Heart Failure Network

Protocol
Renal Optimization Strategies Evaluation in Acute Heart Failure

ROSE-AHF

Compiled by:

The Heart Failure Network Research Group

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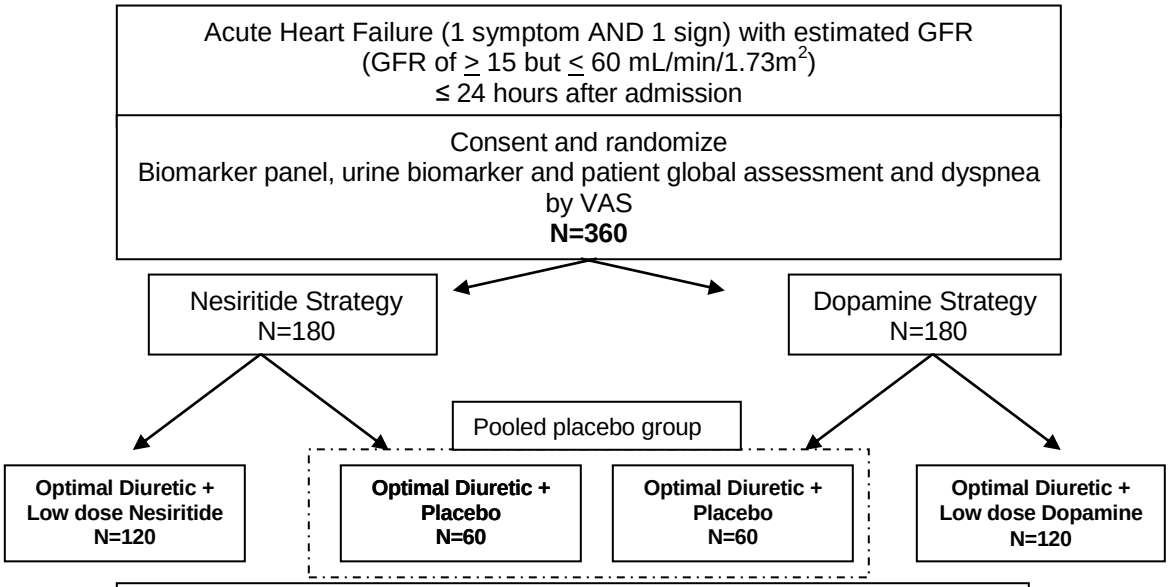
1. EXECUTIVE SUMMARY

Title:	Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE –AHF)
Indication:	Acute heart failure
Location:	Regional clinical centers and associated hospitals in the United States and Canada.
Rationale	Novel adjuvant therapies for use in AHF (adenosine antagonists, vasopressin antagonists, renal blood flow enhancing devices) are being investigated in industry funded trials, yet currently available strategies have not been investigated such as: 1) low dose Dopamine and 2) low dose Nesiritide
Objectives:	To evaluate the safety and efficacy of adjuvant renal-protective therapies with 1) low dose Dopamine and 2) low dose Nesiritide, added to optimal diuretic dosing
Study Design:	Approximately 360 patient double blinded placebo-controlled, multicenter clinical trial with randomization to three treatment arms.
Treatment Regimens:	1. Optimal diuretic dosing + placebo 2. Optimal diuretic dosing + low dose dopamine 3. Optimal diuretic dosing + low dose nesiritide
Primary Endpoints:	**Safety:** Change in serum cystatin C from randomization to 72 hours **Efficacy:** Cumulative urinary volume (UV; +/-indwelling urinary catheter) at 72 hr
Secondary Endpoints:	• Change in serum creatinine from randomization to 72 hr • Cumulative urinary sodium excretion (UNaV) at 72 hr • Patient global well being assessment by Visual Analog Scale (VAS) area under the curve (AUC) over 72 hr • Dyspnea assessment by Visual Analog Scale (VAS) AUC over 72 hr • Change in weight from randomization to 72 hr • Change from randomization in blood urea nitrogen (BUN)/serum cystatin C ratio at 72 hr • Development of cardio-renal syndrome during 72 hrs • Persistent or worsening heart failure within 72 hrs • Treatment Failure within 72 hrs
Tertiary Endpoints:	• Change in serum cystatin C from randomization to 24 and 48 hr • Cumulative UV at 24 and 48 hr • Cumulative urinary sodium excretion (UNaV) at 24 and 48 hr • Patient global well being assessment by Visual Analog Scale (VAS) area under the curve (AUC) over 24 and 48 hr • Dyspnea assessment by Visual Analog Scale (VAS) AUC over 24 and 48 hr • Change in serum creatinine from randomization to 24 and 48 hr • Changes from randomization in bivariate vector of serum cystatin C and cumulative UV at 24 and 72 hr • Changes from randomization in bivariate vector of creatinine and weight at 24 and 72 hrs • Time from randomization to discharge from index hospitalization • Total days alive and free from heart failure hospitalization during the 60 days following randomization • Changes in circulating biomarkers from randomization to 72 hours • Urinary biomarkers (baseline, 72 hours, Day 7 or discharge if earlier) • Mortality during the six months following enrollment

1.1 Study Flow Chart



Acute Heart Failure (1 symptom AND 1 sign) with estimated GFR (GFR of ≥ 15 but ≤ 60 mL/min/1.73m^2)
≤ 24 hours after admission

Consent and randomize
Biomarker panel, urine biomarker and patient global assessment and dyspnea by VAS
N=360

Day 1
24 hr study labs (Cr, BUN, Na), biomarker panel, urine biomarkers and urine collection for UNaV (24 hour urine collection)
Patient global assessment and dyspnea by VAS

At 24 hrs, continue renal study drug (placebo, nesiritide or dopamine)
a. Decrease diuretic dose
b. Increase diuretic dose
c. Change to oral diuretic

Day 2
48 hr study labs (Cr, BUN, Na), biomarker panel, urine biomarkers and urine collection for UNaV (24 hour urine collection)

At 48 hrs, continue renal study drug (placebo, nesiritide or dopamine)
d. Decrease diuretic dose
e. Increase diuretic dose
f. Change to oral diuretic

Day 3
72 hr Study Labs (Cr, BUN, Na), biomarker panel, urine biomarkers, and urine collection for UNaV (24 hour urine collection)

At 72 hours: Open Label Therapy

At Day 7 or discharge if earlier:
Study Labs (Cr, BUN, Na), biomarker panel, urine biomarkers

At 60 day:
Phone Visit to assess vital status and potential rehospitalizations

Mortality data will be collected at 6 months via phone call

2. HYPOTHESES AND OBJECTIVES

2.1 Primary Hypotheses:

- As compared to placebo, low dose dopamine will enhance renal function as measured by change in serum cystatin C and diuretic response to optimal diuretic dosing in patients with AHF and renal dysfunction.

- As compared to placebo, low dose nesiritide will enhance renal function as measured by change in serum cystatin C and diuretic response to optimal diuretic dosing in patients with AHF and renal dysfunction.

2.2 Secondary Objectives

Other secondary objectives of this protocol will be to examine the effect of the above treatments on:

- Change in serum creatinine from randomization to 72 hr
- Cumulative urinary sodium excretion (UNaV) at 72 hr
- Patient global well being assessment by Visual Analog Scale (VAS) AUC over 72 hr
- Dyspnea assessment by Visual Analog Scale (VAS) AUC over 72 hr
- Change in weight from randomization to 72 hr
- Change from randomization in blood urea nitrogen (BUN) / serum cystatin C ratio at 72 hr
- Persistent or worsening heart failure within 72 hrs
- Development of cardio-renal syndrome during 72 hrs
- Treatment failure within 72 hrs

2.3 Tertiary Objectives

Tertiary objectives of the study will be to examine the effect of the above treatments on:

- Change in serum cystatin C from randomization to 24 and 48 hr
- Cumulative UV at 24 and 48 hr
- Cumulative urinary sodium excretion (UNaV) at 24 and 48 hr
- Patient global well being assessment by Visual Analog Scale (VAS) area under the curve (AUC) over 24 and 48 hr
- Dyspnea assessment by Visual Analog Scale (VAS) AUC over 24 and 48 hr
- Change in serum creatinine from randomization to 24 and 48 hr
- Change from randomization in bivariate vector of serum cystatin C and cumulative UV at 24 and 72 hr
- Change from randomization in bivariate vector of creatinine and weight at 24 and 72 hr
- Time from randomization to discharge from index hospitalization
- Total days alive and free from hospitalization for heart failure during the 60 days following randomization
- Changes in circulating biomarkers from randomization to 72 hours

