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The ATHENA-HF Randomized Clinical Trial

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IMPORTANCE Persistent congestion is associated with worse outcomes in acute heart failure (AHF). Mineralocorticoid receptor antagonists administered at high doses may relieve congestion, overcome diuretic resistance, and mitigate the effects of adverse neurohormonal activation in AHF.

OBJECTIVE To assess the effect of high-dose spironolactone and usual care on N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels compared with usual care alone.

DESIGN, SETTING, AND PARTICIPANTS This double-blind and placebo (or low-dose)-controlled randomized clinical trial was conducted in 22 US acute care hospitals among patients with AHF who were previously receiving no or low-dose (12.5 mg or 25 mg daily) spironolactone and had NT-proBNP levels of 1000 pg/mL or more or B-type natriuretic peptide levels of 250 pg/mL or more, regardless of ejection fraction.

INTERVENTIONS High-dose spironolactone (100 mg) vs placebo or 25 mg spironolactone (usual care) daily for 96 hours

MAIN OUTCOMES AND MEASURES The primary end point was the change in NT-proBNP levels from baseline to 96 hours. Secondary end points included the clinical congestion score, dyspnea assessment, net urine output, and net weight change. Safety end points included hyperkalemia and changes in renal function.

RESULTS A total of 360 patients were randomized, of whom the median age was 65 years, 129 (36%) were women, 200 (55.5%) were white, 151 (42%) were black, 8 (2%) were Hispanic or Latino, 9 (2.5%) were of other race/ethnicity, and the median left ventricular ejection fraction was 34%. Baseline median (interquartile range) NT-proBNP levels were 4601 (2697-9596) pg/mL among the group treated with high-dose spironolactone and 3753 (1968-7633) pg/mL among the group who received usual care. There was no significant difference in the log NT-proBNP reduction between the 2 groups (−0.55 [95% CI, −0.92 to −0.18] with high-dose spironolactone and −0.49 [95% CI, −0.98 to −0.14] with usual care, $P = .57$). None of the secondary end point or day-30 all-cause mortality or heart failure hospitalization rate differed between the 2 groups. The changes in serum potassium and estimated glomerular filtration rate at 24, 48, 72, and 96 hours. were similar between the 2 groups.

CONCLUSIONS AND RELEVANCE Adding treatment with high-dose spironolactone to usual care for patients with AHF for 96 hours was well tolerated but did not improve the primary or secondary efficacy end points.

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Author Audio Interview

Supplemental content

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Acute heart failure (AHF) accounts for more than a million hospitalizations in the United States annually.[1] Hospitalizations for HF are associated with a mortality rate or readmission risk of approximately 30% at 60 days and approximately 50% by 6-month postdischarge.[2,3] The already activated renin-angiotensin-aldosterone system in chronic HF may be further accentuated in AHF.[4] Using intravenous loop diuretics intensifies secondary hyperaldosteronism among these patients.[5] Beyond myocardial and vascular adverse effects, hyperaldosteronism directly contributes to diuretic resistance in AHF.[6] Elevated aldosterone levels in AHF are associated with an increased risk of cardiovascular mortality and HF readmission.[7]

The role of low-dose mineralocorticoid receptors antagonists (MRAs) therapy as a neurohormonal antagonist is well established for the treatment of chronic heart failure and reduced ejection fraction. However, the role of high-dose MRA therapy in AHF remains uncertain. Several studies have shown that MRAs taken at high doses result in significant natriuresis and help patients overcome diuretic resistance.[8,9] However, there have been concerns regarding hyperkalemia and renal failure with MRA use, especially with high doses.[10] A single-center, single-blind, nonrandomized clinical trial suggested that the benefits of high-dose MRA therapy in AHF included lower natriuretic peptide levels, less congestion, better renal function, and less need for an intravenous diuretic.[11] Accordingly, we conducted the Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial to test the hypothesis that using high-dose spironolactone in patients with AHF would have a beneficial effect.

Key Points

Question Does adding high-dose spironolactone treatment for patients with acute heart failure lower natriuretic peptide levels and improve outcomes better than usual care?

Findings In this randomized clinical trial, high-dose spironolactone use in acute heart failure was not associated with greater improvement in natriuretic peptide levels, symptoms, congestion, urine output, weight loss, or clinical outcomes than treatment with usual care.

