It also shows that the greatest BP response can be expected in patients with ARR >7 and PRA ≤1.34 ng/mL per hour. Since spironolactone is a cheap and widely available drug, its use could lead to an improved BP control in the global perspective. Whether spironolactone also significantly reduces the diastolic BP and its positive effect on BP leads to a decreased number of cardiovascular events and decreased mortality needs to be explored in further studies.

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