Rationale and Design of the Aldosterone Targeted NeuroHormonal CombinEd with Natriuresis TherApy in Heart Failure (ATHENA-HF) Trial

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Rationale and Design of the Aldosterone Targeted NeuroHormonal CombinEd with Natriuresis Therapy in Heart Failure (ATHENA-HF) Trial

Javed Butler, MD, MPH, MBA (1); Adrian F. Hernandez, MD (2); Kevin J. Anstrom, PhD (2); Andreas Kalogeropoulos, MD, PhD (3); Margaret M. Redfield, MD (4); Marvin A. Konstam, MD (5); W. H. Wilson Tang, MD (6); G. Michael Felker, MD (2); Monica R. Shah, MD (7); Eugene Braunwald, MD (8)

From the Department of Medicine, Stony Brook University, Stony Brook, New York (1); Department of Medicine, Duke University, Durham, North Carolina (2); Department of Medicine, Emory University, Atlanta, Georgia (3); Department of Cardiovascular Diseases, Mayo Clinic, Minnesota (4); Department of Medicine, Tufts University, Boston, Massachusetts (5); Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio (6); Division of Cardiovascular Sciences, National Heart, Lung, and Blood Institute, Baltimore, Maryland; Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts (8)

Running Title: ATHENA HF Trial

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Address correspondence to: Javed Butler, MD, MPH, Cardiology Division, Stony Brook University, T-16, Room 080, Stony Brook, NY 11794. Telephone: (631) 444-1066 Fax: (631) 444-1054 Email: javed.butler@stonybrookmedicine.edu
ABSTRACT
While therapy with mineralocorticoid receptor antagonists (MRA) is recommended for patients with chronic heart failure (HF) with reduced ejection fraction and in post-infarction HF, it has not been studied well in acute HF (AHF) despite being commonly used in this setting. At high doses, MRA therapy in AHF may relieve congestion through its natriuretic properties and mitigate the effects of adverse neurohormonal activation associated with intravenous loop diuretics. The Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure (ATHENA-HF) trial is a randomized, double blind, placebo-controlled study of the safety and efficacy of 100 mg daily spironolactone vs. placebo (or continued low-dose spironolactone use in participants who are already receiving spironolactone at baseline) in 360 patients hospitalized for AHF. Patients are randomized within 24 hours of receiving the first dose of intravenous diuretics. The primary objective is to determine if high-dose spironolactone, when compared to standard care, will lead to greater reductions in N-terminal pro-B-type natriuretic peptide levels from randomization to 96 hours. The secondary endpoints include changes in the clinical congestion score, dyspnea relief, urine output, weight change, loop diuretic dose, and in-hospital worsening HF. Index hospital length of stay and 30-day clinical outcomes will be assessed. Safety endpoints include risk of hyperkalemia and renal function. Differences among patients with reduced versus preserved ejection fraction will be determined.

Key Words: Heart failure, acute heart failure, hospitalization, mineralocorticoid receptor antagonist, aldosterone, natriuretic peptides

Abbreviations:
ACE: Angiotensin converting enzyme
AHF: Acute heart failure
ASCEND-HF: Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure
ATHENA-HF: Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure
eGFR: Estimated glomerular filtration rate
EVEREST: Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan
HF: Heart failure
MRA: Mineralocorticoid receptor antagonists
NT-proBNP: N-terminal pro B-type natriuretic peptide
RELAX-AHF: Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure
RAAS: Renin-angiotensin-aldosterone-system
WHF: Worsening heart failure
Heart failure (HF) accounts for over a million hospitalizations in the United States annually.\textsuperscript{1,2} Hospitalizations for HF are associated with a significantly elevated risk for post-discharge mortality and recurrent hospitalizations. Mortality or readmission risk at 60-days post discharge is \(~30\%\) and may be as high as 50\% by 6 months in these patients.\textsuperscript{3-7} While therapy for chronic HF with reduced ejection fraction has evolved over time favorably impacting survival, outcomes for patients with acute heart failure (AHF) have not changed much in the past two decades. Thus far none of the trials have shown an improvement in post-discharge outcomes in patients with acute heart failure.\textsuperscript{8,9} Thus there remains a pressing need to develop interventions that can improve outcomes safely in this high-risk group of patients.