- Urinary biomarkers (baseline, 72 hours, day 7 or discharge if earlier)
- Mortality during the six months following enrollment

3. BACKGROUND AND SIGNIFICANCE

Acute heart failure (AHF) is the most common cause of hospital admission in patients over age 65, accounting for 1,000,000 admissions, over 6 million hospital days, and $12 billion in costs annually.[1] The prognosis of patients admitted with AHF is dismal, with a 20-30% readmission rate and a 20-30% mortality rate within six months after admission.[2]

Renal dysfunction and AHF

Recent studies have established the prognostic importance of renal function in patients with heart failure. A multivariate analysis of the patients in the second prospective randomized study of Ibopamine on mortality and efficacy (PRIME) by Hillege et al[3] demonstrated that estimated glomerular filtration rate (GFR) is the most powerful predictor of mortality, exceeding functional status and ejection fraction (EF). Furthermore, a retrospective analysis of the studies in left ventricular dysfunction (SOLVD) treatment trial and SOLVD prevention trial by Dries et al[4] confirmed that estimated GFR is an important determinant of survival. Importantly, Dries et. al. demonstrated that a mild reduction of estimated GFR had an impact on survival even in patients who were asymptomatic. In patients who are hospitalized with decompensated CHF, worsening renal function is also associated with worse outcome as reported in separate studies by Gottlieb et al[5] and Smith et al[6]. In both studies, an increase in plasma creatinine of 0.2-0.3 mg/dL predicted worse outcomes.

Various studies have estimated that 25-30% of patients hospitalized for decompensated CHF have worsening of renal function leading to prolonged hospitalization, increased morbidity and mortality. The acute decompensated heart failure national registry (ADHERE) database enrolled 160,000 non-selected patients admitted to the 281 participating hospitals for acute decompensated heart failure. In this registry, more than 70% of the patients had moderate renal dysfunction as defined by estimated GFR of less than 60 ml/min m^2. Using a classification and regression tree analysis to predict outcomes in the ADHERE database, inpatient mortality risk can be predicted from serum creatinine, blood urea nitrogen (BUN) and systolic blood pressure. In this analysis, patients with BUN $\geq$ 43 mg/dL, systolic blood pressure of < 115 mmHg and serum creatinine of $\geq$ 2.75 mg/dL had a 10 fold increase in inpatient mortality.[7]

Renal Adjuvant Therapies

Although there are no FDA approved renal adjuvant therapies for AHF, several novel adjuvant therapies for use in AHF (adenosine antagonists, vasopressin antagonists, renal blood flow enhancing devices) are being investigated in randomized clinical trials. Additionally, there are currently available strategies, with the potential for improving renal function in AHF such as low dose dopamine and low dose nesiritide. However, these strategies have not been investigated.

Cystatin C

Cystatin C is a 13 kDa protein and member of the competitive lysosomal cysteine protease inhibitors. Cystatin C is freely filtered by the glomerulus and has advantages over creatinine when estimating GFR in that its production is not dependent on muscle mass.

In comparison, serum creatinine, the primary tool for evaluation of kidney function in clinical practice, can be affected by extra-renal factors including age, body weight, nutritional status, ethnicity, and gender. Hence, cystatin C measurement is a more accurate estimate of GFR than creatinine-based equations. Importantly, high serum cystatin C is an important prognostic marker. [22; 23]

4. PRELIMINARY STUDIES

4.1 Low dose dopamine

Dopamine is a catecholamine with dose-dependent effects on the systemic and renal vasculature. Dopamine has been shown to exhibit a graded pharmacological response, with a dose-dependent predominant activation of dopaminergic receptors, β-receptors, and α-receptors. Generally, at doses ≤3 µg/Kg/min, dopamine has been found to activate dopamine A1 receptors, which cause vasodilation of the renal arteries and other vascular beds, including mesenteric, coronary, and cerebral beds. In addition, there is stimulation of dopamine A2 receptors that leads to inhibition of norepinephrine release from sympathetic nerve endings. Activation of dopamine A1 and A2 receptors also result in a decline in systemic vascular resistance and an increase in RBF. Dopamine infused at approximately 3 to 5 µg/Kg/min activates β1- and β2- adrenergic receptors, conferring a positive inotropic effect that is responsible for the increase in CO. At a dose >5 µg/Kg/min, dopamine has been reported to exert clinically relevant activation of α1- and α2-adrenergic receptors, which results in arterial vasoconstriction. In healthy participants, low-dose dopamine increases renal blood flow and promotes natriuresis through stimulation of renal A1 and A2 receptors and thus may protect the kidney from acute tubular necrosis.[8]

The concept of low-dose or renal-dose dopamine has persisted since the first clinical description of its use in patients with congestive heart failure.[9] In 2005, Friedrich et. al conducted a systematic review and meta-analysis by using a comprehensive search strategy to determine the effects of low dose dopamine on a broad range of clinical and renal physiologic outcomes and adverse events. 61 trials that randomly assigned 3359 patients were identified. Meta-analyses using random-effects models showed no effect of low-dose dopamine on mortality (relative risk, 0.96 [95% CI, 0.78 to 1.19]), need for renal replacement therapy (relative risk, 0.93 [CI, 0.76 to 1.15]), or adverse events (relative risk, 1.13 [CI, 0.90 to 1.41]). Overall, low-dose dopamine increased urine output by 24% (CI, 14% to 35%) on day 1. Statistically significant improvements in serum creatinine level (4% relative decrease [CI, 1% to 7%]) and measured estimated GFR (6% relative increase [CI, 1% to 11%]) on day 1 were clinically insignificant. There were no significant changes on days 2 and 3 of therapy. The authors concluded that low-dose dopamine offers transient improvements in renal physiology, but no good evidence showing that it offers important clinical benefits to patients with or at risk for acute renal failure.[10]

However, a recent study by Elkyam et al, indicated that low dose dopamine is associated with an increase in renal blood flow in patients with heart failure. (Figure 1) This effect is due to dilation of both the large conductance and small resistance renal blood vessels. They concluded that further evaluation of the efficacy and safety of dopamine for improvement of renal function in hospitalized patients with heart failure is warranted.[11]

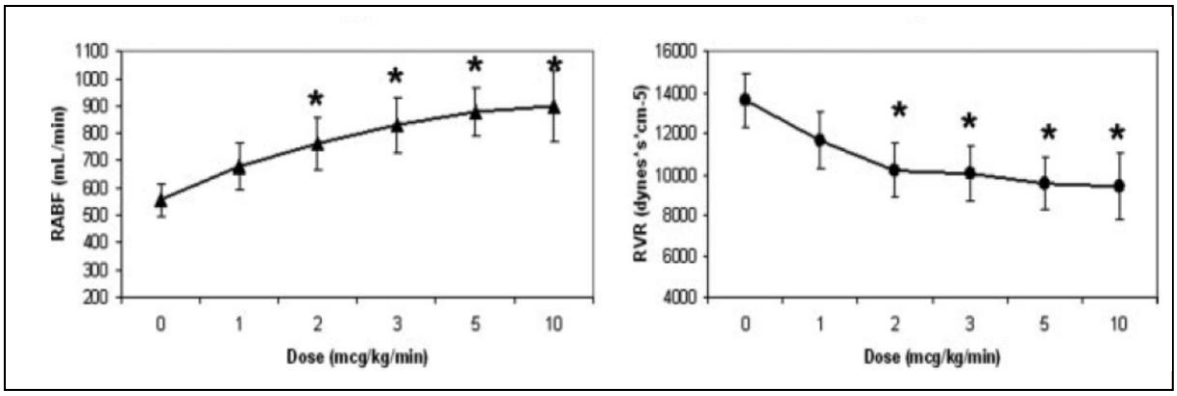


Figure 1. Renal artery blood flow (RABF) and renal vascular resistance (RVR) in response to dopamine infusion. (Elkyam et al [11])

Preliminary findings from the **Dopamine in Acute Decompensated Heart Failure** (DAD-HF) trial were presented at the **Heart Failure Society of America 2009 Scientific Meeting**.

