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Abstract

Background—Worsening renal function in heart failure may be related to increased venous congestion, decreased cardiac output, or both. Diuretics are universally used in acute...
decompensated heart failure, but they may be ineffective and may lead to azotemia. We aim to compare the decongestive properties of a urine output-guided diuretic adjustment to standard therapy for the management of cardiorenal syndrome in acute decompensated heart failure.

**Methods**—Data were pooled from subjects randomized to the stepwise pharmacological care algorithm (SPCA) in the CARRESS-HF trial and those who developed cardiorenal syndrome (rise in creatinine >0.3 mg/dL) in the DOSE-AHF and ROSE-AHF trials. Patients treated with SPCA (n=94) were compared to patients with standard decongestive therapy (SDT) that included intravenous loop diuretic use (DOSE-AHF and ROSE-AHF, n=107) at the time of cardiorenal syndrome and followed for net-fluid balance, weight loss, and changing renal function.

**Results**—The SPCA group had higher degrees of jugular venous pressure (p<.0001) at the time of cardiorenal syndrome. The group that received the SPCA had more weight change (-3.4±5.2 lbs) and more net fluid loss (1.705±1.417 L) after 24 hours than SDT (-0.8±3.4 lbs and 0.892±1.395 L, respectively; p<0.001 for both) with a slight improvement in renal function (creatinine change -0.1±0.3 vs. 0.0±0.3 mg/dL, respectively; p=0.03).

**Conclusions**—Compared to SDT, patients who received an intensification of medication therapy for treating persisting congestion had greater net-fluid and weight loss without being associated with renal compromise.

**Keywords**

acute decompensated heart failure; cardiorenal syndrome; diuretics

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**INTRODUCTION**

A rise in serum creatinine during decongestive therapy occurs in approximately one quarter of patients presenting with acute heart failure and is associated with poor outcomes.\(^1\)\(^-\)\(^3\) Sometimes termed “cardiorenal syndrome” (type 1), this phenomenon occurs as a result of the complex interplay between arterial underfilling, venous congestion, and maladaptive neurohormonal and hemodynamic changes.\(^4\) Yet, relief of congestion via diuretics can help alleviate persistent congestion without deterioration of renal function if adequate fluid loss is achieved.\(^5\), \(^6\) Subsequent to the Diuretic Optimization Strategies Evaluation Acute Heart Failure (DOSE-AHF) trial\(^7\) showing high dose of diuretics provides decongestion without renal dysfunction, other trials have employed this approach including the Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-AHF) trial\(^8\) as standard diuretic therapy (SDT).\(^8\)

Another approach for decongestion has been through stepped pharmacological care that included inotropes and vasodilator therapy such as used in the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF).\(^9\) In this approach, investigators designed a stepped pharmacologic care algorithm (SPCA) that targeted a high volume output by intention (urine) for management of patients’ heart failure. Since the SPCA protocol achieved successful diuresis as demonstrated in CARRESS-HF in comparison to ultrafiltration, we hypothesize that an intense medication therapy regimen via a goal-oriented, urine output-directed SPCA can achieve more effective diuresis than standard
approaches in congested, non-oliguric patients admitted with acute heart failure who experienced a rise in serum creatinine.

METHODS

Study Population

We included three studies conducted within the NHLBI-sponsored Heart Failure Clinical Trials Network. The protocols were approved by the Institutional Review Board at each site, and written informed consent was obtained from all patients prior to randomization. All trials were conducted in the United States and Canada.

The DOSE-AHF trial (conducted from 2008 to 2009 at 26 clinical sites) assessed the effectiveness and renal consequences of high vs. low dose loop diuretic and bolus vs. continuous infusion intravenous loop diuretic dosing in hospitalized patients with acute decompensated heart failure. Of the 308 patients randomly assigned, 151 were assigned to low dose loop diuretic, 157 to high dose loop diuretic, 156 to bolus dosing, and 152 to continuous infusion dosing.

