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ORIGINAL RESEARCH

Ultrafiltration in Acute Heart Failure: Implications of Ejection Fraction and Early Response to Treatment From CARRESS-HF

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BACKGROUND: Ultrafiltration is not commonly used because of higher incidence of worsening renal function without improved decongestion. We examined differential outcomes of high versus low fluid removal and preserved versus reduced ejection fraction (EF) in CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure).

METHODS AND RESULTS: Baseline characteristics in the ultrafiltration arm were compared according to 24-hour ultrafiltration-based fluid removal above versus below the median. Patients were stratified by EF (≤40% or >40%). We compared clinical parameters of clinical decongestion during the hospitalization based on initial (≤24 hours) response to ultrafiltration. Cox-proportional hazards models were used to identify associations between fluid removal <24 hours and composite of death, hospitalization, or unscheduled outpatient/emergency department visit during study follow-up. The intention-to-treat analysis included 93 patients. Within 24 hours, median fluid removal was 1.89 L (Q1, Q3: 1.22, 3.16). The high fluid removal group had a greater urine output (9.08 versus 6.23 L, *P*=0.027) after 96 hours. Creatinine change from baseline to 96 hours was similar in both groups (0.10 mg/dL increase, *P*=0.610). The EF >40% group demonstrated larger increases of change in creatinine (*P*=0.023) and aldosterone (*P*=0.038) from baseline to 96 hours. Among patients with EF >40%, those with above median fluid removal (n=17) when compared with below median (n=17) had an increased rate of the combined end point (87.5% versus 47.1%, *P*=0.014).

CONCLUSIONS: In patients with acute heart failure, higher initial fluid removal with ultrafiltration had no association with worsening renal function. In patients with EF >40%, ultrafiltration was associated with worsening renal function irrespective of fluid removal rate and higher initial fluid removal was associated with higher rates of adverse clinical outcomes, highlighting variable responses to decongestive therapy.

Key Words: congestion ■ heart failure ■ ultrafiltration

Diuretics improve symptoms in most patients with acute heart failure (AHF), yet more aggressive volume removal strategies such as ultrafiltration have not shown to be superior.[1–3] The UNLOAD (Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure) and AVOID-HF (Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure) trials showed that ultrafiltration resulted in more weight loss and net fluid loss as well as more favorable clinical outcomes compared with usual care.[2,3] Because a higher incidence of worsening renal function (WRF) without improved decongestion and increased adverse events related to vascular access complications were observed in CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure),

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CLINICAL PERSPECTIVE

What Is New?

- Higher initial fluid removal with ultrafiltration had no association with worsening renal function.
- In patients with an ejection fraction >40%, ultrafiltration was associated with worsening renal function irrespective of fluid removal.
- In patients with an ejection fraction >40%, higher initial fluid removal rate was associated with higher rates of adverse clinical outcomes.

What Are the Clinical Implications?

- We provide new insights into the mechanics of aggressive fluid removal in patients hospitalized for heart failure.
- The work highlights the variable responses to decongestive therapy.
- Heart failure with more preserved ejection fraction appears to be more prone to complications with aggressive fluid removal.

Nonstandard Abbreviations and Acronyms

AHF	acute heart failure
CARRESS-HF	Cardiorenal Rescue Study in Acute Decompensated Heart Failure
WRF	worsening renal function