**PERSISTENT CONGESTION AND OUTCOMES IN ACUTE HEART FAILURE**

Worsening congestion is the main reason for hospitalization for the majority of AHF patients and diuretics remains the mainstay of therapy. Even with the use of intravenous diuretics, over half of the patients lose \(\leq 5\) lbs. and up to 20\% may actually gain weight during hospitalization.\textsuperscript{10} Despite improvement in symptoms, a large proportion of these patients continue to have persistent congestion at discharge,\textsuperscript{11} which whether measured clinically,\textsuperscript{12,13} with right heart catheterization, or by natriuretic peptide levels,\textsuperscript{14,15} predict post-discharge outcome. Persistent congestion may be sub-clinical, related to diuretic resistance, or when further diuretic use is difficult in the face of worsening renal function.

**IMPORTANCE OF ALDOSTERONE IN ACUTE HEART FAILURE**

The renin-angiotensin-aldosterone-system (RAAS) is activated in HF. In normal subjects, aldosterone levels range between 2-9 ng/dL but in one AHF trial, median levels were 11.0 ng/dL and were over the upper normal range in 33.2\% of patients.\textsuperscript{16} Aldosterone levels are only transiently suppressed with ACE inhibition. Intravenous loop diuretic use in AHF further
intensifies RAAS activation and secondary hyperaldosteronism\textsuperscript{17, 18}, enhancing proximal tubular sodium absorption and decreased distal sodium delivery, impairing the normal escape mechanism from the sodium-retaining effect of aldosterone. Therefore, beyond myocardial and vascular adverse effects, hyperaldosteronism directly contributes to diuretic resistance.\textsuperscript{19} Loop diuretics also block sodium chloride transport at the macula densa, which stimulates the RAAS independent of renal sodium loss\textsuperscript{17}. (Figure 1)

MINERALOCORTICOID RECEPTOR ANTAGONIST USE IN ACUTE HEART FAILURE

The low dose mineralocorticoid receptor antagonists (MRA) used in chronic HF are believed to benefit patients by anti-fibrotic but not natriuretic effects.\textsuperscript{20} Inhibition of mineralocorticoid receptors at higher MRA doses may cause significant natriuresis. Resistance to loop diuretics in AHF may be overcome by natriuretic doses of spironolactone (>50 mg/day).\textsuperscript{19} In a study of 6 HF patients, 200 mg twice a day of spironolactone caused a marked increase in sodium excretion leading to negative sodium balance.\textsuperscript{21} In another study, patients with severe HF who were resistant to high-dose loop diuretics responded with increased natriuresis with the use of 100 mg/day spironolactone.\textsuperscript{22}

The clinical benefit and safety of high dose MRA use in AHF was recently supported by a single-center, single-blind trial of 100 patients treated with standard therapy alone or with addition of spironolactone initiated within 24 hours.\textsuperscript{23} Spironolactone dose was 94.5±23.3 mg on day 1 and 62.7±24.3 mg on day 3. Increase in creatinine by ≥0.3 mg/dL from day 1 to day 3 was more likely to occur in the standard of care arm (20% vs. 4%; P=0.038). Plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) levels were comparable at baseline but were lower in the spironolactone group at day 3 (2488 [4579] pg/ml in controls vs. 1555 [1832] pg/ml in
spironolactone group; \( P=0.05 \). A greater proportion of patients in the spironolactone group were free of congestion at day 3 and a higher proportion had transitioned from intravenous to oral furosemide (82\% vs. 44\%; \( P<0.001 \)). These findings support the safety and potential efficacy of a high-dose spironolactone strategy in AHF. However, this was a single center non-randomized study and the intervention was not blinded to the investigators, which raises concerns for potential bias. While high dose MRA may be effective in the setting of congestion, increased risks of hyperkalemia or elevation in creatinine also need to be studied further.\(^{24}\)

