Protocol for the Heart Failure Clinical Research Network

Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy – HF

ATHENA-HF

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List of Abbreviations

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
ACTH	Adrenocorticotropic hormone
AE	Adverse event
AHF	Acute heart failure syndrome
ARB	Angiotensin receptor blocker
BNP	B-type natriuretic peptide
BUN	Blood urea nitrogen
CC	Coordinating center
CCS	Composite Congestion Score
CRF	Case report form
DBP	Diastolic blood pressure
DCC	Data coordinating center
DCRI	Duke Clinical Research Institute
ECG	Electrocardiogram
ED	Emergency department
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
EPHESUS	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
EVEREST	Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan
GFR	Glomerular filtration rate
HF	Heart failure
HFN	Heart Failure Clinical Research Network
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HR	Heart rate
ICF	Informed Consent Form
IRB	Institutional review board
ITT	Intention to treat
IV	Intravenous
IVRS	Interactive voice recording system
KDOQI	Kidney Disease Outcomes Quality Initiative
LVEF	Left ventricular ejection fraction
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
NSAIDs	Non-steroidal anti-inflammatory drugs
PCI	Percutaneous coronary intervention
PCP	Primary care physician
RAAS	Renin-angiotensin-aldosterone system
RALES	Randomized Aldactone Evaluation Study
RCC	Regional clinical center
SAE	Serious adverse event
SAR	Suspected adverse reaction
SBP	Systolic blood pressure
SUSAR	Suspected unexpected serious adverse reaction
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
VAS	Visual Analog Scale

Table of Contents

1 EXECUTIVE SUMMARY

Title	**Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy – HF (ATHENA-HF)**
Indication	High-dose mineralocorticoid receptor antagonist (MRA) therapy in acute heart failure (AHF)
Location	Approximately 30 clinical centers in the United States and Canada.
Brief Rationale	Mineralocorticoid receptor antagonist (MRA) therapy is recommended in stable chronic systolic heart failure (HF) and post-infarction HF patients for improving morbidity and mortality. The Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial also showed reduction of hospitalization risk in patients with HF and preserved ejection fraction (HFpEF), albeit the primary endpoint was not met. MRA therapy in AHF and in high doses is less well studied. The effectiveness and safety of early high dose MRA therapy in AHF is supported by a single-blind study showing lower risk of worsening renal function and need for loop diuretics, and improved congestion. MRA therapy in AHF may improve outcomes by relieving congestion at higher doses through their natriuretic property, in addition to preventing the deleterious effects of exacerbation of neuro-hormonal activation by loop diuretics. Of note, higher serum aldosterone levels in AHF are associated with worse post-discharge outcomes. Also, *hypokalemia* is common in AHF, whereas serious hyperkalemia (>6.0 mmol/L) was uncommon in previous trials with MRAs, and no death from hyperkalemia has been reported in these trials. Modest eGFR decreases or hyperkalemia in previous trials did not diminish benefits from MRA in HF.
Study Design	Randomized, double blind, placebo-controlled study of high-dose spironolactone vs. placebo (for patients not receiving MRA at home) or low-dose spironolactone (for patients already receiving low-dose spironolactone) in AHF.
Treatment	Patients not on MRA at baseline will be randomized (1:1) to spironolactone 100 mg or placebo and those on low-dose spironolactone at home (12.5 or 25 mg) will be randomized (1:1) to 100 mg spironolactone or 25 mg spironolactone for up to 96 hours, after which further MRA use will be at the discretion of the treating physicians.
Primary 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 to test the hypothesis that high-dose spironolactone will lead to greater reduction in NT-proBNP levels over standard of care.
Secondary Objectives	To determine the effect of high-dose spironolactone in patients with AHF on: 1. Clinical congestion score, dyspnea relief, renal function, urine output, weight change, hyperkalemia, loop diuretic dose, and in-hospital worsening HF from randomization to 96 hours 2. Length of stay, all-cause mortality, all-cause readmissions, outpatient worsening HF (HF readmission, emergency department [ED] visit or observational unit stay or need for outpatient IV diuretics) and MRA use and loop diuretic dose requirements at day 30 post-randomization
Primary Endpoint	Change in NT-proBNP from randomization to 96 hours.
Secondary Endpoints (96 hours)	1. Congestion score 2. Dyspnea relief (7-point Likert and Visual Analog Scale (VAS)) 3. Net urine output 4. Net weight change 5. Loop diuretic dose requirement 6. In-hospital worsening of HF
Tertiary Endpoints (Day 30)	1. All-cause mortality 2. All-cause readmissions 3. Outpatient worsening HF (HF readmissions or ED visits or observational unit stays for HF or need for outpatients IV diuretics) 4. MRA use 5. Loop diuretic dose 6. Index hospitalization length of stay

Day 60 Vital Status	1. Vital status
Safety Endpoints	1. Change in serum creatinine 2. Hyperkalemia (>5.5mmol/L and >6.0mmol/L)
Abbreviated Study Flow	We plan to enroll 360 patients aged 21 years or older who are: 1. Receiving no MRA or low-dose spironolactone (12.5 mg or 25 mg) on admission, 2. Have estimated glomerular filtration rate (eGFR) ≥30 ml/min/1.73m^2 3. Have serum K^+ ≤5.0 mmol/L 4. Admitted with AHF (≥1 symptom and ≥1 sign of congestion), and 5. NT-proBNP ≥1000 or BNP ≥250 (Local Lab) within 24 hours prior to randomization. We aim to test a strategy of high-dose (100 mg) spironolactone vs. placebo for MRA-naïve patients and high-dose (100 mg) spironolactone vs. low-dose (25 mg) spironolactone for those receiving low-dose spironolactone (12.5 mg or 25 mg) at baseline. Patients will be randomized within 24 hours of first I.V. diuretic dose to receive spironolactone or matching placebo in a double-blind fashion. Randomization and treatment will be stratified according to previous MRA use. Patients receiving no MRA at home will be randomly assigned to receive either spironolactone 100 mg or matching placebo in hospital for 96 hours. Patients already receiving low-dose spironolactone (12.5 mg or 25 mg) at home will be randomized to spironolactone 100 mg vs. 25 mg in hospital for 96 hours. Study drug (spironolactone or matching placebo) will be administered as follows: **No Previous MRA Stratum:** 4x25 mg study capsules once daily; starting dose 100 mg spironolactone or placebo; if dose adjustment is required, active drug capsules will be adjusted by pharmacy to achieve the required dose. **Previous Low-dose MRA Stratum:** 4x25 mg study drug capsules once daily; one capsule containing 25 mg spironolactone and 3x25 mg study drug capsules containing spironolactone or placebo; if dose adjustment is required, active drug capsules will be adjusted by pharmacy to achieve the required dose. Repeat electrolytes and creatinine/BUN will be measured every 24 hours until 96 hours (or earlier as stipulated for hyperkalemia management protocol), and study drug dose will be adjusted accordingly. Potassium supplement and potassium containing salt substitutes will be discontinued at randomization, high potassium containing foods will be avoided during the study protocol, and automatic hospital potassium replacement protocols will be stopped for enrolled patients.

Actions Based on Serum Potassium Concentration: 24, 48, and 72 hour Assessments

Serum K^+ Concentration	Action	Protocol
≤ 5.0 mmol/L	Monitor	Continue protocol
5.1 - 6.0 mmol/L	1. Check if sample hemolyzed. 2. Check if K^+ supplement given. 3. Treat per physician preference. 4. Repeat K+	
	If repeat K^+ is ≤ 5.0: →	Continue protocol
	If repeat K^+ value is 5.1 - 6.0: → 1. Treat per physician preference. 2. Repeat K^+ next day and follow protocol accordingly.	**Temporarily hold protocol for this day; reassess next day.** **If Day 4: Permanently Stop Protocol**
	If repeat K^+ value is >6.0: →	**Permanently Stop Protocol**
> 6.0 mmol/L	1. Check if sample hemolyzed. 2. Check if K^+ supplement given. 3. Treat per physician preference.	
	If sample not hemolyzed and patient not on K^+ supplements: →	**Stop protocol**
	If sample hemolyzed or patient receiving K^+ supplements: Repeat K^+	
	If repeat K^+ is ≤ 5.0: →	Continue protocol
	If repeat K^+ value is 5.1 - 6.0: → 1. Treat per physician preference. 2. Repeat K^+ next day and follow protocol accordingly.	**Temporary hold protocol for this day; reassess next day.** **If Day 4: Permanently Stop Protocol**
	If repeat K^+ value is > 6.0: →	**Permanently Stop Protocol**

Other Medications
All other medications, including diuretics, will be left at the discretion of the treating physician throughout the study.

Volume Assessment
If patient is clinically euvolemic in less than 96 hours, consider changing loop diuretics to oral dose.

Discharge <96 Hours
If patient is discharged in less than 96 hours, assess primary and secondary outcomes at the time of discharge.

Renal Function Changes
Modest increase in serum creatinine with active diuresis is seen in many patients with AHF. This change usually reverses over time. In some patients however, a rise in serum creatinine in patients who are diuretic resistant may portend poor prognosis. There remains clinical concern about acute kidney injury with high dose MRA. The decision regarding management of such patients is best left to the discretion of the treating physicians. It is however recommended that:

Serum Creatinine Increased by:	Clinically	Protocol
≤ 0.5 mg/dl	• Diuresing • Improving • Fluid overloaded	Continue protocol
>0.5 mg/dl	• Improving • Fluid overloaded • Not oliguric	May hold protocol or give study drug reduced to half dose, per PI discretion*
>0.5 mg/dl	• Oliguric	Hold protocol – May continue study drug next day per PI discretion based on renal function.