Meaning Routinely using high-dose spironolactone in acute heart failure is not recommended; further studies targeting specifically patients who are resistant to diuretics with high-dose spironolactone are needed.

Methods

Study Oversight

The ATHENA-HF trial was sponsored by the National Heart, Lung, and Blood Institute and conducted by the Heart Failure Clinical Research Network. The protocol was approved by the network's protocol review committee and monitored by the network's data and safety monitoring board. The protocol is in Supplement 1.The ethics committee at each participating site approved the trial and all participants gave written informed consent. Data collection, management, and analyses were performed at the network's coordinating center at Duke Clinical Research Institute.

Study Patients

The eligibility criteria for the ATHENA-HF trial included a clinical diagnosis of heart failure with at least 1 sign and 1 symptom of AHF and with an N-terminal pro-B-type natriuretic peptide (NT-proBNP) level of 1000 pg/mL or more or BNP level of 250 pg/mL or more, regardless of ejection fraction, measured within 24 hours of randomization. Patients were eligible if they were either receiving no spironolactone or receiving low-dose spironolactone (12.5 or 25 mg per day) at home before hospital admission. Patients were also required to have a serum potassium concentration of 5.0 mEq/L (for millimoles per liter, multiply by 1.0) or less, an estimated glomerular filtration rate of 30 mL/min/1.73m^2 or more, and a systolic blood pressure level of more than 90 mm Hg. Patients receiving eplerenone were excluded because, in an acute setting, it may not be easily known if the patient had previously been intolerant to spironolactone. Patients who were already taking more than 25 mg of spironolactone were excluded.

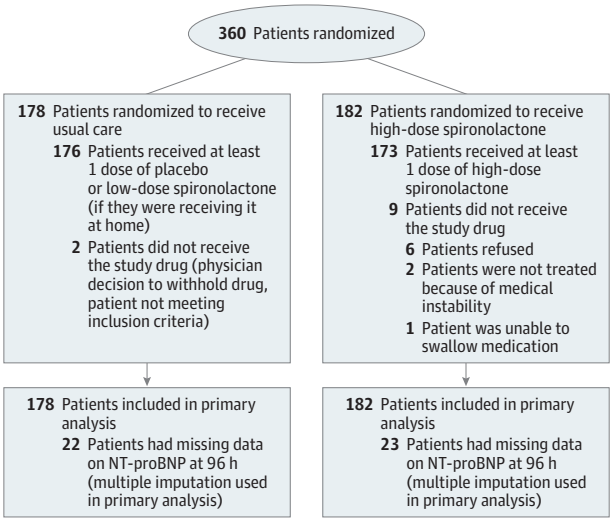
Study Design

The detailed study design for the ATHENA-HF trial has been described previously.[12] Briefly, this was a randomized, double-blind, placebo-controlled trial that assessed the effects of high-dose spironolactone in addition to usual care vs usual care on NT-proBNP levels at 96 hours among patients hospitalized for AHF. The study intervention was initiated within 24 hours of patients receiving the first dose of intravenous diuretics. Patients not taking spironolactone were randomized to 100 mg spironolactone or a placebo. Those taking low-dose spironolactone before their hospital admission were randomized to 100 mg or 25 mg per day in the usual care alone arm; the placebo was not given to these patients to avoid ethical concerns with discontinuing chronic stable therapy. Randomization was double-blind for both comparator strata and was not stratified according to previous low-dose spironolactone treatments. The prescription of all other medications, including diuretics, was left at the discretion of the treating physician. The study drug was discontinued after 96 hours and further MRA use was left to the treating physician's discretion. Data on left ventricular ejection fraction measured within 6 months before randomization were collected; when unavailable, it was assessed during hospitalization. Algorithms were suggested for managing worsening creatinine levels and hyperkalemia during the blinded period.

