Published in final edited form as:

J Card Fail. 2018 July ; 24(7): 428–438. doi:10.1016/j.cardfail.2018.02.002.

Determinants of diuretic responsiveness and associated outcomes during acute heart failure hospitalization: An analysis from the NHLBI Heart Failure Network Clinical Trials

Michael S Kiernan, MD, MS¹, Susanna R Stevens, MS², W.H. Wilson Tang, MD³, Javed Butler, MD⁸, Kevin J Anstrom, PhD², Edo Y Birati, MD⁵, Justin L Grodin, MD⁹, Divya Gupta, MD⁶, Kenneth B Margulies, MD⁴, Shane LaRue, MD⁷, Victor G. Dávila-Román, MD⁷, Adrian F Hernandez, MD², and Lisa de las Fuentes, MD⁷ on behalf of the NHLBI Heart Failure Clinical Trials Network Investigators

¹Tufts Medical Center, Boston, MA

²Duke Clinical Research Institute, Durham, NC

³Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, OH

⁴Stony Brook University, Stony Brook, NY

⁵Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

⁶Emory University, Atlanta, GA

⁷Washington University in St. Louis, St. Louis MO

⁸University of Mississippi, Jackson, MS

⁹University of Texas Southwestern, Dallas, TX

Abstract

Background—Poor response to loop diuretic therapy is a marker of risk during acute heart failure hospitalization. We sought to describe baseline determinants of diuretic response and to further explore the relationship between this response and clinical outcomes.

Methods and Results—Patient data from the NHLBI Heart Failure Network ROSE-AHF and CARRESS-HF clinical trials were analyzed to determine baseline determinants of diuretic response. Diuretic efficiency (DE) was defined as total 72h fluid output per total equivalent loop diuretic dose; subjects were stratified to high and low DE groups by the median value. We then utilized data from the DOSE-AHF to determine if these predictors of DE correlated with response

Corresponding Author: Michael S. Kiernan, MD, MS Tufts Medical Center, Box 244, 800 Washington St., Boston, MA 0211, mkiernan@tuftsmedicalcenter.org, 617-636-8068.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures: J Butler - research support from the National Institutes of Health, European Union; and the FDA, and is a consultant to Amgen, Bayer, Celladon, Covis Medtronic, Janssen, Novartis, Relypsa, StealthPeptide, Takeda, and Trevena; A Hernandez - Research: Amgen, AstraZeneca, BMS, GSK, Novartis, Janssen, Honorarium: Amgen, Novartis, Janssen. All other authors have nothing to disclose.

to a high- versus low-dose diuretic strategy. At 72h, the high DE group had median fluid output of 9071 ml (25th %, 75th%; 7240, 11775) with median furosemide dose of 320 mg (220, 480) compared to 8030 ml (6300, 9915) and 840 mg (600, 1215) for the low DE group. Weight change at 72h was -4.3 kg (25th %, 75th%; -6.5, -1.9) vs. -2.9 kg (-4.9, -1.3) in the high and low DE groups ($p < 0.001$). Cystatin C was independently associated with DE [OR 0.36 per 1mg/L increase; 95% CI: 0.24, 0.56 ($P < 0.001$)]. Independent of baseline characteristics, reduced fluid output, weight loss and DE were each associated with increased 60 day mortality. Among patients with eGFR below the median, those randomized to a high-dose strategy had improved symptoms compared to those randomized to a low-dose strategy.

Conclusions—Elevated baseline cystatin C, as a biomarker of renal dysfunction, is associated with reduced diuretic response during heart failure hospitalization. Higher loop diuretic doses are required for therapeutic decongestion in patients with renal insufficiency. Poor response independently identifies a high-risk population with increased mortality.

Keywords

acute heart failure; renal failure; cystatin C; loop diuretic; congestion

INTRODUCTION

Acute heart failure (AHF) syndromes are driven by the development of a volume overload state(1). Accordingly, fluid removal with loop diuretics is a cornerstone of AHF management(2). The inability to adequately decongest patients during AHF hospitalization is associated with increased risk of death or readmission and congestion at post-discharge follow up is similarly associated with decreased survival(3–5). The sigmoidal-shaped diuretic dose-response curve of patients with chronic HF is shifted downward and to the right, implying that 1) higher doses of loop diuretics are required to achieve maximal natriuretic response and that 2) the overall maximal natriuretic response is reduced (6). The need for escalating doses of loop diuretics to achieve similar natriuretic response defines the development of diuretic resistance, and is associated with increased mortality(7, 8).

Metrics of diuretic responsiveness have been recently suggested to provide incremental prognostic information beyond that provided by changes in weight, fluid balance, or loop diuretic dose alone(9, 10). Testani, et al., reported that loop “diuretic efficiency (DE)”, defined as net fluid loss per milligram of loop diuretic equivalent administered during AHF hospitalization, was independently associated with survival after adjusting for baseline characteristics, diuretic dose, and fluid output(9). Likewise, Valente, et al., reported that weight loss indexed to diuretic dose, better described a dose-response relationship although was prognostically similar to either component variable alone(10).

Utilizing data from the Heart Failure Network (HFN) clinical trials, we sought to provide further insight into cardiorenal interactions during AHF episodes. Data were pooled from the ROSE-AHF (Renal Optimization Strategies Evaluation) and CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) AHF trials to investigate baseline determinants of DE. The relationship between markers of congestion, DE and their impact on clinical outcomes were then explored. Subsequently, cystatin C (CyC)-based estimates of

renal function were used to further evaluate the association between baseline renal insufficiency and diuretic response. Data from subjects enrolled in the DOSE-AHF (Diuretic Optimization Strategies in Acute Heart Failure) trial were utilized to investigate whether patients predicted to be at risk of poor diuretic response have a differential response to alternative dosing strategies.

METHODS

Data Source

These analyses used data from the National Heart, Lung, and Blood Institute (NHLBI) HFN-sponsored ROSE-AHF (NCT01132846), CARRESS-HF (NCT00608491) and DOSE-AHF (NCT00577135) clinical trials. Study designs and primary results were published previously(11–13).

ROSE-AHF enrolled patients within 24 hours of admission for AHF with concomitant renal dysfunction (glomerular filtration rate of 15–60 mL/min/1.73m²). The diagnosis of AHF was based on at least one symptom and one sign of HF regardless of left ventricular ejection fraction (LVEF). Patients were randomized in an open, 1:1 allocation ratio to a dopamine or nesiritide strategy. Within each strategy, participants were randomized in a double-blind, 2:1 ratio to active treatment or placebo. A total of 360 patients were enrolled at 26 sites across North America from September 2010 to March 2013(12).

CARRESS-HF enrolled patients with AHF regardless of LVEF who had persistent congestion with cardiorenal disease. Cardiorenal disease was defined as an increase in serum creatinine concentration of at least 0.3 mg/dL within 12 weeks prior or 10 days after AHF admission. Exclusion criteria included a serum creatinine concentration > 3.5 mg/dL. Patients were randomized to either a stepped pharmacologic therapy strategy or ultrafiltration. The algorithm for stepped pharmacologic therapy has been published previously; diuretics were titrated to maintain a urine output of 3 to 5 L/day (11). Patients (n=188) were enrolled at 22 sites between June 2008 and January 2012.

