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Clinical Research

Spironolactone in Acute Heart Failure Patients With Renal Dysfunction and Risk Factors for Diuretic Resistance: From the ATHENA-HF Trial

Stephen J. Greene, MD,[a,b] G. Michael Felker, MD, MHS,[a,b] Anna Giczewska, MS,[a,c] Andreas P. Kalogeropoulos, MD, MPH, PhD,[d] Andrew P. Ambrosy, MD,[e,f] Hrishikesh Chakraborty, DrPH,[a] Adam D. DeVore, MD, MHS,[a,b] Marat Fudim, MD,[a,b] Steven E. McNulty, MS,[a] Robert J. Mentz, MD,[a,b] Muthiah Vaduganathan, MD, MPH,[g] Adrian F. Hernandez, MD, MHS,[a,b] and Javed Butler, MD, MPH, MBA[h]

[a] *Duke Clinical Research Institute, Durham, North Carolina, USA*

[b] *Division of Cardiology, Duke University School of Medicine, Durham, North Carolina, USA*

[c] *Department of Biomedical Engineering, Faculty of Electronics, Telecommunications and Informatics, Gdansk University of Technology, Gdansk, Poland*

[d] *Division of Cardiology, Stony Brook University, Stony Brook, New York, USA*

[e] *Department of Cardiology, Kaiser Permanente San Francisco Medical Center, San Francisco, California, USA*

[f] *Division of Research, Kaiser Permanente Northern California, Oakland, California, USA*

[g] *Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, Boston, Massachusetts, USA*

[h] *Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA*

See editorial by Clarke, pages 1079–1081 of this issue.

ABSTRACT

Background: Acute heart failure (HF) patients with renal insufficiency and risk factors for diuretic resistance may be most likely to derive incremental improvement in congestion with the addition of spironolactone.

Methods: The **A**ldosterone **T**argeted **N**eurohormonal **C**ombined with **N**atriuresis **T**herapy in **H**eart **F**ailure (ATHENA-HF) trial randomized 360 acute HF patients with reduced or preserved ejection fraction to spironolactone 100 mg daily or usual care for 96 hours. The current analysis assessed the effects of study therapy within tertiles of baseline estimated glomerular filtration rate (eGFR) and subgroups at heightened risk for diuretic resistance.

RÉSUMÉ

Contexte : Les patients présentant une insuffisance cardiaque (IC) aiguë accompagnée d'une insuffisance rénale et de facteurs de risque de résistance aux diurétiques pourraient être plus susceptibles d'obtenir une réduction significative de la congestion grâce à l'ajout de spironolactone.

Méthodologie : L'essai ATHENA-HF (***A**ldosterone **T**argeted **N**eurohormonal **C**ombined with **N**atriuresis **T**herapy in **H**eart **F**ailure*) a été mené auprès de 360 patients présentant une IC aiguë et une fraction d'éjection réduite ou préservée, répartis aléatoirement pour recevoir pendant 96 heures soit de la spironolactone à raison de 100 mg par jour, soit les soins usuels. La présente analyse visait à évaluer les

Relief of signs and symptoms of congestion represents the cornerstone of inpatient care for patients hospitalized for heart failure (HF).[1] However, effective decongestion is oftentimes difficult, and a significant proportion of patients are discharged with persistent congestion and attendant heightened risks of death and HF rehospitalization.[1,2] Likewise, recent investigations have supported diuretic response, defined as the change in weight per 40 mg oral furosemide equivalent, as an objective measure of decongestive efficiency that predicts postdischarge outcomes.[3-5] In these studies, poor diuretic response (ie, diuretic resistance) consistently correlates with several patient characteristics, including poor renal function,

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Corresponding author: Dr Stephen J. Greene, Duke Clinical Research Institute, 200 Morris Street, Durham, North Carolina 27701, USA. Tel.: +1-919-684-8111; fax: +1-919-668-7078.

E-mail: stephen.greene@duke.edu

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Results: Across eGFR tertiles, there was no incremental benefit of high-dose spironolactone on any efficacy endpoint, including changes in log N-terminal pro-B-type natriuretic peptide and signs and symptoms of congestion (all *P* for interaction $\geq$ 0.06). High-dose spironolactone had no significant effect on N-terminal pro-B-type natriuretic peptide reduction regardless of blood pressure, diabetes mellitus status, and loop diuretic dose (all *P* for interaction $\geq$ 0.38). In-hospital changes in serum potassium and creatinine were similar between treatment groups for all GFR tertiles (all *P* for interaction $\geq$ 0.18). Rates of inpatient worsening HF, 30-day worsening HF, and 60-day all-cause mortality were numerically higher among patients with lower baseline eGFR, but relative effects of study treatment did not differ with renal function (all *P* for interaction $\geq$ 0.27).

Conclusions: High-dose spironolactone did not improve congestion over usual care among patients with acute HF, irrespective of renal function and risk factors for diuretic resistance. In-hospital initiation or continuation of spironolactone was safe during the inpatient stay, even when administered at high doses to patients with moderate renal dysfunction.