Study End Points

The primary end point was the proportional change in the log NT-proBNP levels from randomization to 96 hours (or at the hospital discharge if the discharge occurred earlier than 96 hours). Multiple secondary end points from randomization to 96 hours were assessed. These included: (1) a clinical congestion score, calculated by finding the sum of the individual scores for orthopnea, jugular venous distension, and pedal

Figure 1. CONSORT Flow Diagram



NT-proBNP indicates N-terminal pro-B-type natriuretic peptide.

edema on a standardized 4-point scale ranging from 0 to 3[13]; (2) dyspnea relief, measured by a Likert scale (ranging from 1 = markedly improved to 7 = markedly worse) and by the Visual analog scale (ranging from 0 to 100, with higher values indicating a better status); (3) daily cumulative net urine output for up to 96 hours; (4) net weight change from baseline to 96 hours or discharge (whichever came first); (5) furosemide equivalents of the loop diuretic dosage at discharge; and (6) the development of in-hospital worsening HF, with signs and symptoms requiring additional therapy. Exploratory end points included a day-30 postrandomization composite of rates of all-cause mortality, all-cause readmission, or outpatient worsening HF (HF-related readmissions or emergency department visits or the need for outpatient intravenous diuretics). Participants were also contacted by telephone at 60 ± 3 days to assess their vital statuses. Safety end points included changes in serum creatinine levels, estimated glomerular filtration rates, and the incidence of moderate (>5.5 mmol/L) and severe hyperkalemia (>6.0 mmol/L) during the 96-hour treatment period.

Statistical Analysis

It was anticipated that 25% of participants enrolled would be taking low-dose MRAs at randomization. Assuming a 20% further reduction in NT-proBNP levels from randomization in the group receiving MRAs compared with the placebo and a 10% reduction among those taking low-dose MRAs at baseline yielded an overall benefit of 17.5% for the study population. With a 1:1 randomization and a 2-sided type I error rate of 0.05, 360 participants provided approximately 85% power. Randomization was conducted using a permuted block design with stratification based on site and MRA use at enrollment. The primary analysis used a linear regression model with an indicator variable for treatment assignment, an indicator for MRA use before admission, and the log of the baseline NT-proBNP level. We analyzed log-transformed NT-proBNP levels because of better distributional properties and, therefore, improvements in the underlying assumptions of the statistical models involving NT-proBNP. Missing values of the 96-hour NT-proBNP levels (22 in usual care and 23 in the group taking high-dose spironolactone) were imputed using a multiple imputation algorithm. In a sensitivity analysis, values missing because of death were imputed to the worst possible value.[14] This analysis accounted for low-dose MRA before admission using a stratified version of the Wilcoxon-Mann-Whitney test. For binary outcomes, χ^2 tests and the Fisher exact test were used for unadjusted comparisons. Unadjusted time-to-event comparisons were conducted using Kaplan-Meier survival estimates and log-rank tests. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals. Four prespecified subgroup analyses were conducted, including baseline low-dose MRA use, sex, ejection fraction (more than vs less than or equal to 45%), and age (more than vs equal to or less than 65 years). Data are presented as median (interquartile range [IQR]). For primary and secondary end points, a *P* value of less than .05 was considered statistically significant. For subgroup analyses, a treatment by subgroup interaction *P* value of less than .01 was considered significant. All analyses were conducted with SAS, version 9.2 (SAS Institute).

Results

Study Patients

From December 2014 to April 2016, 360 patients were enrolled from 22 sites for an enrollment rate of approximately 1 patient per site per month. A total of 182 patients were randomized to receive high-dose spironolactone plus usual care and 178 to usual care alone (placebo [n = 132] or continued low-dose spironolactone [n = 46]) (**Figure 1**). Baseline characteristics of the patient population are shown in **Table 1**. Note that the use of medication at baseline reflects those that the patients were given at randomization, which was within 24 hours of the patient's first dose of intravenous diuretics. The number of patients receiving spironolactone was lower at randomization than at preadmission, as home medications were discontinued at admission for some patients. The median age of patients was 65 years, 65 (36%) were female, and 101 (56%) were white. The median ejection fraction was 34%; 93 patients (26%) had an ejection fraction of more than 45%. The median systolic blood pressure was 122 mm Hg, heart rate was 79 bpm, serum potassium concentration was 4.0 mEq/L, serum creatinine was 1.2 mg/dL (for micromoles per liter, multiply by 88.4), and the estimated glomerular filtration rate was 56 mL/min.

