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Spironolactone vs Amiloride for Resistant Hypertension
A Randomized Clinical Trial

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IMPORTANCE Amiloride has been proposed as an alternative to spironolactone for treating resistant hypertension. However, no randomized clinical trials have compared the efficacy of spironolactone and amiloride in patients with resistant hypertension.

OBJECTIVE To determine whether amiloride is noninferior to spironolactone in reducing home-measured systolic blood pressure (SBP) in patients with resistant hypertension.

DESIGN, SETTING, AND PARTICIPANTS Prospective, open-label, blinded end-point randomized clinical trial conducted at 14 sites in South Korea. From November 16, 2020, to February 29, 2024, 118 patients with home SBP of 130 mm Hg or greater after a 4-week run-in period with a fixed-dose triple medication combination (angiotensin receptor blocker, calcium channel blocker, and thiazide) were enrolled.

INTERVENTION Patients were randomized in a 1:1 ratio to receive 12.5 mg/d of spironolactone (n = 60) or 5 mg/d of amiloride (n = 58). If home SBP remained 130 mm Hg or greater and serum potassium was less than 5.0 mmol/L after 4 weeks, dosages were increased to 25 mg/d and 10 mg/d, respectively.

MAIN OUTCOMES AND MEASURES The primary end point was the between-group difference in home SBP change at week 12, with a noninferiority margin of −4.4 mm Hg for the lower bound of the confidence interval. Secondary end points included achievement rates of home- and office-measured SBP of less than 130 mm Hg.

RESULTS The median age of the study population was 55 years, with 70% male. There were no differences between groups in demographic characteristics other than use of α-blockers (8.6% in the amiloride group and 0% in the spironolactone group). The mean baseline home SBPs were 141.5 (SD, 7.9) mm Hg and 142.3 (SD, 8.5) mm Hg in the amiloride and spironolactone groups, respectively. At week 12, mean home SBP measurements were changed from baseline by −13.6 (SD, 8.6) mm Hg and −14.7 (SD, 11.0) mm Hg in the amiloride and spironolactone groups, respectively (between-group difference in change, −0.68 mm Hg; 90% CI, −3.50 to 2.14 mm Hg), with amiloride demonstrating noninferiority to spironolactone. Home-measured achievement rates of SBP less than 130 mm Hg in the amiloride and spironolactone groups were 66.1% and 55.2%, respectively, and office-measured achievement rates of SBP less than 130 mm Hg were 57.1% and 60.3%, respectively, with no difference between the 2 groups. One case of hyperkalemia-related discontinuation occurred in the amiloride group, with no cases of gynecomastia in either group.

CONCLUSIONS AND RELEVANCE Amiloride was noninferior to spironolactone in lowering home SBP, suggesting that it could be an effective alternative for treatment of resistant hypertension.

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- Visual Abstract
- Editorial
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Resistant hypertension is defined as inability to achieve blood pressure (BP) control below a target despite use of 3 or more antihypertensive drugs, including diuretics commonly combined with renin-angiotensin system inhibitors and calcium channel blockers, or the need for 4 or more antihypertensive medications to achieve BP control.[1-3] Resistant hypertension affects approximately 10% of patients with hypertension and is associated with a poorer prognosis than nonresistant hypertension.[2,4-6] Spironolactone is the drug of choice when BP is not controlled with maximally tolerated doses of renin-angiotensin system inhibitors, calcium channel blockers, and thiazide-like/-type diuretics.[3,7] In the PATHWAY-2 trial, spironolactone demonstrated significantly better efficacy than doxazosin and bisoprolol in reducing home-measured systolic BP (SBP) in patients with resistant hypertension.[8] However, a major limitation of spironolactone is its relatively high incidence of hyperkalemia and antiandrogenic adverse effects, such as gynecomastia and menstrual irregularities.[9] Therefore, when spironolactone is not tolerated, potassium-sparing diuretics, such as amiloride, can be considered.[7] In a substudy of 146 of 314 participants with resistant hypertension in the PATHWAY-2 trial, the effect of amiloride (10-20 mg once daily) on clinic-measured SBP was assessed over 6 to 12 weeks during an optional open-label run-out phase. The results showed that amiloride, 10 mg once daily, reduced clinic SBP by 20.4 mm Hg (95% CI, 18.3-22.5 mm Hg) compared with 18.3 mm Hg (95% CI, 16.2-20.5 mm Hg) for spironolactone.[10] Unlike spironolactone, amiloride does not have antiandrogenic adverse effects and has a lower incidence of hyperkalemia,[11] potentially making it a better option for resistant hypertension treatment if the BP-lowering efficacy is similar. However, these studies were not randomized, and no randomized clinical trials have compared the efficacy of spironolactone and amiloride in patients with resistant hypertension. Therefore, we designed and conducted a prospective, randomized, open-label, blinded end-point trial in patients with resistant hypertension to compare spironolactone (12.5-25 mg/d) with amiloride (5-10 mg/d) to determine whether amiloride is noninferior to spironolactone in reducing home SBP after 12 weeks of treatment.

Methods

Study Design and Participants

This multicenter trial in patients with resistant hypertension was conducted in 14 tertiary care hospitals in South Korea (eAppendix 1 in Supplement 1). In the initial protocol, the threshold for daytime mean SBP and home SBP for enrollment was 135 mm Hg. On June 21, 2022, it was changed to 130 mm Hg owing to the emphasis on intensive BP lowering in the Korean Society of Hypertension guidelines and other major guidelines for intensive BP lowering.[12-15] The final study protocol and statistical analysis plan are available in Supplement 2.