DOSE-AHF enrolled patients within 24 hours of admission for AHF who had at least one sign and symptom of HF regardless of LVEF. The study used a 2X2 factorial design randomizing patients to a strategy of high-versus low-dose furosemide therapy and continuous (CI) versus intermittent bolus dose administration. Patients were required to have baseline diuretic requirement of 80 mg of oral furosemide equivalents daily. Patients with serum creatinine concentration > 3.0 mg/dL were excluded. A total of 308 patients were enrolled at 26 sites between March 2008 and November 2009(13).

Study Population

Patients enrolled in the ROSE-AHF and the stepped pharmacologic strategy arm of CARRESS-HF trials with non-missing data to calculate DE at 72 hours following randomization were included for the analyses of baseline determinants of DE (Figure 1). This cohort was also used to explore the association between markers of decongestion and clinical outcomes. Patients from the DOSE-AHF trial with non-missing clinical outcomes

data at 72 hours were examined to determine the interaction between correlates of DE and response to diuretic strategy.

Outcomes

DE was defined as total 72 hour fluid output per total loop diuretic dose, expressed as 40 mg furosemide equivalents (1 mg oral bumetanide = 20 mg torsemide = 80 mg furosemide; 1 mg intravenous bumetanide = 20 mg torsemide = 40 mg furosemide; 40 mg of oral furosemide = 20 mg intravenous furosemide)(13). Survival was compared between patients with DE above versus below the median DE. To evaluate for an interaction between diuretic strategy and patients symptoms, patients' global assessment of symptoms, quantified as the area under the curve (AUC) of the score on a visual-analogue scale (VAS) over the course of the 72 hours, was compared between treatment groups. Other secondary markers of clinical decongestion were also compared. Clinical decongestion was defined as jugular venous pressure of less than 8 cm of water, no more than trace peripheral edema, and the absence of orthopnea(12, 13).

Biomarkers

Baseline plasma samples were collected from patients enrolled in all three clinical trials at baseline for measurement of Cys-C and analyzed at a central core laboratory blinded to treatment assignment.

Statistical Analyses

Baseline characteristics were reported as frequency (%) for categorical variables and median [interquartile interval] for continuous variables. Categorical variables were compared using likelihood ratio chi-square tests, and continuous variables were compared using Wilcoxon rank sum tests.

To evaluate determinants of diuretic response, DE was dichotomized into high and low DE based on median value for the study population. Baseline determinants of DE above the median (high DE) were modeled using multivariable logistic regression with backward elimination where a p-value < 0.1 was required for retention. Candidate variables were selected based on clinical relevance and published literature and included age, gender, race, history of hypertension, weight, mean arterial pressure at randomization, LVEF, medications including angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), and β -blockers, and laboratory values including N-terminal pro BNP, blood urea nitrogen (BUN), sodium, hemoglobin, and CysC. Randomized assigned clinical trial arm, thiazide use between randomization and 72h, diabetes, and HF etiology were forced into the model for adjustment.

Markers of decongestion including 72 h fluid output, change in weight, and weight loss indexed per 40 mg intravenous furosemide equivalent administered from randomization through 72 hours were compared between high and low DE groups using Wilcoxon rank sum tests. Categorical measures of congestion were compared with chi-square tests.

Cox proportional hazard modeling was used to explore the relationship between clinical markers of decongestion, DE and mortality. These models were generated with a combined dataset from ROSE-AHF and CARRESS-HF. Models were adjusted for age, mean arterial blood pressure, and BUN. A single mortality model included weight change, diuretic dose, net fluid output, DE, and adjustment variables. We also assessed the association between DE tertile and time to death using Kaplan-Meier curves and a log rank test.

To investigate whether there is a homogenous treatment effect of diuretic strategies across eGFR stratum, the interaction between eGFR and randomized treatment arm from the DOSE-AHF trial (high-versus low-dose administration) was studied in a multivariate model that included both the main effects as well as the interaction term. eGFR was calculated with a CysC based formula and patients were stratified as above or below the median eGFR for the study population(14).

$$Cys\ C \leq 0.8: eGFR = 133 \times (Cys\ C/0.8)^{-0.499} \times 0.996^{Age} [\times 0.932\ if\ female]$$

$$Cys\ C > 0.8: eGFR = 133 \times (Cys\ C/0.8)^{-1.328} \times 0.996^{Age} [\times 0.932\ if\ female]$$

Similarly, the interaction between eGFR and bolus versus CI administration was evaluated in a separate multivariable model. Continuous end-points including change in weight and fluid loss were evaluated using linear regression. Logistic regression was used to compare differences in percent freedom from clinical congestion at 72 h. If the interaction p-value from the regression models was < 0.10, differences between continuous end points within GFR strata was assessed using Wilcoxon rank sum testing. A p-value of < 0.05 was considered statistically significant. SAS version 9.2 software (SAS Institute, Cary, North Carolina) was used for all analyses.

RESULTS

Among the 360 patients enrolled into ROSE-AHF and 94 patients in the pharmacologic arm of CARRESS-HF, 422 patients had data available for determination of DE at 72 hours (Figure 1). The median age of the study population was 69.5 years [25th %, 75th %: 61, 79]. 56% had an underlying ischemic etiology of HF and 39% had LVEF > 40% (Table 1).

Patient characteristics on the basis of the median split of DE (635 ml per 40 mg of furosemide) are displayed in Table 1. Overall, patients with low DE had lower MAP, lower serum sodium, lower GFR, and lower hemoglobin levels. In addition, those with low efficiency had higher BUN, higher albumin, higher serum creatinine, higher CysC, and higher NT-pro-BNP levels. Patients with low DE were less likely to be on ACEi/ARB therapy at time of randomization.

In-hospital Characteristics

Distribution of diuretic response by diuretic dose for the study population is provided in Figures 2a (fluid output) and 2b (change in weight). The average daily dose of IV furosemide equivalents over 72 hours was 280 mg (25th %, 75th %: 200, 405) for the low efficiency group compared to 107 mg (25th %, 75th %: 73, 160) for the high efficiency group ($P = <0.0001$). Median net fluid loss at 72 hours was 635ml/40mg furosemide (25th %, 75th %: 407, 1059). Median weight loss was -0.23 kg/40mg furosemide (25th %, 75th %: -0.49, -0.08). Total fluid output at 72 hours and weight loss (kg) were greater in the high versus low efficiency groups (Table 2). Correlation between net fluid and weight loss at 72 hours: $r = 0.58$. Patients with high DE were more likely to be on ACEi/ARB therapy at discharge or day 7. Comparison of other in-hospital characteristics including receipt of adjunctive thiazide diuretics or open-label intravenous inotropic or vasodilator support, changes in renal function and length of stay are presented in Table 2.