*Each patient will get 4 capsules (4 placebo, 4 active, or 3 placebo +1 active).
If creatinine increases >0.5 mg/dl and investigator wants to continue half dose of study drug, the patient will still get 4 capsules (4 placebo, 2 placebo +2 active, or 3 placebo +1 active). This will be done by the research pharmacy.

Ejection Fraction
All patients with AHF who fulfill the eligibility criteria will be considered for the study irrespective of ejection fraction. However, ejection fraction data will be noted to assess the potential differences in response to the study intervention among patients with HF and preserved vs. reduced ejection fraction.

Ejection fraction data will be obtained from an echocardiogram within 6 months prior to randomization. Nuclear perfusion study, MRI, or MUGA that includes ejection fraction is acceptable. Those patients who do not have an echocardiogram recorded within this time frame will get an echocardiogram, nuclear study, MRI, or MUGA during hospitalization, prior to the 96 hour in-hospital assessment to ascertain ejection fraction.

30 Day Follow-up
Telephone follow-up at 30 (+3 days) post randomization for tertiary endpoints and adverse events.

60 Day Follow-up
Telephone follow-up at 60 (+/-3 days) to assess vital status (death).

2 HYPOTHESES AND OBJECTIVES

2.1 Primary Objective and Hypothesis

The primary objective is to determine whether oral high-dose spironolactone administered early in patients with AHF will lead to greater proportional reduction in NT-proBNP levels from randomization to 96 hours.

Hypothesis: High-dose spironolactone will lead to greater proportional reduction in NT-proBNP levels from randomization to 96 hours over standard of care.

2.2 Secondary Objectives

To determine the effect of high-dose spironolactone in patients with AHF from randomization to 96 hours on:

- Congestion score
- Dyspnea relief
- Net urine output
- Net weight change
- Loop diuretic dose requirements
- In-hospital worsening of HF

2.3 Tertiary Objectives

To determine the effect of high-dose spironolactone in patients with AHF by day 30 post randomization on:

- All-cause mortality
- All-cause readmissions
- Outpatient worsening HF symptoms (HF readmission or emergency department visits or observational unit stay or need for outpatient IV diuretics)
- MRA use
- Loop diuretic dose requirements
- Length of stay at index hospitalization

2.4 Safety Endpoints

- Renal function
- Hyperkalemia (>5.5 mmol/L or >6.0 mmol/L)

3 BACKGROUND AND SIGNIFICANCE

Public Health Impact of Heart Failure

Heart failure is the leading cause of adult hospitalization in the United States and imposes a substantial burden on public health. Heart failure is the number one cause of hospitalization among Medicare beneficiaries and accounts annually for over 1.1 million hospitalizations, over 60,000 deaths, and over $39 billion in healthcare costs. As the population ages and survival from other cardiovascular diseases improves, HF prevalence is expected to rise further.[1, 2]

Heart Failure Hospitalization

Hospitalizations for AHF are associated with significant risk for increased post-discharge mortality and recurrent hospitalization. Multiple studies indicate that mortality or re-admission at 60-days post discharge is ~30% among patients hospitalized for AHF,[3-5] and as high as 50% by 6 months.[6] A series of trials employing a variety of in-hospital interventions, barring one early experience,[7] have been unable to conclusively impact post-hospitalization mortality and/or readmission risk.[4, 8-11] Other than volume optimization,[12] no short-term pharmacological or device-based intervention has affected post-discharge outcomes among these patients.

Congestion and Dyspnea in Acute Heart Failure

Published data suggest that a large proportion of patients continue to have persistent subclinical congestion at the time of discharge.[13] Congestion at the time of discharge, whether measured as clinical signs,[14] natriuretic peptide levels,[15] or with right heart catheterization,[16] is one of the strongest predictors of post-discharge outcomes. This was demonstrated in a post hoc analysis of the placebo group (N=2061) from the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trial, which enrolled AHF patients with EF≤40%.[14] In this study, a modified composite congestion score (CCS) at discharge calculated by summing the individual scores for orthopnea, JVD, and pedal edema (on a standardized 4-point scale ranging from 0 to 3) was predictive of 30-day HF readmission (HR per point 1.06, 95%CI 0.95–1.19), all-cause mortality (HR 1.34, 95%CI 1.14–1.58), and combined morality and HF readmission (HR 1.13, 95%CI 1.03–1.25).[14] The modified CCS used in that study was a simplified version of a CCS previously developed by the Heart Failure Association of the European Society of Cardiology.[17] The same CCS (**Table 1**) will be used in the current study to assess congestion (secondary endpoint).

Table 1. Composite Congestion Score (CCS)

Signs and Symptoms	0	1	2	3
Dyspnea	None	Seldom	Frequent	Continuous
Orthopnea	None	Seldom	Frequent	Continuous
Fatigue	None	Seldom	Frequent	Continuous
JVD (cm H_2O)	<6	6-9	10-15	>15
Rales	None	Bases	To <50%	To >50%
Edema	Absent/Trace	Slight	Moderate	Marked

Reproduced from Ambrosy et al, *Eur Heart J,* 2013, *34*, 835-843.

Similarly, the degree of dyspnea improvement during hospitalization for AHF is considered an important therapeutic goal. In the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) trial, early dyspnea relief (from baseline to 6h) was measured on a 7-point Likert Scale,[18] which we propose to use in the current study (**Table 2**) in addition to the Visual Analog Score (VAS). Refer to Appendix B and C. In ASCEND-HF, early dyspnea relief (defined as moderate or marked improvement) was associated with lower risk-adjusted 30-day mortality/HF hospitalization (HR 0.81; 95% CI 0.68–0.96) and mortality/hospitalization (HR 0.85; 95% CI 0.74–0.99).[18]

Table 2. Dyspnea Relief Scale

• Markedly Improved
• Moderately Improved
• Minimally Improved
• No change
• Minimally Worsened
• Moderately Worsened
• Markedly Worsened

Aldosterone Breakthrough and Sodium Retention in Heart Failure

Although modulation of the renin-angiotensin-aldosterone system (RAAS) with ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) improves morbidity and mortality in HF, in a proportion of patients, aldosterone may only be suppressed transiently with ACE inhibition.[19] Also, loop diuretics in AHF may worsen the already increased RAAS activation and secondary hyperaldosteronism.[20] This "aldosterone breakthrough" can have important consequences on sodium retention as well as the profibrotic actions on the heart, blood vessels, and kidney.[19]

Potential Benefits from Natriuretic MRA Doses

Failure to escape from the sodium-retaining effect of aldosterone due to persistent activation of RAAS causes enhanced proximal tubular sodium absorption and decreased distal sodium delivery. Therefore, beyond myocardial and vascular profibrotic effects, hyperaldosteronism directly contributes to diuretic resistance.[21].The currently recommended low MRA doses (e.g. spironolactone 25 to 50 mg/day) for patients with HF exert their beneficiary primarily through anti-fibrotic but not natriuretic effects.[22] Resistance to loop diuretics is frequently present in HF. For these patients, natriuretic doses of aldosterone antagonists (spironolactone >50 mg/day) may be a potential option. The competitive natriuretic response of aldosterone antagonists is related to activity of the RAAS: the higher the RAAS activity, the higher the dose of aldosterone antagonist required to produce natriuresis.[21] Therefore, natriuretic doses of spironolactone may provide supplementary benefit beyond the effect on myocardial and vascular fibrosis.[23] In a pilot study in 6 patients with various HF etiologies, 200 bid spironolactone alone led to negative sodium balance without clinically significant increases in K^+ (from 3.9±0.2 to 4.1±0.2 mmol/L) or creatinine clearance (87±7 to 87.2±8 mL/min) after 4 days of therapy,[24]

MRA Use and Outcomes in Chronic Heart Failure

MRA therapy is currently recommended in stable but symptomatic HF patients for improving morbidity and mortality,[25, 26] based on large randomized controlled trials in chronic HFrEF[27, 28] and post-infarction HF patients.[29] In patients with HFpEF[30] the recent Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial showed reduction of hospitalization risk with MRA but the primary endpoint was not met.[31] **Table 3** summarizes the outcome-driven, placebo-controlled RCTs evaluating MRAs in HF or left ventricular systolic dysfunction (LVSD).