ultrafiltration is not commonly used.[1] We hypothesized that WRF in the ultrafiltration group was attributable to overaggressive volume removal in certain AHF subgroups. Ultrafiltration may have had different cardiorenal implications in patients with volume redistribution rather than volume overload as the predominant cause of decompensation because the mechanical removal of intravascular volume may lead to vascular underfilling overwhelming the capillary refill rate.[4–6] Patients with AHF and preserved ejection fraction (EF) may be particularly susceptible to rapid volume shifts, leading to worsened renal and cardiovascular outcomes.[7] The present analysis of CARRESS-HF examines differential outcomes of high versus low fluid removal and preserved versus reduced EF.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. CARRESS-HF compared ultrafiltration at a constant rate of 200 mL/h with stepped pharmacological therapy among patients hospitalized for AHF who had already demonstrated WRF. Study groups experienced similar fluid removal and weight reduction, but creatinine increase was more frequent with ultrafiltration.[1] Although 200 mL/h was the target fluid removal rate, many patients did not achieve this rate.[8] For the present analysis, baseline characteristics in the ultrafiltration arm were compared according to 24-hour ultrafiltration-based fluid removal above versus below the median. Patients were stratified by EF (≤40% or >40%). Ultrafiltration therapy was interrupted or discontinued for reasons such as hemodynamic instability, achievement of optimal volume status, evidence of volume depletion, increasing creatinine, and filter clotting or other vascular access dysfunction.[8] Outcomes of interest included net urine output, weight change, and change in serum creatinine, serum urea nitrogen (SUN), N-terminal pro–brain natriuretic peptide, plasma renin activity, and aldosterone from baseline to 96 hours. Further, we evaluated the change in clinical congestion (jugular venous distension, edema, and orthopnea), days from randomization to discharge (named further length of stay), and composite outcome of death, hospitalization, or unscheduled outpatient/emergency department visit during study follow-up (60 days).

Statistical Analysis

The intention-to-treat (ITT) population made the main cohort in our analysis. For the present analysis, patients were stratified by above and below median of fluid removal at 24 hours, and baseline characteristics were compared. Continuous variables were reported as median (25th percentile, 75th percentile) and compared using Wilcoxon rank-sum tests. Categorical variables were presented as frequencies and percentages and compared using the chi-square test or the Fisher's exact test when the frequencies were not sufficient.

Wilcoxon rank-sum test and Pearson chi-square test or Fisher's exact test were also used to compare the changes from baseline to 96 hours of the outcomes of interest between our subgroups of interests. Our subgroups of interest were above and below median fluid removal at 24 hours, >40% and ≤40% baseline EF, EF subgroups were further stratified by above and below median fluid removal at 24 hours.

Unadjusted and adjusted Cox proportional hazards models were used to identify associations between fluid removal within the first 24 hours and composite. Age, sex, body mass index, creatinine, and EF were used as adjustment variables similarly to primary CARRESS-HF publication.[1]

Additionally, a sensitivity analysis was included for the as-treated population, where patients who were randomized

to ultrafiltration but did not go on to receive therapy were excluded. *P* value <0.05 was considered significant. All statistical analyses were performed using SAS (version 9.4).

This primary study (CARRESS-HF) was approved by the institutional board review and patients gave signed informed consent.

RESULTS

Intention-to-Treat Analysis

The ITT analysis of CARRESS-HF included 93 patients treated with ultrafiltration (49.7% of the original trial cohort). There were a total of 58 events over a median of 39 days of follow-up. Within 24 hours, median fluid removal was 1.89 L (Q1, Q3: 1.22, 3.16). Baseline characteristics including age, sex, severity of congestion, race, relevant comorbidities, prior AHF hospitalizations, SUN and creatinine were similar in both the high (n=47) and low (n=46) fluid removal groups (all *P*> 0.05) (Table 1). The high fluid removal group had a greater urine output (9.08 versus 6.23 L, *P*=0.027) and weight loss (13.89 versus 9.67 lbs, *P*=0.044) after 96 hours. Creatinine change from baseline to 96 hours was similar in both groups (0.10 mg/dL increase, *P*=0.610) (Table 2).