Résultats : Dans tous les tertiles du TFGe, l'administration d'une forte dose de spironolactone n'a procuré aucun bienfait supplémentaire à l'égard des paramètres d'efficacité, y compris les variations logarithmiques du fragment N-terminal du propeptide du peptide natriurétique de type B N-Terminal et les signes et symptômes de congestion (toutes les valeurs de *p* pour l'interaction $\geq$ 0,06). L'administration d'une forte dose de spironolactone n'a pas eu d'effet significatif quant à la réduction du propeptide natriurétique de type B N-terminal, sans égard à la pression artérielle, à la présence ou à l'absence de diabète et à la dose du diurétique de l'anse (toutes les valeurs de *p* pour l'interaction $\geq$ 0,38). Les variations des taux sériques de potassium et de créatinine durant l'hospitalisation étaient comparables dans les deux groupes de traitement, et ce, dans tous les tertiles du TFGe (toutes les valeurs de *p* pour l'interaction $\geq$ 0,18). Le taux de patients dont l'IC s'est aggravée durant l'hospitalisation et après 30 jours, ainsi que le taux de mortalité toutes causes confondues à 60 jours, étaient numériquement supérieurs chez les patients présentant un TFGe inférieur au départ, mais les effets relatifs du traitement à l'étude ne variaient pas selon l'état de la fonction rénale (toutes les valeurs de *p* pour l'interaction $\geq$ 0,27).

Conclusions : L'administration d'une forte dose de spironolactone ne s'est pas révélée supérieure aux soins usuels pour réduire la congestion chez les patients présentant une IC aiguë, indépendamment de l'état de leur fonction rénale et des facteurs de risque de résistance aux diurétiques présents. La mise en route ou la poursuite du traitement par la spironolactone chez les patients hospitalisés s'est révélée sans danger durant le séjour à l'hôpital, même lorsque le médicament était administré à de fortes doses à des patients présentant une dysfonction rénale modérée.

lower systolic blood pressure, history of diabetes, and high doses of background loop diuretic therapy.[3-6] Thus, these baseline characteristics may define patient populations where additive decongestive therapies offer greatest likelihood of benefit over standard in-hospital care.

Few studies have prospectively investigated decongestive strategies in the setting of acute HF (AHF) with renal insufficiency and diuretic resistance, and there remain no definitively proven strategies.[7-9] The recently completed **A**ldosterone **T**argeted Neuro**h**ormonal Combine**d** with **Na**triuresis Therapy in **H**eart **F**ailure (ATHENA-HF) trial tested the hypothesis that the addition of high-dose spironolactone would result in greater decongestion, as compared with standard care.[10] Results from the overall trial population showed high-dose spironolactone to be well tolerated but without laboratory or clinical benefits. However, although overall trial results were neutral, it is plausible that incremental decongestive benefit among patients with loop diuretic resistance was nullified by no benefit among patients with preserved renal function and robust response to background diuretic therapy. In this context, the purpose of this *post hoc* analysis from the ATHENA-HF trial was to explore the incremental decongestive effects and safety of high-dose spironolactone over standard therapy in AHF patient subsets with renal dysfunction and high risk for diuretic resistance.

Methods

Study design

The design and primary results of the ATHENA-HF trial have been previously reported.[10,11] Briefly, ATHENA-HF was a prospective, multicentre, randomized trial investigating the efficacy and safety of high-dose spironolactone in addition to usual care vs usual care alone among patients hospitalized for AHF. Patients not taking spironolactone before enrollment were randomized to 100 mg spironolactone daily or placebo; patients already taking spironolactone were randomized to 100 mg spironolactone daily or 25 mg daily. The treatment period was 96 hours. Eligible patients were hospitalized with a clinical diagnosis of HF ($\geq$ 1 sign and $\geq$ 1 symptom) irrespective of ejection fraction (EF) and an N-terminal pro-B-type natriuretic peptide (NT-proBNP) level $\geq$ 1000 pg/mL within 24 hours of randomization. Patients were required to have the serum potassium level $\leq$ 5.0 mEq/L, an estimated glomerular filtration rate (eGFR) $\geq$ 30 mL/min/1.73 m^2 determined by the Modification of Diet in Renal Disease equation, and systolic blood pressure $>$ 90 mm Hg. Patients already receiving eplerenone or $>$ 25 mg daily of spironolactone were excluded. The trial was conducted in accordance with the Declaration of Helsinki and with institutional review board/ethics committee approval at all sites. All patients provided written informed consent.