Table 3. Outcome-Driven Placebo-Controlled RCTs with MRAs in Heart Failure and LVSD

Trial	Patients	Active	Placebo	Tx	FU	Outcome
EMPHASIS-HF (2011) [29]	NYHA II LVEF ≤35%	1364	1373	Eplerenone 50 mg daily	21 mo	Primary: CV mortality or HF readmission (18.3% vs. 25.9%; P<0.001; RRR=34%)
EPHESUS (2003) [27]	LVEF ≤40% post-AMI	3313	3319	Eplerenone 25–50 mg daily	16 mo	Primary: death (14.4% vs. 16.7%; P=0.008; RRR=15%); CV death or CV hospitalization (HF, AMI, stroke, VT/VF) (26.7% vs. 30.0%; P=0.002; RRR=13%)
RALES (1999) [28]	NYHA III-IV, LVEF ≤35%	822	841	Spirono-lactone 25 mg daily	24 mo	Primary: death (35% vs. 46%; P<0.001; RRR=30%)

AMI: acute myocardial infarction; CV cardiovascular; EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS: Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; RALES: Randomized Aldactone Evaluation Study; RRR: relative risk reduction; VF: ventricular fibrillation; VT: ventricular tachycardia

Benefits from Early MRA Administration

In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[27] trial, the benefit with MRA was confined to those patients who received the active drug at 3 to 6 days post-acute myocardial infarction compared to those who received the drug at day 7 to 14.[32] Although the hypothesis was that electrical remodeling takes place before visible left ventricular (LV) remodeling and this consequently reduced sudden cardiac death (SCD), interestingly the readmission rate were also reduced to a similar extent as SCD with early MRA (and only with early MRA),[32] implying that there are other acute protective effects beyond anti-arrhythmic properties with early MRA. Considering that AHF is associated with acute cardiac damage, as evident by detectable troponin (Tn) release in ~50% in recent cohorts with sensitive assays,[33-35] which in turn adversely affected outcomes, [33-35] MRAs could have an immediate protective effect in the early post-AHF period both for SCD and arrhythmias and readmission rates. In fact, in an analysis from Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial, eplerenone markedly reduced the risk of HF hospitalizations in patients with HF to a greater extent than is captured by only studying the time to first hospitalization.[36]

Aldosterone and Acute Heart Failure

In the EVEREST trial, which enrolled patients with LVEF <40% hospitalized for AHF and 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 of 16 ng/mL in 33.2% of patients.[37] 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, providing an observational link between aldosterone pathway activity and outcomes in AHF.[37] 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 HF rehospitalization (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 in adjusted models.[37]

Other Considerations

Hypokalemia is common in AHF, often due to a defect in Na^+/K^+-ATPase activity and intracellular shift of K^+ caused by oxidative stress and neurohormonal activation in combination with loop diuretics.[38] Finally, MRA therapy continues to be underutilized in AHF in general. In a recent study, not only significant underutilization of MRAs in eligible hospitalized HF patients was demonstrated (27%),[39] but also eligible patients without a discharge prescription seldom initiated therapy as outpatients (13%).

4 PRELIMINARY STUDIES

Experience with MRAs in Acute Heart Failure

The role of MRA therapy in AHF is less well studied. A recent observational study showed that initiation of MRA at hospital discharge was not associated with improved mortality or cardiovascular readmission but was associated with improved HF readmission in the long term among older patients with HFrEF.[40] There was an increase in the risk of readmission for hyperkalemia at 30 days (2.9% vs 1.2%; P<0.001) and 1 year (8.9% vs 6.3%; P=.002) in the treated group; however, hyperkalemia was seldom the primary diagnosis for these readmissions, and the absolute increase in hyperkalemia as a primary diagnosis was small.[40]

MRA use in AHF has two potential advantages, improve decongestion through its diuretic effect and counter the neurohormonal activation that characterizes AHF that is enhanced by loop diuretics.[41] The benefit and safety of early MRA use in AHF is supported by a recent single-center, single-blind trial, [42] where 100 patients admitted with AHF were treated with standard therapy or spironolactone initiated within 24 hours. Spironolactone dose was 94.5±23.3 mg at day 1 and 62.7±24.3 mg at day 3. Increase in creatinine ≥0.3 mg/dL from day 1 to day 3 was more likely to occur in controls (20% vs. 4%; P=0.038). Serum potassium did not differ between groups, and plasma NT-proBNP was decreased more in spironolactone group at day 3 (median [IQR], 2488 [4579] vs. 1555 [1832]; P=0.05). A greater proportion of patients in the treatment group were free of congestion at day 3 based on edema, rales, jugular venous pressure, and orthopnea (all P<0.05). A significantly higher proportion of patients had transitioned to oral furosemide by day 3 (82% vs. 44%; P<0.001). These findings support the safety and potential efficacy of a high-dose spironolactone strategy in AHF.

High-dose MRA in Heart Failure

In 18 patients with advanced HF receiving 50-200 mg of spironolactone in addition to standard treatment there was no significant increase in mean serum potassium (4.0 vs. 4.2 mEq/l) or serum creatinine (1.3 vs. 1.4 mg/dl during an average follow up of 41 weeks. [43] In 3 patients, spironolactone treatment was stopped due to a mean increase in serum creatinine (1.9 vs. 2.6 mg/dl) and in one of them, an increase in serum potassium (4.4 vs. 5.2 mEq/l).[43]

Safety Considerations

For safety reasons, it is important to only include patients with eGFR ≥30 ml/min1.73m^2 at enrollment. Of note, modest eGFR decreases in EPHESUS did not affect benefits with MRA or lead to adverse outcomes.[44] In a similar analysis from EMPHASIS-HF, worsening renal function and hyperkalemia were more frequent with eplerenone, but their occurrence did not eliminate the survival benefit of eplerenone.[45] However, the risk of hyperkalemia increases with increasing doses of MRA (see section **Drug-Related Risks** for additional details). Finally, recent registry data demonstrate that the rate of hyperkalemia with MRA use is declining[46] as more experience is gained with these agents in HF and guidelines are more appropriately applied.[47]

5 BASIC STUDY DESIGN

5.1 Screening Phase

Patients ≥21 years old (1) admitted with an AHF diagnosis (verified by ≥1 symptom and ≥1 sign of congestion) and (2) receiving no MRA or low dose spironolactone (12.5 mg to 25 mg daily) at baseline, will be screened. Those with eGFR <30 mL/min/1.73m^2, K^+ >5.0 mmol/L, or systolic blood pressure <90 mmHg will be excluded. Patients will be included if admission or screening BNP ≥250pg/ml or admission NT-proBNP ≥1000pg/ml (Local Lab). Agreeing patients meeting entry criteria will be consented.

5.2 Randomization

After providing informed consent and signing the informed consent form (ICF), all subjects who fulfill all the inclusion criteria and none of the exclusion criteria will be randomized. Following randomization, no potassium supplements should be given to patient throughout the duration of the trial, no potassium containing salt substitutes should be inadvertently given to the patient, and if the hospital has any automatic potassium replacement protocols, they should be stopped for the enrolled patients.

Randomization will be performed using procedures determined by the Coordinating Center (CC).

- Patients receiving no MRA therapy at baseline will be randomized to receive either spironolactone 100 mg or placebo daily for 96 hours.
- Patients already receiving low-dose spironolactone at baseline (12.5 mg or 25 mg daily) will be randomized to 100 mg or 25 mg spironolactone daily for 96 hours.

Within 24 hours prior to randomization, all study participants will undergo:

1. Medical History
2. Review of medications including pre-hospital loop diuretics, MRA, and potassium doses
3. Physical examination, vital signs and body weight
4. Measurement of creatinine, blood urea nitrogen (BUN), and electrolytes
5. Dyspnea Relief Assessments (7-point Likert and Visual Analog Scale)
6. Serum pregnancy test for all women of childbearing potential
7. Collection of samples for measurement of NT-proBNP levels (Core Lab)

Administration of Study Drug:

Study drug will be initiated as follows:

- Patients receiving no MRA therapy at baseline: 4x25 mg study capsules once daily; starting dose 100 mg spironolactone or placebo; if dose adjustment is required, active capsules will be adjusted by pharmacy to achieve the required dose.
- Patients already receiving low-dose spironolactone at baseline: 4x25 mg study capsules once daily; one capsule containing 25 mg spironolactone and 3x25 mg study capsules containing spironolactone or placebo; if dose adjustment is required, active capsules will be adjusted by pharmacy to achieve the required dose.

5.3 Study Intervention – First 96 Hours

Patients will be followed every 24 hours following randomization through 96 hours. Study drug will be administered daily for 96 hours. Study drug administration time is anchored to time of randomization. Dose adjustments (continue, hold, stop) are permitted according to serum K^+ and renal function per section 7.1.

Assessment at 24 hours post randomization includes:

1. Review of medications
2. Body weight
3. Fluid intake/urine output
4. Creatinine, blood urea nitrogen (BUN), and electrolytes
5. Adverse events

If the 24 hour assessment is also the day of discharge, include:

a. Physical exam / Vital signs
b. Dyspnea Relief (7-Point Likert and VAS)
c. Biomarkers (NT-proBNP) (Core Lab)

Assessment at 48 hours post randomization includes:

1. Review of medications
2. Physical exam / Vital signs
3. Body weight
4. Fluid intake/urine output
5. Dyspnea Relief (7-Point Likert and VAS)
6. Creatinine, blood urea nitrogen (BUN), and electrolytes
7. Biomarkers (NT-proBNP) (Core Lab)
8. Adverse events

Assessment at 72 hours post randomization includes:

1. Review of medications
2. Body weight
3. Fluid intake/urine output
4. Creatinine, blood urea nitrogen (BUN), and electrolytes
5. Adverse events

If the 72 hour assessment is also the day of discharge, include:

a. Physical exam / Vital signs
b. Dyspnea Relief (7-Point Likert and VAS)
c. Biomarkers (NT-proBNP) (Core Lab)

Assessment at 96 hours post randomization includes:

1. Medication review
2. Physical exam / Vital signs
3. Body weight
4. Fluid intake/urine output
5. Creatinine, blood urea nitrogen (BUN), and electrolytes
6. Dyspnea Relief (7-Point Likert and VAS)
7. Biomarkers (NT-proBNP) (Core Lab)
8. Adverse events

Volume Assessment

If patient is clinically euvolemic in less than 96 hours, consider changing loop diuretics to oral dose.

