ORAL **S**ODIUM TO **P**RESERVE **R**ENAL **E**FFICIENC**Y** IN **A**CUTE **H**EART **F**AILURE **(OSPREY-AHF)**

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ORAL SODIUM TO PRESERVE RENAL EFFICIENCY IN ACUTE HEART FAILURE

(OSPREY-AHF)

Investigators

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Sponsor: Cleveland Clinic Heart Vascular and Thoracic Institute, Wilson Grant, Kaufman Grant

PROTOCOL SIGNATURE PAGE

I have carefully read the OSPREY-AHF protocol. I agree to conduct this study as outlined herein. Furthermore, I understand that the Cleveland Clinic and the IRB must approve any changes to the protocol in writing before implementation.

_____
W. H. Wilson Tang, MD **(Principal Investigator)**

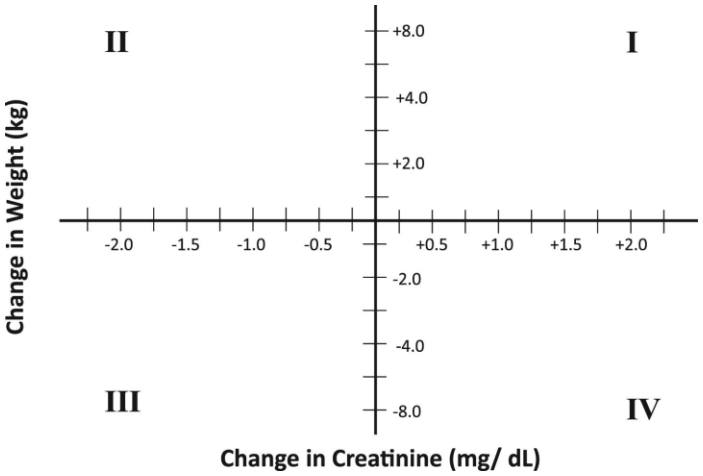
_____
Date

1.0 INTRODUCTION

1.1 Purpose of this Study:

We are proposing a prospective, randomized, double blinded, placebo-controlled single center study evaluating the role of co-administration of oral sodium chloride with intravenous diuretics in patients hospitalized with acute decompensated heart failure. We are approaching this study with the hypothesis that the use of oral sodium chloride leads to improved effective diuresis (as measured by weight loss) and renal function as compared to placebo in patients hospitalized with acute decompensated heart failure undergoing aggressive intravenous diuretic therapy.

Primary endpoint:
Our primary outcome will be a composite outcome of change in weight and change in creatinine from baseline to 96 hours (or discharge) after initiation of sodium chloride capsule administration vs placebo (as analyzed by intention to treat)



The bivariate outcome will be displayed on a two-dimensional grid with individual data points for each patient representing paired changes in both creatinine and weight at 96 hours after randomization (or at discharge) (Fig. 1). A confidence region for the average difference between treatment arms in this bivariate response will be described as an ellipse, and the two treatment arms will be compared with the use of the Hotelling T-square test, which is a multivariate analog of the 2-sample t test used with a single continuous variable.

The null hypothesis is that there is no difference between the treatment groups in this 2-dimensional end point.

Secondary endpoints:

- Change in creatinine [timepoint: enrollment to 96 hours (or discharge)],
- Change in weight [timepoint: enrollment to 96 hours (or discharge)]
- Change in daily urine output [timepoint: day of enrollment, active treatment days 1, 2, 3, 4],
- Change in serum sodium [timepoint: day of enrollment, active treatment days 1, 2, 3, 4],
- Change in thirst distress survey [timepoint: enrollment to 96 hours (or discharge), followup phone call],
- Time to discontinuation of intravenous diuretic therapy [timepoint: enrollment to discharge]
- Total diuretic dosage in oral furosemide equivalents [timepoint: enrollment to 96 hours (or discharge)],
- Daily urine output/daily total furosemide dose [timepoint: day of enrollment, active treatment days 1, 2, 3, 4]
- Guideline directed medical therapy [timepoint: enrollment to discharge]

- Total potassium supplementation required [timepoint: enrollment to 96 hours or discharge]
- Length of index hospitalization [timepoint: enrollment to discharge]
- Heart failure rehospitalizations, unscheduled clinic and emergency department visits [timepoint: discharge to 30 days post discharge]
- Death from any cause [timepoint: enrollment to 90 days post enrollment]
- Initiation of renal replacement therapy or ultrafiltration [timepoint: enrollment to 90 days post enrollment]
- Occurrence of a serious adverse event [timepoint: enrollment to 90 days post enrollment]