Efficacy

Baseline median (IQR) NT-proBNP levels were 4601 pg/mL (IQR, 2697-9596 pg/mL) in the group taking spironolactone and 3753 pg/mL (IQR, 1968-7633 pg/ml) in the group receiving usual care. All randomized patients completed the study. There was no significant difference in the primary end point between the

Table 1. Baseline Patient Characteristics

Baseline Characteristics	No. (%)	
	Usual Care Alone (n = 178)	High-Dose Spironolactone (n = 182)
Demographics		
Age, median (25th-75th)	65 (54-74)	65 (57-76)
Women	64 (36)	65 (36)
Race/ethnicity		
White	99 (56)	101 (55)
Black	77 (43)	74 (41)
Other	2 (1)	7 (4)
Hispanic or Latino	6 (3)	2 (1)
Medical history		
Myocardial infarction	52 (30)	51 (28)
Hypertension	142 (81)	159 (87)
Stroke	26 (15)	29 (16)
Atrial fibrillation	84 (48)	88 (50)
Chronic lung disease	43 (24)	39 (21)
Diabetes mellitus	74 (42)	72 (40)
Chronic kidney disease	54 (31)	43 (24)
Obstructive sleep apnea	41 (25)	41 (25)
Current smoker	25 (15)	31 (17)
Baseline treatment[a]		
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	112 (63)	105 (58)
β-blockers	132 (74)	135 (74)
Mineralocorticoid receptor antagonists	21 (12)	19 (11)
Loop diuretics	169 (95)	177 (97)
Furosemide equivalent dose, median (25th-75th), mg	80 (40-160)	80 (40-160)
Furosemide equivalent dose, mean (SD), mg	118.8 (94.4)	122.5 (113.8)
Thiazide diuretics	3 (2)	3 (2)
Digoxin	19 (11)	15 (8)
Hydralazine	47 (26)	44 (24)
Long-acting nitrates	33 (19)	35 (19)
Calcium channel blockers	23 (13)	36 (20)
Statin	101 (57)	104 (57)
Implanted defibrillator	35 (42)	23 (35)
Biventricular pacemaker	31 (37)	28 (42)
Clinical characteristics		
Heart failure hospitalizations in past year	114 (64)	120 (66)
Left ventricular ejection fraction	30 (20-45)	35 (21-50)
Proportion with ejection fraction at <45%	140 (79)	123 (69)
Ischemic etiology	117 (66)	109 (60)
Systolic blood pressure, median (25th-75th), mm Hg	123 (108-138)	120 (106-138)
Heart rate per minute, median (25th-75th)	80 (70-94)	78 (70-90)
BMI, median (25th-75th), kg/m^{2}[b]	32 (27-38)	30 (25-35)
Jugular venous pulse ≥10 cm	126 (74)	135 (76)
Rales	99 (56)	112 (62)
Edema	142 (80)	139 (77)
Orthopnea	154 (87)	151 (85)
New York Heart Association class III or IV	153 (86)	149 (85)
Fatigue frequent or continuous	151 (86)	156 (86)
Dyspnea frequent or continuous	151 (86)	150 (83)
Dyspnea—visual analog scale, median (25th-75th)	65 (40-75)	60 (45-75)

(continued)

Table 1. Baseline Patient Characteristics (continued)

Baseline Characteristics	No. (%) Usual Care Alone (n = 178)	High-Dose Spironolactone (n = 182)
Laboratory values, median (25th-75th)		
Sodium, mEq/L (to convert to millimoles per liter, multiply by 1.0)	140 (138-142)	140 (138-142)
Potassium, mEq/L (to convert to millimoles per liter, multiply by 1.0)	4.0 (3.6-4.3)	3.9 (3.6-4.3)
Blood urea nitrogen, mg/dL (to convert to millimoles per liter, multiply by 0.357)	22 (17-31)	23 (16-33)
Creatinine, mg/dL (to convert to micromoles per liter, multiply by 88.4)	1.3 (1.0-1.5)	1.2 (1.0-1.5)
Glomerular filtration rate, mL/min/1.73 m^2	55 (46-71)	58 (45-75)
B-type natriuretic peptide, pg/mL (n = 156)[c]	1055 (502-1581)	1131 (680-1986)
N-terminal pro B-type natriuretic peptide, pg/mL (n = 204)[c]	4176 (1936-7456)	4028 (2472-10048)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] At the time of randomization.

[b] $P < .05$.