5.4 Discharge

Study drug will be discontinued after 96 hours and further use of MRA will be left to the treating physician's discretion.

Assessment at Discharge

If discharge occurs after the 96 hour assessment but prior to the 30 day follow-up telephone call, the following will be documented:

1. Medication review (prescribed medications at the time of discharge)
2. Body weight (if available)
3. Creatinine, blood urea nitrogen (BUN), and electrolytes (if available)
4. Adverse events

Ejection Fraction

Ejection fraction data will be obtained from echocardiogram within 6 months prior to randomization. Those patients who do not have an echocardiogram recorded within this time frame will get an echocardiogram, nuclear perfusion study, MRI, or MUGA performed prior to the 96 hour in-hospital assessment to ascertain ejection fraction.

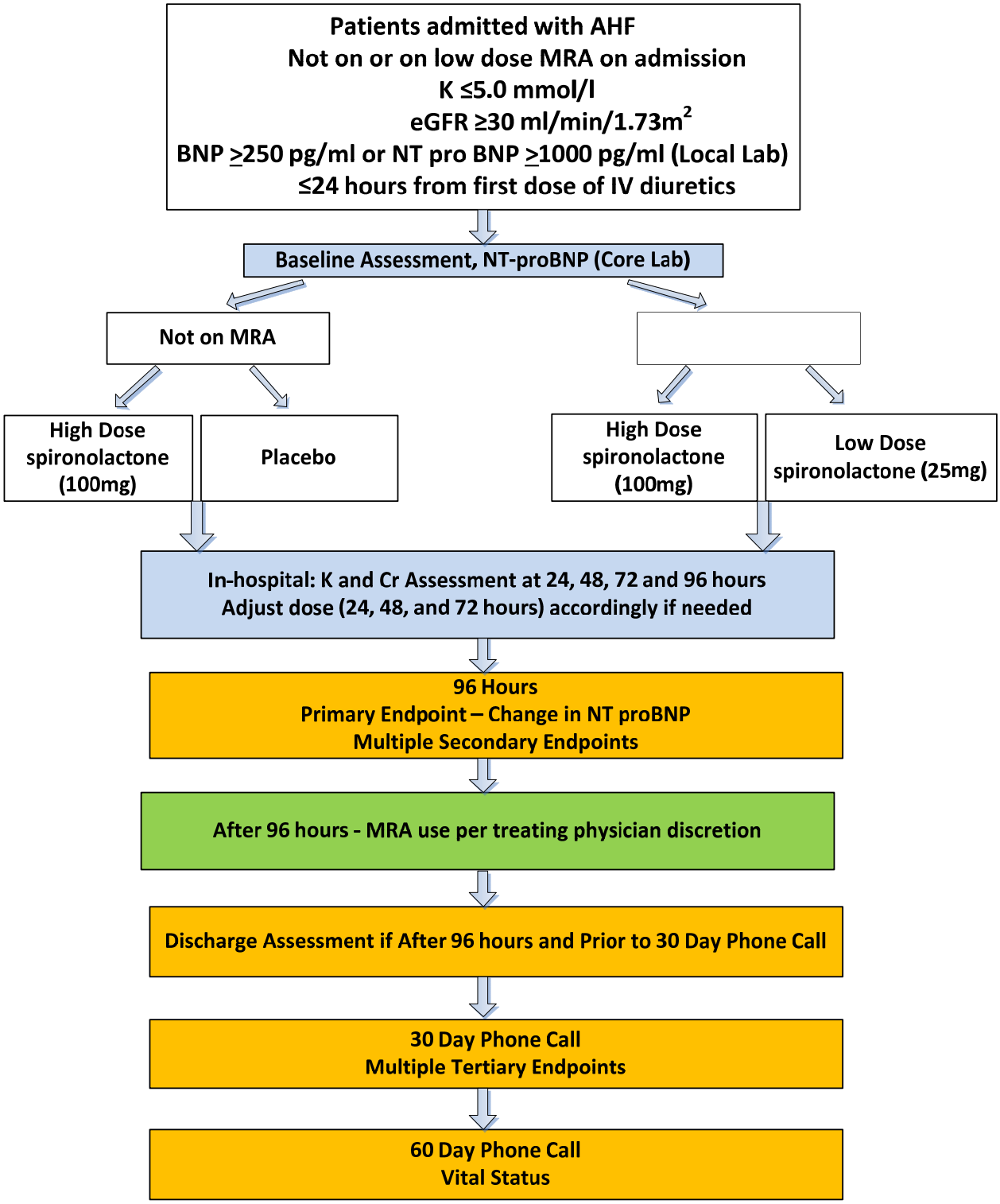
5.5 Follow-Up Telephone Call at Day 30

All participants will be contacted by telephone at day 30 (+3 days) following randomization to assess tertiary endpoints, including medication use and adverse events.

5.6 Follow-Up Telephone Call at Day 60

All participants will be contacted by telephone at day 60 (+/-3 days) following randomization to assess vital status.

5.7 Study Flow Diagram



6 STUDY POPULATION AND ELIGIBILITY CRITERIA

6.1 Study Population

Patients hospitalized for AHF with eGFR ≥30 ml/min/1.73m^2 and K^+ ≤5.0 mmol/L at randomization. Eligible patients will be randomized within 24 hours of first dose of IV diuretic. A total of 360 patients aged 21 years or older receiving no MRA or low-dose spironolactone (12.5 mg to 25 mg daily) at baseline will be enrolled.

6.2 Inclusion Criteria

1. Male or female patient ≥21 years old
2. Admitted to hospital for AHF with at least 1 symptom (dyspnea, orthopnea, or edema) and 1 sign (rales on auscultation, peripheral edema, ascites, pulmonary vascular congestion on chest radiography) of congestion
3. Patient must be randomized within 24 hours of first IV diuretic dose administered for the current episode of decompensation (regardless of where the diuretic was given e.g. office, ED, ambulance, hospital etc.)
4. Estimated GFR of ≥30 mL/min/1.73m^2 determined by the MDRD equation
5. Serum K^+ ≤5.0 mmol/L at enrollment
6. NT-proBNP ≥1000 pg/mL or BNP ≥250 pg/mL, measured within 24 hours from randomization (Local Lab)
7. Not on MRA or on low-dose spironolactone (12.5 mg or 25 mg daily) at baseline

6.3 Exclusion Criteria

1. Taking eplerenone or >25 mg spironolactone at baseline
2. eGFR < 30 ml/min/1.73m2
3. Serum K+ >5.0 mmol/L. If a repeat measurement within the enrollment window is <5.0, the patient can be considered for inclusion.
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 oral or IV 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 inotrope use
14. Complex congenital heart disease
15. Primary hypertrophic cardiomyopathy, infiltrative cardiomyopathy, acute myocarditis, constrictive pericarditis or tamponade
16. Previous adverse reaction to MRAs
17. Enrollment in another randomized clinical trial during index hospitalization

7 TREATMENT INTERVENTIONS

7.1 Intervention

The therapeutic intervention is a double-blind treatment with 100mg or 25 mg spironolactone or placebo. Spironolactone is a synthetic, steroidal MRA agent with additional antiandrogen, weak progestogen properties, and some indirect estrogen and glucocorticoid effects. It acts predominantly as a competitive antagonist of the aldosterone receptor, and therefore also acts as a potassium-sparing diuretic.

Study drug will be given once daily, every 24 hours following randomization, for 96 hours in hospital starting within ≤24 hours from the first dose of I.V. diuretic administered for the current episode of decompensation (e.g. office visit, ED, during transfer before admission, or in-hospital). The daily dose will be adjusted according to the results of daily serum potassium concentration, renal function, and congestion status. The active and placebo study drug will appear identical to preserve the double-blind study design. The initial dosing scheme will be as follows:

- Patients receiving no MRA at home will receive either spironolactone 100 mg or matching placebo (4x25 mg study capsules) once daily for 96 hours.
- Patients already receiving low-dose MRA at home will receive spironolactone 100 mg vs. 25 mg (1x25 mg spironolactone and 3 study capsules) in hospital for 96 hours.

Other Medications

All other medications, including diuretics, will be left at the discretion of the treating physician.