The double-blind DAD-HF trial is randomizing ADHF patients to receive higher-dose IV furosemide (40 mg bolus followed by 20 mg/hour for 8 hours), or lower-dose furosemide (40 mg bolus followed by 5 mg/hour for eight hours) plus dopamine (5 µg/kg per min for eight hours). Eligibility for the study, underway at seven centers in Greece, Germany, and the US, include a diagnosis of ADHF marked by severe recent-onset dyspnea, congestion, admission arterial blood oxygen <90%, and plasma B-type natriuretic peptide (BNP) levels >400 pg/mL, all in the absence of severe renal failure (serum creatinine >200 mol/L or GFR <30 mL/min per 1.73 m^2) or a systolic blood pressure <90 mm Hg. In the preliminary analysis of the first 50 patients randomized at the centers in Greece, as reported by Triposkiadis, the two patient groups were statistically comparable with respect to the prevalence of hypertension, atrial fibrillation, diabetes, chronic lung disease, and the use of ACE inhibitors or angiotensin-receptor blockers, beta blockers, aldosterone antagonists, digoxin, and statins.

The 25 who received full-dose furosemide and the 25 who received the two drugs a low dosage produced statistically comparable volumes of urine.

Cumulative urine output during eight-hour infusion of high-dose furosemide vs low-dose furosemide plus low-dose dopamine*

Hour of infusion	High-dose furosemide (mL), n=25	Low-dose furosemide/dopamine (mL), n=25
2	647	847
4	948	1272
6	1223	1510
8	2214	1888

*All differences between the groups nonsignificant.

A 0.6 mEq/mL drop in serum potassium levels from baseline to 24 hours in the high-dose group was significant (p=0.012), and a 0.3 mEq/mL decrease in the low-dose group was not (p=0.09). Hypokalemia (serum potassium <3.5 mEq/L) developed in two patients who received high-dose furosemide but in none who received low-dose furosemide (p=0.013)

The low-dose regimen was associated with significantly less renal damage by several measures. In the high-dose group, serum creatinine rose significantly from 1.32 mg/dL at baseline to 1.48 mg/dL at 24 hours (p<0.01), but it was more or less stable in the low-dose group, at 1.34 and 1.30 mg/dL, respectively. Blood urea nitrogen (BUN) increased from 43.2 mg/dL at baseline to 51.2 mg/dL at 24 hours (p<0.01) in the high-dose group, but nonsignificantly went from 45.9 to 43.8 mg/dL in the low-dose group.

Measures of worsening renal function at 24 hours for high-dose furosemide vs low-dose furosemide plus low-dose dopamine

Measure	High-dose furosemide (%)	Low-dose furosemide/dopamine (%)	P
sCr, >0.3 mg/dL increase	36	4	0.005
sCr, >25% increase	36	4	0.004
eGFR, >10% decrease	64	28	0.011

sCr=serum creatinine; eGFR=estimated glomerular filtration rate.

Dyspnea improved significantly and to similar degrees in both groups. There were no significant differences in hospital length of stay or clinical outcomes out to 60 days (the study is looking at mortality and all-cause hospitalization at one year as the primary end point and at 60 days as a secondary end point.

4.2 Low dose nesiritide

Controversies regarding the renal effects of nesiritide in AHF:

Brain natriuretic peptide (BNP) is a cardiac peptide with vasodilating, renin inhibiting, natriuretic and diuretic properties.[12] Human recombinant BNP (nesiritide) has been approved by the FDA for the management of acute decompensated heart failure (CHF). [13] The standard recommended dose of nesiritide is a bolus of 2 μg/kg followed by infusion of 0.01 μg/kg/min. While preclinical studies have demonstrated the renal enhancing effects of systemic intravenous (IV) administration of BNP, the clinical trials which led to the FDA approval of BNP for the management of AHF have been conflicting with regards to the renal enhancing properties of BNP. A recent study by Wang et. al. indicates that the standard recommended dose of nesiritide does not improve renal

function in patients treated for acute decompensated CHF. [14] Furthermore, a metanalysis of the clinical trials suggested that nesiritide might even be detrimental to renal function in patients with acute decompensated CHF.[15] One explanation for the discrepancy between the pre-clinical and clinical data could be in part due to the fact that the dose used in these clinical studies resulted in significant decreases in blood pressure (BP) and hence renal perfusion pressure attenuating the renal enhancing effects. [16]

In the BNP-CARDS study, 75 consecutive patients with acute decompensated heart failure and baseline renal dysfunction were enrolled in this randomized, double-blind, placebo-controlled clinical trial. Subjects were randomized to receive nesiritide (0.01 µg/kg/min with or without a 2-µg/kg bolus) or placebo (5% dextrose in water) for 48 hr in addition to their usual care. Predefined primary end points of the trial were a rise in serum creatinine by ≥20% and change in serum creatinine. The groups had similar baseline age (74.9 vs. 75.5 years, respectively), blood pressure (123/64 vs. 125/64 mm Hg) and serum creatinine (1.82 vs. 1.86 mg/dl). There were no significant differences in the incidence of a 20% creatinine rise (23% vs. 25%) or in the change in serum creatinine (−0.05 vs. +0.05 mg/dl). There were no significant differences in the secondary end points of change in weight (−2.19 vs. −1.58 kg), intravenous furosemide (125 vs. 107 mg), discontinuation of the infusion due to hypotension (13% vs. 6%), or 30-day death/hospital readmission (33% vs. 25%). The authors concluded that nesiritide had no impact on renal function in patients with acute decompensated heart failure.[17]

In a Mayo Clinic study, 71 AHF patients with underlying renal dysfunction who were admitted with volume overload were randomized to standard therapy without or with nesiritide (2mcg/kg bolus; 0.01 mcg/kg/min for 48 hours). In all patients, diuretics were administered according to a standardized dosing algorithm. Nesiritide patients had smaller increases in creatinine ($p=0.048$) and blood urea nitrogen ($p=0.02$), but greater blood pressure reduction ($p<0.01$). Nesiritide did not enhance diuretic responsiveness ($p=0.57$) but increased 3'5' cyclic guanosine monophosphate and decreased endothelin more ($p<0.05$ for both). There were no differences in the change in atrial natriuretic peptide, N-terminal proBNP, plasma renin activity, angiotensin II, and aldosterone between groups. The authors concluded that when used as adjuvant "renal protective" therapy in AHF patients with renal dysfunction, the clinically recommended dose of nesiritide reduced blood pressure, did not appear to worsen renal function, and suppressed endothelin but did not enhance diuretic responsiveness nor prevent activation of the renin angiotensin aldosterone system.[18]

Riter et al published a case control clinical study of 15 patients that were treated with low dose nesiritide (13 received 0.005 μg/kg/min and 2 received 0.0025 μg/kg/min both without bolus). Using a retrospective case control design, they compared the low dose group to a group of patients (n=12) who did not receive nesiritide, matching groups for ejection fraction (EF) and baseline estimated GFR. Patients who received low dose nesiritide had lower baseline systolic BP compared to those that did not receive nesiritide (101±3 vs 115±6* mmHg). Low dose nesiritide was well tolerated without a significant decrease in systolic BP (from 101±3 to 97 ±3 mmHg. $P>0.05$) while systolic BP decreased significantly in the group not treated with nesiritide (from 115±6 to 106±6 mmHg, $P<0.05$). Most importantly, patients in the low dose nesiritide group had improvement in renal

function as measured by a decrease in plasma Cr (from 2.6±0.3 to 2.1±0.2 mg/dl, P<0.05) (Figure 2.) and BUN (from 78±9 to 57±8 mg/dl, P<0.05) with increases in estimated estimated GFR (from 27±3 to 35 ±4 ml/min/1/73 m^2, P<0.05). Renal function did not improve in the no nesiritide group. Patients in the low dose nesiritide group required less furosemide dose during the entire hospitalization as compared to the no nesiritide group (136±39 vs 345±115* mg of furosemide) while achieving similar diuresis and change in weight during hospitalization. [19]

