Acute Decompensated Heart Failure
Represents an Enormous Healthcare Burden
Acute decompensated heart failure (ADHF) is the most common cause of hospital admission in persons aged >65 years, accounting for 100,000 admissions and >6 million hospital days.1 The total cost of HF care in the United States is currently estimated at $21 billion and is projected to increase to $53 billion in 2030 with the majority of costs (80%) related to ADHF hospitalizations.2 The prognosis of patients admitted with ADHF is dismal, with a 20% to 30% readmission rate and a 20% to 30% mortality rate within 6 months after admission.3

Renal Dysfunction Is Potently Associated With Adverse Outcomes in ADHF
Studies have established the prognostic importance of renal function in patients with HF. Analysis from the second prospective randomized study of Ibopamine on mortality and efficacy4 was one of the first to demonstrate that estimated glomerular filtration rate (GFR) was the strongest predictor of mortality in ADHF. In the ADHF national registry (ADHERE), 63% of patients with ADHF had moderate renal dysfunction (GFR<60 mL/min m²) on admission and in-hospital mortality was strongly associated with the severity of renal dysfunction.5 A meta-analysis of 16 studies characterizing the association between renal impairment and mortality in patients with HF indicated that 1-year mortality increased incrementally across the range of renal function with a 7% increase in risk for every 10 mL/min decrease in GFR.6 As recently reviewed,7 numerous more recent studies have confirmed the association of renal dysfunction with adverse short- and long-term outcomes in ADHF, an association which seems equally robust in patients with ADHF with reduced or preserved ejection fraction.

Acute Kidney Injury During the ADHF Hospitalization
In patients hospitalized with ADHF, several studies demonstrated that acute kidney injury (AKI) during treatment of ADHF is common, with increases in creatinine ≥0.3 mg/dL occurring in 25% to 30% of patients. Regardless of baseline renal function, AKI is associated with poorer outcomes.7–9 In a recently proposed cardiorenal classification system, AKI during hospitalization for ADHF is termed type 1 or acute cardiorenal syndrome.10 More recently, studies have demonstrated that the prognostic implications of AKI may be modified by its duration (transient versus persistent)11 and associated clinical factors (adequacy of decongestion).12,13 Transient AKI and AKI occurring in the setting of more adequate decongestion were not associated with poorer outcomes, whereas persistent AKI and AKI occurring in the presence of persistent congestion were. However, another large study found that persistent AKI was associated with poorer outcomes, despite evidence of more adequate decongestion.14 Although the factors mediating AKI or type 1 cardiorenal syndrome during an ADHF hospitalization are clearly multifactorial, the adverse prognostic implications of renal dysfunction and AKI during ADHF treatment provide strong rationale for development of therapeutic strategies that enhance decongestion while preserving renal function in ADHF.14

Pathophysiology of Renal Dysfunction in HF and Type 1 Cardiorenal Syndrome
The pathogeneses of underlying renal dysfunction in HF and the mediators of type 1 cardiorenal syndrome are complex.15 The HF state leads to chronic renal hypoperfusion because of impaired cardiac output,16 renal venous congestion,17–19 and neurogenic and humorally mediated renal vasoconstriction. Renal dysfunction related to HF often occurs on the
The Concept of Renal Adjuvant Therapy for ADHF

Although our understanding of the pathophysiology of renal dysfunction and type 1 cardiorenal syndrome is incomplete, existing knowledge provides several pathophysiological targets that may inform design of therapies to preserve renal function and enhance the ability to attain adequate decongestion in ADHF. Inotropes or vasodilators are commonly used to increase cardiac output in ADHF and may enhance renal function via an effect on the heart and systemic vasculature. However, therapies that specifically target the kidney to enhance decongestion and preserve renal function can be considered adjuvant therapies for ADHF. A limited number of renal targeted therapies have been tested in ADHF.