In the EVEREST trial, which enrolled patients with left ventricular ejection fraction of <40\% who were hospitalized for acute heart failure and were receiving standard therapy, median baseline aldosterone blood level was 11.0 ng/dL (25–75 percentile: 2–21 ng/dL) and was over the upper normal range in 33.2\% of patients. Median aldosterone levels increased during hospital stay from 11 ng/dL at baseline to 15 ng/dL at discharge (\( P<0.001 \)) and remained increased 6 months after discharge (16 ng/dL, \( P<0.001 \) vs. baseline). Higher serum aldosterone levels correlated with worse post-discharge outcomes. After a median follow-up of 9.9 months, higher baseline aldosterone levels were associated with an increased risk for mortality and the combined endpoint of cardiovascular mortality plus heart failure readmission in adjusted models (HR 1.49, 95\% CI 1.11–1.99; and HR 1.40, 95\% CI 1.11–1.78, respectively), in the highest quartile when compared with the lowest.\(^{16}\)

**RISK FOR HYPERKALEMIA**

Most of the data on hyperkalemia with MRAs is in chronic HF. In AHF, hypokalemia is more common and is often due to a defect in \( \text{Na}^+ / \text{K}^+ \)-ATPase activity and an intracellular potassium shift caused by oxidative stress and neurohormonal activation in combination with loop diuretic use.\(^{25}\) Spironolactone is rapidly metabolized to several metabolites that produce natriuretic and
antikaliuretic effects. While the natriuretic effects decline over a period of 48-72 hours, the antikaliuretic effects may be observed for several days following discontinuation, underscoring the importance of careful monitoring of potassium levels, especially in patients with chronic kidney disease. In a study in six chronic HF patients, 200mg bid of spironolactone led to negative sodium balance without significant increases in potassium levels (3.9 to 4.1 mmol/L) or changes in creatinine clearance after 4 days. In 18 patients with advanced HF receiving 50-200 mg of spironolactone in addition to standard treatment, there was no significant increase in serum potassium (4.0 vs. 4.2 mEq/l) or creatinine (1.3 vs. 1.4 mg/dl) during an average follow up of 41 weeks. In an AHF study assessing 50-100 mg spironolactone use, serum potassium did not differ between control vs. spironolactone groups (3.9 vs. 4.1 mmol/L respectively) at day 3 (p=0.15).

ENDPOINTS IN ACUTE HEART FAILURE

Congestion is the most common manifestation of AHF and is related with both symptoms and prognosis. Persistent congestion at discharge is associated with worse outcomes. The effectiveness of decongestion can be measured in multiple ways.

Natriuretic Peptide Levels

Natriuretic peptide are markers of wall stretch and have advantage over clinical signs for assessment of congestion due to the lack of sensitivity and inter-rater reliability of examination. Even with symptom relief, readmission and mortality risk remains high if natriuretic peptides stay elevated in patients with AHF. Baseline levels and changes in hospital are both associated with filling pressures and outcomes, with best outcomes seen when natriuretic peptide levels decrease by >30% in hospital. Discharge natriuretic peptide levels are superior to admission levels or change in levels during hospitalization for predicting risk.
Dyspnea

In several studies, dyspnea improvement in AHF was associated with improved outcomes post-discharge. In the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, early dyspnea relief measured on a 7-point Likert scale was associated with lower 30-day mortality or HF hospitalization risk.\textsuperscript{31} In the Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure (RELAX-AHF) trial, serelaxin was associated with both improvement in dyspnea assessed by Visual Analog Scale and lower 6-month mortality risk.\textsuperscript{32} Thus significant and early improvement in dyspnea may predict improved long-term outcomes, besides being a therapeutic goal by itself.

Clinical Congestion Score

In the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial, a modified composite congestion score at discharge calculated by summing the individual scores for orthopnea, jugular venous distension, and pedal edema (on a standardized 4-point scale ranging from 0 to 3) was predictive of 30-day all-cause mortality (HR 1.34, 95\%CI 1.14–1.58), and combined morality and HF readmission risk (HR 1.13, 95\%CI 1.03–1.25).\textsuperscript{12}

Mortality

Mortality reduction is the gold standard outcome for clinical trials in chronic heart failure. Though several previous trials focused primarily on symptom improvement in clinical trials for acute heart failure, it is now well recognized that symptom improvement during hospitalization is an inconsistent predictor of post-discharge mortality.\textsuperscript{33,34} In fact therapies like inotropes may improve symptoms and worsen the risk for mortality. In-hospital mortality for patients with acute heart failure is low but the main concern is the very high (up to 30\% one-year) post discharge
mortality.\textsuperscript{35} Thus assessing post-discharge mortality as both an efficacy and safety outcome in this high-risk group of acute heart failure patients is imperative.