The ROSE-AHF trial (conducted between 2010 and 2013 at 26 clinical sites) assessed the effectiveness of decongestive therapies and renal consequences with placebo compared to additional low-dose dopamine (2 μg/kg/min) or low-dose nesiritide (0.005 μg/kg/min) in hospitalized patients with acute decompensated heart failure and renal dysfunction (glomerular filtration rate 15–60mL/min/1.73 m² as estimated by the Modification of Diet and Renal Disease equation). Of the 360 patients randomly assigned, 122 were assigned to low-dose dopamine and 119 to low-dose nesiritide which were both compared to placebo in a 2:1 fashion.

The CARRESS-HF trial (conducted between 2008 and 2012 at 22 clinical sites) assessed the effectiveness of ultrafiltration as a primary decongestive therapy in comparison to a stepwise urine-output guided diuretic dosing algorithm in patients hospitalized with acute decompensated heart failure and worsening renal function (>0.3 mg/dL rise in serum creatinine) within the prior 6 weeks before or 10 days after admission for heart failure. Of the 188 randomly assigned patients, 94 were enrolled in the ultrafiltration arm and 94 were enrolled in the stepwise urine-output guided diuretic dosing algorithm.

Data Synthesis

In order to compare the effectiveness and renal consequences of an intensification of medical therapy via urine output guided diuretic approach to SDT in patients with cardiorenal syndrome, we completed a post-hoc analysis of a pooled cohort of patients from DOSE-AHF, ROSE-AHF, and CARRESS-HF. Patients in DOSE-AHF and ROSE-AHF who developed cardiorenal syndrome (herein defined as >0.3 mg/dL increase in creatinine from baseline) during hospitalization for acute heart failure were included into the SDT group. Patients randomly assigned to a urine output-guided stepped diuretic dosing approach in CARRESS-HF were included into the stepwise pharmacological care algorithm (“SPCA”) group. Patients were excluded if they were without follow-up examinations, fluid...
and weight assessments, or laboratory measures at least 24 hours after meeting criteria for cardiorenal syndrome (Figure 1).

**Standard Diuretic Therapy**

Patients from DOSE-AHF were randomly assigned to four diuretic dosing strategies. Patients were given the total daily intravenous furosemide dose equivalent to their prior daily loop diuretic dose in the low-dose strategy or to a total daily intravenous furosemide dose that was 2.5 times their prior daily loop diuretic dose in the high-dose strategy. These dosing strategies were randomly assigned to intravenous bolus dosing every 12 hours or continuous intravenous infusion. In contrast, all patients in ROSE-AHF received open-label, intravenous diuretic at a total daily intravenous furosemide dose that was 2.5 times their daily loop diuretic dose prior to hospitalization. Patients naïve to loop diuretics were given a twice daily intravenous dosing of furosemide at 40 mg. There were no urine-output goals in decongestive strategies for both DOSE-AHF and ROSE-AHF trials.

**Stepwise Pharmacological Care Algorithm**

In CARRESS-HF, patients randomly assigned to intravenous diuretic therapy were placed on a urine-output guided stepped pharmacologic approach to intensify their prior medical therapies. Clinicians and practitioners were encouraged to increase or decrease diuretic dose in order to maintain a daily urine output of 3–5 L, with the ultimate goal to achieve euvolemia. The diuretic titration algorithm is listed in Figure 2. This algorithm included provisions for vasoactive or inotropic adjunctive therapies based on the patients’ clinical factors in those who were unable to meet this goal despite aggressive decongestive therapies.

**Outcome Assessment**

All outcomes were assessed from the time point when a patient met criteria for cardiorenal syndrome in DOSE-AHF and ROSE-AHF to 24 hours and at 24 hours from randomization in CARRESS-HF. The effectiveness of decongestion was assessed via change in weight and net fluid loss. Changing renal function was assessed via changes in creatinine and blood urea nitrogen.