Intrarenal adenosine receptors play a role in mediating tubular glomerular feedback wherein increased sodium delivery to the renal tubules with diuretic therapy results in renal vasoconstriction and proximal tubular sodium reabsorption as part of an intrinsic intrarenal homeostatic mechanism. To block this response, an adenosine 1-receptor antagonist (rolofylline) was developed and tested in a large, multicenter trial of patients with AHF and renal impairment. Although rolofylline showed promise in preliminary studies, the pivotal trial showed no effect on symptom resolution, readmission rate, mortality, or renal function when compared with placebo.

Relaxin is an endogenous peptide that modulates cardiovascular adaptation to pregnancy and is a potent vasodilator which may also have beneficial effects on renal function. The Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure (RELAX-AHF) trial program tested recombinant human relaxin-2 (serelaxin) in patients with ADHF with normal or increased (>125 mm Hg) systolic blood pressure and included patients with preserved EF (26% of patients). Overall, relative to placebo, serelaxin improved dyspnea, had no effect on cardiovascular death or HF or renal failure hospitalization at 180 days, reduced 180-day all-cause mortality, and had significant favorable effects on biomarkers reflective of congestion, renal function, hepatic function, and myocardial necrosis. The degree to which renal-specific effects versus systemic vasodilatation mediated the favorable effects of serelaxin in patients with ADHF with normal or elevated blood pressure is unclear.

The clinical development of ularitide has paralleled that of nesiritide in many respects. Ularitide is a chemically synthesized form of urodilatin, a natriuretic peptide of renal origin which binds to the natriuretic peptide A receptor and produces hemodynamic and renal effects similar to those observed in preclinical and early clinical studies of nesiritide. In phase II dose finding studies, doses (7.5, 15, or 30 ng/kg per minute) of ularitide were infused for 24 hours and produced substantial and dose-related reductions in pulmonary capillary wedge pressure, systemic vascular resistance, and systolic blood pressure without effects on urine output and with numerically greater but not statistically significant increases in creatinine. Impairment in renal function was least evident with the 15 ng/kg per minute dose, and this dose is being tested in the ongoing Trial of Ularitide’s Efficacy (TRUE) and safety in patients with AHF (NCT01661634) with a composite primary end point incorporating measures of clinical status.

There has been concern during the effects of diuretics on renal function in ADHF and particularly in patients with ADHF who develop type 1 cardiorenal syndrome. Ultrafiltration represents a strategy to achieve decongestion without exposing the kidneys to diuretics and thus a potential renal protective strategy. A small trial showed more effective decongestion without differential effects on renal function and a significant decrease in ADHF rehospitalizations with ultrafiltration as compared with diuretics in ADHF. A recent study evaluated the effect of ultrafiltration on renal function and adequacy of decongestion in patients with type 1 cardiorenal syndrome. In this study, as compared with stepped pharmacological care, ultrafiltration was associated with more severe AKI, no greater degree of decongestion, and more adverse events. A larger trial is investigating the effect of ultrafiltration versus diuretics on time to HF events after ADHF hospitalization but is not specifically targeting patients with type 1 cardiorenal syndrome (NCT01474200). Thus, the potential to preserve renal function and enhance decongestion with ultrafiltration continues to be of interest in ADHF.

Rationale for the Renal Optimization Strategies Evaluation in AHF Trial: Low-Dose Dopamine or Nesiritide as Renal Adjuvant Therapies

Clinically available agents have physiological properties that support their potential as renal adjuvant therapies to enhance decongestion and to preserve renal function during diuretic therapy for ADHF. Two such therapies, low-dose dopamine and low-dose nesiritide will be independently tested against placebo in the Renal Optimization Strategies Evaluation (ROSE) in AHF trial.