Determinants of high diuretic efficiency

Baseline predictors of high DE are presented in Table 3. Following adjustment for baseline characteristics, lower CysC at time of randomization was independently associated with high DE [Odds ratio 0.36 (per 1mg/L increase) (95% CI: 0.24, 0.56), $p < 0.001$]. ACEi or ARB use at baseline was associated with high DE, as was the absence of thiazide administration from randomization through 72 hours. There was a trend toward significance in the association between high DE and both higher baseline serum sodium as well as the absence of baseline β -blocker administration.

Diuretic efficiency and 60 day mortality

We compared mortality between the high and low DE groups. Kaplan-Meier survival curves are presented in Figure 2. At 60 days, 25 patients (13.1%) died in the low DE group compared to 14 patients (7.0%) in the high DE group ($p = 0.036$). In univariate modeling (as well as when adjusting for baseline characteristics alone), DE, weight change, and fluid output were associated with survival (Table 4). When DE, fluid output, weight loss, and diuretic dose were included in the same model, change in weight maintained the closest association with survival.

Analysis of interaction between eGFR and diuretic treatment group

Among the 308 patients enrolled in the DOSE-AHF study, 293 had baseline CysC and 72 hour clinical end-point data available. Baseline characteristics of the study population are presented in Table 5. Comparing high-dose to low-dose strategies, an interaction between GFR, estimated by a CysC, and the primary clinical trial endpoint, GVAS AUC, was identified (p -value for interaction = 0.03); patients with higher CysC were more likely to benefit from higher doses of diuretics. No difference in the GVAS AUC was seen between high- and low-dose strategies in the high eGFR group ($p=0.67$). Similarly, among patients with low eGFR, 18.8% of those randomized to high-dose were free of congestion at 72 hours compared to 5% of those in the low-dose group ($p=0.04$). An interaction between eGFR and treatment effect on other end-points of decongestion including change in weight and fluid output was not seen (Table 6).

Heterogeneity of treatment effect across eGFR groups was not seen between bolus versus CI administration on any clinical end-points (Table 6), although there was a trend toward an interaction with change in GVAS ($p=0.05$). The treatment effect on this end-point was in opposite directions, whereby CI administration led to greater change in GVAS compared to bolus dosing in the low eGFR group and less change the high eGFR group, although these differences were not significant.

DISCUSSION

Baseline renal insufficiency is common among patients hospitalized with AHF and is reported to be an important determinant of diuretic response(6, 15). Using data pooled from two clinical trials enrolling patients with AHF and renal insufficiency, this report demonstrates a relationship between CysC and response to loop diuretic therapy. This reports confirms past observations regarding the link between chronic kidney disease and diuretic responsiveness while adding information regarding baseline CysC as a potential determinant of diuretic responsiveness. The central findings of this investigation can be summarized as follows: 1) lower DE is associated with reduced renal function, 2) patients with renal insufficiency appear to require higher diuretic doses to achieve therapeutic decongestion, and 3) lower DE is a marker of HF disease severity and is associated with reduced survival.

Cystatin C and other determinants of diuretic responsiveness

Loop diuretics function by inhibiting the luminal $\text{Na}^+, \text{K}^+, 2\text{Cl}^-$ carrier in the thick ascending limb of the loop of Henle, minimizing the entry of sodium into the cell(16). Loop diuretics are protein-bound and enter the urine primarily via tubular secretion in the proximal tubule. Their effect is dose dependent and determined by the rate at which they are delivered to their site of action(17). Numerous pathophysiologic processes emerge during AHF episodes including hemodynamic impairment with reduced renal perfusion and neurohormonal activation—all of which may contribute to cardiorenal interactions and the development of diuretic resistance.

Evaluating data from two distinct cohorts, Testani, et al. defined a novel metric of diuretic responsiveness, termed DE, to quantify the efficiency with which diuretics facilitate urine production(9). Inpatient diuretic dose is influenced by baseline medications as well as physician prescribing practices while fluid output may be dependent on the individual degree of volume overload. The authors thus propose that the primary signal of interest is a marker of response to a given dose of diuretic. In this analysis, BUN was the only determinant of reduced DE after adjustment for other markers of disease severity. Likewise, using data from the Placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with acute heart failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial, Valente, et al., identified a correlation between BUN and a weight-based metric of DE(10). Elevated BUN during AHF therapy is a marker neurohormonal up regulation as well as of worsening renal function, both of which may constrain the diuretic response(18, 19). Additional baseline characteristics that have been associated with poor

diuretic response in other studies include lower blood pressure, diabetes, long-term loop diuretic use, worse renal dysfunction, poorer NYHA classification, and fewer signs of congestion (less edema)(20, 21).

Given the diuretic response observed in the ROSE-AHF and CARRESS-HF cohorts, these populations appear to have more advanced cardiorenal disease than included in prior investigations of diuretic responsiveness. Average diuretic response was $-0.42\text{kg}/40\text{mg}$ of furosemide in both the Efficacy and Safety of Relaxin for the Treatment of Acute Heart Failure (RELAX-AHF) as well as the A Study Testing the Effectiveness of Nesiritide in Patients With Acute Decompensated Heart Failure (ASCENT-HF) trials compared to $-0.23\text{kg}/40\text{mg}$ of furosemide in the present investigation (20, 21). Similarly, median urinary diuretic response was $-1375\text{ml}/40\text{mg}$ of furosemide per 24 hours in the ASCEND-HF trial compared to $-635\text{ml}/40\text{mg}$ of furosemide over 72 hours in the combined cohort from the ROSE-AHF and CARRESS-HF trials (20).

There are known limitations to creatinine-based estimates of renal function including the influence of body mass, diet, variable production, and tubular secretion(14, 22). Furthermore, creatinine-based GFR estimates are problematic in the non-steady state of AHF. Thus, despite the previously reported relationship between renal insufficiency and diuretic dose requirements, serum creatinine has not been identified as a marker of DE, albeit patients included in prior studies had less renal impairment than those included in the present investigation (9, 10). In contrast, CysC is a cysteine protease inhibitor that is ubiquitously produced at an approximately constant rate in nucleated cells. It is freely filtered and neither secreted nor reabsorbed. Because of these properties, CysC-based estimates of GFR have emerged as a potentially more sensitive biomarker of renal insufficiency(14).

We investigated the association between CysC and diuretic response and identified CysC at study randomization as an independent predictor of DE. These findings are similar to those reported from an analysis of the ASCEND-HF (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure) trial that found lower CysC to be associated with greater urine output (23). While CysC has been previously identified as a predictor of clinical-outcomes(24), we demonstrate its relationship to diuretic response among patients with cardiorenal disease and further highlight CysC as a biomarker of interest in AHF.