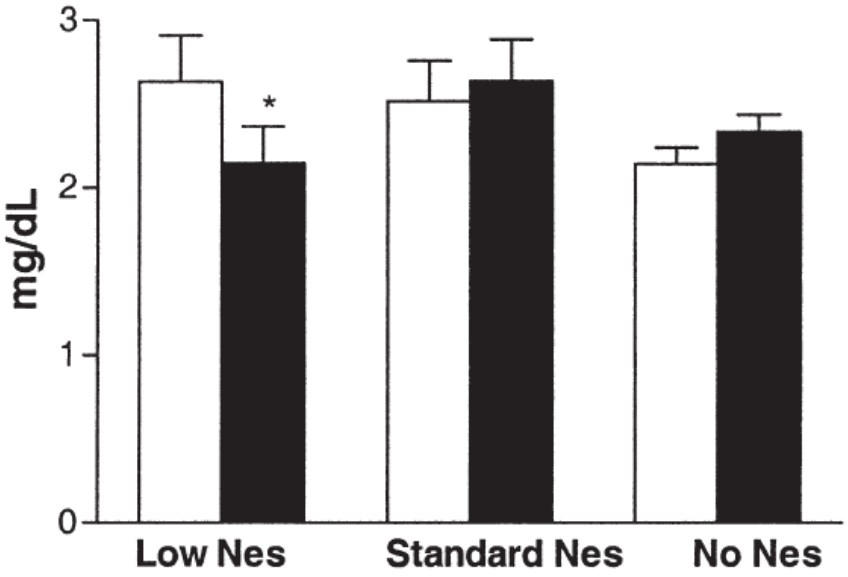


Figure 2. Plasma creatinine at baseline (open bars) and after therapy (solid bars) with low-dose nesiritide (Low Nes), standard-dose nesiritide (Standard Nes) and no-nesiritide (No Nes) groups. *p < 0.05 versus baseline. (Riter et.al.[19])

Chen et al, performed a double-blinded placebo-controlled proof of concept pilot study in patients (n=40) with renal insufficiency preoperatively (defined as an estimated GFR of < 60 mL/min determined by the Cockroft-Gault formula), undergoing cardiopulmonary bypass cardiac surgery. The patients were randomized to placebo (n=20) or IV low dose nesiritide (n=20; 0.005 µg/Kg/min) for 24 hours started after the induction of anesthesia and before cardiopulmonary bypass. Patients in the nesiritide group had an increase of plasma B-type natriuretic peptide and its second messenger cGMP at the end of the 24-hour infusion. These changes were not observed in the placebo group. There was a significant activation of aldosterone in the placebo group at the end of the 24-hour infusion, but not in the nesiritide group. Patients in the nesiritide group also had a decrease in plasma cystatin levels at the end of the 24-hour infusion. (Figure 3) At 48 and 72 hours, there was a decrease in estimated GFR and an increase in plasma cystatin C as compared with end of the 24-hour infusion in the placebo group. In contrast, renal function was preserved in the nesiritide group with no significant change in estimated GFR and a trend for plasma cystatin to increase as compared with end of the 24-hour infusion. This proof of concept pilot study supports the conclusion that perioperative administration of low dose nesiritide is biologically active and decreases plasma cystatin in patients with renal insufficiency undergoing cardiopulmonary bypass

cardiac surgery. Further studies are warranted to determine whether these physiological observations can be translated into improved clinical outcomes.[20]

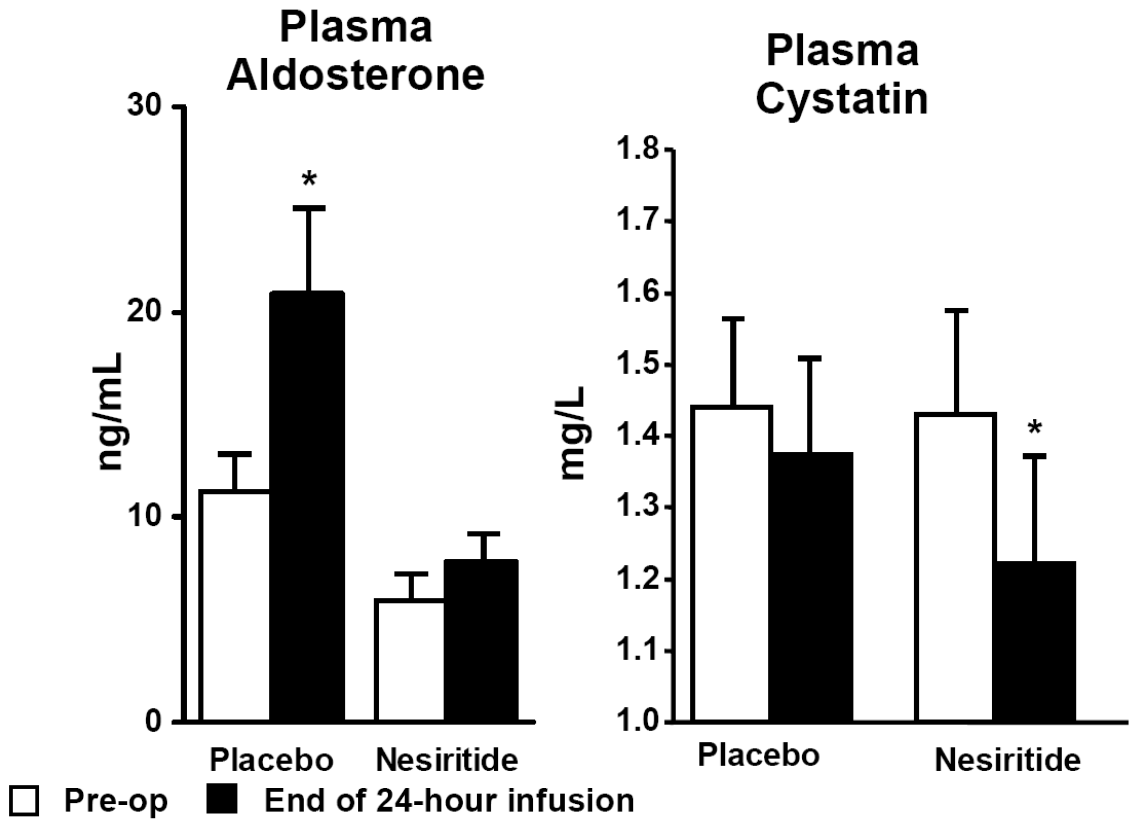


Figure 3. Plasma aldosterone and plasma Cystatin levels pre-operative (Pre-op) and at the end of the 24-hour infusion period. * P<0.05 versus Pre-op. (Chen et.al. [20])

5. BASIC STUDY DESIGN

This study is a randomized, double blind, placebo controlled, multi-center clinical trial of patients with signs and symptoms consistent with AHF within 24 hours of hospital admission. A total of approximately 360 patients will be enrolled in the trial.

Patients will be randomized to one of 3 treatment regimens (120 patients / treatment regime):

1. Optimal diuretic dosing + placebo
2. Optimal diuretic dosing + low dose dopamine
3. Optimal diuretic dosing + low dose nesiritide

Central venous line or PICC line or standard peripheral IV catheter placed in the antecubital fossa, depending on local hospital requirements, will be placed in the patients randomized to the Dopamine strategy group. Standard peripheral IV catheter will be placed in the patients randomized to the Nesiritide strategy group

TThere will be an initial open 1:1 randomization to a Nesiritide Strategy group or a Dopamine Strategy group. Patients in the Dopamine Strategy group will subsequently be randomized to low dose dopamine or placebo in a 2 to 1 blinded fashion. Likewise patients in the Nesiritide Strategy group will be randomized to low dose nesiritide or placebo in a 2 to 1 blinded fashion. All patients will receive open-label diuretic treatment.