Permitted Dose Adjustments

Recommended actions for administration of study drug are based on 24, 48, and 72 hour serum K^+ levels:

Serum K^+ Concentration	Action	Protocol
≤ 5.0 mmol/L	Monitor	Continue protocol
5.1 - 6.0 mmol/L	1. Check if sample hemolyzed. 2. Check if K^+ supplement given. 3. Treat per physician preference. 4. Repeat K+	
	If repeat K^+ is ≤ 5.0: →	Continue protocol
	If repeat K^+ value is 5.1 - 6.0: → 1. Treat per physician preference. 2. Repeat K^+ next day and follow protocol accordingly.	**Temporarily hold protocol for this day; reassess next day.** **If Day 4: Permanently Stop Protocol**
	If repeat K^+ value is >6.0: →	**Permanently Stop Protocol**
> 6.0 mmol/L	1. Check if sample hemolyzed. 2. Check if K^+ supplement given. 3. Treat per physician preference.	
	If sample not hemolyzed and patient not on K^+ supplements: →	**Stop protocol**
	If sample hemolyzed or patient receiving K^+ supplements: Repeat K^+	
	If repeat K^+ is ≤ 5.0: →	Continue protocol
	If repeat K^+ value is 5.1 - 6.0: → 1. Treat per physician preference. 2. Repeat K^+ next day and follow protocol accordingly.	**Temporary hold protocol for this day; reassess next day.** **If Day 4: Permanently Stop Protocol**
	If repeat K^+ value is > 6.0: →	**Permanently Stop Protocol**

Change in Renal Function
The decision regarding management of patients with change in serum creatinine is best left to the discretion of the treating physicians. It is however recommended that:

Serum Creatinine Increased by:	Clinically	Protocol
≤ 0.5 mg/dl	• Diuresing • Improving • Fluid overloaded	Continue protocol
>0.5 mg/dl	• Improving • Fluid overloaded • Not oliguric	May hold protocol or give study drug reduced to half dose, per PI discretion.*
>0.5 mg/dl	• Oliguric	Hold protocol – May continue study drug next day per PI discretion based on renal function.

*Each patient will get 4 capsules (4 placebo, 4 active, or 3 placebo +1 active).
If creatinine increases >0.5 mg/dl and investigator wants to continue half dose of study drug, the patient will still get 4 capsules (4 placebo, 2 placebo +2 active, or 3 placebo +1 active). This will be done by the research pharmacy.

7.2 Drug Dispensing

Drug dispensing will be managed by the CC in collaboration with the contracted drug supply vendor. At randomization and every 24 hours through 96 hours, the pharmacy at each site will provide the study personnel with study drug. Authorized personnel will administer the study drug.

No previous MRA stratum: 4x25 mg study drug capsules once daily; starting dose 100 mg spironolactone or placebo; if dose adjustment is required, active capsules will be adjusted by pharmacy to achieve the required dose.

Previous low-dose MRA stratum: 4x25 mg study drug capsules once daily; one capsule containing 25 mg spironolactone and 3x25 mg study capsules containing spironolactone or placebo; if dose adjustment is required, active capsules will be adjusted by pharmacy to achieve the required dose.

7.3 Drug Storage, Accountability and Destruction

Storage - Study drug is to be stored at room temperature below 25°C (77°F) with excursions permitted to 30°C (86°F). Excessive moisture should be avoided.

Accountability - All study drug provided to the sites must be accounted for in writing. Documentation must be maintained by the investigator and will be monitored by the CC. Forms to record dispensing of study medication will be provided prior to the initial shipment of the study drug. A copy of the completed study drug accountability record will be provided to the CC as part of the study closeout activities.

Destruction - Used and unused study drug can be destroyed at the site according to accepted pharmacy practice, local and national guidelines, using the site's destruction procedure. A copy of the drug destruction SOP should be maintained in the pharmacy section of the Regulatory Binder. Study drug destruction should be documented in the comments section of the Subject Specific Drug Accountability Log.

7.4 Randomization, Stratification and Blinding

Randomization will occur within 24 hours of first I.V. diuretic dose given for the current episode of acute HF decompensation (either in the office, ED, ambulance, or hospital). Randomization to active drug or placebo (1:1 allocation ratio) is stratified by site and spironolactone usage at baseline. Blinding is ensured by preparation of identically appearing placebo and active drug (25 mg study drug capsules). Subjects will be randomized using a permuted block randomization to ensure relatively equal distribution of subjects to each arm within each site. Blinding of the study, with respect to treatment groups will be preserved by the use of matching placebo. Designated site Investigational Pharmacists will be unblinded to dosing assignment to allow for correct dispensing of study drug. The investigator may be asked at the end of the trial if they had obtained any information that may have led to the unblinding of treatment.

7.5 Unblinding

The investigative sites will be given access to the treatment code for their patients for emergency unblinding only by calling the CC. Unblinding should be a very rare occurrence. The potential physiologic actions of the therapy are well characterized. Given the known safety profile of spironolactone, it is anticipated that there should be no need to unblind the study drug. Any suspected study drug-related events should be treated as though the patient received active therapy. Nevertheless, in the rare event of necessary unblinding, the CC medical monitor must be contacted to discuss a given case. Randomization data will be kept strictly confidential, accessible only to authorized persons, until the time of unblinding.

7.6 Concomitant Medications

Patients with AHF should be treated with standard HF guidelines recommended care. Medications should be adjusted during hospitalization as dictated by the guidelines. The following drug interactions have been observed with spironolactone with long-term use:

- ACE inhibitors or ARBs: may be associated with hyperkalemia
- Alcohol, barbiturates, or narcotics: maybe associated with hypokalemia
- Corticosteroids, ACTH: may be associated with hypokalemia
- Pressor amines (e.g. norepinephrine): may reduce vascular responsiveness
- Skeletal muscle relaxants: may amplify muscle relaxant responsiveness
- Lithium: may lead to lithium toxicity
- NSAIDs: may be associated with hyperkalemia
- Cardiac glycosides (e.g. digoxin): may lead to digoxin toxicity
- Anticoagulants (e.g. warfarin, heparin): may reduce the effects of anticoagulation

8 RECRUITMENT AND SCREENING PROCEDURES

8.1 Common Recruitment Procedures

All participants admitted to the participating sites with AHF will be screened. Patients meeting all eligibility criteria will be approached regarding participation and asked to provide written informed consent before any study procedure commences.

8.2 Estimated Enrollment Period

This study will enroll 360 participants at approximately 30 clinical centers in the United States and Canada. It is projected that 25-30 patients per month will be enrolled (1.0 patients per center per month), for a total anticipated enrollment period of approximately 12-15 months.

8.3 Informed Consent Procedures

Informed Consent - HFN center clinicians will explain to eligible patients the purpose of the study, study procedures and evaluations, and the potential risks and benefits of participation, and will answer any questions. If a patient agrees to participate, they will review and sign the site-specific IRB approved ICF before any study specific procedures are conducted.

Confidentiality and HIPAA Requirements - All information collected on study participants will be stored in a confidential manner using the procedures in place at each participating site. Only approved study personnel will have access to data collected as part of the study. A subject ID number on all study documents will identify study participants. Data will be transmitted to the CC in a secure manner, and stored securely at the CC using standard Duke Clinical Research Institute (DCRI) operating procedures.

Protections of Human Subjects - Protections for human subjects of research are required under Department of Health and Human Services (HHS) regulations at 45 CFR 46. Subpart A of the HHS regulations constitutes the Federal Policy (Common Rule) for the Protection of Human Subjects, which has been adopted by an additional 16 Executive Branch Departments and Agencies. Each institution engaged in (non-exempt) HHS-supported human subjects research must provide a written Assurance of Compliance, satisfactory to the Office for Protection from Research Risks (OPRR), that it will comply with the HHS human subjects regulations--45 CFR 46.103(a).

8.4 Summary of the Risks and Benefits

Drug-Related Risks - Spironolactone has been licensed for the treatment of HF for many years. The most common risks of taking spironolactone include hyperkalemia (observed at <1.0% in the RALES trial), hyponatremia, headache, drowsiness, lethargy, diarrhea, cramps, bleeding, gastritis, vomiting, anorexia, nausea, rash, pruritus, and urticaria. With long-term use, gynecomastia, breast tenderness, erectile dysfunction, and post-menopausal bleeding have been reported but are less common. Hirsutism, agranulocytosis, and hyperchloremic metabolic acidosis have also been reported.

A potentially serious side effect sometimes seen in patients treated with spironolactone is hyperkalemia. Patients with impaired renal function are considered to be at higher risk, an observation used to define the exclusion criteria. **Table 4** summarizes the incidence of hyperkalemia in previous major studies with MRA in HF. No death has been attributed to hyperkalemia secondary to MRA use in any trial to date. However, the risk of hyperkalemia does increase with increasing doses of MRA. In the dose-finding RALES study, there was a clear dose-response relationship between spironolactone dose and rates of hyperkalemia.[22] The proportion of patients developing K^+ ≥5.5 was 5%, 13%, 20%, and 24% for doses of 12.5, 25, 50, and 75 mg, respectively ($P<0.001$).[22] However, in the main RALES trial, with appropriate surveillance of potassium and creatinine levels, the use of spironolactone was associated with less hypokalemia and improved survival in patients with severe heart failure even in the setting of moderate hyperkalemia.[48]