ACEi or ARB use at randomization was also associated with high DE. Beyond renal insufficiency, postulated mechanisms for loop diuretic resistance in AHF include activation of the renin-angiotensin- aldosterone system with resultant increase in proximal and distal tubule sodium reabsorption(25–27). Findings regarding the effects of ACE inhibition on renal sodium handling in HF are inconsistent. As it relates to the potential augmentation of natriuresis, ACEi may suppress circulating angiotensin II and aldosterone levels, thus reducing RAAS-mediated tubular salt reabsorption. Furthermore, ACE inhibition decreases afferent renal arteriolar vasoconstriction and increases the glomerular ultrafiltration coefficient, which may also act to augment natriuresis(28–30). Intolerance of ACEi/ARB therapy, however, is a known marker of advanced HF(31). Rather than implying a direct pharmacologic effect of RAAS inhibition on diuretic responsiveness, it is equally plausible

that observed association between ACEi/ARB use and DE is secondary to the underlying patient condition. Similar to prior observations, there was an association between β -blocker therapy use and decreased diuretic response(10). The study population in these analyses represent a high risk cohort reflected by a 60-day mortality rate of 14% in the pharmacologic arm of CARRESS-HF and 10% in the placebo arm of ROSE-AHF(11, 12). It is not clear if β -blocker therapy administration during AHF exacerbation can negatively impact hemodynamic and neurohormonal cardiorenal interactions, via a blunting of heart rate and stroke volume. There remains great uncertainty regarding management of AHF and the role of continued administration of neurohormonal antagonists including β -blocker therapy, particularly among sicker patients with evidence of cardiorenal disease. Whether continuation of these agents has a beneficial, deleterious, or net neutral effect on clinical outcomes requires further prospective investigation. Likewise, thiazide use from randomization through 72 hours was not surprisingly associated with low DE as thiazides are commonly used to overcome diuretic resistance.

Poor Diuretic Response and Clinical Outcomes

Clinical congestion is well-known to be associated with adverse outcomes. Persistent congestion at the time of discharge following AHF hospitalization as well as overload at post-discharge follow up are associated with increased risk of death and recurrent hospitalization(3, 5). Freedom from congestion was strictly defined in the NHLBI Heart Failure Network clinical studies requiring all three of the following criteria to be met: jugular venous pressure less than 8 cm, trace or absent peripheral edema, and no orthopnea. Only 9% of the CARRESS-HF pharmacologic arm and 15% of the DOSE-AHF population were free of all congestion at discharge(12, 13). While evidence of residual congestion at discharge is common following AHF hospitalization(5), this low proportion reflects the severity of illness of the cohort enrolled in these clinical studies. In the Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial comparing ultrafiltration to intravenous diuretic therapy, decreased risk of 90-day clinical events occurred in conjunction with greater volume removal in the ultrafiltration arm(32). Similarly, in a prior analysis of the DOSE-AHF trial, Kociol, et al., observed that improvement in markers of decongestion at the time of discharge was associated with improvement in clinical outcomes(4). The association between relief of congestion and improved outcomes, however, has not been consistent across studies as an analysis of the ESCAPE trial did not find a relationship between weight loss and clinical events(33). Similarly, weight loss associated with Tolvaptan administration in multiple studies has not translated to a reduction in clinical events (34–36).

In the first report of DE, Testani, et al. identified a correlation between diuretic dose, but not net fluid output, and all-cause mortality(9). After multivariable adjustment, DE alone was associated with mortality. Other studies have similarly found an association between poor diuretic response and risk of subsequent death or heart failure rehospitalization (20, 21). The PROTECT analysis found correlations between DE, weight loss, and total diuretic dose with mortality(10). DE, however, did not appear to add incremental prognostic value beyond the component variables. Similar to this later investigation, in the present study, net fluid output was associated with 60-day mortality. The risk of death decreased by 19% for each

additional 1 liter of net fluid produced within 72 hours of randomization. Weight loss was also associated with improved survival, with a 15% decrease in risk of dying per 1 kg lost.

Patients with eGFR may respond better to a high-dose diuretic strategy

The primary DOSE-AHF trial did not find a clinical benefit of a high- versus low-dose administration of loop diuretics in the setting of AHF(13). The trial did, however, provide important data regarding the safety of high-dose diuretic administration. Compared to a low-dose strategy, a high-dose strategy was associated with significantly fewer serious adverse events. Additionally, while the GVAS AUC was not different between groups, improvement in a number of secondary endpoints of decongestion, including weight loss and net fluid loss, were seen with a high-dose strategy. We investigated whether treatment interaction exists between diuretic strategies and baseline GFR, estimated by Cys-C as a biomarker of diuretic response, given the observation from the ROSE-AHF and CARRESS-HF analyses that Cys-C was closely associated with DE.

We identified a heterogeneous treatment effect across eGFR strata, whereby those with lower eGFR had greater clinical improvement with a high-dose diuretic strategy. Patients with higher eGFR responded similarly to high- and low-dose interventions. This finding is consistent with a rightward shift of the loop diuretic dose-response curve, whereby patients with cardiorenal insufficiency require higher doses of loop diuretics to achieve similar peak responses(6). Decreased renal perfusion in HF leads to decreased drug delivery, diminished proximal secretion, and up-regulation of neurohormonal pathways resulting in a sodium avid state. Successful diuresis is dependent on the effective delivery of loop diuretic to inhibit the Na⁺,K⁺,2Cl⁻ co-transporter. While the maximum effective dose differs in patients with HF and renal insufficiency, this may be partially overcome by increasing the diuretic dose(6). In an attempt to achieve maximal early decongestion, these aggregate data seem to suggest that an early, high-dose strategy is reasonable among patients presenting with AHF and concomitant renal insufficiency.

A biomarker of diuretic responsiveness may prove useful to supplement risk stratification of patients presenting to the emergency department with AHF. Patients anticipated to have high DE could more easily be selected either for discharge or ongoing care in an observation unit, while those anticipated to have low DE could more rapidly be transitioned to an inpatient unit. Thus, it is feasible that a biomarker driven strategy could prevent unnecessary hospitalization by facilitating triage of patients anticipated to be more responsive to therapy. Similarly, as a primary intervention of ambulatory disease management is titration of oral diuretics, the value of including CysC based eGFR to improve patient selection for clinical trials also merits further study. Nonetheless, it should also be acknowledged that present findings stem from a post-hoc analysis of clinical trial data and are hypothesis generating and do not imply causality. DOSE-AHF was not designed to evaluate the efficacy of diuretic strategies among patients demonstrating diuretic resistance or renal insufficiency. The lack of an interaction between GFR, diuretic strategy and other secondary end-points of decongestion including differences and fluid output and weight loss, provides caution regarding over interpretation of these findings. Further studies are necessary to confirm the

safety and efficacy of an aggressive diuretic algorithm among patients with cardiorenal disease.