The institutional review boards of all 14 hospitals approved the study. The trial followed the Declaration of

Key Points

Question In patients with resistant hypertension who are taking angiotensin receptor blockers, calcium channel blockers, and thiazides, is amiloride, a potassium-sparing diuretic, noninferior to spironolactone for lowering blood pressure?

Findings In this open-label, blinded end-point, randomized clinical trial involving 118 patients with resistant hypertension, amiloride and spironolactone lowered home-measured systolic blood pressure by 13.6 mm Hg and 14.7 mm Hg from baseline, respectively, with no difference in blood pressure–lowering effect.

Meaning These results support amiloride as a possible alternative to spironolactone as a fourth-line agent in patients with resistant hypertension.

Helsinki,[16] Good Clinical Practice guidelines, and relevant local laws and regulations. The Clinical Trial Centre of the Yonsei University Health System (Seoul, South Korea) provided study coordination, data management, and site management services. Designated trial monitors reviewed the investigational data every month to verify their accuracy, completeness, and adherence to the protocol. This study adhered to the reporting guidelines established by the Consolidated Standards of Reporting Trials (CONSORT).

Patients eligible for enrollment were aged 19 to 75 years and diagnosed with resistant hypertension. eFigure 1 in Supplement 1 shows the study design. Resistant hypertension was defined when, despite treatment with a triple combination of renin-angiotensin system inhibitors, calcium channel blockers, and thiazide-like/-type diuretics, mean daytime SBP was 130 mm Hg or greater on ambulatory BP monitoring performed within 12 months prior to screening. At the first screening, if office-measured SBP was 130 to 180 mm Hg despite consistent use of antihypertensive medication for the previous 4 weeks, patients entered the run-in phase. During the run-in period, the drug regimen was switched to a triple fixed-dose combination of amlodipine, olmesartan, and hydrochlorothiazide at dosages of 5 mg/d, 20 mg/d, and 12.5 mg/d; 5 mg/d, 40 mg/d, and 12.5 mg/d; or 10 mg/d, 40 mg/d, and 12.5 mg/d; respectively, at investigators' discretion. After 4 weeks, participants with a mean home-measured SBP of 130 mm Hg or greater were eligible for randomization. All participants provided written informed consent. Additional information regarding inclusion and exclusion criteria is provided in eAppendix 2 in Supplement 1.

Randomization

Participants were randomly assigned in a 1:1 ratio to receive open-label spironolactone (12.5 mg/d) or amiloride (5 mg/d). Participants were stratified by sex and age for randomization. Interactive web-response permuted-block randomization (mixed blocks of 4 or 6) with stratification based on sex and age (≥60 or <60 years) was used to allocate participants and was managed by an external programmer who was independent from the trial; participating physicians enrolled

participants, and these physicians and study coordinators had access to the interactive web-response system.

Procedures

After 4 weeks of postrandomization treatment with spironolactone, 12.5 mg/d, or amiloride, 5 mg/d, if the mean home SBP was 130 mm Hg or greater and serum potassium was less than 5.0 mmol/L, spironolactone and amiloride doses were increased to 25 mg/d and 10 mg/d, respectively, at investigators' discretion. After 4 more weeks, a safety visit was conducted to measure blood potassium level. Four weeks later, at week 12, home BP was measured and the study ended. Other classes of antihypertensive medications, such as β-blockers and α-blockers, were allowed if administered at a stable dose for at least 4 weeks before the initial screening without any dose changes throughout the study. During the remainder of the study, changes in the doses of olmesartan, amlodipine, and hydrochlorothiazide were not allowed.

A trained nurse conducted office BP measurements after 5 minutes of rest in a sitting position in the research examination room using a validated automated device (HEM 7080-IC, HEM 7121, HEM-7120, HEM-7122, HEM-7141-T; Omron). The mean of 3 BP readings taken at 1-minute intervals after 5 minutes of rest was used in this study.[17-20] Home BP was measured using a validated digital device (HEM-7121, HEM-7122, HEM-7141-T; Omron). Participants were provided with the digital sphygmomanometer device at study visits. They were instructed to measure and record their BP twice daily on paper, in the morning and evening, at the same time and location, for 7 consecutive days before study visits. Blood pressure was not measured during sleep. At study visits, participants were to submit the paper with their recorded BP values to the research team. On each occasion, brachial BP was measured twice, 1 to 4 minutes apart, after 5 minutes of rest in a sitting position. Morning BP was measured twice before participants took antihypertensive medications within 2 hours of waking up, and evening BP was measured twice within 1 hour of bedtime. The mean of these measurements was used for analysis. Participants with at least 8 measurements were included in the analysis. A mean home BP of 130/80 mm Hg or greater was defined as uncontrolled home BP.[14]

Participants were instructed to bring all study drugs prescribed at the previous visit to each subsequent visit. Adherence was calculated using pill count methods, dividing the number of drugs prescribed by the number of drugs expected to have been taken between the previous and current visits.[21]

Outcomes

The primary end point was the difference between spironolactone and amiloride in terms of changes in home SBP from baseline to week 12. The secondary end point was the target achievement rate for home- and office-measured SBP at week 12. The target home and office SBP and diastolic BP were 130 mm Hg and 80 mm Hg, respectively. For the safety analysis, development of gynecomastia and serum potassium level of 5 mmol/L or greater were assessed at weeks 4, 8, and 12. Additionally, the percentage of participants who discontinued or

reduced their medication owing to elevated serum potassium levels was assessed.