Renal Dose Dopamine as a Renal Adjuvant Therapy in ADHF

Dopamine is an endogenous catecholamine with different pharmacological effects on the systemic and renal vasculatures. Dopamine has been shown to exhibit sequential dose-dependent activation of dopaminergic, β adrenergic, and α adrenergic receptors. At low doses, dopamine activates the dopamine receptors, resulting in vasodilatation of the renal, mesenteric, coronary, and cerebral vascular beds by stimulating dopamine A1 receptors and inhibition of norepinephrine release from sympathetic nerve endings by stimulating dopamine A2 receptors. At intermediate doses, dopamine activates β1-adrenergic receptors, providing inotropic and potentially proarrhythmic effects. At high doses, dopamine activates α1- and α2-adrenergic receptors providing systemic arterial vasoconstriction. Criteria for low- (<3 μg/kg per minute), intermediate- (4–5 μg/kg per minute), and high- (>5 μg/kg per minute) dose dopamine have been suggested, but individual responses may vary. In patients with stable chronic HF with reduced ejection fraction, Elkayam documented decreases in renal vascular resistance and increases in renal blood flow at
do increase until the infusion rate reached 5 μg/kg per minute even though systemic vascular resistance was lower than at baseline at all doses.31

Several studies have investigated the potential renal protective effects of low-dose dopamine in patients considered at risk for development of renal failure. A systematic review and meta-analysis of these studies (61 trials; 3359 patients) indicated that most of the trials focused on patients undergoing surgery (40 trials) or receiving intravenous contrast (8 trials) with only 1 trial that included patients with ADHF. In this heterogeneous group of studies, dopamine did increase sodium excretion and decrease creatinine, but did not alter mortality or the need for renal replacement therapy as compared with placebo.32

Two small, single-center, open-label studies compared the renal effects of the combination of low-dose dopamine in patients with ADHF receiving diuretic therapy.33,34 Both studies demonstrated preservation or improvement of renal function with low-dose dopamine, whereas deterioration of renal function was observed with diuretic therapy alone.

The Damping in Acute Decompensated Heart Failure (DAD-HF) trial randomized 60 patients with ADHF to receive high-dose intravenous furosemide (40-mg bolus followed by 20 mg/h for 8 hours) or low-dose intravenous furosemide (40-mg bolus followed by 5 mg/h for 8 hours) plus dopamine (5 μg/kg per minute for 8 hours).35 Urine volume was similar between the 2 groups, although the incidence of AKI over the subsequent hospitalization course was higher in the high-dose furosemide group (30%) than in the low-dose furosemide plus dopamine group (6.7%). The DAD-HF II study was recently presented as an abstract at the late breaking trial session of the European Society of Cardiology HF 2013 Congress. The trial, which was conducted at 4 centers in Greece, randomized 161 patients with ADHF to 1 of the 3 treatment arms: high-dose furosemide (20 mg/h); low-dose furosemide (5 mg/h), and low-dose furosemide plus low-dose dopamine (5 μg/kg per minute). The infusions were stopped after 8 hours, after which treatment was left to the discretion of the physician. Although AKI was significantly more common in the high-dose group than in the 2 other groups at 24 hours (24% versus 7%–11%; P<0.0001), this difference did not persist throughout the hospitalization.

There were no between-group differences in the initial relief of symptoms of congestion, as well as in clinical outcomes (including all-cause mortality, cardiovascular mortality, and HF rehospitalization) at 60 days or 1 year. The trial was stopped short of its enrollment goal of n=450 because an interim analysis showed that the primary outcome of all-cause mortality and HF rehospitalization at 60 days was unlikely to show a difference between the groups and because the group receiving dopamine had significantly higher heart rates, a finding which may suggest activation of β1-adrenergic receptors by the relatively high dose of dopamine used in the trial (Giamouzis et al, The DAD-HFII trial Late Breaking Trials 2, HF 2013. Abstract 285. http://clinicaltrials.gov/show/NCT01060293).