Limitations—Limitations of these analyses include all of those inherent to observational, post-hoc studies utilizing clinical trial data sets; as the impact of randomization is lost, despite adjustment for baseline characteristics, residual confounding likely remains when comparing outcomes between patients with and without DE. Furthermore, patients with missing DE data were likely different than those without missing data, and excluding these patients may have introduced bias in to the analyses. ACEi/ARB use at discharge or day 7 was higher in the high DE group. While this may reflect less severe heart failure in the high DE group, underscored by intolerance to ACEi/ARB therapy in the low DE cohort, it cannot be excluded that more frequent ACEi/ARB administration in the high DE cohort led to the observed differences in clinical outcomes between DE groups. Additionally, data were pooled from two small randomized clinical trials enrolling heterogeneous populations at disparate time points during hospitalization. Enrollment criteria for CARRESS-HF included evidence of worsening renal function in the setting of diuretic dose escalation prior to or after HF hospitalization. The selection bias associated with enrolling patients defined as having cardiorenal disease likely amplified the association between renal dysfunction and diuretic requirements. Furthermore, given the known association of worsening renal function during acute HF and mortality, this may have confounded the relationship between DE and subsequent outcomes(37). Limiting the analyses, however, to a single clinical trial from the larger ROSE-AHF dataset did not significantly alter the primary findings (data not shown). Finally, diuretic response was treated as a linear relationship, when in reality the dose-response curve of loop diuretics is sigmoidal and dependent on individual patient characteristics.

Conclusions

Baseline CysC, a biomarker of renal function, correlates with response to loop diuretic therapy during AHF hospitalization. Patients with renal impairment require higher doses of diuretics to achieve therapeutic decongestion. Poor diuretic response to AHF therapy identifies a high risk population and is associated with reduced survival.

Acknowledgments

FUNDING: This research was supported in part by grants from the National Institutes of Health (coordinating center: U10 HL084904; regional clinical centers: U01 HL084861, U10 HL110312, 13 U10 HL110342, U10 HL110262, U10 HL110302, U10 HL110309, U10 HL110336, U10 HL110338)

Abbreviations

AHF	acute heart failure
CI	continuous infusion
CysC	cystatin C
eGFR	estimated glomerular filtration rate

References

1. Chaudhry SI, Wang Y, Concato J, Gill TM, Krumholz HM. Patterns of weight change preceding hospitalization for heart failure. *Circulation*. 2007 Oct 2; 116(14):1549–54. [PubMed: 17846286]
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013 Oct 15; 128(16):1810–52. [PubMed: 23741057]
3. Bettencourt P, Azevedo A, Pimenta J, Frieso F, Ferreira S, Ferreira A. N-terminal-pro-brain natriuretic peptide predicts outcome after hospital discharge in heart failure patients. *Circulation*. 2004 Oct 12; 110(15):2168–74. [PubMed: 15451800]
4. Kociol RD, McNulty SE, Hernandez AF, Lee KL, Redfield MM, Tracy RP, et al. Markers of decongestion, dyspnea relief, and clinical outcomes among patients hospitalized with acute heart failure. *Circ Heart Fail*. 2013 Mar; 6(2):240–5. [PubMed: 23250981]
5. Lucas C, Johnson W, Hamilton MA, Fonarow GC, Woo MA, Flavell CM, et al. Freedom from congestion predicts good survival despite previous class IV symptoms of heart failure. *Am Heart J*. 2000 Dec; 140(6):840–7. [PubMed: 11099986]
6. Ellison DH. Diuretic therapy and resistance in congestive heart failure. *Cardiology*. 2001; 96(3–4): 132–43. [PubMed: 11805380]
7. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation*. 2006 Mar 21; 113(11):1424–33. [PubMed: 16534009]
8. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. *J Am Coll Cardiol*. 2012 Sep 18; 60(12):1031–42. [PubMed: 22840531]
9. Testani JM, Brisco MA, Turner JM, Spatz ES, Bellumkonda L, Parikh CR, et al. Loop diuretic efficiency: a metric of diuretic responsiveness with prognostic importance in acute decompensated heart failure. *Circ Heart Fail*. 2014 Mar 1; 7(2):261–70. [PubMed: 24379278]
10. Valente MA, Voors AA, Damman K, Van Veldhuisen DJ, Massie BM, O'Connor CM, et al. Diuretic response in acute heart failure: clinical characteristics and prognostic significance. *Eur Heart J*. 2014 May 14; 35(19):1284–93. [PubMed: 24585267]
11. Bart BA, Goldsmith SR, Lee KL, Givertz MM, O'Connor CM, Bull DA, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012 Dec 13; 367(24): 2296–304. [PubMed: 23131078]
12. Chen HH, Anstrom KJ, Givertz MM, Stevenson LW, Semigran MJ, Goldsmith SR, et al. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE acute heart failure randomized trial. *JAMA*. 2013 Dec 18; 310(23):2533–43. [PubMed: 24247300]
13. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011 Mar 3; 364(9): 797–805. [PubMed: 21366472]
14. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating glomerular filtration rate from serum creatinine and cystatin. *C N Engl J Med*. 2012 Jul 5; 367(1): 20–9. [PubMed: 22762315]
15. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Card Fail*. 2007 Aug; 13(6):422–30. [PubMed: 17675055]
16. Ellison DH. Diuretic drugs and the treatment of edema: from clinic to bench and back again. *Am J Kidney Dis*. 1994 May; 23(5):623–43. [PubMed: 8172204]
17. Brater DC. Diuretic therapy. *N Engl J Med*. 1998 Aug 6; 339(6):387–95. [PubMed: 9691107]
18. Brisco MA, Coca SG, Chen J, Owens AT, McCauley BD, Kimmel SE, et al. Blood urea nitrogen/creatinine ratio identifies a high-risk but potentially reversible form of renal dysfunction in patients with decompensated heart failure. *Circ Heart Fail*. 2013 Mar; 6(2):233–9. [PubMed: 23325460]