Table 4. Incidence of Hyperkalemia in Trials with MRA in HF

Trial	Patients	Active	Placebo	Tx	Mean FU	Results
TOPCAT (2014) [29]	NYHA II-IV, LVEF >45%	1722	1723	Spironolactone 15-45mg	3.3 yr	K>5.5 18.7% spiro vs. 9.1% placebo
Aldo-DHF (2013) [30]	NYHA II-III LVEF ≥50% Grade ≥1 DD or AF, low VO_2	213	209	Spironolactone 25 mg daily	12 mo	K >5.0: 44 (21%) vs. 22 (11%); P=0.005 K >5.5: 4 (2%) vs. 3 (1%); P=0.99
ARTS (2013) [49]	NYHA II-III LVEF ≤40% moderate CKD	265	63 spiro; 65 placebo	BAY 94-8862 2.5–10 mg daily	4 wk	Any event reported as 'hyperkalaemia': 11.1% in the spiro group
EMPHASIS-HF (2011) [29]	NYHA II LVEF ≤35%	1364	1373	Eplerenone 50 mg daily	21 mo	K >5.5: 11.8% vs. 7.2%; P<0.001; D/c b/c of K: 1.1% vs. 0.9%; P=0.57
Udelson et al (2010) [50]	NYHA I-II LVEF ≤35%	116	109	Eplerenone 50 mg daily	9 mo	Unclear definition: 14 (12.0%) vs. 6 (5.5%)
Vizzardi et al (2010) [51]	NYHA I-II LVEF ≤40%	79	79	Spironolactone 25–100 mg daily	6 mo	1 patient d/c because of K >5.5
AREA IN-CHF (2009) [52]	NYHA II LVEF ≤45%	231	236	Canrenone 25-50 mg daily	12 mo	K >5.5: 23 (10.1%) vs. 8 (3.5%); P<0.01 K >6.0: 3 vs. 2 pt
Gao et al (2007) [53]	NYHA II-IV LVEF <45%	58	58	Spironolactone 20 mg daily	6 mo	1 patient in the spiro group
EPHESUS (2003) [27, 44, 54]	LVEF ≤40% post-AMI	3313	3319	Eplerenone 25–50 mg daily	16 mo	K >5.5: 15.6% vs. 11.2%; P<0.001; K >6.0: 5.5% vs. 3.9%; P=0.002
RALES (1999) [28, 55]	NYHA III-IV LVEF ≤35%	822	841	Spironolactone 25 mg daily	24 mo	K >6.0: 2% vs. 1%; P=0.42

AMI: acute myocardial infarction; AREA-in-CHF: Antiremodelling Effect of Aldosterone Receptors Blockade with Canrenone in Mild Chronic Heart Failure; CKD: chronic kidney disease; EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS: Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; RALES: Randomized Aldactone Evaluation Study; TOPCAT: Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist

Pregnancy

This protocol may be hazardous to an unborn child. The FDA has assigned spironolactone to pregnancy category C. Animal studies at the maximum human dose showed feminization of male fetuses during early pregnancy and indications of endocrine dysfunction in both male and female offspring during late pregnancy that persisted into adulthood. There are no controlled studies of spironolactone in humans to determine whether there are significant risks to a fetus carried by a mother who is participating in this study. Therefore, female participants must be postmenopausal, surgically sterilized or have a negative serum pregnancy test prior to inclusion in the trial.

Other Study-Related Risks

Blood draws: The risks of drawing blood include bleeding at the puncture site, bruising and pain. These occur in a very small portion of the population.

9 EVALUATIONS AND PROCEDURES

A complete schedule of assessments is provided in **Appendix A.** All protocol described assessments should be anchored using the randomization date and time. All patients will be assessed every 24 hours following randomization for 96 hours:

- 24-hour assessment should occur between 22 and 26 hours post randomization
- 48-hour assessment should occur between 46 and 50 hours post randomization
- 72-hour assessment should occur between 70 and 74 hours post randomization
- 96-hour assessment should occur between 94 and 98 hours post randomization

9.1 Baseline Evaluation and Procedures Conducted Prior to Randomization

Within 24 hours prior to randomization, all study participants will undergo:

1. Medical History
2. Review of medications including pre-hospital loop diuretics, MRA, and potassium doses
3. Physical examination, vital signs and body weight
4. Measurement of creatinine, blood urea nitrogen (BUN), and electrolytes
5. Dyspnea Relief Assessments (7-point Likert and Visual Analog Scale)
    a. Measured off oxygen for 3 minutes. If the patient develops severe dyspnea prior to 3 minutes off oxygen, the patient will complete the dyspnea relief worksheets at the point of severe dyspnea.
6. Serum pregnancy test for all women of childbearing potential
7. Collection of samples for measurement of NT-proBNP levels (Core Lab)

9.2 Assessment at 24 Hours Post Randomization

1. Review of medications
2. Body weight
3. Fluid intake/urine output
4. Creatinine, blood urea nitrogen (BUN), and electrolytes
5. Adverse events

If the 24 hour assessment is also the day of discharge, include:

a. Physical exam / Vital signs
b. Dyspnea Relief (7-Point Likert and VAS)
c. Biomarkers (NT-proBNP) (Core Lab)

9.3 Assessment at 48 Hours Post Randomization

1. Review of medications
2. Physical exam / Vital signs
3. Body weight
4. Fluid intake/urine output
5. Dyspnea Relief (7-Point Likert and VAS)
6. Creatinine, blood urea nitrogen (BUN), and electrolytes
7. Biomarkers (NT-proBNP) (Core Lab)
8. Adverse events

9.4 Assessment at 72 Hours Post Randomization

1. Review of medications
2. Body weight
3. Fluid intake/urine output
4. Creatinine, blood urea nitrogen (BUN), and electrolytes
5. Adverse events

If the 72 hour assessment is also the day of discharge, include:

a. Physical exam / Vital signs
b. Dyspnea Relief (7-Point Likert and VAS)
c. Biomarkers (NT-proBNP) (Core Lab)

9.5 Assessment at 96 Hours Post Randomization

1. Medication review
2. Physical exam / Vital signs
3. Body weight
4. Fluid intake/urine output
5. Creatinine, blood urea nitrogen (BUN), and electrolytes
6. Dyspnea Relief (7-Point Likert and VAS)
7. Biomarkers (NT-proBNP) (Core Lab)
8. Adverse events

9.6 Volume Assessment

If patient is clinically euvolemic in less than 96 hours, consider changing loop diuretics to oral dose.

9.7 Ejection Fraction

Ejection fraction data will be obtained from echocardiogram within 6 months prior to randomization. Those patients who do not have an echocardiogram recorded within this time frame will get an echocardiogram, nuclear perfusion study, MRI, or MUGA performed prior to the 96 hour in-hospital assessment to ascertain ejection fraction.

9.8 Discharge

Study drug will be discontinued after 96 hours and further use of MRA will be left to the treating physician's discretion.

If discharge occurs after the 96 hour assessment but prior to the 30 day assessment, the following will be documented:

1. Medication review (prescribed medications at the time of discharge)
2. Body weight (if available)
3. Creatinine, blood urea nitrogen (BUN), and electrolytes (if available)
4. Adverse events

9.9 Follow-Up Telephone Call at Day 30

All participants will be contacted by telephone at day 30 (+3 days) post randomization to assess:

1. Vital status (death)
2. Any readmissions
3. Any HF readmissions or ED visits or observational unit stays for HF or need for outpatient IV diuretics
4. MRA use at day 30
5. Loop diuretic dose at day 30
6. Any adverse events

9.10 Follow-Up Telephone Call at Day 60

All participants will be contacted by telephone at day 60, (+/- 3 days) post randomization to assess vital status (death).

10 OUTCOME DETERMINATIONS

10.1 Primary Endpoint

The primary endpoint for this study will be the proportional change in NT-proBNP from randomization to 96 hours. The Core Laboratory at Vermont will determine NT-proBNP levels for calculation of the endpoint from samples obtained at randomization, 48 hours, and 96 hours, respectively. (NT-proBNP will be obtained at the 24 hour or 72 hour assessment if that assessment is the same day as discharge.)

10.2 Secondary Endpoints (From Randomization to 96 Hours)

1. Congestion score
2. Dyspnea relief
3. Net urine output
4. Weight change
5. Loop diuretic dose requirements
6. In-hospital worsening HF, defined as worsening HF signs and symptoms requiring additional therapy in the judgment of the treating physician.

10.3 Tertiary Endpoints (Day 30 (+3) Post Randomization)

1. All-cause mortality by day 30
2. All-cause readmissions by day 30
3. Outpatient worsening HF (HF readmission or emergency department visits or observational unit stay or need for outpatient IV diuretics) by day 30
4. MRA use at day 30
5. Loop diuretic dose requirements at day 30
6. Length of stay for index hospitalization

10.4 Safety Endpoints

1. Change in serum creatinine from randomization to 96 hours post randomization.
2. Incidence of hyperkalemia (>5.5mmol/L or >6.0mmol/L) from randomization to 96 hours post randomization.

11 PARTICIPANT SAFETY AND ADVERSE EVENTS

11.1 Institutional Review Boards

All HFN sites will submit the study protocol, informed consent form, and other study documents to the IRB for approval. Any amendments to the protocol, other than minor administrative changes, must be approved by each IRB before they are implemented.

11.2 Definitions

11.2.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in a subject whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of the study drug.

11.2.2 Suspected Adverse Reaction

A suspected adverse reaction (SAR) is any adverse event for which there is a reasonable possibility that the drug caused the event. “Reasonable possibility” suggests there is a causal relationship between the drug and the adverse event. “Suspected adverse reaction” implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

11.2.3 Serious Adverse Events (SAE)

An adverse event or suspected adverse reaction is considered serious if the investigator or sponsor believes any of the following outcomes may occur:

- Death
- Life-threatening AE: Places the subject at immediate risk of death at the time of the event. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Inpatient hospitalization or prolongation of hospitalization.
- Congenital anomaly or birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition above.

This determination is based on the opinion of either the investigator or sponsor (e.g., if either believes it is serious, it must be considered serious).