Study endpoints

The prespecified primary efficacy endpoint for the main ATHENA-HF trial and the present *post hoc* analysis was the proportional change in the log NT-proBNP level from baseline to 96 hours or hospital discharge (whichever occurred first). Prespecified secondary congestion endpoints were measured from baseline to 96 hours/hospital discharge, and included (1) change in the absolute NT-proBNP level, (2) change in clinical congestion score, (3) dyspnea at 96 hours (7-point Likert scale), (4) change in dyspnea (100-point visual analogue scale), (5) net urine output, (6) change in body weight, and (7) change in furosemide equivalent diuretic dose. Secondary clinical endpoints included (1) inpatient worsening HF, defined as worsening signs and symptoms requiring additional therapy; (2) 30-day worsening HF, defined as the composite of HF readmission, emergency department visit, or outpatient receipt of intravenous diuretic therapy; and (3) 60-day all-cause mortality. Safety endpoints included (1) changes in serum potassium, creatinine, and eGFR from baseline to 96 hours/hospital discharge; (2) serious adverse events at 30 days; and (3) hyperkalemia $\geq$ 5.5 mEq/L at 30 days.

Statistical analysis

Spironolactone treatment effect by baseline eGFR. Patients were categorized by tertile of baseline eGFR, and baseline characteristics were compared. Continuous variables were reported as median (25th percentile, 75th percentile) and compared using Wilcoxon rank-sum tests. Categorical variables were presented as frequencies and percentages, and compared using the proportion difference test or Fisher's exact test.

Within each eGFR tertile, patients were further stratified by the study treatment arm and the effect of treatment was compared for all efficacy and safety endpoints. Interactions between tertiles and treatment arms were evaluated using general linear models for continuous outcomes and logistic models for categorical outcomes. For each endpoint, imputation for missing data was not performed and analyses were derived from patients with complete data for a given measure. To evaluate consistency of efficacy and safety results for high-dose spironolactone with alternate eGFR cutpoints, sensitivity analyses using clinical eGFR definitions aligned with the stages of chronic kidney disease were performed (ie, eGFR 30-44, 45-59, and $\geq$ 60 mL/min/1.73 m^2). Further sensitivity analyses included separate evaluations among patients with EF $<$ 45% and $\geq$ 45% by baseline eGFR tertile.

Spironolactone treatment effect by risk factors for diuretic resistance. To further evaluate the study treatment effect among patients with risk factors for diuretic resistance other than low eGFR, regression modelling with the multiple imputation method for missing values of the change in log NT-proBNP was used (rate of missing values, 12.5%). The effect of high-dose spironolactone on the primary endpoint was tested across multiple prespecified subgroups of interest, including systolic blood pressure ($\geq$ or $<$ median), presence vs absence of diabetes mellitus (DM), and baseline loop diuretic dose ($\geq$ or $<$ median). Interaction *P* values, with adjustments for baseline log NT-proBNP and stratification factor from the randomization scheme, were computed to assess the treatment effect for the change in log NT-proBNP for specific subgroups.

Associations between baseline eGFR and study endpoints. Unadjusted and adjusted hazard ratios using Cox regression models were used to compare eGFR tertiles for time-to-event endpoints of 30-day worsening HF and 60-day all-cause mortality. Linearity and proportional hazards assumptions were tested for all models and no violations were found. Furthermore, unadjusted and adjusted general linear regression models were used to assess the association between the eGFR tertile and the change in log NT-proBNP. All adjusted Cox regression and general linear regression models used 6 prespecified covariates measured at baseline, including age, systolic blood pressure, history of DM, history of atrial fibrillation, ischemic HF etiology, and proportion of patients with HF with preserved EF. All statistical analyses were performed using SAS version 9.4 or later (SAS Institute, Cary, NC). Two-tailed $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics by eGFR tertile (defined as eGFR $\leq$ 50, eGFR 51-71, and eGFR $\geq$ 72 mL/min/1.73 m^2) for all 360 patients enrolled in the ATHENA-HF trial are presented in Supplemental Table S1. Patients with worse renal function tended to be older and were more likely to be white with preserved EF, ischemic HF etiology, and history of atrial fibrillation. The baseline NT-proBNP level markedly increased from the highest to lowest eGFR tertile, but signs and symptoms of congestion were similar between groups with the exception of less orthopnea among those with worse renal function. Rates of baseline loop diuretic use were similar between eGFR tertiles, but dosing increased with progressively worse renal function. Patients in the lowest eGFR tertile were least likely to be receiving background angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker therapy, but rates of background mineralocorticoid receptor antagonist therapy were similar across groups.

Effects of spironolactone on congestion and clinical events

Data on in-hospital changes in congestion and clinical events are displayed in Table 1. Regardless of treatment assignment, patients in all eGFR tertiles tended to have at least moderate reductions in the NT-proBNP level from baseline to 96 hours. Similarly, all groups tended to have improvements in clinical congestion, including improvements in dyspnea and clinical congestion score and weight loss. Median (25th-75th) urine output from baseline to 96 hours ranged from 4018 (1586-7416) to 7060 (2211-8736) mL in all subgroups.