**Statistical Analysis**

Data are presented as median [interquartile range] or mean ± standard deviation for continuous variables and number [percent] for categorical variables. The Kruskal-Wallis, chi-square, and ANOVA tests were used to compare characteristics and outcomes between groups. For biomarker outcomes, linear regression models were used to calculate change from cardiorenal syndrome diagnosis till 24 hours after with adjustment for the value at cardiorenal syndrome diagnosis. All analyses compared characteristics and outcomes between the SDT and SPCA groups. Two-sided p-values <0.05 were considered statistically significant. All statistical analyses were conducted using SAS software, version 9.2 (SAS Institute Inc., Cary, NC).
RESULTS

Our cohort was comprised of 208 patients from the DOSE-AHF, ROSE-AHF, and CARRESS-HF trials. There were 91 patients from CARRESS-HF included in this study who underwent decongestion via the stepwise pharmacological care algorithm with follow-up data 24 hours after randomization. The SDT group (N=107) was comprised of 55 patients from DOSE-AHF and 52 patients from ROSE-AHF who developed cardiorenal syndrome during the course of treatment. Patients in the SPCA group met criteria for the cardiorenal syndrome at the time of randomization, in accordance with entry criteria of the CARRESS-HF trial. In the SDT group, 35 patients met criteria for the cardiorenal syndrome by 24 hours after randomization, 48 patients met the criteria for the cardiorenal syndrome by 48 hours after randomization, and 24 patients met criteria for the cardiorenal syndrome by 72 hours after randomization. There were an additional 22 patients randomly assigned in ROSE-AHF who met criteria for cardiorenal syndrome at 72 hours who were not included in this analysis because of the end of the follow-up period (i.e. no urine output or weight or renal data beyond this time point).

Before meeting criteria for cardiorenal syndrome, patients in the SDT group had better renal function based on creatinine (1.6 [1.3, 2.1] mg/dL) and cystatin C (1.8 [1.4, 2.3] mg/L) in comparison to the SPCA group (creatinine 2.3 [1.8, 2.7] mg/dL and cystatin C 2.3 [1.8, 2.7] mg/L, p<.0001 for both). Yet, median aminoterminal pro-B-type natriuretic peptide levels were not significantly different between the SDT and SPCA groups at that point (3,968 [1,151, 8,440] vs. 4,307 [2,017, 8,791] pg/mL, respectively; p=0.3).

Baseline Characteristics

Baseline characteristics were compared at the time of cardiorenal syndrome for the SDT group and for the SPCA group at randomization and are shown in Table 1. This cohort was representative of a contemporary population of patients hospitalized with severe chronic heart failure complicated by cardiorenal syndrome. Baseline demographics, medical histories, inotrope or IV vasoactive medication use, and heart failure disease severity were similar between the two groups, respectively (p>0.05 for all). Also, there were no differences in implantable cardioverter-defibrillator use or prehospitalization heart failure medications including pre-hospitalization diuretic dose (p>0.05 for all). As expected (due to the inclusion criteria for CARRESS-HF), we observed that the SPCA group had worse renal function (creatinine 2.3 [1.8, 2.7] mg/dL and cystatin C 2.3 [1.8, 2.7] mg/L) than the SDT group (creatinine 1.6 [1.3, 2.1] mg/dL and cystatin C 1.8 [1.4, 2.3] mg/L; p<.0001 for both) at randomization prior to receiving their assigned decongestive therapies. There were 26/198 (13%) who were on vasoactive medications or inotropes by 72 hours of randomization and 5 of these 26 were on these infusions prior to randomization.

At the time of cardiorenal syndrome (Table 1), serum sodium (138 vs. 138 mEq/L), creatinine (2.2 vs. 2.3 mg/dL), and blood urea nitrogen (46 vs. 50 mg/dL) were similar between the SDT and SPCA groups, respectively (p>0.05 for all). Although the median body weight was not different at the time of cardiorenal syndrome between groups (218.4 vs 229.5 lbs, p=0.14; for SDT and SPCA, respectively), patients given SPCA were more
centrally congested than patients who received SDT as they had higher jugular venous pressures (p<.0001, Table 1).