Sample Size Estimation

In the PATHWAY-2 substudy, amiloride during the run-out phase lowered SBP by a mean of 11.2 mm Hg (95% CI, 8.7-13.7 mm Hg) compared with placebo in the randomized phase of the trial.[8,10] Because 50% of the lower margin was 4.4 mm Hg, the noninferiority margin was set at 4.4 mm Hg, with an SD of 9 mm Hg, 80% power, and a 1-sided t-test α = .05. The sample size was calculated assuming that mean changes in home SBP for amiloride and spironolactone would be equivalent. The null hypothesis was that amiloride would be inferior to spironolactone by more than the set inferior margin. We determined that 59 participants were required in each group, assuming a 10% dropout rate, to achieve a final enrollment of 53 participants per group.
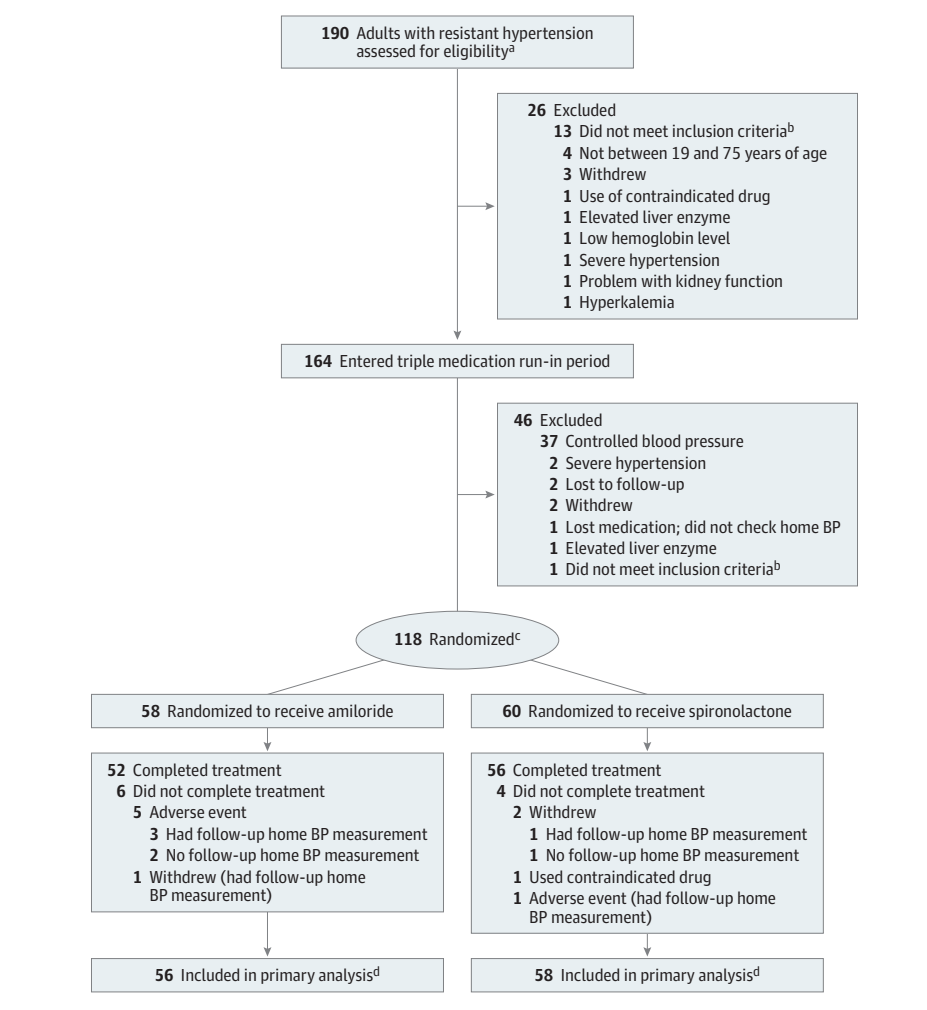
Statistical Analysis

All analyses in this study were conducted in accordance with the statistical analysis plan (Supplement 2). Clinical end points were analyzed using the last-observation-carried-forward method. The primary analysis was conducted on the full analysis set, which included participants who had taken the investigational drug at least once and had at least 1 follow-up measurement of mean home SBP at week 4 or week 12. All data were analyzed using an intention-to-treat approach, following precisely predefined criteria. The primary end point—assessing the noninferiority of amiloride compared with spironolactone in terms of changes in home SBP from baseline to week 12—was evaluated using analysis of covariance. The analysis-of-covariance models were adjusted for the corresponding baseline BP. The primary end-point analysis was performed using a 1-sided test (α = .05; α = .025 for sensitivity) comparing the lower bound of the confidence interval with the noninferiority margin of −4.4 mm Hg. For the secondary end point, the target BP achievement rate at week 12 was assessed using the $χ^2$ test. The primary end point was also calculated in prespecified subgroups. Intergroup differences between continuous variables were analyzed using the t test or the Wilcoxon rank sum test. Intragroup differences were analyzed using the paired t test or the Wilcoxon signed rank test. Descriptive statistics included sample sizes, arithmetic means and standard deviations for continuous variables, and frequencies and percentages for categorical variables, which were calculated for all baseline demographics. All analyses were conducted with SAS version 9.4 (SAS Institute Inc) or R version 4.1.0 (R Foundation for Statistical Computing).