There was no significant difference in the primary endpoint of the change in log NT-proBNP between high-dose spironolactone and usual care, regardless of baseline eGFR

Table 1. Primary and secondary endpoints by baseline renal function

Outcomes	High-dose spironolactone GFR ≤ 50 (N = 60) GFR 51-71 (N = 55) GFR ≥ 72 (N = 67)	Usual care GFR ≤ 50 (N = 58) GFR 51-71 (N = 65) GFR ≥ 72 (N = 55)	*P* value	Interaction *P* value
Primary endpoint: log NT-proBNP				
Baseline				
GFR ≤ 50	8.87 (8.26, 9.48)	8.53 (7.80, 8.94)	0.010	
GFR 51-71	8.22 (7.94, 8.86)	8.31 (7.59, 9.05)	0.615	
GFR ≥ 72	8.18 (7.39, 8.77)	7.76 (7.27, 8.35)	0.107	
96 h (or earlier discharge)				
GFR ≤ 50	8.52 (7.74, 9.14)	7.93 (7.49, 8.53)	0.013	
GFR 51-71	7.80 (7.19, 8.63)	7.66 (7.06, 8.50)	0.499	
GFR ≥ 72	7.40 (6.85, 7.97)	6.93 (6.52, 7.51)	0.030	
Change				0.797
GFR ≤ 50	−0.43 (−0.80, −0.13)	−0.42 (−0.72, −0.04)	0.810	
GFR 51-71	−0.54 (−1.00, −0.14)	−0.38 (−0.99, −0.09)	0.610	
GFR ≥ 72	−0.70 (−1.10, −0.47)	−0.76 (−1.16, −0.33)	0.785	
Secondary endpoints: measures of congestion				
NT-proBNP (pg/mL)				
Baseline				
GFR ≤ 50	7097 (3860, 13,140)	5063 (2451, 7637)	0.010	
GFR 51-71	3720 (2811, 7031)	4073 (1973, 8545)	0.615	
GFR ≥ 72	3563 (1627, 6452)	2342 (1432, 4231)	0.107	
96 h (or earlier discharge)				
GFR ≤ 50	4994 (2290, 9290)	2781 (1794, 5065)	0.013	
GFR 51-71	2440 (1326, 5588)	2121 (1161, 4914)	0.499	
GFR ≥ 72	1642 (939, 2889)	1018 (680, 1830)	0.030	
Change				0.073
GFR ≤ 50	−2189 (−6529, −610)	−833 (−2679, −204)	0.045	
GFR 51-71	−1701 (−3004, −617)	−1089 (−2981, −162)	0.503	
GFR ≥ 72	−1951 (−3676, −582)	−1059 (−2979, −482)	0.195	
96-h change in clinical congestion score*				0.063
GFR ≤ 50	−5 (−7, −3)	−7 (−9, −3)	0.122	
GFR 51-71	−6 (−9, −4)	−5 (−7, −4)	0.312	
GFR ≥ 72	−5 (−8, −4)	−7 (−8, −5)	0.139	
96-h dyspnea—Likert†				0.103
GFR ≤50	2 (1, 3)	1 (1, 3)	0.025	
GFR 51-71	2 (1, 2)	2 (1, 2)	0.702	
GFR ≥ 72	2 (1, 3)	2 (1, 3)	0.409	
96-h change in dyspnea—VAS‡				0.793
GFR ≤ 50	12 (0, 27)	15 (5, 25)	0.333	
GFR 51-71	18 (5, 35)	20 (10, 37)	0.812	
GFR ≥ 72	15 (2, 28)	12 (0, 30)	0.752	
96 h net urine output (mL)				0.687
GFR ≤ 50	5702 (2780, 7455)	4018 (1587, 7416)	0.189	
GFR 51-71	4631 (2825, 7770)	5101 (3005, 7166)	0.959	
GFR ≥ 72	7060 (2211, 8737)	6745 (3734, 8983)	0.978	
96-h change in weight (kg)				0.599
GFR ≤50	−3.9 (−7.3, −0.9)	−2.7 (−4.4, −0.4)	0.084	
GFR 51-71	−2.9 (−5.5, −0.8)	−2.4 (−5.6, −0.8)	0.878	
GFR ≥ 72	−3.7 (−5.7, −1.1)	−3.4 (−5.3, −0.9)	0.629	
96-h change in furosemide equivalent diuretic dose (mg)				0.058
GFR ≤ 50	−80 (−173, 95)	−80 (−160, 0)	0.525	
GFR 51-71	−80 (−200, 0)	−80 (−160, 4)	0.784	
GFR ≥ 72	−60 (−160, 0)	−40 (−120, 0)	0.110	
Secondary endpoints: clinical events				
Inpatient worsening HF events§				0.270
GFR ≤ 50	17 (29.3%)	10 (17.5%)	0.137	
GFR 51-71	9 (17.0%)	13 (20.3%)	0.646	
GFR ≥ 72	7 (11.1%)	8 (14.8%)	0.550	
30-d HF hospitalization, ED visit, or death				0.612
GFR ≤ 50	7 (13.2%)	7 (12.5%)	0.912	
GFR 51-71	2 (3.8%)	4 (7.0%)	0.680	
GFR ≥ 72	10 (16.7%)	6 (12.0%)	0.489	

Table 1. Continued.