[c] Site-based qualifying values.

2 groups (log NT-proBNP change: −0.55, 95% CI, −0.92 to 0.18 in the group taking spironolactone and −0.49, 95% CI, −0.98 to −0.14 in the group receiving usual care; $P = .57$). Changes in log NT-proBNP levels were similar in analyses using only complete cases (ie, without imputation) (−0.56, 95% CI, −0.96 to −0.19 in the group taking spironolactone and −0.50, 95% CI, −0.99 to 0.14 in the group receiving usual care; $P = .57$). None of the secondary end points, including dyspnea score (Likert and visual analog scales), clinical congestion score, net urine output, weight change, requirement for loop diuretics, and in-hospital worsening heart failure were different between the 2 groups (**Table 2**). Notably, the NT-proBNP levels presented in Table 1 (on-site qualification values before randomization) vs Table 2 (core laboratory values before treatment initiation) were drawn at different times, and patients in the 2 groups may have had different treatments and responses to them in the interim. At discharge, the mean furosemide dosage (in intravenous furosemide equivalents) was 89.5 mg for those taking spironolactone vs 98.0 mg for those receiving the placebo. In the group taking spironolactone, 26 patients (14%) were discharged receiving spironolactone (1 receiving 50 mg daily, 17 receiving 25 mg daily, and 8 receiving 12.5 mg daily) vs 35 (20%) in the placebo group (2 receiving 50 mg, 25 receiving 25 mg, and 8 receiving 12.5 mg). At 96 hours, thiazide use was 3% among those receiving the usual care and 4% among those taking high-dose spironolactone. The median (interquartile range [IQR]) time from randomization to discharge was 4 (IQR, 2-7) days in both groups. Two and 7 patients receiving usual care and 2 and 5 patients taking high-dose spironolactone died during the index hospitalization and through day 30, respectively. There was no difference in time to the first HF readmission, emergency department visit, or death between the 2 groups (adjusted HR, 1.22; 95% CI, 0.68-2.19; $P = .50$) (**Figure 2**). There was no difference in all-cause mortality rates at 60 days. There was no difference in 30-day MRA use between the 2 groups (57 [36%] receiving usual care alone vs 51 [31%] taking high-dose spironolactone, $P = .24$).

Safety

High-dose spironolactone was well tolerated. The changes in serum potassium, creatinine, and estimated glomerular filtration rate from baseline to 24, 48, 72, and 96 hours is shown in **Table 3**. Only 1 patient in the group receiving usual care and 0 in the group taking high-dose spironolactone experienced serum potassium levels between 5.5 and 5.9 mEq/L, and no one had a potassium concentration of more than 6.0 mEq/L during the 96 hours of study treatment. Serious adverse events by 30 days were reported in 84 patients (47%) in the group receiving usual care and 79 patients (43%) taking high-dose spironolactone ($P = .47$). Worsening renal function, defined as an increase of 0.3 mg/dL in creatinine from baseline through 96 hours, occurred in 51 of 182 patients (28%) in taking high-dose spironolactone and 57 of 178 patients (32%) receiving usual care ($P = .42$). No differences between groups were observed in terms of changes in heart rate or blood pressure levels during treatment.

Subgroup Analysis

No differences were observed in the primary end point between patients randomized to high-dose spironolactone or usual care stratified by age, sex, or use of low-dose spironolactone at baseline (eFigure in the Supplement). The change in log NT-proBNP levels at 96 hours or at an earlier discharge in the groups receiving spironolactone and usual care, respectively, among patients with an ejection fraction of 45% or less was −0.55 (95% CI, −0.92 to −0.19) and −0.54 (95% CI, −0.99 to −0.15), and among those with an ejection fraction of more than 45% was −0.53 (95% CI, −1.03 to −0.14) and −0.42 (95% CI, −0.64 to −0.03) (interaction $P = .08$). The results were similar when only complete cases were analyzed without imputation (ejection fraction of ≤45%: spironolactone, −0.56 [95% CI, −0.92 to −0.20] vs usual care, −0.56 [95% CI, −1.01 to −0.15]; ejection fraction of >45%: spironolactone, −0.57 [95% CI, −1.11 to −0.19] vs usual care, −0.43 [95% CI, −0.64 to −0.09]).