Results

Between November 16, 2020, and February 29, 2024, 118 participants met the inclusion criteria and were randomized to receive spironolactone (n = 60) or amiloride (n = 58) (**Figure 1**). Four participants in the spironolactone group and 6 in the amiloride group did not complete the study (eTable 1 in Supplement 1). Overall, 114 participants were included in

Figure 1. Flow of Participants Through a Trial of Amiloride vs Spironolactone for Resistant Hypertension

<table>
<tr><td colspan="3">190 Adults with resistant hypertension assessed for eligibility[a]</td></tr>
</table>

26 Excluded
 13 Did not meet inclusion criteria[b]
  4 Not between 19 and 75 years of age
  3 Withdrew
  1 Use of contraindicated drug
  1 Elevated liver enzyme
  1 Low hemoglobin level
  1 Severe hypertension
  1 Problem with kidney function
  1 Hyperkalemia

164 Entered triple medication run-in period

46 Excluded
 37 Controlled blood pressure
  2 Severe hypertension
  2 Lost to follow-up
  2 Withdrew
  1 Lost medication; did not check home BP
  1 Elevated liver enzyme
  1 Did not meet inclusion criteria[b]

118 Randomized[c]

58 Randomized to receive amiloride

60 Randomized to receive spironolactone

52 Completed treatment
 6 Did not complete treatment
  5 Adverse event
   3 Had follow-up home BP measurement
   2 No follow-up home BP measurement
  1 Withdrew (had follow-up home BP measurement)

56 Completed treatment
 4 Did not complete treatment
  2 Withdrew
   1 Had follow-up home BP measurement
   1 No follow-up home BP measurement
  1 Used contraindicated drug
  1 Adverse event (had follow-up home BP measurement)

56 Included in primary analysis[d]

58 Included in primary analysis[d]

[a] Resistant hypertension was defined as daytime mean systolic blood pressure (SBP)≥130 mm Hg on a 24-hour ambulatory blood pressure measurement within 12 months and office SBP of 130 to 180 mm Hg despite taking 3 or more antihypertensive medications of different classes, including diuretics, for at least 4 weeks without dose changes.

[b] Participants who did not meet the daytime SBP criteria of 24-hour ambulatory blood pressure measurement within 12 months, had a change in dose of 3 or more antihypertensive drugs including a diuretic for at least 4 weeks, or did not meet the office SBP criteria.

[c] The 1:1 randomization was stratified by sex and age (<60 years vs ≥60 years).

[d] Participants included in the primary analysis received the study drug at least once and had at least 1 measurement of home SBP after baseline. Four participants in the amiloride group and 2 in the spironolactone group who did not complete the study but completed at least 4 weeks of the study and had home SBP measurements were included in the primary analysis.

the full analysis/safety set and 94 were included in the per-protocol analysis. The primary outcome was analyzed using the full analysis set.

The median ages of participants in the spironolactone and amiloride groups were 55 and 53 years, respectively (**Table 1**). The study population was predominantly male, comprising 70.0% and 70.7% of the spironolactone and amiloride groups, respectively. The number of antihypertensive medications used prior to study enrollment did not differ between the 2 groups. The mean baseline office SBP was 144.5 (SD, 9.5) mm Hg and 145.8 (SD, 9.9) mm Hg in the spironolactone and amiloride groups, respectively (*P* = .44). No significant intergroup differences were observed in other demographic data.

The mean dosage of the fixed-dose triple combination of amlodipine, olmesartan, and hydrochlorothiazide used during the run-in period before randomization did not differ between the 2 groups (Table 1). Comparing other antihypertensive drugs, use of α-blockers was significantly higher in the amiloride group at baseline (*P* = .03). The mean baseline home SBP for the amiloride and spironolactone groups was 141.5 (SD, 7.9) mm Hg and 142.3 (SD, 8.5) mm Hg, respectively. eTable 2

in Supplement 1 shows the median number of home BP measurements per week at baseline and weeks 4 and 12.

At week 12, mean home SBP decreased by 13.6 (SD, 8.6) mm Hg and 14.7 (SD, 11.0) mm Hg in the amiloride and spironolactone groups, respectively (**Figure 2** and **Table 2**). No significant between-group difference was observed in the change in mean home SBP (−0.68 mm Hg; 90% CI, −3.50 to 2.14 mm Hg). Because the lower limit of the 90% CI for the difference in home SBP reduction was greater than −4.4 mm Hg, amiloride satisfied the predefined criteria for noninferiority. In the sensitivity analysis, the 2-sided 95% CI was calculated, revealing that the lower limit of the 95% CI was greater than −4.4 mm Hg, thereby confirming the noninferiority of amiloride compared with spironolactone (Table 2). The per-protocol analysis showed similar results (eTable 3 in Supplement 1). At week 4, 48.3% and 30.9% of participants in the spironolactone and amiloride groups required an increase in their doses, respectively, with no significant intergroup difference (eTable 4 in Supplement 1).

Regarding the secondary end points, no significant difference was observed between the 2 groups in the achievement