Patients with EF ≤40% (n=59) versus > 40% (n=35) had a median of 2.28 L (Q1, Q3: 1.22, 3.29) versus 1.75 L (Q1, Q3: 1.14, 2.80) fluid removed in the first

Table 1. Baseline Characteristics Stratified by the Fluid Removal in the First 24 hours (Above and Below Median)

	Below Median* (N=46)	Above Median* (N=47)	*P* Value
Demographics			
Age in years, median (25th, 75th)	72.5 (61.0–79.0)	68 (61.0–76.0)	0.205
Male sex, n/N (%)	34/46 (73.9%)	38/47 (80.9%)	0.424
White race, n/N (%)	34/46 (73.9%)	37/47 (78.7%)	0.585
Medications received before hospitalization			
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, n/N (%)	24/46 (52.2%)	27/47 (57.4%)	0.609
Beta blocker, n/N (%)	35/46 (76.1%)	38/47 (80.9%)	0.576
Aldosterone antagonist, n/N (%)	10/46 (21.7%)	11/47 (23.4%)	0.848
Diuretic use, n/N (%)	40/46 (87.0%)	45/47 (95.7%)	0.158
Furosemide equivalent diuretic dose, median (25th, 75th)	120.0 (40.0–180.0)	120.0 (80.0–240.0)	0.361
Medical history			
Ejection fraction, median (25th, 75th)	34.0, (20.0–55.0)	27.0 (20.0–45.0)	0.378
Hospitalization for heart failure in previous y, n/N (%)	34/46 (73.9%)	35/46 (76.1%)	0.81
Ischemia as cause of heart failure, n/N (%)	31/46 (67.4%)	34/47 (72.3%)	0.603
Diabetes mellitus, n/N (%)	31/46 (67.4%)	29/47 (61.7%)	0.566
Atrial fibrillation, n/N (%)	30/46 (65.2%)	23/47 (48.9%)	0.113
Percutaneous transluminal coronary angioplasty, n/N (%)	12/46 (26.1%)	20/47 (42.6%)	0.095
Coronary artery bypass grafting, n/N (%)	15/46 (32.6%)	20/47 (42.6%)	0.322
Sustained ventricular tachycardia or ventricular fibrillation arrhythmia, n/N (%)	4/46 (8.7%)	5/47 (10.6%)	1.000
Aortic or mitral valve disease, n/N (%)	15/44 (34.1%)	21/46 (45.7%)	0.263
Weight, lbs, median, (25th, 75th)	206.6, (179.5–265.4)	207.7 (162.5–264.3)	0.707
Peripheral edema (moderate +), n/N (%)	41/46 (89.1%)	39/47 (83.0%)	0.392
Rales, n/N (%)	26/46 (56.5%)	28/47 (59.6%)	0.766
Orthopnea (2 pillows +), n/N (%)	36/45 (80.0%)	39/43 (90.7%)	0.157
Dyspnea visual analog scale, median, (25th, 75th)	46.5 (28.0–70.0)	54.0 (30.0–76.0)	0.282
New York Heart Association class (III, IV), n/N (%)	45/45 (100.0%)	45/45 (100.0%)	-
Biomarkers			
Creatinine, mg/dL, median, (25th, 75th)	2. (1.6–2.4)	1.9 (1.5–2.4)	0.737
N-terminal pro–brain natriuretic peptide, pg/mL, median,	5702.0 (3011.0–11701.0)	4013 (2236.0–9950.0)	0.259
Plasma renin activity, median, (25th, 75th)	4.9 (1.8–17.0)	9.3 (2.9–17.1)	0.256
Aldosterone, median, (25th, 75th)	213.6 (124.4–419.9)	216.4 (151–416.3)	0.718

*Median for patients with ultrafiltration is equal to 1.89 L. Wilcoxon rank-sum test was used to compare differences between continuous variables and chi-square test or Fisher's exact test were used to compare differences between categorical variables.