1.2 Importance and Rationale of Study

Dietary sodium restriction is a common therapeutic intervention in the management of patients hospitalized with decompensated heart failure. This is despite limited supportive data and inconsistent society guidelines.[1–3] Randomized clinical trial data has shown that dietary sodium restriction in patients hospitalized with heart failure was not associated with differences in weight, clinical congestion, time to clinical stability but was associated with increased thirst.[4] Numerous studies demonstrate that sodium restriction is associated with increased renin-angiotensin-aldosterone system activation as well as increases in inflammatory markers.[5,6] These findings challenge of the role of sodium restriction in hospital management of heart failure and have lead to trials that consider a therapeutic role of providing sodium to patients with acute heart failure for its effect in attenuating neurohormonal activation during aggressive diuresis. A central example is the SMAC-HF study from Italy, which showed that in 1771 patients with acute NYHA class IV heart failure, the addition of hypertonic saline (150ml of 1.4%-4.6% NaCl twice a day in addition to diet liberalization led to statistically significant increased urine output and weight loss in addition to reductions in creatinine, length of stay, mortality and readmissions.[7] These findings are controversial but similarly favorable results with the use of hypertonic saline in aiding diuresis have been seen in Japan with improved diuresis with continuous hypertonic saline infusions.[8] Despite these results, use of sodium chloride supplementation in acute heart failure remains limited. This may be because the practice challenges ingrained clinical practice, but a more likely reason is that the manner of sodium chloride delivery in these trials (hypertonic saline) is often reserved for the ICU setting and central venous access for delivery. While small volumes of hypertonic saline are likely safe to be administered in a non-ICU setting, the results would be more broadly applicable and utilized if the manner of sodium supplementation did not require intensive monitoring or central venous access, ie oral supplementation. Therefore, the purpose of the "**O**ral **S**odium to **P**reserve **R**enal **E**fficienc**Y** in **A**cute **H**eart **F**ailure" (OSPREY-AHF) is to evaluate the efficacy and safety of oral sodium chloride supplementation compared to placebo in patients with acute decompensated heart failure. While we are specifically interested in sodium chloride and its hypothesized role in attenuating a neurohormonally mediated diuretic resistance commonly seen in patients requiring high dose diuretic therapy, we also intend that by focusing on oral sodium chloride supplementation we may clarify the role of dietary sodium restriction in hospitalized patients with acute heart failure.

2.1 Inclusion/Exclusion Criteria

Inclusion Criteria:

- Age ≥ 18 years old AND
- Admitted to cardiology floor (non-ICU) with primary diagnosis of decompensated heart failure AND
- NT-proBNP >1000 ng/L AND
- Initiation of continuous furosemide infusion at a rate of 10mg/hr or higher.

Exclusion Criteria:

- Serum sodium (Na+) level less than 120 or greater than 145.
- Average systolic blood pressure >180 mmHg or DBP >100mmHg over past 24 hours.
- Anticipated length of stay less than 72 hours.
- Use of vasopressin antagonist
- Current use of sodium chloride tablets.
- Active diagnosis of diabetes insipidus
- Inability to tolerate oral diet or swallow pills
- Presence of malabsorptive gastrointestinal disorder (Crohn's disease, short gut syndrome)
- The use of iodinated radiocontrast material in the past 72 hours or anticipated use of intravenous contrast during the current hospitalization
- Admission with intention to undergo open heart surgery.
- Use of intravenous inotropes, vasopressors or vasodilators at enrollment
- A baseline estimated glomerular filtration rate <15 mL/min/1.73m² according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula at the moment of inclusion
- Use of renal replacement therapy at time of enrollment.

3.0 Study Procedures

Prior to the initiation of participation, a signed and dated informed consent and permission to use protected health information must be obtained. Randomization will occur via REDCAP Randomization Tool

4.1 Study Evaluations

All study evaluations will be as per clinical standard of care. Research procedures will include the randomization of sodium chloride vs placebo as well as adverse event reporting.