Table 2. Primary and Secondary Outcomes

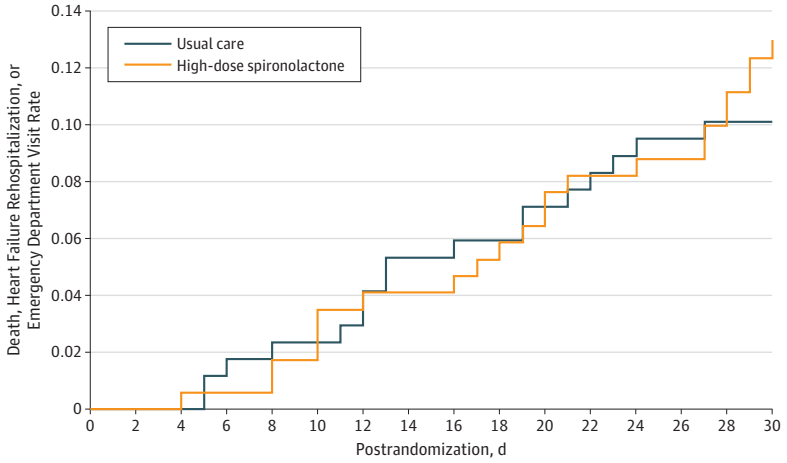
Outcomes	Median (25th-75th)		*P* Value
	Usual Care Alone	High-Dose Spironolactone	
Primary End Point: Log N-Terminal Pro B-Type Natriuretic Peptide			
Baseline	8.23 (7.58 to 8.94)	8.43 (7.90 to 9.17)	
96-h (or earlier discharge)—with multiple imputation for missing values	7.64 (6.93 to 8.45)	7.89 (7.19 to 8.68)	
Change—with multiple imputation for missing values	−0.49 (−0.98 to −0.14)	−0.55 (−0.92 to −0.18)	.57
96-h (or earlier discharge)—no imputation, complete cases only	7.55 (6.91 to 8.31)	7.81 (7.06 to 8.59)	
Change—with multiple imputation for missing values	−0.50 (−0.99 to −0.14)	−0.56 (−0.96 to −0.19)	.57
Secondary End Points: N-Terminal Pro B-Type Natriuretic Peptide, pg/mL			
Baseline	3753 (1968 to 7633)	4601 (2697 to 9596)	
96-h (or earlier discharge)—with multiple imputation for missing values	2080 (1025 to 4675)	2672 (1326 to 5896)	
Change—with multiple imputation for missing values	−1072 (−3182 to −231)	−1796 (−3883 to −571)	.76
96-h (or earlier discharge)—no imputation, complete cases only	1898 (1003 to 4046)	2461 (1168 to 5366)	
Change—with multiple imputation for missing values	−1060 (−2856 to −238)	−1774 (−3763 to −586)	.61
Clinical congestion score			
Baseline	11 (9 to 12)	10 (9 to 12)	
96-h (or earlier discharge)	4 (2 to 6)	4 (2 to 7)	
Change	−6 (−8 to −4)	−6 (−8 to −4)	.41
Dyspnea			
Likert Score (96-h or earlier discharge)	2 (1 to 3)	2 (1 to 3)	.31
Visual analog scale			
Baseline	65 (40 to 75)	60 (45 to 75)	
96-h (or earlier discharge)	83 (70 to 90)	80 (65 to 90)	
Change	15 (5 to 30)	15 (2 to 30)	.61
Net urine output, mL (cumulative)			
24-h	1183 (510 to 1955)	1100 (483 to 2131)	.76
48-h	2282 (1155 to 4135)	2484 (1203 to 4411)	.44
72-h	3810 (2011 to 5565)	4171 (2053 to 6040)	.53
96-h	5584 (2924 to 8132)	6086 (2780 to 8420)	.57
Weight change, kg			
Baseline	939.9 (77.6-113.6)	88.5 (73.8-107.5)	
96-h (or earlier discharge)	90.2 (76.0-110.5)	84.0 (71.9-104.7)	
Change	−2.8 (−5.1 to −0.8)	−3.3 (−5.9 to −0.9)	.33
Furosemide equivalent diuretic dose, mg			
Baseline	160 (120 to 320)	160 (100 to 320)	
96-h (or earlier discharge)	80 (40 to 240)	80.0 (40 to 200)	
Change	−80 (−160 to 0.0)	−80.0 (−160 to 0)	.77
Worsening heart failure, No. (%)			
Inpatient	31 (18)	33 (19)	.76
Outpatient (through day 30)	17 (10)	19 (11)	.76