Table 2. Association With Outcomes Stratified by Fluid Removal in the First 24 Hours (Above and Below Median) and Ejection Fraction (≤40% Versus >40%)

	Volume Removed in First 24 h			Baseline Ejection Fraction		
	Low Volume Removal (n=46)	High Volume Removal (n=47)	*P* Value*	EF ≤40% (n=59)	EF >40% (n=35)	*P* Value*
Net urine output at 96 h, L	6.23 (3.87, 9.87)	9.08 (5.91,10.52)	0.027	6.98 (4.09, 10.3)	7.28 (4.63,10.6)	0.420
Δ Weight, lbs	↓9.67 (–13.60, –5.73)	↓13.89 (–22.71, –7.28)	0.044	↓11.55 (–15.40, –5.95)	↓11.68 (–18.30, –7.05)	0.690
Δ Creatinine, mg/dL	↑0.10 (–0.12, 0.53)	↑0.10 (–0.31, 0.57)	0.601	↓0.04 (–0.31, 0.42)	↑0.19 (–0.01, 0.96)	0.023
Δ Serum urea nitrogen	↑9.50 (–2.00, 22.00)	↑12.00 (–3.00, 24.00)	0.756	↑4.00 (–3.00, 19.00)	↑17.50 (1.00–32.00)	0.029
ΔN-terminal pro–brain natriuretic peptide, pg/mL	↓273.70 (–2149.00, 1172.00)	↓656.00 (–1516.00, 54.30)	0.331	↓836.00 (–2748.00, 30.30)	↓108.40 (–1046.00, 266.00)	0.068
Δ Plasma renin activity, ng/mL/hr	↑1.68 (–0.53, 10.37)	↑8.66 (–0.09, 19.8)	0.134	↑2.21 (–0.18, 13.49)	↑6.06 (0.16, 14.01)	0.537
Δ Aldosterone, ng/dL	↓0.55 (–98.07, 47.5)	↓23.54 (–90.84, 161.91)	0.780	↓31.76 (–199.90, 50.75)	↑2.87 (–35.58, 108.27)	0.038
Congestion at 96 h	39/43 (90.7%)	35/39 (89.7%)	1.000	45/50 (90%)	29/32 (90.6%)	1.000
Length of stay, d†	8 (6, 13)	6 (4, 9)	0.010	7 (5, 11)	7 (5, 13)	0.624
Death, hospital, or emergency department/ urgent care	28/46 (60.9%)	34/46 (73.9%)	0.182	40/59 (67.8%)	22/34 (64.7%)	0.761

Δ–change from baseline to 96 hours. EF indicates ejection fraction.
* *P* value represents Median for patients with ultrafiltration is equal 1.89L. Wilcoxon rank-sum test or Pearson chi-square test or Fisher's exact test.
†days from randomization to discharge.

24 hours. Weight change and urine output at 96 hours were similar regardless of EF. The EF >40% group demonstrated larger increases in creatinine (*P*=0.023), SUN (*P*=0.029), and aldosterone (*P*=0.038) at 96 hours (Table 2). Among patients with EF >40%, those with above median fluid removal (n=17) when compared with below median (n=17) had an increased rate of death, hospitalization, or unscheduled outpatient/ emergency department visit during study follow-up (87.5% versus 47.1%, *P*=0.014) (Table 3). The hazard ratio (HR) was 2.45 (95% CI, 1.00–6.00; *P*=0.05), but risk was attenuated after adjustment (HR, 2.00; 95%

Table 3. Association With Outcomes Stratified by Ejection Fraction (≤40% Versus >40%)