19. Testani JM, Cappola TP, Brensinger CM, Shannon RP, Kimmel SE. Interaction between loop diuretic-associated mortality and blood urea nitrogen concentration in chronic heart failure. *J Am Coll Cardiol*. 2011 Jul 19; 58(4):375–82. [PubMed: 21757114]
20. ter Maaten JM, Dunning AM, Valente MA, Damman K, Ezekowitz JA, Califf RM, et al. Diuretic response in acute heart failure—an analysis from ASCEND-HF. *Am Heart J*. 2015 Aug; 170(2): 313–21. [PubMed: 26299229]
21. Voors AA, Davison BA, Teerlink JR, Felker GM, Cotter G, Filippatos G, et al. Diuretic response in patients with acute decompensated heart failure: characteristics and clinical outcome—an analysis from RELAX-AHF. *Eur J Heart Fail*. 2014 Nov; 16(11):1230–40. [PubMed: 25287144]
22. Shemesh O, Golbetz H, Kriss JP, Myers BD. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int*. 1985 Nov; 28(5):830–8. [PubMed: 2418254]
23. Tang WH, Dupont M, Hernandez AF, Voors AA, Hsu AP, Felker GM, et al. Comparative assessment of short-term adverse events in acute heart failure with cystatin C and other estimates of renal function: results from the ASCEND-HF trial. *JACC Heart Fail*. 2015 Jan; 3(1):40–9. [PubMed: 25453534]
24. Lassus J, Harjola VP, Sund R, Siirila-Waris K, Melin J, Peuhkurinen K, et al. Prognostic value of cystatin C in acute heart failure in relation to other markers of renal function and NT-proBNP. *Eur Heart J*. 2007 Aug; 28(15):1841–7. [PubMed: 17289743]
25. Abdallah JG, Schrier RW, Edelstein C, Jennings SD, Wyse B, Ellison DH. Loop diuretic infusion increases thiazide-sensitive Na(+)/Cl(-)-cotransporter abundance: role of aldosterone. *J Am Soc Nephrol*. 2001 Jul; 12(7):1335–41. [PubMed: 11423562]
26. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. *Ann Intern Med*. 1985 Jul; 103(1):1–6. [PubMed: 2860833]
27. Martinez-Maldonado M, Gely R, Tapia E, Benabe JE. Role of macula densa in diuretics-induced renin release. *Hypertension*. 1990 Sep; 16(3):261–8. [PubMed: 2203682]
28. Ichikawa I, Yoshioka T, Fogo A, Kon V. Role of angiotensin II in altered glomerular hemodynamics in congestive heart failure. *Kidney Int Suppl*. 1990 Nov; 30:S123–6. [PubMed: 2259071]
29. Motwani JG, Fenwick MK, Morton JJ, Struthers AD. Furosemide-induced natriuresis is augmented by ultra-low-dose captopril but not by standard doses of captopril in chronic heart failure. *Circulation*. 1992 Aug; 86(2):439–45. [PubMed: 1638713]
30. Suki WN. Renal hemodynamic consequences of angiotensin-converting enzyme inhibition in congestive heart failure. *Arch Intern Med*. 1989 Mar; 149(3):669–73. [PubMed: 2537612]
31. Kittleson M, Hurwitz S, Shah MR, Nohria A, Lewis E, Givertz M, et al. Development of circulatory-renal limitations to angiotensin-converting enzyme inhibitors identifies patients with severe heart failure and early mortality. *J Am Coll Cardiol*. 2003 Jun 04; 41(11):2029–35. [PubMed: 12798577]
32. Costanzo MR, Guglin ME, Saltzberg MT, Jessup ML, Bart BA, Teerlink JR, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol*. 2007 Feb 13; 49(6):675–83. [PubMed: 17291932]
33. Hasselblad V, Gattis Stough W, Shah MR, Lokhnygina Y, O'Connor CM, Califf RM, et al. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. *Eur J Heart Fail*. 2007 Oct; 9(10):1064–9. [PubMed: 17719273]
34. Pang PS, Konstam MA, Krasa HB, Swedberg K, Zannad F, Blair JE, et al. Effects of tolvaptan on dyspnoea relief from the EVEREST trials. *Eur Heart J*. 2009 Sep; 30(18):2233–40. [PubMed: 19561338]
35. Konstam MA, Kiernan M, Chandler A, Dhingra R, Mody FV, Eisen H, et al. Short-Term Effects of Tolvaptan in Patients With Acute Heart Failure and Volume Overload. *J Am Coll Cardiol*. 2017 Mar 21; 69(11):1409–19. [PubMed: 28302292]
36. Felker GM, Mentz RJ, Cole RT, Adams KF, Egnaczyk GF, Fiuzat M, et al. Efficacy and Safety of Tolvaptan in Patients Hospitalized With Acute Heart Failure. *J Am Coll Cardiol*. 2017 Mar 21; 69(11):1399–406. [PubMed: 27654854]

37. Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. *Eur Heart J*. 2014 Feb; 35(7):455–69. [PubMed: 24164864]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Perspectives

Competency in Medical Knowledge

Diuretic resistance, defined as poor response to loop diuretic therapy, is a marker of heart failure disease severity and associated with decreased survival.

Competency in Patient Care

Compared to those without kidney disease, heart failure patients with renal insufficiency require higher dose loop diuretics to facilitate clinical decongestion.

Translational Outlook

Prospective investigations may seek to define the role of cystatin C as a biomarker to guide patient selection for clinical trials as well as to monitor renal response to therapeutic interventions during acute heart failure episodes.

Highlights

- Renal impairment is associated with reduced diuretic responsiveness in acute heart failure.
- Diuretic resistance is a marker of heart failure disease severity and associated with increased mortality.
- Heart failure patients with concomitant kidney disease require higher loop diuretic dosing to facilitate decongestion.

Figure 1.

Consort diagram detailing the pooled study population from the ROSE-AHF and CARRESS-HF cohorts used for the predictors of diuretic efficiency and associated outcomes analyses.

Figure 2.

a Scatter plot of net IV furosemide dose equivalent by fluid output in the first 72 hours.

b Scatter plot of net IV furosemide dose equivalent by weight change in the first 72 hours.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 3.
(Central Figure) Kaplan-Meier curves for survival stratified by median diuretic efficiency. The KM mortality rate at 60 days is 13.1% in the low DE group and 7.0 % in the high DE group.

Table 1

Baseline Patient Characteristics (CARRESS-HF and ROSE-AHF)