Table 1. Baseline Participant Characteristics

Characteristics	Amiloride (n = 58)	Spironolactone (n = 60)
Age, median (IQR), y	53 (44-69)	55.0 (43-63)
Sex, No. (%)		
Female	17 (29.3)	18 (30.0)
Male	41 (70.7)	42 (70.0)
Medical history, No. (%)[a]		
Dyslipidemia	34 (58.6)	31 (51.7)
Type 2 diabetes	21 (36.2)	14 (23.3)
Heart failure	4 (6.9)	4 (6.7)
Peripheral vascular disease	4 (6.9)	3 (5.0)
Stroke	2 (3.4)	3 (5.0)
Chronic obstructive pulmonary disease	2 (3.4)	0
Myocardial infarction	0	1 (1.7)
Current smoking, No. (%)	7 (12.1)	13 (21.7)
No. of antihypertensive medication classes used, median (IQR)	3.0 (3.0-4.0)	3.0 (3.0-4.0)
Amlodipine/olmesartan/hydrochlorothiazide dosage, mg/d, No. (%)		
5/20/12.5	29 (50.0)	33 (55.0)
5/40/12.5	17 (29.3)	17 (28.3)
10/40/12.5	12 (20.7)	10 (16.7)
Other type of antihypertensive medications, No. (%)		
β-Blockers	17 (29.3)	18 (30.0)
α-Blockers	5 (8.6)	0
Nitrates	2 (3.4)	0
Body mass index, mean (SD)[b]	30.3 (4.6)	29.0 (4.8)
Waist circumference, mean (SD), cm	97.3 (11.6)	96.2 (14.2)
Blood pressure, mean (SD), mm Hg		
Office		
Systolic	145.8 (9.9)	144.5 (9.5)
Diastolic	87.6 (10.8)	88.1 (9.0)
24-Hour[c]		
Systolic	144.6 (11.6)	144.0 (13.0)
Diastolic	85.2 (10.4)	86.8 (9.4)
Daytime[c]		
Systolic	148.8 (11.7)	146.8 (13.2)
Diastolic	88.2 (10.6)	88.7 (9.5)
Nighttime[c]		
Systolic	134.5 (15.5)	136.1 (15.8)
Diastolic	78.0 (11.6)	80.9 (9.9)
Serum creatinine, mean (SD), mg/dL	0.8 (0.2)	0.9 (0.2)
Estimated glomerular filtration rate, mL/min/1.73 m²		
Mean (SD)[d]	98.4 (12.3)	93.1 (16.0)
<60, No. (%)	0	2 (3.3)
Serum aldosterone, median (IQR), ng/dL[e]	14.9 (10.3-17.9)	18.3 (11.8-20.7)
Plasma renin activity, median (IQR), ng/mL per h[e]	2.9 (1.4-8.4)	2.1 (0.6-7.0)

SI conversion: To convert creatinine to micromoles per liter, multiply by 88.4.

[a] Information on medical history was obtained through interviews.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Values measured by ambulatory blood pressure monitoring at the first assessment for eligibility.

[d] Calculated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation.

[e] Data are from the full analysis set, with 1 participant from the spironolactone group missing aldosterone/renin data (amiloride group: n = 56; spironolactone group: n = 57).

rate of the target home SBP of less than 130 mm Hg and in the achievement rate of the target office SBP of less than 130 mm Hg (eTable 5 in Supplement 1). The per-protocol analysis also showed no differences in secondary end points between the 2 groups (eTable 5 in Supplement 1). eFigure 2 in Supplement 1 presents changes in office SBP in each group during the study period. At week 12, mean office SBP measurements were 129.2 (SD, 10.1) mm Hg and 127.2 (SD,

10.4) mm Hg in the spironolactone and amiloride groups, respectively, with no significant intergroup difference.

Subgroup analyses by age, sex, diabetes, and waist circumference did not reveal any significant differences in the change in mean home SBP from baseline to 12 weeks (Figure 3). However, smoking status (P = .049 for interaction), body mass index (P = .03 for interaction), and aldosterone to renin ratio (P = .04 for interaction) showed a significant difference in

Figure 2. Change in Home SBP in Patients Treated With Amiloride vs Spironolactone
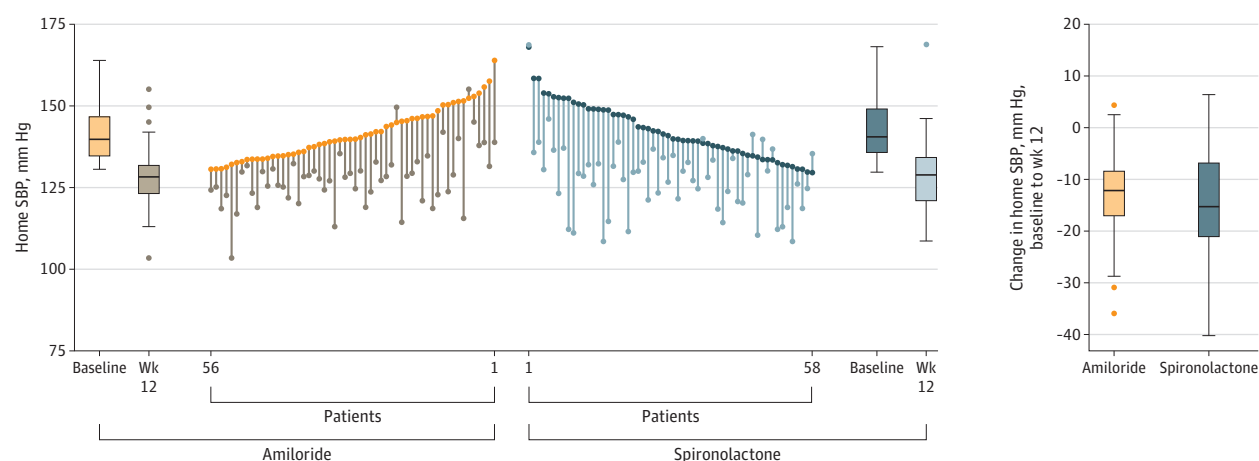
The parallel dot plot contains 1 vertical line for each patient, extending from the home systolic blood pressure (SBP) measurement at baseline to the home SBP at 12 weeks. Descending lines indicate a reduction in home SBP over time; ascending lines indicate an increase. Baseline home SBP measurements are shown in ascending order for the amiloride group and descending order for the spironolactone group. The tops and bottoms of the boxes in the box plots indicate the IQR, with the line indicating the median. Whiskers extend to the upper and lower adjacent values, the location of the furthest point within a distance of 1.5 IQRs from the first and third quartiles. Dots indicate more extreme values.