Discussion

In this study, which represents the first double-blind multicenter trial assessing the efficacy and safety of high-dose spironolactone in AHF, there was no benefit or risk seen with an active intervention over usual care for the primary or secondary end points. These include changes in NT-proBNP levels, urine output, weight changes, symptoms, or congestion score. These results contrast with some of the earlier mechanistic and clinical data that suggested that there would be increased urine output and less congestion by using high-dose MRA therapy. High-dose spironolactone therapy was well tolerated without any significant risk of hyperkalemia or worsening renal function among the population of patients who met the eligibility criteria for the ATHENA-HF trial.

The eligibility criteria for ATHENA-HF were chosen to represent a generalizable population with AHF. The inclusion criteria of a glomerular filtration rate of more than 30 mL/min resulted in a cohort with a median rate of 56 mL/min. Both study groups had significant diuresis and lost more than 2.7 kg of weight in the first 96 hours or by an earlier discharge. It is possible that targeting patients with a resistance to diuretics with lower glomerular filtration rates may lead to better results with high-dose spironolactone. No difference was seen in the use of diuretic dosages between the 2 study arms, so it does not

Figure 2. Time to First Heart Failure Rehospitalization, Emergency Department Visit, or Death



No. at risk

Usual care	178	176	171	166	165	164	163	159	159	158	156	155	153	152	147	137
High-dose spironolactone	182	175	173	171	171	167	164	163	163	161	159	156	156	155	153	141

There were no significant differences noted in the postdischarge outcomes among patients randomized to receive the usual care alone vs the group who received high-dose spironolactone. Receiving high-dose spironolactone vs usual care had a hazard ratio of 1.22 (95% CI, 0.68-2.19; *P* = .50).

Table 3. Changes in Serum Potassium Concentration and Renal Function

Change	Median (25th-75th)		Mean (SD)		*P* Value
	Usual Care Alone	High-Dose Spironolactone	Usual Care Alone	High-Dose Spironolactone	
Change in Serum Potassium, mEq/L (to Convert to Millimoles per Liter, Multiply by 1.0)					
24-h	0.00 (−0.40 to 0.30)	0.00 (−0.30 to 0.30)	0.01 (0.56)	−0.00 (0.47)	.50
48-h	0.10 (−0.30 to 0.40)	0.10 (−0.10 to 0.40)	0.04 (0.52)	0.16 (0.46)	.02
72-h	0.20 (−0.40 to 0.55)	0.20 (−0.20 to 0.60)	0.09 (0.62)	0.22 (0.52)	.08
96-h	0.20 (−0.30 to 0.60)	0.30 (0.00 to 0.70)	0.15 (0.69)	0.31 (0.54)	.08
Change in Serum Creatinine, mg/dL (to Convert to Micromoles per Liter, Multiply by 88.4)					
24-h	0.05 (−0.05 to 0.20)	0.05 (−0.03 to 0.17)	0.07 (0.18)	0.06 (0.17)	.76
48-h	0.02 (−1.10 to 0.20)	0.10 (−0.03 to 0.02)	0.10 (0.27)	0.09 (0.20)	.67
72-h	0.08 (−0.08 to 0.22)	0.10 (−0.03 to 0.28)	0.13 (0.33)	0.12 (0.26)	.85
96-h	0.10 (−0.02 to 0.33)	0.10 (−0.05 to 0.27)	0.16 (0.30)	0.15 (0.30)	.77
Change in Estimated Glomerular Filtration Rate, mL/min/1.73 m^2					
24-h	−1.95 (−8.46 to 2.79)	−2.58 (−7.83 to 1.53)	−2.75 (9.43)	−2.54 (10.80)	.87
48-h	−1.59 (−9.65 to 3.71)	−4.12 (−8.87 to 1.89)	−3.34 (12.52)	−3.33 (11.15)	.95
72-h	−3.70 (−12.06 to 4.09)	−3.71 (−10.67 to 0.87)	−4.47 (13.37)	−4.53 (12.05)	.82
96-h	−5.53 (−13.11 to 0.79)	−4.35 (−11.06 to 1.74)	−5.56 (13.85)	−4.13 (11.58)	.56