	Ejection Fraction ≤40% Volume Removed in the First 24 h			Ejection Fraction >40% Volume Removed in the First 24 h		
	Low Volume Removal (n=29)	High Volume Removal (n=30)	*P* Value*	Low Volume Removal (n=17)	High Volume Removal (n=17)	*P* Value*
Net urine output at 96 h, L	6.00 (2.60, 8.07)	8.90 (5.93,12.07)	0.031	7.12 (5.44, 11.06)	8.62 (4.35,10.46)	0.917
Δ Weight, lbs	↓8.82 (–12.57, –5.29)	↓13.89 (–22.93, –9.92)	0.014	↓11.68 (–14.90, –7.80)	↓11.17 (–22.49, –7.05)	0.858
Δ Creatinine, mg/dL	↓0.08 (–0.19, 0.42)	↑0.06 (–0.46, 0.37)	0.771	↑0.19 (0.02, 1.24)	↑0.20 (–0.08, 0.86)	0.767
Δ Serum urea nitrogen	↑2.00 (–2.00, 14.80)	↑4.50 (–9.00, 21.57)	0.732	↑18.00 (9.00, 31.00)	↑17.00 (0.00, 32.00)	0.547
ΔN-terminal pro–brain natriuretic peptide, pg/mL	↓677.50 (–2748.00, 1325.50)	↓836.00 (–2765.00, –291.00)	0.643	↓435.90 (–1202.00, 359.50)	↓54.30 (–942.90, 266.00)	0.635
Δ Plasma renin activity, ng/mL/hr	↑1.40 (–0.78, 5.36)	↑8.66 (–0.15, 22.36)	0.187	↑3.19 (–0.76, 16.24)	↑6.27 (1.17, 13.09)	0.707
Δ Aldosterone, ng/dL	↓29.05 (–229.60, 44.40)	↓34.46 (–114.9, 143.03)	0.535	↓0.55 (–58.88, 53.09)	↑57.93 (–35.58, 379.10)	0.149
Congestion at 96 h	24/26 (92.3%)	21/24 (87.5%)	0.661	16/17 (94.1%)	13/15 (86.7%)	0.589
Length of stay, days†	8 (6, 11)	6 (4, 10)	0.072	11 (7, 13)	5 (4, 8)	0.008
Death, hospital, or emergency department/ urgent care	19/29 (65.5%)	21/30 (70.0%)	0.713	8/17 (47.1%)	14/16 (87.5%)	0.014

Δ–change from baseline to 96 hours. Groups are further stratified by fluid removal in the first 24 hours (above and below median).
**P* value represents Wilcoxon rank-sum test or Pearson chi-square test or Fisher's exact test.
†days from randomization to discharge.

Table 4. Hazard Ratio for Low and High Fluid Removal in 24 hours With Separation for Type of Treatment and Reduced and Preserved Ejection Fraction—Intention-to-Treat Population

	LVEF ≤40				LVEF >40			
	Unadjusted		Adjusted*		Unadjusted		Adjusted	
Outcome	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Ultrafiltration								
Time to first of death, rehospitalization, unscheduled outpatient/emergency department visit	0.94 (0.50–1.77)	0.854	1.26 (0.62–2.56)	0.524	2.45 (1.00–6.00)	0.050	2.00 (0.71–5.65)	0.192

HR indicates hazard ratio; and LVEF, left ventricular ejection fraction.

*Adjustment covariates include age, sex, baseline body mass index, baseline creatinine, and baseline LVEF. Reference groups: female and below median in total fluid removal in the first 24 hours.

CI, 0.71–5.65; *P*=0.19) (Table 4). There was no difference in renal function (*P*=0.771 for EF ≤40% and *P*=0.767 for EF > 40%.

Sensitivity Analysis—as-Treated Analysis

For the as-treated analysis 8 patients were removed from the original cohort to make a total of 86 patients treated with ultrafiltration (46.0% of the total CARRESS-HF trial cohort). Within 24 hours, median fluid removal was 2.11 L (Q1, Q3: 1.31, 3.34). Baseline characteristics including age, sex, severity of congestion, race, relevant comorbidities, prior AHF hospitalizations, SUN, and creatinine were similar in both the high (n=45) and low (n=41) fluid removal groups (all *P*>0.05). The high fluid removal group had a trend toward greater urine output (9.08 versus 6.85 L, *P*=0.101) and weight loss (13.89 versus 10.80 lbs, *P*=0.094) after 96 hours. Creatinine change from baseline to 96 hours was similar in both groups (0.10 versus 0.13 mg/dL increase, *P*=0.538) (Table S1) .