Table 2. Home Blood Pressure Change From Baseline to Week 12

End points	Amiloride (n = 56)			Spironolactone (n = 58)			Difference in change, spironolactone − amiloride[a]	
	Baseline	Week 12	Change	Baseline	Week 12	Change	With 90% CI	With 95% CI
Primary end point								
Total home systolic blood pressure, mean (SD), mm Hg[b]	141.5 (7.9)	128.0 (8.9)[c]	−13.6 (8.6)[c]	142.3 (8.5)	127.6 (10.8)[d]	−14.7 (11.0)[d]	−0.68 (−3.50 to 2.14)	−0.68 (−4.05 to 2.69)
Secondary end points								
Systolic blood pressure, mean (SD), mm Hg								
Morning[e]	142.9 (9.8)	129.1 (11.2)[c]	−13.8 (9.6)[c]	142.0 (9.3)	127.7 (10.8)[d]	−14.3 (12.0)[d]	−0.95 (−4.03 to 2.13)	−0.95 (−4.63 to 2.73)
Evening[f]	140.2 (8.1)	126.7 (8.0)[c]	−13.5 (9.1)[c]	142.6 (9.3)	127.6 (11.7)[d]	−15.0 (11.2)[d]	−0.29 (−3.18 to 2.60)	−0.29 (−3.74 to 3.16)
Diastolic blood pressure, mean (SD), mm Hg								
Total home[b]	86.1 (9.1)	79.2 (7.6)[c]	−6.8 (6.1)[c]	87.0 (8.6)	80.4 (8.1)[d]	−6.7 (7.3)[d]	0.52 (−1.30 to 2.33)	0.52 (−1.65 to 2.68)
Morning[e]	87.8 (9.7)	81.1 (8.7)[c]	−6.7 (6.5)[c]	87.3 (8.6)	81.1 (8.1)[d]	−6.2 (7.4)[d]	0.33 (−1.57 to 2.24)	0.33 (−1.94 to 2.61)
Evening[f]	84.3 (9.4)	77.4 (7.6)[c]	−6.9 (6.9)[c]	86.7 (9.2)	79.5 (8.6)[d]	−7.1 (7.9)[d]	0.82 (−1.14 to 2.78)	0.82 (−1.62 to 3.16)

[a] Analysis-of-covariance model, adjusted for corresponding baseline blood pressure, 2-sided.

[b] Mean of morning and evening measurements.

[c] Four missing values were imputed by the last-observation-carried-forward method.

[d] Two missing values were imputed by the last-observation-carried-forward method.

[e] Mean of 2 measurements between 7 AM and 9 AM or within 2 hours of waking.

[f] Mean of 2 measurements between 9 PM and 11 PM or within 1 hour before sleep.
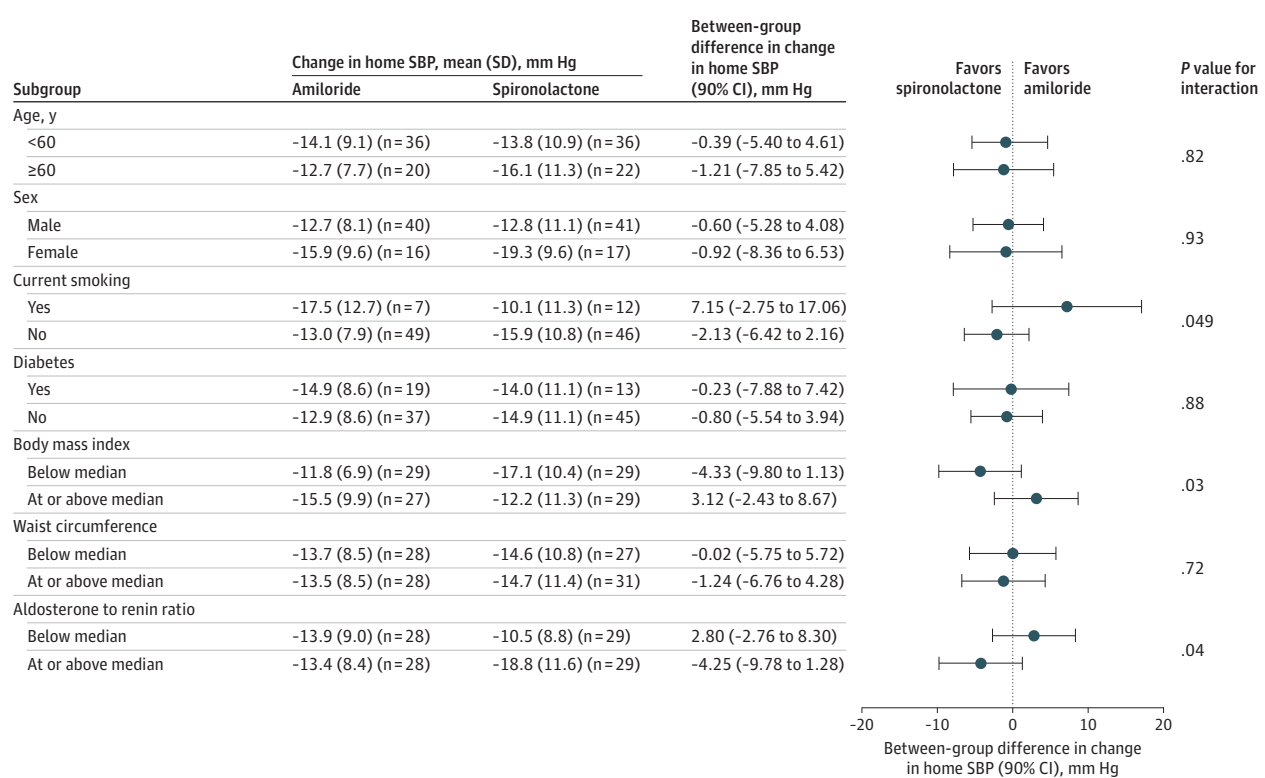
BP-lowering effects between spironolactone and amiloride (Figure 3). The per-protocol analysis did not show any significant associations with the aldosterone to renin ratio or body mass index (eFigure 3 in Supplement 1).