Outcomes	High-dose spironolactone GFR ≤ 50 (N = 60) GFR 51-71 (N = 55) GFR ≥ 72 (N = 67)	Usual care GFR ≤ 50 (N = 58) GFR 51-71 (N = 65) GFR ≥ 72 (N = 55)	*P* value	Interaction *P* value
60-d all-cause mortality				0.635
GFR ≤ 50	6 (10.0%)	6 (10.3%)	0.951	
GFR 51-71	1 (1.8%)	4 (6.2%)	0.373	
GFR ≥ 72	1 (1.5%)	0 (0.0%)	1.000	

Data expressed as n (%) or median (25th, 75th). Data derived from patients with complete data for each endpoint (ie, no imputation). Change refers to the change in measure from baseline to 96 h or hospital discharge, whichever occurred first.

ED, emergency department; GFR, estimated glomerular filtration rate; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VAS, visual analogue scale

* Clinical congestion score was calculated by finding the sum of the individual scores of orthopnea, jugular venous distention, and pedal edema on a standardized 4-point scale ranging from 0 to 3.

† Measured by the Likert scale ranging from 1 = markedly improved to 7 = markedly worse.

‡ Measured by VAS ranging from 0 to 100 with higher values indicating better status.

§ Defined as worsening HF with signs and symptoms requiring additional therapy.

tertile (*P* for interaction = 0.80). Likewise, there was no differential effect of high-dose spironolactone by baseline renal function for any of the secondary congestion endpoints (all *P* for interaction ≥ 0.058). Rates of inpatient worsening HF, 30-day worsening HF, and 60-day all-cause mortality were numerically higher among patients with lower eGFR, but there was no interaction with study treatment (all *P* for interaction ≥ 0.27). Sensitivity analyses for all primary and secondary endpoints using clinical eGFR cutpoints of 30-44 (N = 71), 45-59 (N = 109), and ≥ 60 mL/min/1.73 m^2 (N = 180) are presented in Supplemental Table S2. Further sensitivity analyses for efficacy endpoints limited to patients with EF < 45% and ≥ 45% are displayed in Supplemental Tables S3 and S4, respectively. Results of all sensitivity analyses were consistent with the primary analysis, with no suggestion of an advantage for high-dose spironolactone for any endpoint, irrespective of the eGFR group.

Figure 1 displays results for the primary efficacy endpoint among subgroups at heightened risk of diuretic resistance. In addition to a neutral effect among patients with lower eGFR, there was no benefit of high-dose spironolactone regardless of stratification by median systolic blood pressure, DM status, or median loop diuretic dose.

Renal function, changes in natriuretic peptide level, and clinical events

Compared with patients in the highest eGFR tertile, lower eGFR tertiles were associated with less reduction in log NT-proBNP from baseline to 96 hours/discharge (Table 2). This relationship persisted after adjustment for clinical factors. Regarding clinical endpoints, eGFR ≤ 50 was independently associated with greater risk of 60-day all-cause mortality. Baseline renal function was not associated with the risk of 30-day worsening HF events.

Safety of spironolactone

Changes in serum potassium and serum creatinine from baseline to 96 hours/discharge were similar between high-dose spironolactone and usual care for all eGFR tertiles (all *P* for interaction ≥ 0.18) (Table 3). Patients in the highest eGFR tertile tended to have less reduction in GFR with high-dose spironolactone, whereas the change in eGFR within lower tertiles was similar between treatment arms (*P* for interaction = 0.033). Only 1 patient randomized to usual care and 0 patients randomized to high-dose spironolactone developed a serum potassium level between 5.5 and 5.9 mEq/L during the 96-hour treatment period; no patient developed a serum potassium level ≥ 6.0 mEq/L. Serious adverse events through 30 days were similar between study treatment groups for all eGFR tertiles (all *P* for interaction = 0.68). Rates of hyperkalemia through 30 days were similarly low (≤ 2%) for high-dose spironolactone and usual care, irrespective of eGFR tertile. Sensitivity analyses for safety endpoints using clinical eGFR cutpoints (Supplemental Table S5) and stratified by EF < 45% (Supplemental Table S6) and ≥ 45% (Supplemental Table S7) did not demonstrate any statistically significant treatment interactions (all *P* for interaction ≥ 0.14).

Discussion

In this cohort of patients hospitalized for AHF, 50% had an eGFR < 60 mL/min/1.73 m^2 and approximately 20% of patients had an eGFR < 45 mL/min/1.73 m^2. Patient profile and clinical outcomes differed by baseline renal function, with worse renal function associated with older age, higher likelihood of preserved EF, and higher all-cause mortality at 60 days. Worse baseline renal function correlated with a greater elevation in the baseline NT-proBNP level and was independently associated with less in-hospital NT-proBNP reduction as compared with patients with better renal function. Regarding study treatment, the addition of high-dose spironolactone did not offer decongestive or clinical advantages over usual care alone among AHF patients with impaired renal function, nor was it effective in subsets at heightened risk for poor response to standard loop diuretic therapy. However, the safety profile of the in-hospital use of spironolactone was reassuring, with no signal of excess hyperkalemia, worsening renal function, or adverse clinical events during the inpatient stay, even in patients with moderate renal dysfunction.