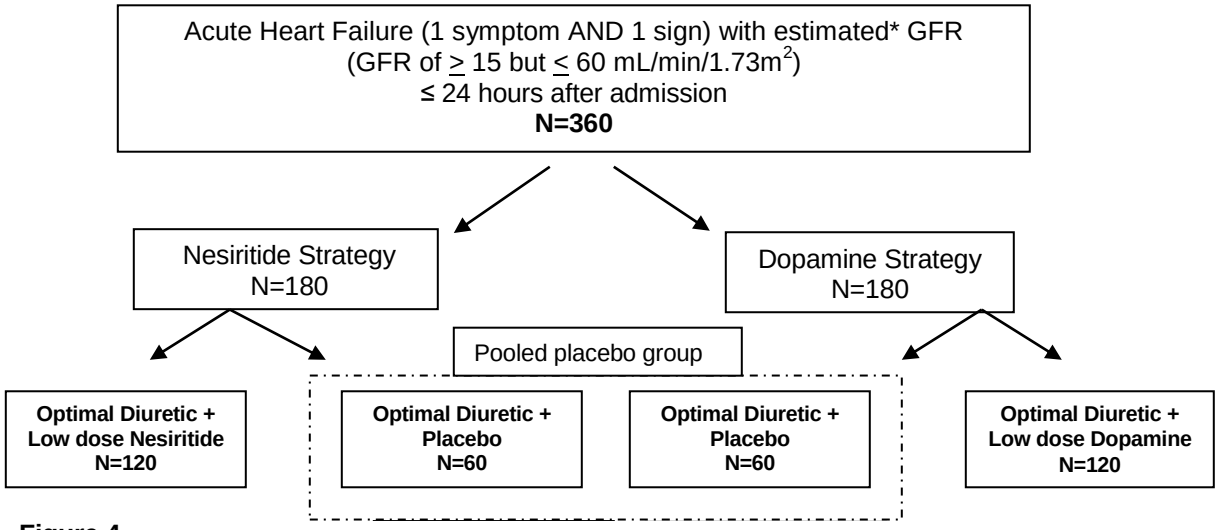


Figure 4

For testing the primary hypotheses outlined in Section 2.1, the placebo patients will be pooled, so that patients randomized to receive dopamine will be compared with the pooled placebo group, and similarly, patients randomized to receive nesiritide will be compared to the pooled placebo group.

The study treatment regimen will be administered for *a total duration of* 72 hours, unless clinical reasons require discontinuation earlier.

The investigator may modify the diuretic dose at 24 and / or 48 hours. The primary assessment for both efficacy and safety will occur at 72 hours after randomization. **After** the primary assessment at 72 hours, all treatment will be open label at the treating physician's discretion.

The primary safety endpoint will be change in serum cystatin C from randomization to 72 hours, based on a standardized, blinded core lab assessment. The primary endpoint for efficacy will be cumulative urinary volume (UV; indwelling urinary catheter) at 72 hours.

Patients will be followed daily during hospitalization for assessment of serious adverse events.

All patients will have a telephone visit at day 60 to assess vital status and any potential rehospitalizations. Mortality data will be collected at 6 months via telephone call.

6. STUDY POPULATION AND ELIGIBILITY CRITERIA

6.1 Inclusion Criteria

- A diagnosis of heart failure as defined by the presence of at least 1 symptom (dyspnea, orthopnea, or edema) AND 1 sign (rales on auscultation, peripheral edema, ascites, pulmonary vascular congestion on chest radiography)
- Prior clinical diagnosis of heart failure Must be identified within 24 hours of hospital admission (24 hour clock begins when the admission orders are placed)
- Estimated GFR of $\geq$ 15 but $\leq$ 60 mL/min/1.73m^2 determined by the MDRD equation
- Male or female patient ≥18 years old
- Willingness to provide informed consent
- Ability to have a PICC or central line placed (if needed) within 12 hours of randomization and study drug infusion started
- Anticipated hospitalization of at least 72 hours

6.2 Exclusion Criteria

- Received IV vasoactive treatment or ultra-filtration therapy for heart failure since initial presentation
- Anticipated need for IV vasoactive treatment or ultra-filtration for heart failure during this hospitalization
- Systolic BP <90 mmHg
- Hemoglobin (Hgb) < 9 g/dl
- Renal replacement therapy
- History of renal artery stenosis $\geq$ 50%
- Hemodynamically significant arrhythmias including ventricular tachycardia or defibrillator shock within 4 weeks
- Acute coronary syndrome within 4 weeks as defined by electrocardiographic (ECG) ST-segment depression or prominent T-wave inversion and/or positive biomarkers of necrosis (e.g., troponin) in the absence of ST-segment elevation and in an appropriate clinical setting (chest discomfort or anginal equivalent)
- Active myocarditis
- Hypertrophic obstructive cardiomyopathy
- Greater than moderate stenotic valvular disease
- Restrictive or constrictive cardiomyopathy
- Complex congenital heart disease
- Constrictive pericarditis
- Non-cardiac pulmonary edema
- Clinical evidence of digoxin toxicity
- Need for mechanical hemodynamic support
- Sepsis
- Terminal illness (other than HF) with expected survival of less than 1 year

- Previous adverse reaction to the study drugs
- Use of IV iodinated radiocontrast material in last 72 hours or planned during hospitalization
- Enrollment or planned enrollment in another randomized clinical trial during this hospitalization
- Inability to comply with planned study procedures
- Pregnancy or nursing mothers

7. TREATMENT INTERVENTIONS

This study will be a placebo controlled study. Treatment interventions will be described in sections 7.1 – 7.3.

7.1 Randomization to 24 hours

Patients will be randomized as described above to one of 3 treatment combinations:

- Optimal diuretic dosing + placebo
- Optimal diuretic dosing + low dose dopamine
- Optimal diuretic dosing + low dose nesiritide

All patients will be started on a 2 liter per day fluid restriction and a 2 gm per day sodium diet. Decisions regarding the use of standard heart failure medications such as ACE inhibitors, beta blockers and digoxin will be left to the discretion of the treating physicians.

Vascular access

Central venous line or PICC line or standard peripheral IV catheter placed in the antecubital fossa, depending on local hospital requirements, will be placed in the patients randomized to the Dopamine strategy group. Standard peripheral IV catheter will be placed in the patients randomized to the Nesiritide strategy group

Urinary Catheter

Use of an indwelling urinary catheter will be encouraged in all patients but a patient may decline and remain in study.

Study Drug Dose and Supplies

The study site investigational pharmacy will prepare low dose dopamine (2µg/kg/min), low dose nesiritide (0.005 µg/kg/min without bolus) or placebo (Dextose 5% water). Hospital stock should be used. Clinical personnel, investigators, and the patients will be blinded.

Based on the results from the recently completed DOSE study, the optimal dose of diuretic will be as follows:

IV furosemide (or equivalent) at a dose equivalent to 2.5 x the total daily *outpatient* oral furosemide (or furosemide equivalent) dose twice daily or equivalent dosing over a 24 hour period. The maximum total daily dose to be administered is 600 mg. and the

minimum total daily dose to be administered is 80 mg. (at frequency determined by the local physician) . For patients who have not been taking outpatient loop diuretics, they will receive 80 mg/day of IV furosemide (or equivalent) dose. If the outpatient dose has changed over the week prior to admission, the outpatient dose will be defined as that being utilized 7 days prior to randomization. For patients receiving outpatient loop diuretics other than furosemide, conversion to furosemide equivalents will be as follows:

1 mg torsemide = 2 mg furosemide

1 mg bumetanide = 40 mg furosemide

At 24 hrs, the treating physician can chose to change the diuretic dose

a. Continue current dose without change
b. Decrease diuretic dose
c. Increase diuretic dose
d. Change to oral diuretic

7.2 48 hours

At 48 hrs, the treating physician can chose to change the diuretic dose

a. Continue current dose without change
b. Decrease diuretic dose
c. Increase diuretic dose
d. Change to oral diuretic

7.3 72 hours and afterwards

After 72 hours, all patient care decisions will be at the discretion of the treating physician.

7.4 Patient Safety, Concomitant Therapies, and Rescue Therapy

Although investigators are encouraged to follow the assigned treatment strategy for the duration of the treatment period (72 hours), **in all cases the patient's safety based on the clinical judgment of the treating physician will take priority over the specific treatment assignment.**

Patients requiring other intravenous vasoactive medications for heart failure (inotropes, vasodilators, etc) will be excluded. Patients requiring such drugs for clinical reasons during the randomization period will meet the secondary endpoints of "worsening or persistent heart failure" and "treatment failure" (see endpoint section).

In the Nesiritide strategy group, if the subject develops significant hypotension as defined by systolic BP of <85 mmHg or light headedness, dizziness or visual symptoms, the infusion will be stopped. After 3 hours, if systolic BP is > 90 mmHg and there is resolution of symptoms, the IV infusion will be restarted at 0.0025 µg/kg/min (50% of the previous dose). If the systolic blood pressure after 3 hours is <90 mmHg or hypotension recurs, then the infusion will be terminated and this will be captured as "treatment failure"

In the Dopamine strategy group, if the subject develops tachycardia as defined by heart rate of >120 beats per min the infusion will be stopped. After 3 hours, if heart rate is < 120 beats per min, the IV infusion will be restarted at 1 µg/kg/min (50% of the previous dose). If the heart rate is >120 beats per min after 3 hours or if tachycardia recurs, then the infusion will be terminated and this will be captured as "treatment failure"

As this is a randomized trial comparing initial strategies, in either case the interpretation of the primary endpoints with regard to both efficacy and renal function will be on an "intention to treat" basis.