In summary, although the findings of the DAD-HF trials may lessen enthusiasm for testing the effect of low-dose dopamine on renal function and decongestion efficacy in ADHF, we believe that the ROSE AHF trial is better suited than the DAD-HF trials to test the effect of this therapy in ADHF for several reasons. The duration of dopamine therapy will be much longer (72 hours) in ROSE AHF providing sustained renal vasodilatation. The dose of dopamine used in ROSE AHF is more clinically relevant because it is the most commonly used renal dose and provides renal vasodilatation with less risk of β-adrenergic stimulation which may offset favorable benefits. Unlike the DAD-HF trials, the ROSE AHF trial tests only the effect of dopamine versus placebo when added to optimal diuretic dosing, whereas in the DAD-HF trials, the effects of dopamine were confounded by different diuretic doses in those treated or not with dopamine, and diuretic doses were not calibrated to patient’s outpatient diuretic requirements.

Low-Dose Nesiritide as a Renal Adjuvant Therapy in ADHF

Brain natriuretic peptide (BNP) is a cardiac peptide with vasodilating, renin, and aldosterone inhibiting natriuretic and diuretic properties.36 Human recombinant BNP (nesiritide) was approved by the Food and Drug Administration for the management of ADHF because of its acute hemodynamic effects to lower systemic and atrial pressures.37 The approved recommended dose of nesiritide is a bolus of 2 μg/kg followed by infusion of 0.01 μg/kg per minute. In the trial which supported labeling of nesiritide for ADHF, this dose produced reduction in systolic blood pressure exceeding 13.5 mm Hg in 25% of patients.37

Although preclinical studies have demonstrated the renal enhancing effects of intravenous administration of BNP, most human studies have not shown evidence of favorable renal effects with approved dose of nesiritide. Wang et al38 administered approved dose of nesiritide or placebo for 24 hours each on consecutive days in a randomized, double-blind, crossover study performed in patients with type 1 cardiorenal syndrome. Changes in renal blood flow, urinary volume, and GFR were not different during the nesiritide and placebo study periods. A small, double-blind, placebo-controlled study randomized 75 patients with ADHF and renal dysfunction to a 48-hour infusion of the approved dose of nesiritide or placebo in addition to usual care. There was no significant difference in the incidence of type 1 cardiorenal syndrome between the nesiritide or the placebo groups.39

In a randomized, open-label study, 71 patients with ADHF with underlying renal dysfunction were randomized to a standardized diuretic regimen with or without the approved dose of nesiritide for 48 hours. Nesiritide patients had smaller increases in creatinine, despite greater blood pressure reduction but nesiritide did not enhance diuretic responsiveness.40

The Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) randomized 7141 patients with ADHF to the approved dose of nesiritide or placebo and demonstrated that although there was minimal improvement in dyspnea in patients who received nesiritide, there was no change in renal function and mortality. Importantly, the incidence of hypotension in nesiritide-treated patients was 26.6% significantly greater than that observed in placebo-treated patients.41 An ancillary analysis from ASCEND showed that full-dose nesiritide was not associated with improved urine output after adjusting for diuretic dose, baseline blood pressure, and baseline renal function but did
not examine treatment blood pressure or investigator reported hypotension as covariates affecting renal response to natriuretic peptides.42

In experimental HF, favorable renal effects of natriuretic peptides are attenuated in the presence of reduced renal perfusion pressure and restored when renal perfusion pressure is kept constant.43 Intrarenal infusion of nesiritide to avoid systemic hypotension is associated with natriuresis, diuresis, and increases in GFR.44 Building on the concept of preserving renal protective effects of natriuretic peptides by limiting systemic hypotension, Riter et al45 compared intravenous administration of low-dose nesiritide (0.0025–0.005 µg/kg per minute without a bolus) with the approved dose or no nesiritide in a case control study of patients with ADHF matched for severity of underlying renal dysfunction. As compared with patients not treated with nesiritide, standard dose nesiritide reduced systolic blood pressure (121–112 mmHg), whereas low-dose nesiritide did not (97–99 mmHg), despite lower blood pressure at baseline. Low-dose nesiritide was associated with significant improvements in creatinine and blood urea nitrogen, whereas these parameters did not improve in the standard dose nesiritide group. Finally, low-dose nesiritide therapy was associated with similar diuresis, despite a diuretic dose that was <50% of that used in patients who received full-dose nesiritide.45