Potential issues specific to spironolactone metabolism notwithstanding,[12] it was posited that robust diuretic response to standard therapy among patients with preserved renal function prevented detection of incremental decongestion with high-dose spironolactone in the overall ATHENA population. The current *post hoc* analysis does not support this

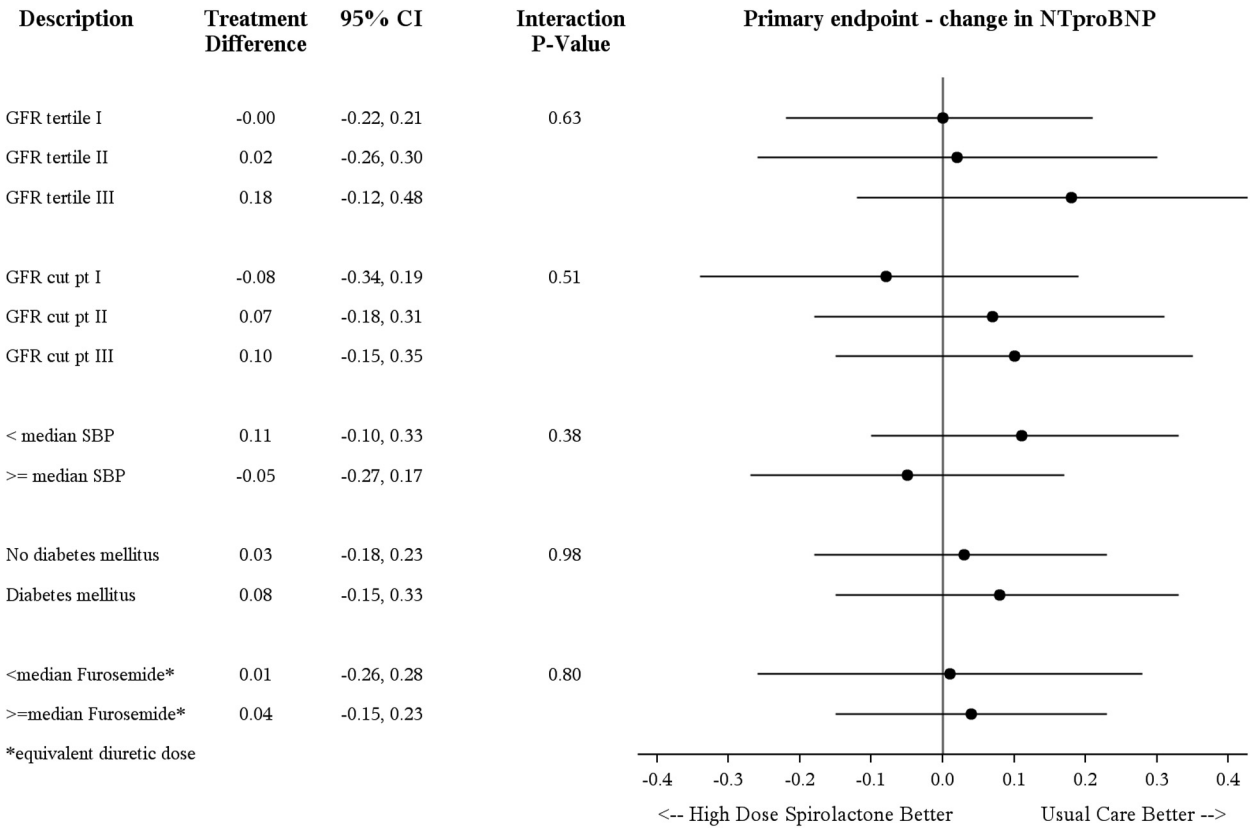

Figure 1. Forest plot of prespecified subgroup analyses. The median SBP was 122 mm Hg, and the median daily furosemide equivalent dose was 80 mg. The *X*-axis represents the treatment difference for the change in log NT-proBNP. CI, confidence interval; GFR, glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.

hypothesis. Reflecting on the present results, patient characteristics of the lowest eGFR tertile deserve attention. Despite an attempt to identify a subset who would demonstrate diuretic resistance, this was not accomplished. Notably, patients in the lowest eGFR tertile had reasonable urine output with 96 hours of standard care (ie, median > 4.0 L, 25% with urine output > 7.4 L). Likewise, limited by trial selection criteria mandating eGFR $\geq$ 30 mL/min/1.73 m^2, the severity of renal dysfunction in the lowest eGFR tertile was modest with a median eGFR of 44, median serum creatinine of 1.6 mg/dL, and median blood urea nitrogen level of 32 mg/dL. Stratification by other factors previously associated with poor diuretic response (including lower systolic blood pressure, history of DM, and high background dosing

Table 2. Associations between baseline renal function and primary and clinical endpoints (combined high-dose spironolactone and usual care groups)