**Effectiveness of Decongestion and Renal Function Changes**

Both treatment methods resulted in both negative weight change and net fluid loss 24 hours after meeting criteria for cardiorenal syndrome (Figure 3). However, when compared to SDT, the SPCA arm resulted in a larger net negative weight change (-3.4 vs -0.8 lbs, p=0.0001) and more net fluid loss (1.705 vs. 0.892 L, p<.0001). Despite the pharmacologic decongestion in both groups, there was minimal change in renal function. Indeed, there was also improved serum creatinine in the SPCA group (-0.1 ± 0.3 mg/dL) compared to the SDT group (0.0 ± 0.3 mg/dL, p=0.03), but this difference was small and there were no additional differences in changing blood urea nitrogen between treatment groups (3.4 vs 1.5 mg/dL, p=0.1 for SDT and SPCA, respectively). Inotrope or IV vasoactive medication use 24 hours after meeting criteria for cardiorenal syndrome was similar for the two groups (10.3% vs 7.7%, p=0.53 for SDT and SPCA, respectively). There was no interaction between the use of vasoactive or inotrope medications and creatinine change (P=0.17). Assuming a correction for multiple comparisons (p<0.01), net weight change and net fluid loss are still significantly different. In a sensitivity analysis assessing these outcomes 48 hours after meeting criteria for cardiorenal syndrome, the outcome comparisons were comparable. Compared to the SDT group (N=53), the SPCA group (N=91) still had a higher weight change (-7.4±8.7 vs. -1.7±4.8 lbs, p<.0001) and larger net fluid loss (3.892 vs. 1.770 L, p<.0001) without any differences in creatinine change (-0.1±0.4 vs. -0.1±0.5 mg/dL, p=0.8) or blood urea nitrogen change (2.9±14.7 vs. 5.5±11 mg/dL, p=0.3).

**DISCUSSION**

In this pooled analysis of the 3 contemporary clinical trials conducted in a standardized fashion by the National Heart, Lung, and Blood Institute (NHLBI)–sponsored Heart Failure Research Network, we compared target-based intensification of medication therapy with standard diuretic therapy for the management of persisting congestion in patients with acute heart failure with rising serum creatinine. The main finding from this analysis is that intensifying medical therapies while targeting a 3–5 L/day urine output is associated with a greater amount of weight loss and a higher net fluid loss than standard diuretic therapy alone without any further worsening renal function. It is important to highlight that these patients remained congested by physical examination and maintained their ability to produce urine output despite a rise in serum creatinine levels during decongestion. These findings imply that a diuretic treatment goal in the setting of persistent congestion can be safely achieved by a regimented escalating and/or adjunctive diuretic/vasoactive drug therapies.

The pathophysiology of acute cardiorenal syndrome in heart failure results from complex hemodynamic and neurohormonal interactions between the failing heart and the kidney.(4) Although worsening renal function was traditionally believed to result from decreasing cardiac output or diuretic-induced intravascular volume depletion,(10) recent insights suggest that venous congestion has an important contributing role especially in the setting of an increasing serum creatinine during decongestive therapy.(11, 12) It is also important to
point out that the occurrence of rising serum creatinine has been more closely linked to inadequate fluid loss than drop in right atrial pressure. (5) Progressive and persistent hemodynamic perturbations often stimulate activation of neurohormonal mechanisms that are meant to preserve cardiac output and renal perfusion, but can also lead to a vicious cycle of further increased cardiac filling pressures and reduced cardiac output. (13) However, if congestion persists and the ability for the kidney to mobilize fluid remains intact (i.e. diuretic-responsive), aggressive decongestive strategies may even overcome such counter-regulatory mechanisms. (14)

Decongestion has an important role in interrupting the cardiorenal cascade by lowering right and left-sided cardiac filling pressures (known as the “reverse Bernheim phenomenon”) and reducing both central venous and intra-abdominal pressure. (15) Yet, escalating standard diuretic therapy may or may not always achieve this goal in part due to diminished diuretic responsiveness, (16) post-diuretic sodium retention, (17) or simply iatrogenic worsening azotemia (or hemoconcentration) from intravascular volume depletion. (18) Nevertheless, there is growing evidence that the ability to achieve adequate volume removal can be associated with improvement in renal function, (5) and can achieve favorable outcomes even in the setting of worsening renal function as indicated by rise in serum creatinine. (6) Our present finding that the SPCA group achieved greater weight change and net fluid loss than that in the SDT group also supports the main findings from DOSE-AHF study that suggest safe use of high-dose diuretic therapy with no significant renal compromise following escalating doses to achieve adequate decongestion. (7)