11.2.4 Laboratory Test Abnormalities

For laboratory test abnormalities that meet the definition of an SAE, that required the subject to have the investigational product discontinued or interrupted or required the subject to receive specific corrective therapy, the clinical diagnosis rather than the laboratory term will be used by reporting investigator (e.g., anemia versus low hemoglobin value).

11.2.5 Assessment of Causal Relationship

A medically qualified investigator must assess the relationship of any AE to the use of study drug, based on available information, using the following guidelines:

- **Not related:** There is not a reasonable causal relationship to the investigational product and the adverse event.
- **Unlikely related:** No temporal association or the cause of the event has been identified, or the drug or biologic cannot be implicated.
- **Possibly related:** There is reasonable evidence to suggest a causal relationship between the drug and adverse event.
- **Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

11.2.6 Expectedness

The expectedness of an AE or SAR shall be determined according to the specified reference document containing safety information (e.g., most current investigator's brochure or product label). Any AE that is not identified in nature, severity, or specificity in the current study drug reference document(s) (e.g. Package insert) is considered unexpected. Events that are mentioned in the investigator's brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but not specifically mentioned as occurring with the particular drug under investigation are considered unexpected.

11.3 Anticipated Adverse Events and Procedure Effects

The following AEs are anticipated, disease-related events in patients admitted with AHF:

- **Arrhythmias:** This refers to both atrial and ventricular arrhythmias.
- **Sudden Cardiac Death:** This refers to witnessed cardiac arrests and sudden deaths without an otherwise apparent cause such as trauma or malignancy.
- **Acute Coronary Syndrome:** This refers to unstable angina, non ST segment elevation myocardial infarction (NSTEMI), and ST segment elevation myocardial (STEMI).
- **Cerebrovascular Event:** This refers to cerebrovascular accidents (stroke) of any cause (hemorrhagic, ischemic, or embolic) and transient ischemic attack (TIA).
- **Venous Thromboembolism:** This includes both deep venous thrombosis and pulmonary embolus.
  Lightheadedness, Presyncope, or Syncope: This includes dizziness, lightheadedness, or fainting from any cause.
- **Acute kidney injury as defined by KDOQI guidelines:** This refers to acute kidney injury, typically defined as a rise in creatinine > 0.3 mg/dL over 48 hours, or progressive loss of renal function over time.
- **In hospital worsening HF:** This refers to treatment for acute heart failure such as receiving intravenous diuretics.
- **Hyperkalemia** (K^+ >5.5 mmol/L)

All anticipated disease related events, will not be captured as AEs/SAEs during the study, but will be entered on the appropriate eCRF module.

11.3.1 Recording and Reporting of Adverse Events

The site investigator is responsible for monitoring the safety of participants enrolled into the study. Non-serious AEs will not be collected on the eCRF but should be documented in the source documents and followed according to local standard of care. All SAEs need to be reported from the time of randomization through the Day 30 assessment, including subjects who are discontinued prematurely from the study. Unless exempted, as described in section 12.3, all SAEs whether or not deemed drug-related or expected must be reported by the investigator or qualified designee within 1 working day of first becoming aware of the event. The investigator or qualified designee will enter the required information regarding the SAE into the appropriate module of the eCRF. If the eCRF system is temporarily unavailable, the event, including the investigator-determined causality to study drug should be reported via the back-up paper SAE form to DCRI Safety Surveillance at 1-866-668-7138. Upon return of the availability of EDC system, the SAE information must be entered into the eCRF.

11.3.2 Follow-up

When additional relevant information becomes available, the investigator will record follow-up information according to the same process used for reporting the initial event as described above. The investigator will follow all reportable events until resolution, stabilization or the event is otherwise explained. DCRI Safety Surveillance will follow all SAEs until resolution, stabilization, until otherwise explained, or until the last subject completes the final follow-up, whichever occurs first. DCRI Safety Surveillance will report all SAEs to the CC, DCRI HFN Clinical Operations Team, and notify the DCRI Safety Medical Monitor and NHLBI designee of all related SAEs within 1-2 business day(s) of receipt. Investigators are also responsible for

promptly reporting adverse events to their reviewing IRB/EC in accordance with local requirements. The DSMB will be provided detailed safety data approximately every 6 months throughout the study and will be notified when a trend in hyperkalemia and/or study drug discontinuation related to hyperkalemia is identified.

11.3.3 Suspected Unexpected Serious Adverse Reaction

Adverse events which meet the criteria of serious, related to study drug, and unexpected for that drug, per product labeling, qualify for expedited reporting to the regulatory authorities. The site Investigator will assess all SAE's occurring at his/her site and evaluate for "unexpectedness" and relationship to study drug. The site Investigator is required to complete and submit a voluntary MedWatch Report for events confirmed by DCRI Safety Medical Monitor, as serious, study drug related and unexpected at: https://www.accessdata.fda.gov/scripts/medwatch/.

A copy of this report should be kept at the site and also forwarded to the DCRI Coordinating Center and to DCRI Safety Surveillance.

Canadian sites will be required to submit 2 forms: CIOMS1and Adverse Reaction form to Health Canada per GCP and as mandated by the protocol. After completing report to the FDA, http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/form/ctadr_dceim-eng.php will be accessed to follow the instructions for completion of the Health Canada Adverse Reaction Report. A copy of the CIOMS1 report will be maintained with the subject's file at the site and fax a copy to the DCRI at 919-668-1982.

11.3.4 Pregnancy

This is a 4-day in hospital study and pregnancy will be ruled out prior to randomization. Thus pregnancy occurrence during the study period is not expected and only those patients who are either post-menopausal or surgically sterile or have a negative pregnancy test will be included in this study. Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported to DCRI within the same timelines as a serious adverse event. The pregnancy will be recorded on the appropriate paper pregnancy tracking form. The pregnancy will be followed until final outcome. Any associated SAEs that occur to the mother or fetus/child will be recorded in the SAE eCRF, within InForm.

12 STATISTICAL CONSIDERATIONS

12.1 Overview

All planned analyses will be prospectively defined and approved by the CC, NHLBI study team, and the protocol PI prior to unblinding of data. In addition, exploratory analyses will be performed to help explain and understand findings observed from the planned analyses. Statistical tests with a 2-sided p-value <0.05 will be considered statistically significant, unless otherwise stated. Summaries of continuous variables will be displayed using the mean, standard deviation, median, and 25th-75th percentiles. For nominal variables, the number and percentages in each category will be presented. Analyses will be performed using SAS software (SAS Institute, Inc, Cary, NC).

12.2 Analysis of Primary Endpoint

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 covariates for treatment assignment, an indicator for MRA at baseline, 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. The analysis will account for low-dose MRA at enrollment using a stratified version of the Wilcoxon-Mann-Whitney test.

12.3 Analysis of Secondary and Tertiary Endpoints

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 spironolactone vs. placebo with the estimated odds ratio and associated 95% confidence interval. The adjustment models will include an indicator variable for home MRA usage. 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:

- Baseline MRA usage
- Sex
- HFpEF vs. HFrEF
- Age ≥ or < 65

12.4 Analysis of Safety Data and Statistical Monitoring Plan

Interim data analysis for efficacy and futility will not be conducted due to relatively small size and short duration of this phase-II clinical trial. The safety analyses will be based on the entire randomized population. Safety will be evaluated by comparing the occurrence of AEs and changes in laboratory values of the active arm compared to placebo.

Treatment emergent AEs are defined as all AEs that occurred, for the first time, on or after the first dose of study medication; or occurred on or after the first dose of study medication with a greater severity compared with the occurrences prior to the first dose. The number and percentage of participants experiencing treatment emergent AEs will be tabulated by treatment group, body system, and preferred term. The percentages between treatment groups will be compared using Fisher's mid-pt test. The number and percentage of participants experiencing treatment emergent AEs will also be tabulated by severity and relationship to the study drug.

12.5 Sample Size and Power Calculations

Prior HFN data suggest that the standard deviation for the proportional change (on the log scale) in NT-proBNP from randomization to 96 hours is approximately 0.60. We anticipate that 25% of subjects enrolled in the study will be on low-dose MRA at the time of randomization. Assuming a 20% improvement 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 smaller 10% improvement in the subset on low-dose MRA at baseline would yield 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 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 would provide 90% power to detect a difference in the setting where a randomly selected individual on the high dose spironolactone arm 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 1-2%.

For continuous secondary endpoints, the study will have approximately 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. The sample size of 360 subjects will not provide adequate power to detect clinically important differences for tertiary endpoints such as all-cause mortality and re-admissions at 30 days.

13 DATA MANAGEMENT PROCEDURES

13.1 Overview of Data Management

The CC will have primary responsibility for data management, including the development of data collection systems, data monitoring processes, and data storage and back-up. State-of-the-art technology will be used for the management of the network's data.

Electronic Case Report Form (eCRF): The CC management team will develop eCRF modules necessary for ATHENA-HF. Common fields and data elements will be used across the HFN trials to promote data standardization and allow cross-network analyses. Study eCRF components will include an enrollment and demographics form; forms for recording relevant history, HF symptoms, physical exam results, laboratory results, and other baseline presenting characteristics; follow-up forms for use during regular follow-up visits; forms to track the participant's clinical course over time; and event forms for recording the circumstances and details surrounding the occurrence of a death or hospitalization.