**Readmissions**

Similar to mortality, readmission post discharge from an acute heart failure hospitalization also remains a critical endpoint, both from a clinical and an economic perspective.\textsuperscript{36} From a clinical perspective, recurrent hospitalizations are associated with a change in the natural history trajectory of the disease process, with each hospitalization portending a worse prognosis subsequently.\textsuperscript{37} From an economic perspective, recurrent hospitalizations account for the largest proportion of direct cost of care for heart failure. Considering that heart failure is the number one discharge diagnosis in the United States for the Medicare beneficiaries, there are now financial penalties imposed by the Centers for Medicare and Medicaid Services for hospitals that have a high rate of readmission post discharge after an acute heart failure hospitalization. Thus effective therapies for these patients should preferably translate into a reduction in risk for readmissions.

**In-hospital Worsening Heart Failure**

Acute worsening heart failure (WHF) is reported in a sizable portion of patients hospitalized for heart failure, and is increasingly being recognized as an entity that is associated with an adverse in-hospital course.\textsuperscript{35} WHF is generally defined as worsening heart failure symptoms and signs requiring an intensification of therapy, and is reported to be seen in anywhere from 5\% to 42\% of heart failure admissions.\textsuperscript{37} Recent data suggest that some experimental therapies may reduce the risk of development of WHF among hospitalized heart failure patients, and this is associated with a reduction in the risk of subsequent post-discharge cardiovascular mortality.\textsuperscript{38} In this respect, WHF holds promise as an endpoint for acute heart failure clinical trials. However, a better understanding of the pathophysiology and a consensus on the definition of WHF is still
needed and until then, it serves as a potential secondary endpoint.

THE ALDOSTERONE TARGETED NEUROHORMONAL COMBINED WITH NATRIURESIS THERAPY IN HEART FAILURE (ATHENA-HF) TRIAL

Study Design

The ATHENA-HF trial is a randomized, double blind, placebo controlled trial assessing the impact of high dose spironolactone vs. placebo (or continued low dose spironolactone use) on natriuretic peptide levels among patients hospitalized for AHF. The study schema is presented in the Central Illustration.

Objective

To determine if high-dose spironolactone administered to patients with AHF will lead to greater reductions in N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels from randomization to 96 hours compared to standard of care. In order to assess the early use of natriuretic doses of spironolactone in AHF and its impact on preventing diuretic resistance, the study intervention is initiated within 24 hours of the first dose of intravenous diuretics.

Eligibility and Intervention

Eligibility criteria are listed in Table 1. Patients hospitalized with at least one sign and one symptoms of AHF with an NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL measured within 24 hours from randomization are eligible. Patients who are either not on spironolactone therapy at home or those who are on low dose spironolactone (12.5 or 25 mg per day) are eligible. Patients must have serum potassium concentration ≤5.0mmol/L, an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m² and systolic blood pressure >90 mmHg.

Patients who are not on spironolactone at home are randomized to 100mg spironolactone or placebo. Those already on 12.5 or 25 mg per day spironolactone are randomized to 100 mg or
25 mg per day but not to placebo, to avoid ethical concerns with discontinuing chronic therapy. Patients on eplerenone will not be included as in the acute setting it may not be easily known if the patient has been previously intolerant to spironolactone. Patients already taking >25 mg of spironolactone will be excluded due to potential overlap with natriuretic potential of intermediate dose spironolactone use.

**Baseline Evaluations**

Baseline evaluation includes history, physical examination, vital signs and body weight assessment, review of medications, measurement of renal function and electrolytes, dyspnea assessments (7-point Likert and Visual Analog Scale measured off oxygen for >3 minutes), pregnancy test for women of childbearing potential, and collection of blood for core laboratory measurement of NT-proBNP level.

**Duration of Intervention**

The median length of stay for HF hospitalization in the United States is 4.3 days.\(^{39}\) In order to have comparable efficacy assessment within the two arms and avoid comparing outcomes among patients with potentially different lengths of stay, and to conform with the prevalent norms of the duration of hospitalization, the duration of intervention and the primary endpoint assessment was chosen to be 96 hours.

**Volume Assessment and Dose Adjustment**

All other medications, including diuretics, are left at the discretion of the treating physician. The study drug is discontinued after 96 hours and further MRA use is left to the treating physician’s discretion. If the patient is clinically euvoletic in <96 hours, the investigators may consider changing loop diuretics to oral dosing.