8. RECRUITMENT AND SCREENING PROCEDURES

8.1 Common Recruitment/Screening Procedures

All patients admitted to the participating Heart Failure Clinical Research Network centers with signs and symptoms suggestive of AHF will be screened by a study coordinator. Given the short time period after admission (≤ 24 hours) for inclusion in the study, it is anticipated that screening in the Emergency Department and screening more than once daily will be effective recruitment strategies. Patients meeting eligibility criteria will be approached regarding participation in this study.

8.2 Estimated Enrollment Period

This study will enroll 360 patients at 9 Regional Clinical Centers (RCCs) and associated satellite centers in the United States and Canada. It is projected that 18 patients per month will be enrolled (2 pts/RCC/month), for a total anticipated enrollment period of approximately 20 months.

8.3 Informed Consent Procedures

8.3.1 Informed Consent

All patients will have the purpose of the study, the study interventions and evaluations, and the potential risks and benefits of participation explained to them and their questions answered. If they consent to participation in this study, they will review and sign the informed consent form (ICF). A template for the ICF appears in Appendix D.

8.3.2 Confidentiality and HIPAA Requirements

All information collected on study participants will be stored in a confidential manner using procedures in place at each participating RCC and associated satellite centers. Only approved study personnel will have access to data collected as part of the ROSE Study. Study participants will be identified by a Subject ID # on all study documents. Data will be

transmitted to the DCC in a secure manner, and stored securely at the DCC using standard DCRI operating procedures.

8.3.3 Protections of Human Subjects

All research proposed in this application will be performed in accordance with applicable human subjects protection regulations.

A copy of the protocol, proposed informed consent form, other written information and any proposed advertising material must be presented to each site's Institutional Review Board (IRB) for written approval prior to enrollment of subjects. A copy of the written approval of the protocol and informed consent must be retained by the site in a study file. The investigator must submit and obtain approval from the IRB for subsequent protocol amendments and changes to the consent before implementing such changes. The investigator will notify the IRB of deviations from the protocol or serious adverse events occurring at the site. Each site must have IRB approval prior to enrolling any patients in the study.

8.3.4 Summary of the Risks and Benefits

As renal function is an important prognostic factor in patients with AHF, the patients randomized to the treatment groups may potentially benefit from the study. The risks of the study are:

- Low dose dopamine: **Common**: Chest pain, increase in blood pressure, fast or irregular heart rates, injection site reaction and hair follicles could stand erected

- Low dose nesiritide: **Common:** Low blood pressure nausea, dizziness; headache; insomnia; worsening of renal function at doses that are higher than what is used in this study. **Uncommon:** irregular heart rhythm, allergic reaction and increased risk of death
- The risks of blood drawing include bleeding at the puncture site, bruising and pain. These risks occur in a very small portion of the population. Patients with a hemoglobin < 9 g/dl will be excluded.
- The risk for PICC line placement include bruising, fainting, pain, swelling, scarring, bleeding, infection, a decrease in blood pressure, slowing of heartbeats, sweating and a feeling of weakness or lightheadedness. Uncommon risk includes infection at the site of the needle stick. These reactions generally do not cause any permanent harm. If a central line is needed, there may be additional risk of pneumothorax.
- This protocol may be hazardous to an unborn child. There is no medical information 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 or have been surgically sterilized or have a serum negative pregnancy test.

9. BASELINE EVALUATIONS AND RANDOMIZATION

A complete schedule of assessments throughout the study is given in Appendix A.

9.1 Randomization

After providing informed consent and signing the ICF, all study subjects will be randomized using procedures determined by the DCC to one of 3 treatment groups. **Patients will be randomized to the nesiritide or dopamine strategy in a 1:1 allocation ratio. Within each strategy, subjects will be randomized to active drug vs. placebo in a 2:1 allocation ratio.** A permuted block randomization method stratified by site will be used to ensure relatively equal distribution of subjects to each arm within each clinical site.

9.2 Baseline Assessments

At the time of randomization, all study subjects will undergo

- Directed history and physical examination, focused on signs and symptoms of congestion
- Vital signs (including O_2 saturation and weight)
- Concomitant cardiovascular medications
- Serum Cystatin C (core laboratory)
- Serum creatinine, BUN, and electrolytes (local laboratory)
- Patient Global Well being assessment (PGA) by VAS (see Appendix C)
- Dyspnea assessment by VAS (see Appendix C)
- Blood sample for biomarkers core laboratory
- Urine Biomarkers

10. FOLLOW UP EVALUATIONS

The 24-hour assessment should occur between 22 and 26 hours after randomization. The 48-hour assessment should occur between 46 and 50 hours after randomization. The 72-hour assessment should occur between 70 and 74 hours after randomization.

The protocol described assessments and urine collection times should be based on the randomization date and time as the anchor. Urine should be collected from randomization through 72 hours. In instances where the start of study drug is delayed 6 or more hours after randomization, an additional urine collection for assessing urinary sodium excretion is required. This urine collection would begin at the 72 hour from randomization point and end at the conclusion of the 72 hour study drug infusion point.

10.1 24, 48 and 72 hours

Between randomization and 72 hours, all study subjects will undergo the following assessments daily:

- Directed history and physical examination, focused on signs and symptoms of congestion
- Vital signs (including O_2 saturation and weight)

- Serum Cystatin C (core laboratory)
- Serum creatinine, BUN, and electrolytes (local laboratory)
- PGA assessment by VAS at 24, 48, and 72 hours
- Dyspnea assessment by VAS at 24, 48 and 72 hours
- Fluid balance between randomization and 24 hours (net intake – net output), 24 and 48 hours, and 48 and 72 hours
- Blood sample for biomarkers core laboratory
- Changes in cardiovascular medications
- Assessment for serious adverse events
- Urine biomarkers
- Urine collection for UNaV

10.2 Day 7 or Day of Discharge (if earlier than 7 days)

- Directed history and physical examination, focused on signs and symptoms of congestion
- Vital signs (including O_2 saturation and weight)
- Serum Cystatin (core laboratory)
- Creatinine, BUN, and electrolytes (local laboratory)
- Blood sample for biomarkers (core laboratory)
- Urine biomarkers
- Changes in cardiovascular medications
- Assessment for serious adverse events

10.3 Day 60

Patients will receive a telephone call to assess vital status and to check for potential rehospitalizations.

10.4 6 months

Mortality data will be collected at 6 months following randomization via telephone call.

11. OUTCOME DETERMINATIONS

11.1 Primary Endpoints

This study will use co-primary endpoints

- **Safety:** Change in serum cystatin C from randomization to 72 hours, based on a blinded biomarker core lab assessment

- **Efficacy:** Cumulative urinary volume (UV; indwelling urinary catheter) at 72 hours

Rationale for Primary Endpoints:

Change in serum cystatin C from randomization to 72 hours was chosen as the primary safety endpoint due to the observed association between AHF therapy with diuretics and worsening renal function and the known association of worsening renal function with other adverse outcomes.

For the assessment of short term efficacy, a variety of endpoints have been utilized in prior AHF studies. These include urine volume, change in weight and patient self assessments of symptoms, typically either dyspnea or global well being (termed patient global assessment (PGA). The ROSE-AHF study will use urine volume over 72 hours as the primary endpoint for efficacy. The rationale for this choice is urine output is related to the enhancement of renal function. Change in weight and patient self assessments of symptoms using a visual analog scale (VAS) will be secondary endpoints.