Study Procedures	Time Point 1 Screening/ Enrollment	Time Point 2 Salt vs Placebo Day1	Time Point 3 Salt vs Placebo Day 2	Time Point 4 Salt vs Placebo Day 3	Time Point 5 Salt vs Placebo Day 4	Time Point 6 Active Treatment Completion Day 5	Time Point 7 Discharge	Time Point 8 Outpatient followup (routine)	Timepoint 9 Followup Phonecall
Informed Consent and Randomization	x								
Collection of baseline characteristics from medical	x								

record (prior medications, PMH, demographics, EF, baseline /admission labs)									
Administer Thirst Distress Survey	x					x			
Vitals and 24 Hour Fluid Balance (Intake/Output)	x	x	x	x	x	x	x	x	
Administration of Salt vs Placebo (2g TID w/ meals)		x	x	x	x				
Collection of Urine electrolytes		x	x	x	x	x			
BMP/NT-ProBNP (per usual clinical care)	x	x	x	x	x	x	x	x	
Review of Current Medications and Diet Order	x	x	x	x	x	x	x	x	
Blood draw for biomarker analysis*		x				x			
Adverse Events		x	x	x	x	x	x	x	x
Reason for discontinuation of study drug			x	x	x	x			
Length of hospital stay							x		
Phone Contact Readmission?									x

* Blood draws for biomarker analysis will be limited to the first 50 patients enrolled.

5.0 Statistical Analysis and Endpoints

5.1 Sample Size and Primary Endpoint:

Population: Acutely decompensated heart failure patients with or at risk for diuretic resistance or congestive nephropathy.

Hypothesis: Use of oral sodium chloride will lead to increased fluid volume removal and attenuate diuretic related renal dysfunction.

Study Design: Prospective, randomized, double blind, placebo controlled, single-center study

Endpoint: Net change in weight and change in creatinine from baseline to 96 hours after initiation of sodium chloride capsule supplementation [or discharge] vs placebo (as analyzed by intention to treat)

Power: 80% (2-sided alpha 0.05)

Sample Size Estimate: 85

Trial	Endpoint	SD	alpha	Power	Difference	Sample size
UNLOAD	Wt change (kg)	3.5	0.5	80	2.2	80
DOSE	Wt change (kg)	4	0.5	80	2.2	104
CARESS-HF	Wt change (kg)	5.1	0.5	80	2.2	168
ATHENA-HF	Wt change (kg)	3.4	0.5	80	2.2	74
Aliti	Wt change (kg)	2.85	0.5	80	2.2	52
3T	Wt change (kg)	2.7	0.5	80	2.2	48
AVERAGE		3.77	0.5	80	2.2	**84**
UNLOAD	Cr change (mg/dl)	0.6	0.5	80	0.3	126
CARESS-HF	Cr change (mg/dl)	0.53	0.5	80	0.3	98
Athena-HF	Cr change (mg/dl)	0.3	0.5	80	0.3	32
AVERAGE		0.476	0.5	80	0.3	**80**

Based on data from the above clinical trials which evaluated diuretic strategies in decompensated heart failure, we believe that 85 patients will give us 80% power to detect a 2.2 kg (5 lb) difference in weight and a 0.3mg/dl difference in serum creatinine levels at 96 hours.

5.2 Safety Endpoints

1. Initiation of dialysis or RRT.
2. Need for mechanical intubation or new initiation of positive pressure ventilation.
3. Need for IV vasoactive medications
4. ICU transfer
5. Death

5.4 Analytical Plan
See above

6.0 Safety Reporting

6.1 Adverse Events

An adverse event (AE) is any event, side effect, or untoward medical occurrence in a subject in a clinical trial whether or not it is considered to have a causal relationship to the study drug, device or procedure. An AE can therefore be any unfavorable and unintended sign, symptom, laboratory findings outside of normal range, physical examination finding, or disease temporally associated with the use of the study drug, device or procedure whether or not the event is considered related to the study drug, device or procedure. Tracking of adverse events will be done after randomization.

6.1.2 Serious Adverse Events

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is defined as any adverse event occurring that results in any of the following outcomes:

1) Death
2) ICU transfer
3) Respiratory failure
4) Initiation of renal replacement therapy
5) A persistent or significant disability or incapacity

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 appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.1.3 Documenting and Reporting of Adverse Events

Adverse events reporting will begin from the time the patient is randomized until the subject has completed the final study visit.

For the purposes of this study, adverse events that are in the opinion of the investigator clinically significant will be tracked including hyperkalemia, acute kidney injury, and hypotension requiring cessation of drug.