Electronic Data Capture (EDC) System: The data will be collected in a validated, 21 CFR Part 11 compliant, Electronic Data Capture (EDC) system. The CC has an internal team of skilled data managers and programmers that will design and produce a tailored network system that provides operational efficiency and meaningful reporting of metrics.

Data Management Process: The EDC system will be used for data entry and simple reports. All data will be entered into the eCRF by personnel at the clinic sites. Any out-of-range values and missing key variables will be flagged and addressed in real-time at the site during data entry. When a query is generated on a particular variable, a flag is raised in a database field; the system tracks the queries and produces reports of outstanding queries. Queries can also be generated from manual or statistical review of the data forms.

The CC will create reports to identify trends in the data that may require additional clarification and training. These reports will be available to the sites and to the study leadership as we work with the sites to correct negative trends and eliminate future data errors. The CC will perform internal database quality-control checks during the study to identify systematic deviations requiring corrections.

Data Quality Control

A three-step approach to data quality control will be implemented.

1. Training: Prior to the start of enrollment, the investigators and study coordinators will be trained on the clinical protocol and data collection procedures. Recent site surveys indicate that most coordinators are very familiar with the EDC system, so training is typically targeted to a specific protocol. For coordinators new to the InForm Database, the CC may provide training with hands-on database interaction and demonstration of key EDC system functionality. Personnel at the clinical sites will enter the data mandated by the protocol into the eCRFs. The data will be abstracted from the participant's medical charts and other source documents. All CRFs will be completed according to the current Good Clinical Practice (cGCP) guidelines. The CC will conduct follow-up training and training for new study personnel as needed.
2. Monitoring: A CC monitor will visit sites as needed during the enrollment period to ensure that data collection is being handled properly, to provide in-service training, and to address questions from site investigators and coordinators. Additional details will be outlined in the Clinical Monitoring Plan.
3. Managing Data: A series of computerized validation checks (DCFs) will be programmed by the CC to check for missing data, inconsistencies in the data or data that is out of range. After the data have been exported from the EDC system to SAS for statistical summarization and data analysis, further cross-checking of the data will be performed by the CC with discrepant observations being queried through the EDC system.

13.2 Data Security

Access to databases will be controlled centrally by the CC through user passwords linked to appropriate privileges. This protects the data from unauthorized changes and inadvertent loss or damage. Database and web servers will be secured by a firewall and through controlled physical access. Database back-up will be performed daily using standard procedures in place at the CC. All disk drives that provide network services, and all user computers, will be protected using virus-scanning software.

13.3 Publication Policy

Dissemination of preliminary information can adversely affect the objectivity of study data. For this reason, investigators will not be allowed to perform subset analyses at any point before the conclusion of the study, and any data, other than safety data, cannot be used for publication or reporting outside of this study until the study is completed or discontinued by the DSMB or HFN Steering Committee.

14 STUDY ADMINISTRATION

14.1 Data and Safety Monitoring Board

A DSMB has been appointed by the NHLBI for the HFN, and will function as the DSMB for this trial. This committee consists of a group of highly experienced individuals with extensive pertinent expertise in HF and clinical trials. The DSMB will advise the HFN Steering Committee regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial.

14.2 Coordinating Center

The DCRI serves at the CC for this trial as specified by the NIH/NHLBI HFN grant.

14.3 Core Laboratories

Biomarker Core Laboratory - The University of Vermont will serve as the Core Laboratory for measurement of HFN biomarkers. Blood specimens will be collected at baseline, 48 hours, and 96 hours, processed at the clinical centers according to the procedures provided by the Core Lab, and shipped to the Core Laboratory on dry ice. (NT-proBNP will be obtained at the 24 hour or 72 hour assessment if that assessment is the same day as discharge.)

15 REGULATORY ISSUES

15.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and documented procedures in the manual of operations. These procedures are designed to ensure adherence to Good Clinical Practice, as described in the following documents:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

15.2 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to the Coordinating Center before study initiation. This committee must approve any amendments to the protocol, other than administrative ones.

15.3 Informed Consent

The investigator or designee must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If written consent is not possible, oral consent can be obtained if witnessed by a signed statement from one or more persons not involved in the study, mentioning why the patient was unable to sign the form. No patient can enter the study before his/her informed consent has been obtained. The informed consent forms are part of the protocol, and must be submitted by the investigator with it for IRB/IEC approval. The CC will supply proposed informed consent forms, which comply with regulatory requirements, and are considered appropriate for the study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by the CC before submission to the IRB/IEC, and a copy of the approved version must be provided to the CC after IRB/IEC approval.

16 REMOTE MONITORING

DCRI or its designee will monitor the study remotely according to the prospective clinical monitoring plan (CMP) for the following purposes:

- Real-time monitoring of compliance with study protocol inclusion/exclusion criteria is enabled via triggers and range checks programmed in the InForm database.
- Assist site personnel who will verify data identified within query reports against source documents through frequent telephone and email contact.
- Verify that written informed consent was obtained before initiation of any screening procedures that are performed solely for the purpose of determining eligibility for the clinical study and/or prior to the patient's randomization to a procedure.

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18 APPENDICES

Appendix A. Schedule of Assessments

Baseline assessments, excluding echocardiogram, must be completed within 24 hours prior to randomization. All visits are anchored from the time of randomization.

	In-hospital						Day 30[10] (+3 days)	Day 60[11] (+/- 3 days)
	Baseline	**24 hours**	**48 hours**	**72 hours**	**96 hours**	**Discharge Assessment (post 96 hours)**	**Telephone Follow Up**	**Telephone Follow Up**
Informed Consent	X							
Medical History	X							
Medication Review	X[1A]	X	X	X	X	X[1B]	X	
Physical Exam / Vital Signs	X	X[2]	X	X[2]	X			
Body Weight	X	X	X	X	X	X[9]		
Fluid intake/urine output		X	X	X	X			
Cr, BUN, electrolytes	X	X[3]	X[3]	X[3]	X	X[9]		
Dyspnea Relief (7-point Likert and Visual Analog Scale)[4]	X	X[2]	X	X[2]	X			
Serum pregnancy test[5]	X							
BNP or NT-proBNP (Local Lab)	X							
Biomarkers (NT-proBNP) (Core Lab)	X	X[2]	X	X[2]	X			
Study drug administration	X	X	X	X				
Clinical events[6]							X	
Adverse events[7]		X	X	X	X	X	X	
Randomize	X							
Echocardiogram[8]			X					
Telephone call to assess vital status								X

[1A]Baseline medication review represents pre-hospital medications
[1B]Discharge Assessment (post 96 hours) represents prescribed medications at the time of discharge
[2]Complete ONLY if day of discharge
[3]Draw labs 1-2 hours prior to scheduled 24, 48, and 72 hour assessments
[4]Assess dyspnea supine, off oxygen for 3 minutes or until severe dyspnea
[5]For women of childbearing potential
[6]Death, any readmissions, and emergency care for HF (readmission or ED visits or observational unit stay or need for outpatient IV diuretics)
[7]Non-serious AEs will not be collected on the eCRF but should be documented in the source documents and followed according to local standard of care. All SAEs need to be reported from the time of randomization through the Day 30 assessment.
[8]Echocardiogram performed within 6 months prior to randomization or prior to the 96 hour assessment to ascertain ejection fraction. Nuclear perfusion study, MRI, or MUGA measuring ejection fraction also acceptable.
[9]Discharge Assessment, if post 96 hour assessment, includes documentation of available Cr/BUN/electrolytes and weight (plus medication review and adverse event assessment)
[10]Performed day 30 (+3 days) post randomization
[11]Performed day 60 (+/-3 days) post randomization

Appendix B: Dyspnea Relief 7-Point Likert Scale

HEART FAILURE NETWORK	**ATHENA HF** Dyspnea Relief 7 Point Likert Scale

Subject ID: _____ - _____ **Subject Initials:** _____
site # *subject #*

Date Completed: ____ /_____ /_____ **Time:** ___: ____
day *month* *year*

Check One: ☐ **Baseline** ☐ **24 Hour** ☐ **48-Hour** ☐ **72 Hour** ☐ **96-Hour Assessment**

Assess dyspnea after being off oxygen for 3 minutes or at the point of severe dyspnea, if prior to 3 minutes.

We would like to measure how you think your breathing is. Please mark the description that best indicates how you are breathing right now.

☐	Markedly Improved
☐	Moderately Improved
☐	Minimally Improved
☐	No Change
☐	Minimally Worse
☐	Moderately Worse
☐	Markedly Worse

Appendix C: Dyspnea Relief Visual Analog Scale

HEART FAILURE NETWORK	**ATHENA HF** Dyspnea Relief Visual Analog Scale

Subject ID: _____ - _____ **Subject Initials:** _____
site # *subject #*

Assessment Date: _____ /_____ /_____ **Time:** ____: _____
day *month* *year*

Check One: ☐ **Baseline** ☐ **24 Hour** ☐ **48-Hour** ☐ **72 Hour** ☐ **96-Hour Assessment**

Assess dyspnea after being off oxygen for 3 minutes or at the point of severe dyspnea, if prior to 3 minutes.

Please draw a horizontal line on the scale to show how you think your breathing is right now. The number "0" equals the worst your breathing has ever felt and the number "100" equals the best your breathing has ever felt.