The NAPA (Nesiritide Administered Peri-Anesthesia in Patients Undergoing Cardiac Surgery) study demonstrated that patients with left ventricular systolic dysfunction undergoing coronary artery bypass grafting using cardiopulmonary bypass had improvement in renal function and clinical outcomes when treated with nesiritide at 0.01 µg/kg per minute without bolus. These effects were more pronounced in patients with reduced renal function at baseline.46 In a small, double-blind, placebo-controlled study of patients with renal insufficiency undergoing cardiopulmonary bypass surgery, as compared with placebo, low-dose nesiritide (as used in ROSE AHF) preserved renal function in the perioperative period.47

In summary, although studies of full-dose nesiritide have not provided evidence of beneficial effects of nesiritide on renal function or diuretic responsiveness, full-dose nesiritide is consistently associated with significant hypotension, a factor known to adversely affect renal function and blunt responsiveness to diuretics and natriuretic peptides. Preliminary studies using low-dose nesiritide in patients with ADHF and cardiac surgery have provided a consistent signal of benefit. Thus, the rationale for testing the effect of low-dose nesiritide in ROSE AHF trial is strong.

**ROSE AHF: Study Objectives**

The ROSE AHF study uses a novel study design to address 2 independent objectives. One primary objective is to test the hypothesis that as compared with placebo, addition of low-dose dopamine to optimal diuretic dosing preserves or enhances renal function, as measured by change in serum cystatin-C and cumulative urinary volume during a 72-hour treatment period in patients with ADHF and renal dysfunction. The other primary objective of the ROSE AHF study is to test the hypothesis that as compared with placebo,
To test the 2 primary hypotheses, the placebo patients will be pooled. Patients randomized to receive dopamine will be compared with the pooled placebo group. Similarly, patients randomized to receive nesiritide will be compared with the pooled placebo group.

**ROSE AHF: Background Therapy**

All patients received optimal open-label diuretic treatment. On the basis of the results of the Diuretic Optimization Strategies Evaluation trial, the protocol-specified optimal total daily intravenous diuretic dose of furosemide (or equivalent) is equal to 2.5×the total daily oral outpatient furosemide (or equivalent) dose at 7 days before admission. One half of the total daily diuretic dose is administered twice daily as a bolus for at least 24 hours. The range of allowed daily furosemide doses is 80 to 600 mg. Patients naive to outpatient loop diuretics received 80 mg/d of intravenous furosemide. After 24 hours, diuretic dosing may be adjusted by the managing provider. All patients are placed on a 2000-mg sodium diet and 2000-mL fluid restriction. The use of other medications is at the discretion of the managing physician. After the primary end point assessment at 72 hours, study drug is discontinued and all treatment is at the treating provider’s discretion.

**ROSE AHF: Study Assessments**

After consent, patients undergo baseline history and physical, measurement of vital signs, phlebotomy for biomarkers (including cystatin C; HFN Core Biomarker Laboratory, University of Vermont) and electrolytes (local laboratory) and patient global well-being and dyspnea visual analogue scale (VAS) measurements. These assessments and adverse event assessments are repeated at 24, 48, and 72 hours. A baseline urine sample is collected for urinary biomarkers and daily 24-hour urine collections for urinary volume, urinary sodium excretion, and urinary biomarkers are performed for 72 hours.

A more limited data set is collected at day 7 or discharge, whichever occurs first. All patients have a telephone assessment of vital status and hospitalizations at 60 days and vital status at 6 months after discharge.

**ROSE AHF: End Points**

The goal of renal adjuvant therapy in AHF is to enhance decongestion (efficacy) while preserving renal function (safety). Thus, for both of the hypotheses tested in ROSE AHF, 72-hour cumulative urinary volume as an index of decongestion efficacy and change in cystatin-C from randomization to 72 hours as a measure of renal function preservation will serve as the coprimary end points.