Patients with EF ≤40% (n=55) versus >40% (n=31) had a median of 2.30 L (Q1, Q3: 1.33, 3.34) versus 1.73 L (Q1, Q3: 1.14, 3.34) fluid removed in the first 24 hours. Weight change from baseline to 96 hours and urine output at 96 hours were similar regardless of EF group *P*>0.05 for both outcomes). The EF >40% group demonstrated larger increases in creatinine (*P*=0.020), SUN (*P*=0.060), and aldosterone (*P*=0.036) at 96 hours (Table S1). Among patients with EF >40%, those with above median fluid removal (n=15) when compared with below median (n=16) had a trend toward increased rate of death, hospitalization, or unscheduled emergency department visit during study follow-up (85.7% versus 50.0%, *P*=0.058). Among patients with EF ≤40%, those with high volume removal had a similar rate of death, hospitalization, or unscheduled emergency department visit during follow-up (70.0% versus 65.5%, *P*=0.713) (Table S2).

The unadjusted HR was 2.12 (95% CI, 0.84–5.36; *P*=0.11) and after adjustment HR was 1.83 (95% CI, 0.63–5.33; *P*=0.27) (Table 5). There was no significant change in renal function in either group.

DISCUSSION

In this clinical trial population of patients with AHF treated with ultrafiltration, the main findings in the ITT analysis

Table 5. Hazard Ratio for Low and High Fluid Removal in 24 hours With Separation for Type of Treatment and Reduced and Preserved Ejection Fraction—as-Treated Population

	LVEF ≤40				LVEF >40			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
Outcome	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Ultrafiltration								
Time to first of death, rehospitalization, unscheduled outpatient/emergency department visit	1.10 (0.57–2.11)	0.777	1.35 (0.66–2.75)	0.409	2.12 (0.84–5.36)	0.111	1.83 (0.63–5.33)	0.269

HR indicates hazard ratio; and LVEF, left ventricular ejection fraction.

*Adjustment covariates include age, sex, baseline body mass index, baseline creatinine, baseline LVEF. Reference groups: female and below median in total fluid removal in the first 24 hours.

were (1) higher initial volume removal was associated with greater weight loss and urine output without WRF; (2) patients with EF >40% were most likely to develop WRF; and (3) patients with EF >40% receiving high initial volume removal were at increased risk for subsequent adverse clinical outcomes. In the as-treated analysis, the observed clinical outcomes were attenuated, with the exception of the association between EF >40% and a higher risk of WRF. This first multicenter analysis comparing the response to ultrafiltration among patients with heart failure with preserved EF versus heart failure with reduced EF identified a high-risk cohort for ultrafiltration therapy and supports a differential congestive physiology between AHF subgroups.

Similar to prior studies, rapid intravascular fluid removal also increased urine production.[9] The current results from CARRESS-HF build on prior work showing that in AHF urine output increase was independent of cardiac output and not seen in patients without congestion, which suggests an important role of venous congestion removal on the glomerular filtration rate.[9] Patients with AHF may experience congestion and resultant cardiovascular decompensation via volume overload, redistribution, or a combination thereof.[10] In other words, volume overload is not always the underlying etiology of cardiovascular decompensation but can be the results of a change in vascular capacitance.[4,11,12] In particular, patients with HFpEF are suggested to be especially fluid sensitive, given increased vascular stiffness leading to more interstitial volume expansion with less intravascular fluid retention and may decompensate with the addition of small volume fluid than patients with heart failure with reduced EF.[7] In AHF, the result may be a decreased fluid uptake from the interstitium, leading to WRF in the setting of aggressive fluid removal regardless of method. Fixed fluid removal with ultrafiltration in CARRESS-HF may thus have led to intravascular hypovolemia by exceeding the capillary refill rate. This analysis suggests that patients with HFpEF are more sensitive to up-front volume shifts. Further, WRF during decongestion is not necessarily a marker of renal injury but could be a marker of appropriate decongestion. Nevertheless, a change in creatinine was the primary end point in the CARRESS-HF and remains an important clinical surrogate guiding volume removal.