The correlation between baseline biomarkers and the BP-lowering effect of amiloride or spironolactone showed different phenomena (eFigure 4 in Supplement 1). The higher the baseline plasma renin activity or the lower the aldosterone to renin ratio, the less BP was lowered by spironolactone treat-

ment, whereas the BP-lowering effect of amiloride showed no correlation with baseline plasma renin activity or aldosterone to renin ratio. The baseline aldosterone level was not related to the BP-lowering effect of spironolactone or amiloride.

In the spironolactone group, 1 participant discontinued study treatment due to dizziness and acute kidney injury; in the amiloride group, 2 participants discontinued study treatment due to dizziness and 1 discontinued due to hyperkalemia. Only 1 participant had a serious adverse event in the

Figure 3. Difference in Home SBP Change Between Amiloride and Spironolactone Treatment in Prespecified Subgroups

Subgroup	Change in home SBP, mean (SD), mm Hg		Between-group difference in change in home SBP (90% CI), mm Hg	Favors spironolactone / Favors amiloride	P value for interaction
	Amiloride	Spironolactone			
Age, y					
<60	-14.1 (9.1) (n=36)	-13.8 (10.9) (n=36)	-0.39 (-5.40 to 4.61)		.82
≥60	-12.7 (7.7) (n=20)	-16.1 (11.3) (n=22)	-1.21 (-7.85 to 5.42)		
Sex					
Male	-12.7 (8.1) (n=40)	-12.8 (11.1) (n=41)	-0.60 (-5.28 to 4.08)		.93
Female	-15.9 (9.6) (n=16)	-19.3 (9.6) (n=17)	-0.92 (-8.36 to 6.53)		
Current smoking					
Yes	-17.5 (12.7) (n=7)	-10.1 (11.3) (n=12)	7.15 (-2.75 to 17.06)		.049
No	-13.0 (7.9) (n=49)	-15.9 (10.8) (n=46)	-2.13 (-6.42 to 2.16)		
Diabetes					
Yes	-14.9 (8.6) (n=19)	-14.0 (11.1) (n=13)	-0.23 (-7.88 to 7.42)		.88
No	-12.9 (8.6) (n=37)	-14.9 (11.1) (n=45)	-0.80 (-5.54 to 3.94)		
Body mass index					
Below median	-11.8 (6.9) (n=29)	-17.1 (10.4) (n=29)	-4.33 (-9.80 to 1.13)		.03
At or above median	-15.5 (9.9) (n=27)	-12.2 (11.3) (n=29)	3.12 (-2.43 to 8.67)		
Waist circumference					
Below median	-13.7 (8.5) (n=28)	-14.6 (10.8) (n=27)	-0.02 (-5.75 to 5.72)		.72
At or above median	-13.5 (8.5) (n=28)	-14.7 (11.4) (n=31)	-1.24 (-6.76 to 4.28)		
Aldosterone to renin ratio					
Below median	-13.9 (9.0) (n=28)	-10.5 (8.8) (n=29)	2.80 (-2.76 to 8.30)		.04
At or above median	-13.4 (8.4) (n=28)	-18.8 (11.6) (n=29)	-4.25 (-9.78 to 1.28)		

Between-group difference in change in home SBP (90% CI), mm Hg
-20 -10 0 10 20

The difference in change in home systolic blood pressure (SBP) between the 2 groups from baseline to week 12 and the confidence interval were calculated using the analysis-of-covariance model adjusted for baseline home SBP.

amiloride group, which was ankle fracture (eTable 6 in Supplement 1). Drug dosage up-titration was not performed for 3 participants in the spironolactone group and 2 in the amiloride group because of hyperkalemia (eTable 6 in Supplement 1). No participants developed gynecomastia during the study period. The overall drug adherence rate was excellent, with an adherence rate of less than 80% for 1 participant in each study group by the end of the study period (eTable 7 in Supplement 1).

Discussion

To our knowledge, this is the first randomized trial to compare spironolactone and amiloride in participants with resistant hypertension. The key findings are as follows. First, amiloride was not inferior to spironolactone in reducing home SBP after 12 weeks of treatment in participants with treatment-resistant hypertension. Second, amiloride was not inferior in terms of target SBP achievement rate after 12 weeks of treatment. Third, low-dose spironolactone and amiloride both showed meaningful BP lowering in participants with resistant hypertension, demonstrating an excellent safety profile and tolerability. Fourth, spironolactone tended to show better efficacy with decreasing renin and increasing aldosterone to renin ratio, whereas the efficacy of amiloride was consistent regardless of renin and aldosterone-renin status. A strength of this study was the inclusion of participants with uncontrolled hypertension who had satisfactory adherence during a 4-week run-in phase with a fixed-dose triple combination of amlodipine, olmesartan, and hydrochlorothiazide and who demonstrated a home SBP greater than 130 mm Hg. Therefore, the likelihood of drug resistance owing to poor adherence or white-coat effect was ruled out. Additionally, we excluded uncontrolled white-coat hypertension cases by enrolling participants with uncontrolled home BP at the time of randomization.