appear that high-dose spironolactone led to a selective early reduction in loop diuretic doses in the active intervention. No differences were noted between patients who were MRA naïve vs those taking low-dose spironolactone at baseline; hence, the neutral results cannot be attributed to long-term MRA use among a proportion of patients. It is possible that 100-mg of spironolactone is not a high enough dose and that higher dosages are needed. This possibility is intriguing, considering that previous smaller HF studies have used up to 200 mg of spironolactone, similar to the dosages used in cirrhosis.[8] This approach may be explored in the future, considering the safety of the 100 mg spironolactone dose in the ATHENA-HF trial. Emerging data that show novel potassium binders reducing the risk of hyperkalemia may further facilitate such a study.[10] Spironolactone is a prodrug that is converted to active metabolite canrenone, which is responsible for its mineralocorticoid effects.[15] Considering that the mean duration of AHF hospitalization in the United States is 4 to 5 days,[16] using intravenous canrenoate with a faster onset of action may be more beneficial. Similarly, new nonsteroidal MRA finerenone that does not require conversion to an active metabolite may be more useful in the AHF setting.[17]

There were no safety concerns raised by using high-dose spironolactone in this trial. There is a substantial risk of hyperkalemia, even with lower doses of spironolactone in patients with chronic heart failure.[10] With the active changes in glomerular filtration rate and blood pressure commonly encountered in the setting of AHF, the risk of hyperkalemia with high-dose spironolactone is concerning. However, our study confirms that in the hospital setting, high-dose spironolac-

tone use is safe in patients with relatively preserved renal function and with the implementation of other precautions and protocols, such as those used in this trial. These data are encouraging for future research with either a higher-dose MRA in AHF than used in ATHENA-HF, or among patients with worse renal function and diuretic resistance.

There were no differences in the efficacy or safety of high-dose spironolactone therapy among any of the prespecified subgroups based on age, sex, or previous use of MRA. Interestingly, while no differences were seen among patients with an ejection fraction rate of 45% or less and among patients with an ejection fraction rate of more than 45%, spironolactone intervention led to a numerically higher reduction in log NT-proBNP levels with a trend toward a significant treatment-by-subgroup interaction. Though the trial was not powered to assess differences among patients with reduced vs preserved ejection fraction rate, these data are intriguing, as the Renal Optimization Strategies Evaluation trial also showed a differential trend with low-dose dopamine use in patients with AHF between those with preserved vs reduced ejection fraction rate.[18] While it is a standard for chronic HF trials to study patients with reduced and preserved ejection fraction separately, a number of recent AHF trials have included patients regardless of ejection fraction rates. The results of the ATHENA-HF trials provide data to encourage further study of the differences between these 2 patient populations in the AHF setting.

Limitations

Our study has several limitations. First, the duration of the treatment (96 hours or until discharge, whichever came first) was relatively short. Considering that spironolactone may take few days to convert to its active metabolites, especially in the presence of hepatic congestion, we cannot exclude the possibility that a longer treatment duration may have shown differences between the 2 groups. Second, data on the primary end point (changes in NT-proBNP levels) were missing for approximately 12% of the study population. However, imputed, worst-possible-value, and raw analyses all pointed to a neutral effect of spironolactone on NT-proBNP levels. Third, for the trial to better represent the real-world population with AHF, we included some patients (25%) who were already receiving low-dose MRA at home, and this may have influenced the treatment effect, thus contributing toward the neutral results. Notably, there was no differential effect of high-dose spironolactone between low-dose and no baseline MRA strata. Fourth, our study was not powered to explore differences according to ejection fraction rates. Finally, we excluded patients with a glomerular filtration rate of 30 mL/min or less and therefore our results, especially regarding safety, cannot be extrapolated to these patients.

Conclusions

High-dose spironolactone in AHF was not associated with improvement in either the primary or the secondary outcomes in the ATHENA-HF trial. This intervention was safe and well tolerated. Future research should study higher dosages and patients with diuretic resistance and should explore differences between patients with preserved vs reduced ejection fraction rates.

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