Characteristic	All patients (N=422)	Low DE (N=211)	High DE (N=211)	p *
Age (years)	70 (61, 79)	69 (61, 81)	70 (61, 77)	0.77
Male sex	307 (73)	149 (71)	158 (75)	0.33
Weight (kg)	92 (78, 115)	91 (77, 114)	93 (79, 115)	0.55
Body Mass Index (kg/m ²)	31.6 (26.8, 38.7)	31.4 (26.9, 38.0)	31.6 (26.6, 39.5)	0.74
Years since initial HF diagnosis	4.37 (1.76, 8.36)	5.04 (2.61, 8.84)	3.99 (1.11, 8.25)	0.007
White race	317 (75)	162 (77)	155 (74)	0.43
Hypertension	348 (82)	176 (83.4)	172 (81.5)	0.61
Ischemic etiology for HF	238 (56)	119 (56.4)	119 (56.4)	1.00
Ejection fraction > 40%	164 (39)	80 (37.9)	84 (40.2)	0.63
Diabetes	245 (58)	126 (59.7)	119 (56.4)	0.49
Heart rate (bpm)	74 (66, 84)	73 (65, 84)	75 (66, 86)	0.51
Mean arterial pressure (mm Hg)	81.3 (74.3, 89.7)	80.2 (74.0, 86.7)	82.7 (75.3, 92.7)	0.02
JVP 8 cm water	386 (96)	197 (96.6)	189 (95.0)	0.43
Edema 2+	316 (75)	154 (73.3)	162 (77.1)	0.37
S3 auscultation	98 (24)	51 (24.5)	47 (22.9)	0.70
Ascites	122 (31)	62 (30.7)	60 (30.3)	0.93
Rales	228 (55)	110 (52.9)	118 (56.5)	0.46
Dyspnea VAS	58 (36, 80)	53 (35, 76)	62 (37, 80)	0.08
Global VAS	50.5 (31, 70)	50 (30, 68)	52 (33, 71)	0.13
LVEF (%)	34.5 (23, 55)	33 (20, 53)	35 (23, 55)	0.26
Moderate or severe tricuspid regurgitation	198 (47)	104 (49.8)	94 (44.5)	0.28
β-blocker therapy at randomization	345 (82)	178 (84.4)	167 (79.1)	0.17
ACEi or ARB at randomization	207 (49)	84 (39.8)	123 (58.3)	0.0001
Aldosterone antagonist at randomization	119 (28)	62 (29)	57 (27)	0.59
Thiazide diuretic in 24 hours prior to randomization	53 (13)	25 (11.8)	28 (13.3)	0.66
Baseline Laboratory Results				
Sodium (mEq/L)	138 (136, 141)	138 (135, 141)	139 (136, 141)	0.009
BUN (mg/dL)	40 (29, 56)	45 (32, 63)	35.6 (28.0, 50.0)	<0.0001
Creatinine (mg/dL)	1.78 (1.41, 2.30)	1.86 (1.50, 2.40)	1.70 (1.40, 2.20)	0.01
Cystatin C (mg/L)	1.82 (1.47, 2.30)	2.05 (1.57, 2.44)	1.66 (1.36, 2.06)	<0.0001
eGFR (mL/min/1.73m ²)	39.2 (28.9, 51.5)	37.2 (27.5, 48.9)	41.5 (30.4, 53.7)	0.002
NT pro BNP (pg/mL)	4725 (2038, 9833)	5255 (2419, 11352)	4217 (1715, 8878)	0.04
Hemoglobin (g/dL)	11.4 (10.2, 12.7)	11.3 (10.0, 12.5)	11.6 (10.4, 12.9)	0.04
Albumin (g/dL)	3.5 (3.2, 3.9)	3.60 (3.10, 4.00)	3.50 (3.20, 3.70)	0.02
Total Bilirubin (mg/dL)	0.9 (0.6, 1.4)	0.90 (0.60, 1.45)	0.90 (0.60, 1.40)	0.43
AST (U/L)	28 (21, 39)	27.5 (21.0, 39.0)	28 (22, 40)	0.69

Abbreviations: ACEi – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, AST – aspartate aminotransferase, bpm – beats per minute, BUN – blood urea nitrogen, DE – diuretic efficiency, eGFR – estimated glomerular filtration rate, HF- heart failure; JVP – jugular venous pressure, LVEF – left ventricular ejection fraction, VAS – visual analogue scale.

*
p-value comparing low versus high DE groups.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2**In-hospital Characteristics by Diuretic Efficiency**

Characteristic	Low DE (N=211)	High DE (N=211)	p [*]
Diuretic efficiency (randomization to 72h) (mL/40 mg furosemide)	407 (268, 522)	1059 (785, 1568)	NA
Net IV furosemide dose equivalent (randomization to 72h) (mg)	840 (600, 1215)	320 (220, 480)	<0.0001
Discharge oral diuretic dose in IV furosemide dose equivalents (mg)	100 (60, 200)	50 (30, 80)	<0.0001
Thiazide use from randomization to 72h (%)	78 (37.0)	39 (18.5)	<0.0001
Total fluid output in 72 hours (mL)	8030 (6300, 9915)	9071 (7240, 11775)	0.0001
Net fluid loss from randomization to 72h (mL)	3766 (2427, 5555)	5341 (3444, 7692)	<0.0001
Weight change at 72h (kg)	-2.9 (-4.9, -1.3)	-4.3 (-6.5, -1.9)	0.0002
Weight loss (kg) per 40 mg furosemide	-0.14 (-0.23, -0.05)	-0.47 (-0.91, -0.23)	<0.0001
Treated with IV inotropes/vasodilators	41.0 (19.4)	28.0 (13.3)	0.09
Increase creatinine ≥ 0.3 mg/dl prior to day 7 or discharge	79.0 (37.6)	48.0 (22.9)	0.001
Change in creatinine from randomization to 72h (mg/dL)	0.04 (-0.20, 0.25)	-0.10 (-0.30, 0.11)	0.0002
Discharge or day 7 creatinine (mg/dL)	1.90 (1.54, 2.47)	1.70 (1.32, 2.10)	<0.0001
Change in GFR (mL/min/1.73m ²) at 72h	-0.77 (-5.30, 4.21)	3.30 (-3.20, 10.40)	<0.0001
Discharge or day 7 BUN (mg/dL)	54.5 (40.0, 71.0)	39.0 (29.0, 55.5)	<0.0001
β-blocker at discharge or day 7 (%)	158 (82.3)	142 (79.8)	0.54
ACEi or ARB at discharge or day 7 (%)	59 (30.7)	95 (53.4)	<0.0001
Aldosterone antagonist at discharge or day 7 (%)	58 (30.2)	56 (31.5)	0.79
Thiazide at discharge or day 7 (%)	29 (13.9)	20 (9.6)	0.17
Net IV furosemide dose equivalent at discharge or day 7 (mg)	100 (60, 200)	40 (30, 80)	<0.0001
JVP ≥ 8 cm water at discharge or day 7 (%)	122 (65.9)	75 (41.4)	<0.0001
Edema ≥ 2+ at discharge or day 7 (%)	55 (27.0)	42 (20.9)	0.15
Congestion free at discharge or day 7 (%)	19 (9.4)	52 (26.4)	<0.0001
Global VAS at 72/96 hours (%)	70 (50, 85)	80 (61, 90)	0.0009
Days from randomization to discharge (%)	7 (5, 13)	5 (4, 7)	<0.0001

* P-values come from Wilcoxon rank sum tests or chi-square tests.

Thiazides include metolazone, chlorothiazide, and hydrochlorothiazide.

Vasodilators/inotropes include milrinone, dobutamine, dopamine, nitroglycerin, nesiritide, nitroprusside.

VAS was assessed at 72 hours in the ROSE-AHF protocol and at 96 hours in CARRESS-HF.

Abbreviations: BUN – blood urea nitrogen, DE – diuretic efficiency, IV – intravenous, JVP – jugular venous pressure, VAS – visual analogue scale.

Table 3

Multivariable Predictors of High Diuretic Efficiency (N=401)

Baseline characteristic	Odds ratio (95% CI)	p
Cystatin C (per 0.1 mg/L increase)	0.90 (0.87, 0.94)	<0.0001
Thiazide use from randomization through 72h	0.43 (0.26, 0.72)	0.001
ACEi or ARB use at randomization	1.96 (1.26, 3.07)	0.003
Sodium (per 1 mEq/L increase)	1.06 (1.00, 1.12)	0.05
Beta blocker use at randomization	0.58 (0.33, 1.02)	0.06
Ejection fraction > 40%	1.50 (0.95, 2.36)	0.08
Ischemic etiology of HF	1.17 (0.75, 1.81)	0.49
Diabetes	1.10 (0.71, 1.72)	0.66

Model selected using logistic regression with backward elimination where a p-value<0.1 was required for retention. Model was also adjusted randomized clinical trial treatment arm (CARRESS pharmacologic arm, ROSE placebo, dopamine, or nesiritide). Diabetes and ischemic etiology of HF were forced into the model for adjustment. Thiazide use included any use of metolazone, hydrochlorothiazide, or chlorothiazide.