Results from the CARRRESS-HF trial demonstrated similar amounts of volume removal between mechanical ultrafiltration and an aggressive stepwise, urine output target-guided diuretic dosing algorithm in patients with acute heart failure complicated by cardiorenal syndrome. (9) This is an important departure from the traditional viewpoint that aggressive diuresis itself is the primary instigator of cardiorenal syndrome. In fact, patients randomly assigned to the ultrafiltration even had transient increases in serum creatinine while patients receiving the SPCA did not. Such observations may support the concept that transient rise in serum creatinine may not be the best indicator for acute kidney injury or compromise in the setting of acute heart failure. (19)

This is a post-hoc analysis and is, thus, hypothesis generating. By comparing the SPCA arm of CARRRESS-HF with patients from DOSE-AHF and ROSE-AHF who experienced the same rise in serum creatinine in this analysis, we also provided a parallel look at what the impact of a medication intensification approach would achieve incrementally. Nevertheless, the results of this study must be interpreted within the context of several notable limitations. This is a retrospective, post hoc analysis pooled from cohorts of three randomized controlled trials with slightly different heart failure populations despite recruiting from sites within the same clinical trials network. We cannot exclude the possibility that baseline differences between patients in the SDT and SPCA groups affected the findings despite similarities between the groups demonstrated in Table 1. For example, the greater degree of congestion at baseline in the SPCA group may have contributed to the greater decongestion achieved in this group. In addition, differences in the rate at which cardiorenal syndrome developed or changes in medications prior to the worsening of renal function could have influenced the
differences in outcomes observed between the STD and SPCA groups. Despite these concerns, it is still important that the increased decongestion with SPCA was not achieved at the expense worsening renal function.

CONCLUSION

Compared to SDT, a urine output-guided SPCA achieved greater net-fluid and weight loss without provoking more renal compromise in patients developing the cardiorenal syndrome during an episode of acute decompensated heart failure and persisting congestion. To our knowledge, this represents the first analysis exploring the safety and effectiveness of an SPCA in this common and challenging clinical setting. These findings also support the use of aggressive decongestive pharmacological therapies for treating the cardiorenal syndrome in non-oliguric patients. This analysis also highlights the potential efficacy of goal-directed treatment algorithms to better achieve adequate decongestion and underscores the need to better understand the pathophysiology of worsening renal function in patients with acute decompensated heart failure. These results should provoke further investigations defining whether a goal-directed SPCA can improve long-term outcomes across the spectrum of acute heart failure.

Acknowledgments

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HIGHLIGHTS

- Targeted therapies may promote more decongestion in AHF with cardiorenal syndrome.
- This approach to decongestion may not provoke more azotemia than standard care.
- Urine-output was stable despite prior azotemia and intense diuretic titration.
- Target-guided decongestive regimens may be safe and effective in this population.
Figure 1. Consort Diagram of the Two Treatment Groups Derived from the 3 Trials
Abbreviations: CARRESS-HF, Cardiorenal Rescue Study in Acute Decompensated Heart Failure; DOSE-AHF, Diuretic Optimization Strategies Evaluation Acute Heart Failure; ROSE-AHF, Renal Optimization Strategies Evaluation in Acute Heart Failure; SPCA, stepwise pharmacological care algorithm; and CRS, cardiorenal syndrome.
Figure 2. The Urine Output-Guided Stepwise Pharmacological Care Algorithm for Diuretic Adjustment
*Presence of persisting volume overload
†Dopamine or dobutamine at 2 μg/kg/min if SBP < 110 mmHg and LVEF<40% or RV systolic dysfunction; or nitroglycerin of nesiritide if SBP > 120 mmHg (any LVEF) and severe symptoms.
‡Hemodynamic guided iv therapy left ventricular assist device, dialysis, or ultrafiltration cross over
Figure 3. Changes in Decongestion and Renal Function Changes during Decongestive Therapies for Cardiorenal Syndrome