LIMITATIONS

These results must be interpreted in the context of several limitations. First, this is a retrospective analysis in which we evaluated differing effects of ultrafiltration therapy in the first 24 hours. We did not extend our analysis to ultrafiltration therapy >24 hours as many patients in CARRESS-HF had ultrafiltration discontinued in subsequent days for various reasons. Notably, a 20% crossover rate limited ITT analysis. The sensitivity analysis using the as-treated, excluding 8 patients who did not receive ultrafiltration upon randomization limited some of the findings previously seen with the ITT analysis. This underlines the limited samples size of analysis and demands additional verification in a larger trial of ultrafiltration such as the AVOID-HF trial.[2]

CONCLUSIONS

In the ITT analysis of patients with AHF and cardiorenal syndrome, higher initial fluid removal with ultrafiltration had no association with WRF. In patients with an EF >40%, ultrafiltration was associated with WRF irrespective of fluid removal. Further, higher initial fluid removal rate was associated with higher rates of adverse clinical outcomes, highlighting variable responses to decongestive therapy.

ARTICLE INFORMATION

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Supplementary Material

Table S1–S2

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Supplemental Material

Table S1. Association with outcomes stratified by fluid removal in the first 24 hours (above and below median) and ejection fraction (EF ≤ 40% vs > 40%).

	Volume removed in first 24 hours			Baseline Ejection Fraction			
	Low Volume Removal (n=41)	**High Volume Removal (n=45)**	**p-value***		**EF ≤40% (n=55)**	**EF >40% (n=31)**	**p-value***
Net UOP at 96 h (L)	6.85 (4.18, 10.57)	9.08 (5.93,11.01)	0.101	Net UOP at 96 h (L)	7.03 (4.18, 10.52)	8.06 (5.33,11.49)	0.296
Δ Weight (lbs)	↓10.80 (-14.11, -6.39)	↓13.89 (-22.71, -7.94)	0.094	Δ Weight (lbs)	↓12.02 (-16.09, -5.95)	↓12.57 (-18.30, -7.80)	0.644
Δ Creatinine (mg/dL)	↑0.13 (-0.11, 0.56)	↑0.10 (-0.29, 0.57)	0.539	Δ Creatinine (mg/dL)	↓0.04 (-0.29, 0.43)	↑0.20 (0.02, 1.01)	0.020
Δ BUN	↑10.00 (0.00, 22.00)	↑14.00 (0.00, 24.00)	0.681	Δ BUN	↑10.00 (0.00-22.00)	↑14.00 (0.00 – 24.00)	0.681
Δ NT-proBNP (pg/mL)	↓268.70 (-1840.00, 1172.00)	↓701.00 (-1516.00,-82.30)	0.187	Δ NT-proBNP (pg/mL)	↓268.70 (-1840.00, 1172.00)	↓701.00 (-1516.00, -82.30)	0.187
Δ PRA (ng/mL/hr)	↑2.21 (-0.16, 11.20)	↑8.66 (0.49, 16.43)	0.263	Δ PRA (ng/mL/hr)	↑2.21 (0.16, 11.20)	↑8.66 (0.49, 16.43)	0.264
Δ Aldosterone (ng/dL)	↑1.44 (-82.60, 50.75)	↓18.56 (-90.33, 161.91)	0.861	Δ Aldosterone (ng/dL)	↑1.44 (-82.60, 50.75)	↓18.56 (-90.33, 161.91)	0.861
Congestion at 96 h	35/38 (92.1%)	33/37 (89.2%)	0.711	Congestion at 96 h	35/38 (92.1%)	33/37 (89.2%)	0.711
Length of Stay (days)**	8 (6, 13)	6 (4, 9)	0.010	Length of Stay (days)**	8 (6, 13)	6 (4, 9)	0.010
Death, hosp, or ED/urgent care	25/41 (61.0%)	33/44 (75.0%)	0.165	Death, hosp, or ED/urgent care	25/41 (61.0%)	33/44 (75.0%)	0.165