**Ejection Fraction**
Ejection fraction measured within 6 months prior to randomization is obtained. Those without this information undergo ejection fraction assessment by any modality during the hospitalization. Patients will be eligible regardless of ejection fraction and therefore this determination does not need to precede randomization. Ejection fraction assessment is performed for a pre-specified secondary analysis to ascertain possible differential effects of intervention in patients with reduced vs. preserved ejection fraction.

**Renal Function and Hyperkalemia**

Modest increase in serum creatinine with diureses seen in many patients with AHF that usually reverses over time. In some patients however, a rise in serum creatinine portend poor prognosis. There remains clinical concern about acute kidney injury with high dose MRA use in AHF. The decision regarding management of patients with worsening creatinine is left to the discretion of the treating physicians. It is recommended that,

a. If serum creatinine is increased ≤0.5 mg/dl and the patient is diuresing and improving, and is still fluid overloaded, continue study drug per protocol

b. If serum creatinine is increased >0.5 mg/dl and the patient is diuresing and clinically improving but is still fluid overloaded, consider decreasing study drug to 50 mg

c. If the patient becomes oliguric with worsening serum creatinine and develops acute kidney injury criteria, hold study drug and reassess in 24 hours

To closely follow the patients to mitigate the risk of hyperkalemia, electrolytes are measured at least every 24h until 96h and at discharge. Potassium supplementation and potassium containing salt substitutes are discontinued and high potassium containing foods are avoided during the study protocol. Study drug dose is adjusted based on serum potassium level as shown in Table 2.
Endpoints

Efficacy

The primary endpoint of ATHENA-HF is the proportional change in NT-proBNP from randomization to 96 hours. Multiple secondary endpoints from randomization to 96 hours are also assessed, including, a) clinical congestion score; b) dyspnea relief by Likert and by Visual Analog Scales; c) net urine output; d) weight change; e) loop diuretic dose need in furosemide dose equivalents, and f) development of in-hospital worsening HF, defined as worsening HF signs and symptoms requiring additional therapy.

Exploratory analyses include a day-30 post randomization telephone call to ascertain, a) all-cause mortality, b) all-cause readmissions, c) outpatient worsening HF, defined as HF readmission or emergency department visits or need for outpatient IV diuretics, d) MRA use and loop diuretic dose requirement at day 30 and e) length of stay for index hospitalization. All participants are also contacted by telephone at 60±3 days to assess vital status.

Safety

Safety endpoints include change in serum creatinine and incidence of hyperkalemia (>5.5mmol/L or >6.0mmol/L) from randomization to 96 hours post randomization.

STATISTICAL CONSIDERATIONS

Sample Size and Power Calculations

Prior HF network data suggest that the standard deviation for the proportional change (on the log scale) in NT-proBNP from randomization to 96 hours is approximately 0.55 to 0.60. It is anticipated that 25% of subjects enrolled will be on low-dose MRA at randomization. Assuming a 20% reduction in NT-proBNP from enrollment in the MRA group compared to placebo for the subset of patients not on an MRA at enrollment and a 10% improvement in the subset on low-
dose MRA at baseline yields an overall benefit of 17.5% for the study population. With a 1:1 randomization and a two-sided type I error rate of 0.05, a total sample size of 360 subjects would provide approximately 85% power. These calculations are based on the two-sample t-test. For the sensitivity analysis using the worst-rank approach for missing values due to death, the total sample size of 360 subjects provides 90% power to detect a difference in the setting in which a randomly selected individual on high dose spironolactone has a 60% chance of having a better response than a randomly selected individual on the placebo/low-dose arm. Both calculations allow for a consent withdrawal rate of approximately 2%. For continuous secondary endpoints, the study will have ≈90% power to detect differences of 0.35 standard deviations between treatment groups. These calculations assume a common variance and normally distributed errors for the two-sample t-test with a two-sided type I error rates of 0.05.

There is potential for greater reductions in natriuretic peptide levels in patients in the placebo arm of the study based on the special expertise for heart failure management at the sites where patients are being enrolled, though this is a concern with most heart failure trials where the placebo arm outcomes are better than seen in real-life based on similar concerns.