Table 4
Associations of Diuretic Efficiency, Fluid Output, and Weight Loss with 60-day Mortality (N=422^{*})

Variable	Adjusted only for trial treatment arm		Adjusted for baseline characteristics [†]		Adjusted for baseline dose, net fluid output, and weight change characteristics [‡] , DE, diuretic	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Diuretic efficiency over 72 hours (per 100 ml/40 mg increase)	0.87 (0.80, 0.95)	0.002	0.90 (0.83, 0.98)	0.02	0.88 (0.76, 1.01)	0.07
Net IV furosemide dose equivalent from randomization to 72h (per 400 mg increase)	1.26 (1.01, 1.56)	0.04	1.10 (0.87, 1.39)	0.42	0.80 (0.52, 1.23)	0.31
Net fluid output at 72 h (per 1 liter increase)	0.86 (0.77, 0.96)	0.007	0.85 (0.76, 0.96)	0.008	0.99 (0.84, 1.17)	0.93
Weight change at 72 h (per 1 kg decrease)	0.87 (0.80, 0.94)	0.0005	0.85 (0.78, 0.93)	0.0003	0.87 (0.78, 0.97)	0.01

^{*} Up to 19 observations are excluded from some models due to missing data.

[†] Adjusted for age, mean arterial blood pressure, and BUN.

Abbreviations: DE – diuretic efficiency; h- hours; HR – hazard ratio.

Table 5**Baseline Patient Characteristics (DOSE)**

Characteristic	All patients (N=293)
Age (years)	68 (57, 77)
Male sex	217 (74)
Weight (kg)	93 (79, 109)
Body Mass Index (kg/m ²)	31.3 (26.6, 36.4)
White race	215 (73)
Hypertension	233 (80)
Ischemic etiology for HF	166 (57)
Ejection fraction > 40%	98 (34)
Diabetes	153 (52)
Heart rate (bpm)	76 (68 – 85)
Mean arterial pressure (mm Hg)	83.3 (75.7, 94.7)
JVP 8 cm water	257 (91)
Edema 2+	232 (79)
S3 auscultation	59 (21)
Ascites	85 (33)
Rales	170 (58)
Dyspnea VAS	49 (30, 71)
Global VAS	47 (27, 60)
LVEF (%)	30 (20, 50)
Moderate or severe tricuspid regurgitation	108 (37)
Beta blocker at randomization	244 (83)
ACEi or ARB at randomization	186 (63)
Thiazide diuretic in 24 hours prior to randomization	47 (16)
Baseline Laboratory Results	
Sodium (mEq/L)	138 (136, 141)
BUN (mg/dL)	32 (21, 52)
Creatinine (mg/dL)	1.40 (1.08, 1.87)
Cystatin C (mg/L)	1.48 (1.12, 1.90)
eGFR (mL/min/1.73m ²)	43.8 (30.6, 64.4)
NT pro BNP (pg/mL)	4461 (2446, 9907)
Hemoglobin (g/dL)	11.4 (10.1, 13.1)
Albumin (g/dL)	3.5 (3.1, 3.8)
Total Bilirubin (mg/dL)	1.1 (0.6, 1.5)
AST (U/L)	28 (21.5, 45.5)

Abbreviations: ACEi – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, AST – aspartate aminotransferase, bpm – beats per minute, BUN – blood urea nitrogen, DE – diuretic efficiency, eGFR – estimated glomerular filtration rate, JVP – jugular venous pressure, LVEF – left ventricular ejection fraction, VAS – visual analogue scale.

Table 6

Interaction between eGFR and diuretic strategy in the DOSE-AHF Trial

72 hour endpoint	Low eGFR*			High eGFR*			Interaction p [†]
	Low dose (N=72)	High dose (N=74)	p [‡]	Low dose (N=73)	High dose (N=74)	p [‡]	
GVAS AUC	4127±1546	4575±1421	0.07	4249±1344	4259±1399	0.67	0.03
Change in GVAS	15.8±24.5	22.9±29.6	0.07	19.7±22.4	28.7±26.4	0.11	0.07
DVAS AUC	4515±1695	4757±1502		4478±1408	4547±1551		0.26
Change in DVAS	11.2±20.0	16.7±29.8		23.9±23.0	27.9±28.0		0.19
Cumulative fluid output (L)	7.25±2.17	8.79±3.60		8.40±3.31	10.1±3.4		0.59
Weight change (kg)	-1.76±3.61	-3.55±4.33		-3.99±4.25	-4.51±3.59		0.57
Change in creatinine (mg/dL)	0.03±0.33	0.06±0.33		0.07±0.29	0.09±0.28		0.54
Free of congestion	3/60 (5.0%)	12/64 (18.8%)	0.02	10/62 (16.1%)	8/59 (13.6%)	0.69	0.04
72 hour endpoint	Low eGFR*			High eGFR*			Interaction p [‡]
	Bolus (N=76)	CI (N=70)	p [‡]	Bolus (N=71)	CI (N=76)	p [‡]	
GVAS AUC	4322±1603	4388±1381		4176±1276	4328±1453		0.92
Change in GVAS	18.8±29.0	19.8±25.2	0.87	26.8±29.1	22.0±19.8	0.37	0.05
DVAS AUC	4601±1585	4678±1625		4329±1358	4687±1572		0.32
Change in DVAS	13.4±25.1	14.5±25.6	0.98	29.6±29.9	22.3±19.9	0.23	0.09
Cumulative fluid output (L)	8.38±3.33	7.63±2.71	0.19	8.73±3.56	9.82±3.23	0.05	0.06
Weight change (kg)	-2.59±4.04	-2.72±4.15		-3.60±3.22	-4.89±4.46		0.19
Change in creatinine (mg/dL)	0.04±0.32	0.05±0.34		0.06±0.29	0.10±0.28		0.75
Free of congestion	6/65 (9.2%)	9/59 (15.3%)		11/59 (18.6%)	7/62 (11.3%)		0.18

* Low and high CKD-EPI cystatin-C GFR are based on a median split at 43.81

† P-values are for the interaction term of eGFR (as a continuous variable) and bolus v. continuous randomized treatment and low v. high dose randomized treatment in models that include both main effects and the interaction. Continuous endpoints come from linear regression and congestion free comes from logistic regression.

‡ P-values within eGFR groups are only presented where the interaction p-value < 0.10 and come from Wilcoxon rank sum tests.

Abbreviations: AUC – area under the curve, DVAS – dyspnea visual analogue scale, GVAS – global visual analogue scale.