7.0 Administration

7.1 Maintaining the Security of Patient Data

Data will be stored on a REDCAP database. There is an instance of this database maintained as a resource at Cleveland Clinic. REDCAP is maintained by Cleveland Clinic but is accessible on and off campus in secure fashion. The data will be entered into the database after completion of study procedures. This data will be entered into REDCap by the investigators. The study principle investigator, co-investigators, statistician(s) and study monitoring staff are the only individuals that will have permission to access the data, and will be able to do so by request.

7.1.1 Data Collection

Demographic and clinical variables will be extracted from the electronic medical record. Adverse event information will be provided by the patient and verified by medical record review/record request if from outside the facility. A RedCap database will be built with eCRFs used to collect study information. Patients will be identified in the EDC by their RedCap assigned record ID. Database maintenance will be delegated to members of the study team.

Variables to be collected: For complete data collection, a REDCAP data-dictionary is included in IRB submission

Hospitalization:

1. MRN
2. Sex
3. Age
4. Race/Ethnicity
5. Date of admission
6. Date of discharge
7. Date of Randomization and Medication administration
8. Length of Hospital Stay (in days)
9. Labs: CMP, CBC
10. Imaging: EF by echo, Other echo parameters for valve function, RV function, and chamber dilation
11. NT-Pro-BNP at admission and discharge and 30 day followup
12. Heart Failure Classification (Ischemic, Non-Ischemic)
13. Non-invasive blood pressure (SBP/DBP MAP), Fluid balance, Urine output/Fluid intake at Admission, Day 1-5, discharge and followup
14. Medical history
15. Concomitant Medications
16. Use of temporary mechanical support, IV vasoactive medications
17. Adverse events (hyperkalemia, angioedema, acute kidney injury, sustained hypotension requiring cessation of drug)
18. Diet Order

Any HF Follow-Up Visit Within 4 Weeks (as part of routine clinical care)

1. NT-proBNP
2. CMP
3. Current Medications
4. Non-invasive blood pressure (SBP/DSP), weight
5. Concomitant Medications
6. Adverse Events (hyperkalemia, angioedema, acute kidney injury, sustained hypotension requiring cessation of drug)

30+ day phone call

1. 30 day readmission

2. Adverse Events

7.3 Informed Consent

Patients will be asked to consider participating in this study when they are being treated with intravenous furosemide infusion. During the consent discussion, prospective patients will be provided with a copy of the informed consent to read before making a decision. Once all patient questions have been answered, patients will be asked to sign an informed consent document prior to agreeing to enroll in the study.

7.3 Investigator Assurances

The PI is responsible for reviewing and authorizing all requests from others to obtain data from this database. Any additional users, known as Sub-Investigators, must submit to the PI a written request along with a signed Sub-Investigator Statement of Assurance. The PI is responsible for authorizing the release of data to Sub-Investigators and tracking these uses with a brief description of their activity.
The PI confirms no data from this database will be released without a written request from the sub-investigator and that the data provided will not contain identifiers unless consent from subjects has been obtained.

8.0 Monitoring Plan

- Review of all original signed ICFs (informed consent forms) for completeness and accuracy, including review of the version signed.
- Verify adequate documentation of the informed consent process and perform 100% SDV (source data verification) of the same.
- Source verify data entered into RedCap
- Verify compliance with current regulations and GCP (Good Clinical Practice) guidelines.
- Review all inclusion and exclusion criteria, SAEs and endpoints for 100% subjects.

8.1 Safety Monitoring

An internal Data Safety Monitoring committee will be comprised of Cleveland Clinic physicians who are not participating in the study as they do not rotate in inpatient clinical services or only practice in the intensive care settings (outside of the study cohort): Rory Hachamovitch MD, Chair of the DSM committee, and members including Michael Militello PharmD, and Paul Cremer, MD MPH. Participant safety will be protected and monitored during the entire study period during their hospital admission and by 90-day phone calls to the patients. There will be a biweekly review of the safety and tolerability outcome measures by the study coordinator. These safety and tolerability outcomes and any other adverse events that occur will be recorded in the patient's electronic medical record. Any adverse events that occur will be investigated to identify possible etiology and relationship to study procedures and reported to the IRB and the DSM committee within 10 working days of their discovery, with the exception of any deaths, which will be reported within 5 working days of their discovery.

Data Base-Case Report Form Completion

Only site staff listed on the Signature and Delegation Log are authorized to enter data or make corrections to CRFs/CRF review will include review for legibility, completeness and consistency with source documents. CRFs should be completed on all subjects that have been randomized.

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