11.2 Secondary Endpoints

- Change in serum creatinine from randomization to 72 hr
- Cumulative urinary sodium excretion (UNaV) at 72 hr
- Patient global well being assessment by VAS AUC over 72 hr
- Dyspnea assessment by VAS AUC over 72 hr
- Change in weight from randomization to 72 hr
- Change from randomization in blood urea nitrogen (BUN) / serum cystatin C ratio at 72 hr
- Development of Cardio-renal syndrome: defined as increase in serum creatinine > 0.3 mg/dl from randomization at any time point during 72 hours after randomization
- Persistent or worsening heart failure defined as need for rescue therapy (additional IV vasoactive agent for heart failure treatment, ultrafiltration, mechanical circulatory or respiratory support) over 72 hours after randomization.
- Treatment Failure**,** a composite comprised of ANY ONE of the following during the 72 hours after randomization:
    - development of cardio-renal syndrome as defined above
    - worsening/persistent heart failure as defined above
    - Significant hypotension requiring discontinuation of study drug
    - Significant tachycardia requiring discontinuation of study drug
    - death

11.3 Tertiary Endpoints

- Change in serum cystatin C from randomization to 24 and 48 hr
- Cumulative UV at 24 and 48 hr
- Cumulative urinary sodium excretion (UNaV) at 24 and 48 hr
- Patient global well being assessment by VAS AUC over 24 and 48 hr
- Dyspnea assessment by VAS AUC over 24 and 48 hr
- Change in serum creatinine from randomization to 24 and 48 hr
- Changes from randomization in the bivariate vector of serum cystatin C and cumulative UV at 24 and 72 hr

For each intervention group and placebo, the change in serum cystatin C at 24 and 72 hours and UV at 24 and 72 hours for each patient will be plotted on a two dimensional coordinate grid along with estimates of the mean effect and a 95% confidence ellipse (separate plots will be produced for the 24-hour data and the 72-hour data). This graphical presentation will allow visual and statistical assessment of the "trade off" between change in serum cystatin C and UV. Comparisons will be constructed for dopamine vs. placebo and nesiritide vs. placebo to visualize the differences between treatment strategies.

- Changes from randomization in the bivariate vector of creatinine and weight at 24 and 72 hr

For each ingtervention group and placebo, weight loss at 24 and 72 hours and change in creatinine at 24 and 72 hours for each patient will be plotted on a two dimensional coordinate grid along with estimates of the mean effect and a 95% confidence ellipse. This graphical presentation will allow visual and statistical assessment of the "trade off" between change in weight and change in renal function. Comparisons between dopamine vs. placebo and nesiritide vs. placebo will be constructed as described above to visualize the differences between treatment strategies.

- Time from randomization to discharge from index hospitalization
- Total days alive and free from heart failure hospitalization during the 60 days following randomization
- Changes in circulating biomarkers from randomization to 72 hours
- Changes in Urine biomarkers from randomization to 72 hours, day 7, or discharge if earlier

- Mortality during the six months following enrollment

12. METHODS TO PROMOTE ADHERENCE AND MINIMIZE BIAS

12.1 Adherence

Since this study will be an inpatient study of relatively brief duration, it is not anticipated that any specific interventions will be required to promote adherence.

12.2 Blinding

For each of the two strategies (nesiritide vs. placebo and dopamine vs. placebo), the treatment assignments will be double-blinded.

PARTICIPANT SAFETY AND ADVERSE EVENTS

12.3 Institutional Review Boards

All Heart Failure Clinical Research Network sites will submit the study protocol, informed consent form, and other relevant study documents to their Institutional Review Board (IRB) for approval.

12.4 Adverse Events

12.4.1 Definitions

An Adverse Event (AE) is any sign, symptom, syndrome, or illness that occurs or worsens during the use of the test intervention (drug, biologic, or device) regardless of causality. A medical condition that is already present prior to treatment administration is not defined as an adverse event unless this medical condition worsens after the patient has been administered the test intervention. The details of these signs and symptoms will however be captured in the patient's CRF for inclusion in the database as baseline conditions. Clinically significant laboratory abnormalities (for example, abnormal ECHOs, ECGs, out of range blood parameters etc.) that occur or worsen during the use of a test intervention are also adverse events.

A Serious Adverse Event (SAE) is any adverse event that:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of hospitalization which is not specifically required by the protocol nor is it elective.
- Results in permanent impairment of a body function or permanent damage to a body structure
- Requires medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure
- Additionally, important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when they jeopardize the patient or require medical or surgical intervention to prevent one of the serious outcomes listed above. Examples of such medical events include: allergic bronchospasm requiring intensive treatment in an emergency

room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse. Medical and scientific judgment must be exercised when classifying events as serious.

The relationship between an adverse event and the study intervention, either surgical or medical, will be determined by the Investigator on the basis of his or her clinical judgment and the following definitions:

- *Possibly Related*: There is a reasonable possibility that the adverse event may have been caused by the study intervention. The temporal relationship of the adverse event to study intervention makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide sufficient explanation for the observed event.

- *Not Possibly Related*: It is unlikely that the event was caused by the study intervention. The temporal relationship of the adverse event to the study intervention makes causal relationship unlikely and other drugs, therapeutic interventions or underlying conditions provide a more likely explanation for the event.

An *Unexpected Adverse Event*: is when the nature or severity of the event is not consistent with the applicable study intervention, expected clinical course or current product labeling.

The following adverse events are anticipated, disease related-events in patients with acute decompensated heart failure and therefore do not require reporting on the Adverse Event form of the CRF (although some may require reporting as study endpoints):

- Atrial fibrillation
- Ventricular tachycardia
- Myocardial infarction
- Acute coronary syndrome
- Electrolyte disturbance
- Acute renal failure
- Worsening heart failure

12.4.2 Recording and Reporting

The Site Investigator is responsible for monitoring the safety of patients enrolled into the study at the study sites. All SAEs will be documented in the source documents and, with the exception of the anticipated events, captured on the SAE page of the CRF. Non-serious AEs should be documented in the source documents and followed according to local standard of care.

All SAEs that result in death or are unexpected for and related to study drug (dopamine or nesiritide) must be reported on a HFN Expedited Event form and faxed to DCRI Safety Surveillance at 1-866-668-7138.

Additionally, adverse events which meet the criteria of serious, related to study drug (dopamine or nesiritide), and unexpected for that drug, qualify for expedited reporting to the regulatory authorities. The Site Investigator will assess all SAEs 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 the events identified 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 Data Coordinating Center.

Investigators are also responsible for promptly reporting adverse events to their reviewing IRB/EC in accordance with local requirements.

A Data and Safety Monitoring Board (DSMB) will review detailed safety data at regular intervals throughout the study.

13. STATISTICAL CONSIDERATIONS

13.1 Overview

Summaries of continuous variables will be displayed using the mean, standard deviation, median, and 25th - 75th percentiles. For nominal variables, the number and frequency of subjects in each category will be presented. Statistical tests with p-values < 0.05 will be considered statistically significant, unless otherwise stated. Analyses will be performed using SAS software (SAS Institute, Inc, Cary, NC).

13.2 Analysis of Primary Endpoints

The primary analysis will be conducted on an intention-to-treat basis. A general linear model with an indicator for randomization to the nesiritide strategy or dopamine strategy, as well as an indicator for the specific treatments being compared, will be used to examine the effect of each treatment on the primary safety and efficacy outcomes. For the primary comparisons, placebo subjects will be pooled across the nesiritide and dopamine strategies. Comparisons of low-dose dopamine vs. placebo and low-dose nesiritide vs. placebo will each be conducted using a Type I error rate of 0.025.

13.3 Sample Size Justification

A difference of 0.3 mg/L in serum cystatin C is considered to be clinically meaningful. With a conservative estimate of 102 subjects per treatment group and a standard deviation for the change between randomization and 72 hours of 0.62 mg/L (see Owan et.al. 2008 for an estimate at 48 hours)[18], the study would have 88% power to detect a clinically significant difference between low-dose dopamine vs. placebo (or low-dose nesiritide vs. placebo) at the 0.025 two-sided level. A standard deviation for the change of 0.59 mg/L would provide 91% power and any standard deviation of less than 0.68 mg/L would provide greater than 80% power to detect a clinically meaningful difference. Based on prior Heart Failure Network clinical trials, the amount of missing data is expected to be less than 15% for the change in serum cystatin C from randomization to 72 hours. Therefore a sample size of 120 subjects per treatment group will provide adequate power for the serum cystatin C analyses.

In the clinical trial of Owan et.al.[18] the estimated standard deviation for the change in cumulative fluid balance from randomization to 72 hours was approximately 2900 mL.[18] Based on prior Heart Failure Network clinical trials, the amount of missing data is expected to be less than 10% for the cumulative UV at 72 hours. With a Type I error rate of 0.025 and a sample size of 108 evaluable subjects per treatment arm, the study would have 90% power to detect a treatment difference of > 1400 mL and 80% power to detect a difference of > 1224 mL. These power calculations were based on a 2-sample t-test for the hypothesis of equal means.