Cumulative urinary volume reflects diuretic responsiveness during the course of study drug administration and the potential for decongestion, is subject to fewer potential measurement errors than fluid balance, weight change, or physical examination changes, and is more clinically relevant than changes in biomarkers, such as BNP. Symptom relief is affected by numerous factors and shown to be poorly correlated to adequacy of decongestion. Thus, this end point, while novel, is well designed to reflect the postulated effect of the study intervention.

Cystatin-C is freely filtered by the glomerulus and (unlike creatinine) is not dependent on muscle mass and its determinants (age, nutritional status, ethnicity, and sex). Cystatin-C and change in cystatin-C are potent prognostic markers in AHF, and change in cystatin-C was a secondary end point in an ADHF trial. Given the potential advantages of cystatin-C as a more specific marker of renal function, this novel end point is used as the primary safety end point in ROSE AHF, and change in creatinine is a secondary end point.

Secondary end points are listed in Table 2. Tertiary end points will include changes in primary and secondary end points at other time periods (24 and 48 hours), biomarkers reflective of HF severity and renal function, length of stay, readmissions and mortality at 60 days and mortality at 6 months.

Prespecified subgroup analyses will be conducted to determine whether the treatment effect on the primary end points is maintained at different subgroups. The ROSE AHF trial is powered to detect a difference in the primary end point with 80% power at 2-sided 5% significance.

**Table 2. Secondary End Points**

<table>
<thead>
<tr>
<th>End Point Description</th>
<th>Timepoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in serum creatinine from randomization to 72 h</td>
<td>Cumulative UNaV at 72 h</td>
</tr>
<tr>
<td>Patient global wellbeing assessment</td>
<td>VAS AUC over 72 h</td>
</tr>
<tr>
<td>Dyspnea assessment</td>
<td>VAS AUC over 72 h</td>
</tr>
<tr>
<td>Change in weight from randomization to 72 h</td>
<td>Change in BUN/Cystatin-C ratio from randomization to 72 h</td>
</tr>
<tr>
<td>Persistent or worsening HF within 72 h</td>
<td>Development of type 1 cardiorenal syndrome during 72 h</td>
</tr>
<tr>
<td>Treatment failure within 72 h</td>
<td>AUC indicates area under the curve; BUN, blood urea nitrogen; HF, heart failure; UNaV, urinary sodium excretion; and VAS, visual analog scale.</td>
</tr>
</tbody>
</table>
and selected secondary end points is modified by pertinent covariates, including blood pressure, age, and blood urea nitrogen levels.

**ROSE AHF: Statistical Considerations**

**Sample Size Justification**
A difference of 0.3 mg/L in serum cystatin-C is considered to be clinically meaningful because a change of cystatin-C of ≥0.3 at 48 hours in patients hospitalized with AHF was associated with a statistically significant, 2-fold increase in 180-day mortality.6 On the basis of prior HFN AHF trials, missing data for the change in serum cystatin-C from randomization to 72 hours are expected to be <15%. Assuming 15% missing data (leaving 102 subjects per treatment group) and a SD for the change between randomization and 72 hours of 0.62 mg/L,40 the study would have 88% power to detect a clinically significant difference in the change in cystatin-C between low-dose dopamine versus placebo (or low-dose nesiritide versus placebo) at the 2-sided 0.025 level of significance. A SD for the change in cystatin-C of 0.59 mg/L would provide 91% power and any SD of <0.68 mg/L would provide >80% power to detect a clinically meaningful difference.

In a previous study in AHF,60 the SD for the change in cumulative fluid balance from randomization to 72 hours was ≈2900 mL. On prior HFN clinical trials, the amount of missing data are expected to be <10% for the cumulative urine volume 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.