P-value calculated via ANOVA for weight change and fluid loss. P-value calculated via linear regression with adjustment for the baseline value at time of cardiorenal syndrome diagnosis for creatinine and blood urea nitrogen. Abbreviation: SPCA: stepwise pharmacological care algorithm and BUN: blood urea nitrogen.
Table 1
Baseline Characteristics of Study Participants at the Time of Cardiorenal Syndrome Diagnosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>SDT (N=107)</th>
<th>SPCA (N=91)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Age [years]</td>
<td>68 [56, 77]</td>
<td>66 [57, 78]</td>
<td>0.84</td>
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<tr>
<td>Male N(%)</td>
<td>72 (67.3)</td>
<td>65 (71.4)</td>
<td>0.53</td>
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<tr>
<td>Ischemic Cardiomyopathy</td>
<td>62 (57.9)</td>
<td>45 (49.5)</td>
<td>0.23</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>75 (70.1)</td>
<td>60 (65.9)</td>
<td>0.53</td>
</tr>
<tr>
<td>ICD</td>
<td>46 (43.0)</td>
<td>28 (30.8)</td>
<td>0.08</td>
</tr>
<tr>
<td>Weight [lbs]</td>
<td>218.4 [177.7, 258.4]</td>
<td>229.5 [190.4, 291.6]</td>
<td>0.14</td>
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<tr>
<td>ACE Inhibitor or ARB§</td>
<td>60 (56.1)</td>
<td>41 (45.1)</td>
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<tr>
<td>Beta-blocker§</td>
<td>89 (83.2)</td>
<td>68 (74.7)</td>
<td>0.14</td>
</tr>
<tr>
<td>MRA§</td>
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<td>23 (25.3)</td>
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</tr>
<tr>
<td>Prehospitalization loop diuretic dose [furosemide equivalents, mg]</td>
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<td>100 [60, 160]</td>
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<td>Inotrope or IV Vasoactive Medication</td>
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<tr>
<td>JVP 8–12 cm H₂O</td>
<td>50 (53.2)</td>
<td>18 (20.7)</td>
<td>&lt;.0001</td>
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<tr>
<td>JVP 13–16 cm H₂O</td>
<td>14 (14.9)</td>
<td>27 (31.0)</td>
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</tr>
<tr>
<td>JVP &gt; 16 cm H₂O</td>
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<td>39 (44.8)</td>
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<td>NYHA Class II§</td>
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<td>NYHA Class III§</td>
<td>63 (63.0)</td>
<td>56 (65.1)</td>
<td>0.39</td>
</tr>
<tr>
<td>NYHA Class IV§</td>
<td>32 (32.0)</td>
<td>30 (34.9)</td>
<td></td>
</tr>
<tr>
<td>LVEF [%]§</td>
<td>35 [21, 53]</td>
<td>35 [25, 55]</td>
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<tr>
<td>Sodium [mEq/L]</td>
<td>138 [135, 139]</td>
<td>138 [136, 140]</td>
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<tr>
<td>Creatinine [mg/dL]</td>
<td>2.2 [1.8, 2.6]</td>
<td>2.3 [1.8, 2.7]</td>
<td>0.45</td>
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<tr>
<td>BUN [mg/dL]</td>
<td>46 [33, 67]</td>
<td>50 [39, 64]</td>
<td>0.49</td>
</tr>
</tbody>
</table>

* Values are median [interquartile range] or N(%) and P-values calculated via the Kruskal-Wallis or chi-square tests.
† Abbreviations: SDT: standard diuretic therapy; SPCA: stepwise pharmacological care algorithm; ICD: implantable cardioverter-defibrillator; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; MRA: mineralocorticoid antagonist; JVP: jugular venous pressure; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; and BUN: blood urea nitrogen.
‡ Missing data: Weight: N=4; JVP: N=17; LVEF: N=2; Sodium: N=1; and BUN: N=1.
§ Randomization characteristics.