**Statistical Analysis**

The primary analysis will be based on a regression model using an outcome variable based on the log of the proportional change in NT-proBNP from randomization to 96 hours. The primary analysis will use a linear regression model with an indicator variable for treatment assignment, an indicator for MRA use prior to admission, and the log of the baseline NT-proBNP level. Missing values of the 96-hour NT-proBNP levels will be imputed using a multiple imputation algorithm. In a sensitivity analysis, values missing due to death will be imputed to the worst possible value. This analysis will account for low-dose MRA at enrollment using a stratified
version of the Wilcoxon-Mann-Whitney test.

General linear models and nonparametric approaches will be used to analyze the continuous outcomes. For binary outcomes, chi-square tests and Fisher’s exact test will be used for unadjusted comparisons. For adjusted comparisons, logistic regression analysis will be used to compare with the estimated odds ratio and 95% confidence interval. Unadjusted time-to-event comparisons will be conducted using Kaplan-Meier survival estimates and log-rank tests. For adjusted analyses, Cox proportional hazards regression models will be used to estimate hazard ratios. Sensitivity analyses will be employed to assess the influence of informatively missing values on the results. Subgroup analyses will be conducted based on baseline factors including: MRA use prior to hospitalization, sex, preserved vs. reduced ejection fraction, and age ≥ or <65 years. Interim data analysis for efficacy and futility will not be conducted due to small size and short duration of this trial. The safety analyses will be based on the entire randomized population.

**Trial Status**

The first patient in ATHENA HF trial was enrolled on December 13, 2014 and the last patient was enrolled in May 2016. Follow up of the patients is ongoing.

**CONCLUSION**

There remains a need to find novel interventions that effectively and safely promote diuresis and improve outcome in AHF. MRA therapy has shown benefit across the spectrum of chronic HF with reduced ejection fraction and a suggestion of benefit in those with preserved ejection fraction as well in certain regions. There are sound theoretical reasons to expect benefit with high dose MRA therapy in AHF as well. If the ATHENA-HF trial shows promising results, it will lay the groundwork for a more definite outcome trial in AHF. This is even more intriguing considering the development of the novel selective MRA, finerenone that has shown benefit in
early phase trials in patients with worsening HF and chronic kidney disease,\(^{44}\) as well as the growing literature on the efficacy and safety of chronic use of novel potassium binders to help mitigate the complications related to the use of RAAS inhibitors.
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FIGURE LEGENDS

Figure 1: Mechanism of Diuretic Resistance and Potential Benefit with Mineralocorticoid Antagonists


Central Illustration: ATHENA-HF Trial Schema

AHF: acute heart failure; BNP: B-type natriuretic peptide; Cr: creatinine; eGFR: estimated glomerular filtration rate; K+: potassium; MRA: mineralocorticoid receptor antagonist;

NTproBNP: N terminal pro B-type natriuretic peptide
Figure 1

A flowchart showing the relationship between cardiac failure, loop diuretic administration, inhibition of macula densa, negative sodium balance, RAAS, secondary hyperaldosteronism, distal sodium delivery, hypertrophy of distal nephron, increased expression of NaCl transporter, and loop diuretic resistance.
Central Illustration

Patients admitted with AHF
Not on or on low dose MRA on admission
- K ≤5.0 mmol/l
- eGFR ≥30 ml/min/1.73m²
- BNP ≥250 pg/ml or NT pro BNP ≥1000 pg/ml (Local Lab)
- ≤24 hours from first dose of IV diuretics

Baseline Assessment, NT-proBNP (Core Lab)

Not on MRA
- High Dose spironolactone (100mg)
- Placebo

On low dose MRA
- High Dose spironolactone (100mg)
- Low Dose spironolactone (25mg)

In-hospital: K and Cr Assessment at 24, 48, 72 and 96 hours
- Adjust dose (24, 48, and 72 hours) accordingly if needed