**Analysis of Primary End Points**
The primary analysis will be conducted on an intention-to-treat basis. A general linear model with an indicator for the specific treatments being compared versus placebo will be used to examine the treatment effect for the coprimary end points. For the primary comparisons, placebo subjects will be pooled across the nesiritide and dopamine strategy arms. Comparisons of low-dose dopamine versus placebo and low-dose nesiritide versus placebo will each be conducted using a Type I error rate of 0.025 for each coprimary end point. Comparison of change in cystatin-C (the difference in paired values of cystatin-C at baseline and 72 hours) will be adjusted for baseline cystatin-C. Sensitivity analyses will be performed using multiple imputations to account for missing data.

**Analysis of Secondary and Tertiary End Points**
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 versus placebo and estimate the associated odds ratio and 95% confidence intervals. 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 because of death. Sensitivity analyses, including the worst-rank score analysis, will be used to assess the influence of informatively missing values on the results. For all secondary and tertiary end points, a P value <0.05 will be considered statistically significant.

**Exploratory Analyses**
If both the low-dose dopamine and low-dose nesiritide treatment are statistically superior to placebo, an exploratory analysis will be conducted to compare the 2 active treatment arms.

**ROSE AHF Ancillary Study**

**Reliable Evaluation of Dyspnea in the ROSE AHF Trial**
This objective of this prospective, ancillary study is to evaluate novel end points for assessing treatment effect in ADHF trials. Most ADHF trials with dyspnea relief as an end point have not demonstrated a benefit of therapies on dyspnea relief. This may indicate that dyspnea improves adequately with standard therapy, and thus is not a critical unmet need in the treatment of ADHF. Alternatively, inability to demonstrate improvement in dyspnea may reflect shortcomings in the tools used to assess dyspnea in hospitalized patients with ADHF. Although the dyspnea VAS score is accepted as a valid assessment of change in ADHF symptoms,5 there is no standardization of conditions (oxygen supplementation, position, activity) at the time of the VAS assessment. Furthermore, in ≤48% of patients with ADHF, other symptoms (body swelling or fatigue) are reported as the most bothersome symptom;52 thus, assessment of dyspnea may not reflect their clinical status or response to therapy.

The ADHF Syndromes International Working Group has proposed a more rigorous provocative Dyspnea Severity Score in which dyspnea is assessed under standardized and incrementally more strenuous conditions.53 In the Reliable Evaluation of Dyspnea in the ROSE AHF (RED-ROSE) study, patients enrolled in the ROSE AHF study undergo sequential assessment of dyspnea using a slight modification of the provocative Dyspnea Severity Score, as well as assessment of their most bothersome symptoms using symptom-specific VAS tools. Changes in these metrics will be compared with those in the standard dyspnea and well-being VAS scores during the course of the hospitalization. Furthermore, the association of changes in the provocative Dyspnea Severity Score and most bothersome symptom VAS scores with objective measures of decongestion (N-terminal pro-BNP, fluid, and weight loss) will be assessed and compared with the standard dyspnea and well-being VAS scores.

**Conclusions**
There are currently no Food and Drug Administration-approved renal adjuvant therapies for patients with ADHF and renal dysfunction. The ROSE AHF study will determine if low-dose dopamine or low-dose nesiritide, both of which are clinically available, enhances decongestion and preserves renal function in this high-risk population. The ROSE AHF trial has several strengths, including the multicenter design, rigorous entry criteria, and efficient use of National Heart, Lung, and Blood Institute resources by pooling the placebo groups for comparison with each tested therapy, a strategy which reduces the number of patients needed to address the hypotheses by 25%.
Furthermore, because of the different biological mechanisms of low-dose dopamine and low-dose nesiritide, this study will provide mechanistic insights into the pathophysiology of renal dysfunction in ADHF. Enrollment in ROSE AHF has been completed. The results of the ROSE AHF trial are expected to provide clinically relevant information on appropriate management of patients with ADHF.

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**Disclosures**

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**References**


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