Δ - change from baseline to 96h
*p-value represents Wilcoxon Rank-Sum test or Pearson chi-square test or Fisher's exact test
**days from randomization to discharge

UOP = urine output; NT-proBNP = N terminal pro brain natriuretic peptide; PRA = plasma renin activity; ED = emergency department.

Table S2. Association with outcomes stratified by ejection fraction (EF ≤ 40% vs > 40%). Groups are further stratified by fluid removal in the first 24 hours (above and below median).

Ejection Fraction <=40% Volume removed in the first 24 hours				Ejection Fraction >40% Volume removed in the first 24 hours			
	Low Volume Removal (n=26)	**High Volume Removal (n=29)**	**p-value***		**Low Volume Removal (n=16)**	**High Volume Removal (n=15)**	**p-value***
Net UOP at 96 h (L)	6.17 (4.09, 8.80)	8.80 (5.92,13.61)	0.118	Net UOP at 96 h (L)	7.15 (6.06, 11.55)	9.28 (4.98,10.98)	0.903
Δ Weight (lbs)	↓9.20 (-13.60, -5.29)	↓13.89 (-23.15, -9.70)	0.041	Δ Weight (lbs)	↓12.13 (-16.60, -8.35)	↓14.19 (-22.49,-7.28)	0.878
Δ Creatinine (mg/dL)	↓0.08 (-0.19, 0.43)	↑0.06 (-0.39, 0.46)	0.907	Δ Creatinine (mg/dL)	↑0.19(0.03, 1.42)	↑0.20 (-0.08, 0.86)	0.678
Δ BUN	↑7.50 (-1.00, 18.00)	↑5.00 (-3.00, 21.57)	0.919	Δ BUN	↑14.50 (6.50, 30.50)	↑20.00 (0.00, 38.00)	0.969
Δ NT-proBNP (pg/mL)	↓332.90 (-2352.00, -1479.00)	↓836.00 (-2765.00, -291.00)	0.317	Δ NT-proBNP (pg/mL)	↓268.70 (-1358.00, 565.00)	↓108.4 (-942.90, -2.00)	0.963
Δ PRA (ng/mL/hr)	↑1.96 (-0.78, 10.31)	↑8.33 (-0.16 - 23.19)	0.344	Δ PRA (ng/mL/hr)	↑6.06 (-0.53, 16.74)	↑7.90 (4.26, 13.09)	0.782
Δ Aldosterone (ng/dL)	↓12.75 (-236.7, 45.39)	↓31.22 (-102.8, 152.47)	0.476	Δ Aldosterone (ng/dL)	0.00 (-35.16, 58.69)	↑108.27 (-18.56, 379.10)	0.097
Congestion at 96 h	21/23 (91.3%)	20/23 (87.0%)	1.000	Congestion at 96 h	15/16 (93.8%)	12/13 (92.3%)	1.000
Length of Stay (days)**	8 (5, 11)	6 (4, 9)	0.064	Length of Stay (days)**	10 (7, 13)	6 (4, 8)	0.034
Death, hosp, or ED/urgent care	17/26 (65.4%)	21/29 (72.4%)	0.5733	Death, hosp, or ED/urgent care	8/16 (50.0%)	12/14 (85.7%)	0.058

Δ - change from baseline to 96h
*p-value represents Wilcoxon Rank-Sum test or Pearson chi-square test or Fisher's exact test
**days from randomization to discharge

UOP = urine output; NT-proBNP = N terminal pro brain natriuretic peptide; PRA = plasma renin activity; ED = emergency department.