Primary endpoint	Unadjusted change (95% CI); *P* value	Adjusted change (95% CI); *P* value*
Absolute change in log NT-proBNP		
GFR $\leq$ 50	0.37 (0.20, 0.55); < 0.001	0.22 (0.01, 0.43); 0.041
GFR 51-71	0.30 (0.10, 0.50); 0.004	0.23 (0.01, 0.45); 0.041
GFR $\geq$ 72	Referent	Referent
Clinical endpoints	**Unadjusted hazard ratio (95% CI); *P* value**	**Adjusted hazard ratio (95% CI); *P* value***
30-d HF hospitalization, ED visit, or death		
GFR $\leq$ 50	1.01 (0.52-1.97); 0.968	0.98 (0.43-2.21); 0.960
GFR 51-71	0.66 (0.31-1.41); 0.287	0.51 (0.22-1.18); 0.117
GFR $\geq$ 72	Referent	Referent
60-d all-cause mortality		
GFR $\leq$ 50	12.75 (1.66-98.07); 0.014	12.11 (1.37-107.22); 0.025
GFR 51-71	5.14 (0.60-43.95); 0.135	5.54 (0.57-53.88); 0.140
GFR $\geq$ 72	Referent	Referent

CI, confidence interval; DM, diabetes mellitus; ED, emergency department; GFR, estimated glomerular filtration rate; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Adjusted for age, systolic blood pressure, history of DM, history of atrial fibrillation, ischemic HF etiology, and proportion of patients with HF with preserved ejection fraction.

Table 3. Safety endpoints by baseline renal function

	High-dose spironolactone GFR ≤ 50 (N = 60) GFR 51-71 (N = 55) GFR ≥ 72 (N = 67)	Usual care GFR ≤ 50 (N = 58) GFR 51-71 (N = 65) GFR ≥ 72 (N = 55)	*P* value	Interaction *P* value
Inpatient (ie, study treatment phase)				
96-h change in serum potassium (mEq/L)				0.948
GFR ≤ 50	0.10 (−0.10, 0.70)	0.10 (−0.30, 0.60)	0.582	
GFR 51-71	0.40 (0.00, 0.70)	0.20 (−0.30, 0.50)	0.157	
GFR ≥ 72	0.40 (0.00, 0.60)	0.10 (−0.40, 0.80)	0.316	
96-h change in serum creatinine (mg/dL)				0.182
GFR ≤ 50	0.20 (−0.10, 0.40)	0.13 (−0.04, 0.41)	0.777	
GFR 51-71	0.20 (0.04, 0.46)	0.04 (0.00, 0.30)	0.133	
GFR ≥ 72	0.00 (−0.09, 0.11)	0.12 (−0.01, 0.20)	0.026	
96-h change in GFR (mL/min/1.73 m^2)				0.033
GFR ≤ 50	−4.09 (−9.58, 3.96)	−4.74 (−10.10, 1.33)	0.765	
GFR 51-71	−9.35 (−17.43, −1.88)	−1.58 (−13.55, 0.00)	0.118	
GFR ≥ 72	0.00 (−11.70, 13.01)	−10.05 (−19.16, 0.84)	0.053	
30-d adverse event rates				
Serious adverse event				0.682
GFR ≤ 50	11 (18.3)	5 (8.6)	0.123	
GFR 51-71	4 (7.3)	4 (6.2)	1.000	
GFR ≥ 72	6 (9.0)	4 (7.3)	1.000	
Hyperkalemia ≥ 5.5 mEq/L				—
GFR ≤ 50	1 (1.7)	0 (0.0)	—	
GFR 51-71	0 (0.0)	1 (1.5)	—	
GFR ≥ 72	0 (0.0)	1 (1.8)	—	

Data expressed as median (25th, 75th). Data derived from patients with complete data for each endpoint (ie, no imputation). Change refers to the change in measure from baseline to 96 h or hospital discharge, whichever occurred first.

GFR, glomerular filtration rate.

of loop diuretic therapy) also failed to detect an efficacy signal, potentially due to small numbers of patients in the overall cohort with true diuretic resistance. A low prevalence of diuretic resistance has been seen in prior HF trials of decongestive therapies and may have similarly contributed to neutral results in the **R**enal **O**ptimization **S**trategies **E**valuation (ROSE) study of low-dose dopamine and nesiritide.[9] Despite the ROSE program requiring renal dysfunction for enrollment, median eGFR was roughly 45 mL/min/1.73 m^2 and patients receiving placebo produced a median 8.3 L of urine with 72 hours of standard therapy.[9] Together with the ROSE findings, the current data from ATHENA-HF suggest that isolated moderate renal insufficiency may be an inadequate selection criterion for future trials of additive decongestive therapies in AHF. Rather, enrollment of patients with confirmed oliguria despite usual care may maximize chances of demonstrating incremental benefit on congestive endpoints and may more closely align with the unmet therapeutic need in clinical practice. Likewise, given the reassuring in-hospital safety profile of high-dose spironolactone seen here, future evaluation of efficacy and safety of spironolactone among AHF patients with severe renal dysfunction (ie, eGFR < 30 mL/min/1.73 m^2) may be considered.