The pathophysiology of resistant hypertension is characterized by excess aldosterone and fluid retention, which are not sufficiently controlled with maximally tolerated thiazide-like/-type diuretics. In the PATHWAY-2 study, the BP-lowering efficacy of spironolactone correlated with an increase in the aldosterone to renin ratio, a marker of volume excess. Spironolactone, unlike doxazosin and bisoprolol, reduced thoracic fluid overload.[10] Thus, the efficacy of spironolactone can be attributed to its ability to block excess aldosterone and reduce fluid volume.[8] However, spironolactone can lead to poor adherence owing to adverse effects such as hyperkalemia, gynecomastia, and menstrual irregularities.[22] Based on the results of the PATHWAY-2 substudy, the European Society of Cardiology/European Society of Hypertension guidelines in 2018 and 2023 recommended using amiloride as an alternative to spironolactone, especially if the latter was not tolerated.[7] However, no randomized clinical trial has directly

compared the efficacy of spironolactone vs amiloride. A direct comparison is crucial because a previous meta-analysis indicated that spironolactone is superior to amiloride in lowering placebo-adjusted office SBP.[11] Additionally, no prior study has compared their efficacy in lowering home BP. Amiloride is a potassium-sparing diuretic that inhibits the epithelial sodium channels of the distal convoluted tubules and collecting ducts of the kidney.[23] These channels are key regulators in sodium reabsorption and are important in regulating salt sensitivity and salt-sensitive hypertension.[24]

This study used lower doses of spironolactone and amiloride, compared with those used in the PATHWAY-2 study, because low-dose spironolactone has been shown to effectively lower BP while minimizing adverse effects. In an uncontrolled study by Nishizaka et al,[25] low-dose spironolactone (12.5-25 mg/d) administered to participants with resistant hypertension resulted in a mean SBP reduction of 25 (SD, 20) mm Hg and a mean diastolic BP reduction of 12 (SD, 12) mm Hg at 6 months. Additionally, an analysis of 1411 participants from the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm who received spironolactone as the fourth-line antihypertensive drug at a median dose of 25 mg/d for a median duration of 1.3 years revealed a mean SBP reduction of 21.9 mm Hg and a mean diastolic BP reduction of 9.5 mm Hg.[26] Regarding hyperkalemia, the Randomized Aldactone Evaluation Study reported a 5% incidence of hyperkalemia with spironolactone, 12.5 mg/d, compared with 24% for spironolactone, 75 mg/d.[9,27] The results of this study showed that low-dose spironolactone and amiloride demonstrated excellent efficacy in lowering BP, with the degree of BP reduction by spironolactone comparable with that in the PATHWAY-2 study. Additionally, with all randomized participants demonstrating good adherence and minimal adverse effects, low-dose spironolactone and amiloride appear to be viable treatment options for resistant hypertension, at least in the short term. In the present study, low-dose spironolactone showed a lower rate of adverse effects than expected, which may be a result that could weaken the need for amiloride as a substitute for spironolactone. The noninferior BP-lowering effect of amiloride compared with spironolactone was consistent regardless of age, sex, and diabetes status. An interesting finding from this study was that while the efficacy of spironolactone was stronger with an increase in the aldosterone to renin ratio and lower plasma renin activity, similar to the findings from the PATHWAY-2 study, the efficacy of amiloride appeared consistent regardless of these factors.[8] The results suggest that spironolactone may be more efficacious in participants with an increased degree of aldosterone excess; however, the efficacy of amiloride

is independent of aldosterone activation. Further research on choosing antihypertensive medications based on baseline aldosterone to renin ratio or plasma renin activity may enhance treatment success in resistant hypertension. In addition, smoking and increased body mass index are known to activate the renin-angiotensin-aldosterone system. Therefore, it is interesting to note that in participants who were currently smoking and participants with a higher body mass index, amiloride showed a greater BP-lowering effect than spironolactone, possibly because the efficacy of amiloride may be less affected by activation of the renin-angiotensin-aldosterone system than spironolactone.[28,29]

Limitations

This study has some limitations. First, we did not compare the efficacy of higher doses of spironolactone (50 mg vs 20 mg), as used in the PATHWAY-2 trial. Therefore, we cannot determine whether the 2 drugs have comparable efficacies at higher doses, as suggested by the PATHWAY-2 study. However, our objective was to assess the effectiveness of lower doses of spironolactone and amiloride in lowering BP in resistant hypertension. This finding has important clinical implications, as lower drug doses are associated with fewer adverse effects, which are major impediments to using these drugs in the real world. Second, we excluded participants with an estimated glomerular filtration rate of less than 50 mL/min/1.73 m^2; hence, our results may not be generalizable to patients with chronic kidney disease. In this regard, the AMBER study among patients with more severe chronic kidney disease showed significant rates of hyperkalemia in patients treated with spironolactone.[30] Third, hydrochlorothiazide, 12.5 mg/d, was used as one of the background antihypertensive medications in this study. Because patients with resistant hypertension who were treated with more potent and longer half-life drugs such as indapamide or chlorthalidone or with higher doses of hydrochlorothiazide were not included in this study, additional verification of the difference in BP-lowering effects between amiloride and spironolactone may be necessary. Fourth, this trial included only South Korean patients. Therefore, it may not reflect differences in drug responses according to ethnicity.

Conclusions

In this randomized clinical trial involving participants with true resistant hypertension, amiloride demonstrated noninferior efficacy in lowering BP at 12 weeks compared with spironolactone.

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