13.4 Analysis of Secondary and Tertiary Endpoints

General linear models and nonparametric approaches will be used to analyze the continuous outcomes. For binary outcomes, logistic regression analysis will be used to compare each treatment vs. placebo and estimate the odds ratio and 95% confidence interval for low-dose dopamine vs. placebo and low-dose nesiritide vs. placebo comparisons. Time-to-event comparisons will be conducted using Kaplan-Meier curves and log-rank tests. For analyses of patient global well being VAS and dyspnea VAS, the value of zero will be imputed for all measurements missing due to death. Sensitivity analyses, including the worst-rank score analysis [(21)] will be employed to assess the influence of informatively missing values on the results. In particular the worst-rank score analysis will account for missing data due to deaths.

13.5 Exploratory Analyses

Analyses comparing the low-dose dopamine and low-dose nesiritide groups will be considered exploratory as they do not directly address the two primary hypotheses of ROSE. However, if both the low-dose dopamine and low-dose nesiritide treatment are statistically superior to placebo, a secondary analysis will be conducted to compare the two active treatment arms.

Further analyses will be conducted to determine whether the effect of low dose dopamine or low dose nesiritide is modified by each of the following covariates:

- Admission blood pressure
- Age (≤ 70 v. > 70)
- Pre-randomization GFR

Estimation of subgroup effects will be conducted within the linear models framework.

For each of the three treatment groups, the relationship between baseline GFR and 72 hour cumulative UV will be estimated using linear regression models. Additional analyses will compare the placebo subjects randomized to the dopamine strategy vs. the placebo patients randomized to the nesiritide strategy to determine whether the presence of the PICC line alters patient outcomes.

13.6 Statistical Monitoring Plan

Interim data analysis for efficacy will not be conducted due to relatively small size and short duration of this phase II clinical trial. Safety data will be periodically assessed by the Data and Safety Monitoring Board based on reporting of adverse events and treatment-level summary data.

14. DATA MANAGEMENT PROCEDURES

ROSE-AHF is a prospective, randomized, controlled study where data will be collected, analyzed, and interpreted by the Duke Clinical Research Institute which functions as the DCC for the Heart Failure Network. 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 Heart Failure Network. This is necessary since dissemination of preliminary information may inappropriately affect the objectivity of the study. For this reason Study Investigators or other parties will not be allowed to perform subset analyses at any point before the conclusion of this study.

All prospective publications or presentations must be reviewed and approved by the Heart Failure Network Publications and Steering Committees.

15. STUDY ADMINISTRATION

15.1 Data and Safety Monitoring Board (DSMB)

A DSMB will be appointed by the NHLBI. This will be a group of individuals with pertinent expertise in heart failure and clinical trials. The DSMB will advise the sponsor 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.

15.2 Data Coordinating Center

The Duke Clinical Research Institute will function as the Data Coordinating Center (DCC) for this trial as specified by the NHLBI.

15.3 Core Laboratories

This study will utilize a biomarker core laboratory designated by the NHLBI and the DCC. Plasma specimens at baseline, 24 hours, 48hours, 72 hours, day 7 (or discharge if earlier) will be processed according to the procedures provided by the core laboratory and sent to the core laboratory on dry ice for analysis. These tests will include those agreed upon by the Heart Failure Network Biomarker Working Group

Urine collection: We will collect five (5) urine samples: Baseline, 24, 48, 72, day 7 or discharge if earlier for assay of selected urinary biomarkers determined by the Heart Failure Network Biomarker Working Group. These urine samples will be obtained as close as possible to (if not simultaneous with) collection of serum biomarkers. Collection should come from clean voided urine or Foley catheter. Samples will be sent to the Biomarker Core Facility for processing.

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17. APPENDICES

17.1 Appendix A. Schedule of Assessments

	Baseline	24 hours (+ / -) 2 hrs	48 hours (+ / -) 2 hrs	72 hours	Day 7 or discharge	60 days (+ / -) 7 days	6 months (+/-) 7 days
Informed Consent	X						
History and physical	X	X	X	X	X		
CV Medication History	X	X	X	X	X		
Vital Signs	X	X	X	X	X		
Oxygen saturation	X	X	X	X	X		
Body weight	X	X	X	X	X		
VAS for PGA	X	X	X	X			
VAS for Dyspnea	X	X	X	X			
Urine output and Fluid balance/24 hours		X	X	X			
Cr, BUN, electrolytes	X	X	X	X	X		
Plasma collection for HFN Biomarkers	X	X	X	X	X		
Urine Biomarkers	X	X	X	X	X		
Urine collection for UNaV		X	X	X			
Serious Adverse events		X	X	X	X		
Rehospitalization Check						X	
Phone visit to assess vital status						X	X

17.2 Appendix B. List of Abbreviations

Abbreviation	Definition
ACE	angiotensin-converting enzyme
ADHF	acute decompensated heart failure
AHF	acute heart failure
AICDs	automatic implantable cardioverter-defibrillators
AUC	area under the curve
BNP	B-type natriuretic peptide
CO	cardiovascular flow
CRP	C-reactive protein
CRS	Cardio-renal syndrome
DOSE	Diuretic Optimization Strategies Evaluation
ED	Emergency Department
EF	ejection fraction
JVP	Jugular venous pressure
LVEDP	left ventricular end diastolic pressure
LVEF	left ventricular ejection fraction
IV	Intravenous
IVRS	Interactive voice response system
KIM	Kidney injury marker
NIV	noninvasive positive pressure ventilation
NYHA	New York Heart Association
PGA	Patient global assessment
PAC	pulmonary artery catheter
PCWP	Pulmonary capillary wedge pressure
RBF	renal blood flow
SVR	systemic vascular resistance
US	United States
VAS	visual analogue scale
UV	urinary volume

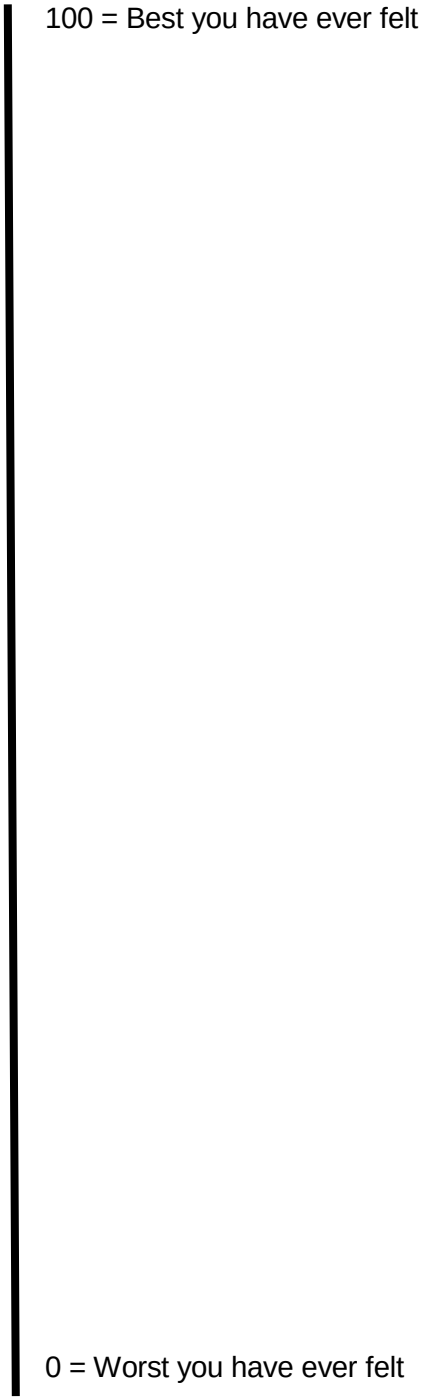
Site Number: _ _ _ **Patient Number: _ _ _ - _ _ _**

Assessment Date: _ _ (day)/_ _ (month) _ _ _ _ (year) **Time: _ _: _ _**

17.3 Appendix C. VAS Instruments

VAS – Global Well Being (PGA)

Please draw a line on the scale to show how you feel right now. The number “0” equals the worst your have ever felt and the number “100” equals the best you have ever felt.



Site Number: _ _ _ **Patient Number: _ _ _ - _ _ _**

Assessment Date: _ _ (day)/_ _ (month) _ _ _ _ (year) **Time: _ _: _ _**

VAS - Dyspnea

Please draw a line on the scale to show how your breathing feels 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.

100 = I am not breathless at all

0 = I am as breathless as I have ever been

17.4 Appendix D. Informed Consent Form

Separate attachment.