Although efficacy findings were neutral, the present data add significant strength to previously reported ATHENA-HF results regarding the relative safety of in-hospital use of spironolactone.[10] In the current analysis, there were no heightened risks of hyperkalemia or worsening renal function (1) despite administration of spironolactone doses above those generally used in clinical practice and (2) even among patients with reduced baseline eGFR where safety concerns are greatest. Despite proven survival benefits and strong guideline recommendations, use of MRA therapy among eligible HF with reduced EF patients in routine practice has remained consistently low, with concerns over hyperkalemia and worsening renal function as significant factors.[13-15] After publication of the **T**reatment **o**f **P**reserved **C**ardiac Function Heart Failure With an **A**ldosterone Antagonis**t** (TOPCAT) trial, guidelines now also endorse consideration of spironolactone among HF with preserved EF patients.[16,17] To improve long-term adherence to guideline-directed medical therapy, the HF hospitalization has been championed as a key opportunity to optimize chronic HF medical therapy.[2,18,19] Nonetheless, only one-third of eligible hospitalized HF patients may be prescribed an MRA at discharge.[20,21] Prior observational data demonstrate strong associations between MRA prescription at discharge and longitudinal postdischarge adherence, but randomized data regarding safety of inpatient MRA use are scarce.[22,23] In this context, the current analysis from ATHENA-HF provides strong evidence for the relative safety of in-hospital initiation or continuation of MRA therapy during a hospitalization for AHF. Specifically, these findings inform in-hospital care for the substantial proportion of HF patients in routine practice with concomitant renal dysfunction. In combination with appropriate postdischarge laboratory and clinical surveillance, the present data support current guidelines regarding in-hospital initiation of MRA therapy in this high-risk subset as a generally safe means of improving quality of care.[18,24]

Aside from study treatment effects, associations between baseline renal function and study endpoints warrant mention. The present findings are consistent with prior HF literature linking poor baseline renal function with increased risk of subsequent clinical events.[25] However, unique to this analysis is the independent association between worse baseline renal function and less in-hospital reduction in NT-proBNP. Although previous work has shown correlation between worse baseline renal function and higher baseline natriuretic

peptide levels, our data have more direct application to future HF clinical trials using reduction in NT-proBNP as an endpoint.[26] Similar to a previous analysis suggesting that prevalent atrial fibrillation/flutter may impact ability of an HF clinical trial to meet an NT-proBNP defined endpoint, the current study highlights baseline renal dysfunction as an additional independent factor potentially limiting sensitivity of a trial to detect significant reduction in NT-proBNP, irrespective of any cardiac effects of study therapy.[27]

Limitations

Limitations of this analysis should be recognized. First, these results should be viewed in the context of the ATHENA-HF inclusion criteria for eGFR $\geq$ 30 mL/min/1.73 m^2. The efficacy and safety findings seen here may not generalize to patients with more severe renal impairment. Nonetheless, this eGFR cutpoint is consistent with clinical guidelines for spironolactone and facilitates applicability to routine practice. Second, the trial protocol did not require postdischarge use of spironolactone. Thus, postdischarge clinical and safety data must be interpreted in the setting of most patients no longer actively receiving study drug. Third, despite multivariable modelling with prespecified covariates, associations between renal function, clinical outcomes, and NT-proBNP change may be subject to residual confounding, and this retrospective observational work cannot definitively determine cause-effect relationships. Fourth, given the moderate size of the overall trial cohort, subgroup analyses were subject to modest numbers of patients and limited statistical power to detect treatment effects. This issue also increased vulnerability to imbalances in baseline NT-proBNP levels (as was seen among patients in the lowest eGFR tertile receiving high-dose spironolactone), which may favour regression to the mean during follow-up and limit utility of change in NT-proBNP as an endpoint. Fifth, eGFR estimated at the time of hospital admission for HF may differ from renal function measured under chronic stable conditions, and the Modification of Diet in Renal Disease equation may be less accurate in the setting of rapidly changing renal function. Thus, the degree to which acute cardiorenal instability contributed to the categorization of patients in this analysis and the results is unclear. Lastly, these data do not reflect the treatment effect of spironolactone among patients with confirmed diuretic resistance during hospitalization. However, the decision to forego such analysis was prespecified, as it was noted that stratification of patients by a feature measured after study randomization would be an improper subgroup analysis. Thus, the present analysis was limited to characteristics measured at study baseline that are risk factors for subsequent diuretic resistance.

Conclusions

In this AHF clinical trial population, renal dysfunction was associated with a distinct patient profile, less in-hospital reduction of NT-proBNP levels, and worse clinical outcomes. High-dose spironolactone did not offer incremental improvement in congestion over usual care, irrespective of renal function and risk factors for diuretic resistance. In-hospital initiation or continuation of spironolactone was safe during the inpatient stay, even when administered at high doses to patients with moderate renal dysfunction.

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Supplementary Material

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