96 Hours
- Primary Endpoint – Change in NT proBNP
- Multiple Secondary Endpoints

After 96 hours - MRA use per treating physician discretion

Discharge Assessment if After 96 hours and Prior to 30 Day Phone Call

30 Day Phone Call
- Multiple Tertiary Endpoints

60 Day Phone Call
- Vital Status
Table 1: Eligibility Criteria for the ATHENA-HF Trial

**Inclusion Criteria**

1. Male or female patient $\geq$ 21 years old
2. Admitted to hospital for acute heart failure with at least one symptom and one sign of congestion
3. Patient must be randomized within 24 hours of first intravenous diuretic dose administered for the current episode of decompensation, regardless of where the diuretic was given e.g. office, emergency department, ambulance or hospital.
4. Estimated glomerular filtration rate of $\geq$ 30 mL/min/1.73m$^2$ determined by the Modified Diet and Renal Disease equation
5. Serum potassium concentration of $\leq$ 5.0 mmol/L at enrollment
6. NT-proBNP $\geq$ 1000 pg/mL or BNP $\geq$ 250 pg/mL, measured within 24 hours from randomization
7. Not on mineralocorticoid receptor antagonists or on low-dose spironolactone (12.5 mg or 25 mg daily) at baseline

**Exclusion Criteria**

1. Taking eplerenone or $>$ 25 mg spironolactone at baseline
2. Estimated glomerular filtration rate $<$ 30 ml/min/1.73m$^2$
3. Serum potassium concentration of $>$ 5.0 mmol/L
4. Systolic blood pressure $<$ 90 mmHg
5. Hemodynamically significant arrhythmias or defibrillator shock within 1 week
6. Acute coronary syndrome currently suspected or within the past 4 weeks
7. Severe liver disease (ALT or AST $>$ 3 x normal, alkaline phosphatase or bilirubin $>$ 2x normal)
8. Active infection (current use of antimicrobial agents)
9. Active gastrointestinal bleeding
10. Active malignancy other than non-melanoma skin cancers
11. Current or planned mechanical circulatory support within 30 days
12. Post cardiac transplant or listed for transplant and expected to receive one within 30 days
13. Current intravenous inotrope use
14. Complex congenital heart disease
15. Primary hypertrophic cardiomyopathy, infiltrative cardiomyopathy, acute myocarditis, constrictive pericarditis or cardiac tamponade
16. Previous adverse reaction to mineralocorticoid receptor antagonists
17. Enrollment in another randomized clinical trial
Table 2: Protocol for Study Drug Adjustment based on Serum Potassium Concentration

<table>
<thead>
<tr>
<th>Serum Potassium concentration</th>
<th>Action</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 5.0 mmol/L</td>
<td>Continue protocol</td>
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<td></td>
<td></td>
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<td>5.1-6.0 mmol/L</td>
<td>Check if sample hemolyzed</td>
<td>Hold protocol</td>
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<tr>
<td></td>
<td>Check if K⁺ supplement given</td>
<td>Repeat K within 6 hours</td>
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<tr>
<td></td>
<td>Treat per physician preference</td>
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<td></td>
<td>If repeat value is ≤5.0 -</td>
<td>Continue protocol</td>
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<td></td>
<td>If repeat value is 5.1-6.0</td>
<td>Hold protocol</td>
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<tr>
<td></td>
<td>Treat according to physician preference</td>
<td>Repeat K next day and follow protocol</td>
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<tr>
<td></td>
<td>If day 4 – Stop study protocol</td>
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<tr>
<td></td>
<td>If repeat value is &gt;6.0</td>
<td>Stop study drug</td>
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<tr>
<td>&gt; 6.0 mmol/L</td>
<td>Check if sample hemolyzed</td>
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<tr>
<td></td>
<td>Check if K⁺ supplement given</td>
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<tr>
<td></td>
<td>Treat per physician preference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If sample not hemolyzed and patient not on K⁺ supplements</td>
<td>Stop study drug</td>
</tr>
<tr>
<td></td>
<td>If sample hemolyzed or patient receiving K⁺ supplements</td>
<td>Repeat K within 6 hours</td>
</tr>
<tr>
<td></td>
<td>If repeat value is ≤5.0</td>
<td>Continue protocol</td>
</tr>
<tr>
<td></td>
<td>If repeat value is between 5.1-6.0</td>
<td>Hold protocol</td>
</tr>
<tr>
<td></td>
<td>Repeat K next day and follow protocol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If day 4 – Stop study drug</td>
<td></td>
</tr>
<tr>
<td></td>
<td>If repeat value is &gt;6.0</td>
<td>Stop study drug</td>
</tr>
</tbody>
</table>