

MINI-FOCUS ISSUE: DECOMPENSATED HEART FAILURE

# Decongestion Strategies and Renin-Angiotensin-Aldosterone System Activation in Acute Heart Failure



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## ABSTRACT

**OBJECTIVES** The purpose of this study was to assess the relationship between biomarkers of renin-angiotensin-aldosterone system (RAAS) activation and decongestion strategies, worsening renal function, and clinical outcomes.

**BACKGROUND** High-dose diuretic therapy in patients with acute heart failure (AHF) is thought to activate the RAAS; and alternative decongestion strategies, such as ultrafiltration (UF), have been proposed to mitigate this RAAS activation.

**METHODS** This study analyzed 427 AHF patients enrolled in the DOSE-AHF (Diuretic Optimization Strategies in Acute Heart Failure) and CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) trials. We assessed the relationship between 2 markers of RAAS activation (plasma renin activity [PRA] and aldosterone) from baseline to 72 h and 96 h and decongestion strategy: high- versus low-dose and continuous infusion versus bolus furosemide for DOSE-AHF and UF versus stepped pharmacologic care for CARRESS-HF. We determined the relationships between RAAS biomarkers and 60-day outcomes.

**RESULTS** Patients with greater RAAS activation at baseline had lower blood pressures, lower serum sodium levels, and higher blood urea nitrogen (BUN) concentration. Continuous infusion furosemide and UF were associated with greater PRA increases (median: +1.66 vs. +0.66 ng/ml/h with continuous vs. bolus infusion, respectively,  $p = 0.021$ ; +4.05 vs. +0.56 ng/ml/h with UF vs. stepped care, respectively,  $p = 0.014$ ). There were no significant differences in RAAS biomarker changes with high- versus low-dose diuretic therapy (both:  $p > 0.5$ ). Neither baseline log PRA nor log aldosterone was associated with increased death or HF hospitalization (hazard ratio [HR] for a doubling of 1.05; 95% confidence interval [CI]: 0.98 to 1.13;  $p = 0.18$ ; and HR: 1.13; 95% CI: 0.99 to 1.28;  $p = 0.069$ , respectively). The change in RAAS biomarkers from baseline to 72 and 96 h was not associated with outcomes (both:  $p > 0.5$ ).

**CONCLUSIONS** High-dose loop diuretic therapy did not result in RAAS activation greater than that with low-dose diuretic therapy. UF resulted in greater PRA increase than stepped pharmacologic care. Neither PRA nor aldosterone was significantly associated with short-term outcomes in this cohort. (Determining Optimal Dose and Duration of Diuretic Treatment in People With Acute Heart Failure [DOSE-AHF]; [NCT00577135](#); Effectiveness of Ultrafiltration in Treating People With Acute Decompensated Heart Failure and Cardiorenal Syndrome [CARRESS]; [NCT00608491](#)) (J Am Coll Cardiol HF 2015;3:97-107) © 2015 by the American College of Cardiology Foundation.

## ABBREVIATIONS AND ACRONYMS

**ACE-I** = angiotensin-converting enzyme inhibitor

**AHF** = acute heart failure

**ARB** = angiotensin receptor blocker

**LVEF** = left ventricular ejection fraction

**RAAS** = renin-angiotensin-aldosterone system

**UF** = ultrafiltration

**WRF** = worsening renal function

Activation of the renin-angiotensin-aldosterone system (RAAS) plays a fundamental role in the pathophysiology of heart failure (1,2). Various strategies for decongestion in acute heart failure (AHF) patients, such as loop diuretic therapy or ultrafiltration (UF), have been posited to lead to greater or lesser degrees of RAAS activation (3,4). For instance, reviews of loop diuretic agents cite the potential of these agents, especially at high doses, to cause RAAS activation (5,6), a potential mechanism of the observational link between diuretic dosing and adverse outcomes (7-9). Data supporting this

concept, however, generally predate current pharmacotherapy for heart failure (10,11). Additionally, RAAS

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activation is frequently cited as a primary driver of worsening renal function (WRF) in AHF patients (i.e., the cardiorenal syndrome) (12). Contemporary data to support this statement are also limited. Finally, the association between the degree of RAAS activation and outcomes after AHF hospitalization in patients treated with contemporary heart failure therapy is unknown. We aimed to investigate the relationships between biomarkers of RAAS activation, decongestion strategy, WRF, and clinical outcomes in AHF patients enrolled in the DOSE-AHF (Diuretic Optimization Strategies in Acute Heart Failure) and CARRESS-HF (Cardiorenal Rescue Study in Acute Decompensated Heart Failure) trials. We hypothesized that low-dose diuretics and UF would be associated with less RAAS activation than high-dose diuretics and stepped pharmacologic care, respectively, and that greater RAAS activation would be associated with increased in-hospital WRF and worse post-discharge outcomes.

## METHODS

**DATA SOURCE AND STUDY POPULATION.** This analysis used data from the DOSE-AHF (NCT00577135)

and CARRESS-HF (NCT00608491) trials sponsored by the National Heart, Lung, and Blood Institute (NHLBI) Heart Failure Network. The study designs and primary results were published previously (5,13-15). Briefly, DOSE-AHF was a prospective, randomized, double-blind, controlled trial that enrolled patients admitted with AHF regardless of left ventricular ejection fraction (LVEF). Patients were eligible if they had a history of chronic heart failure requiring outpatient oral loop diuretic therapy ( $\geq 80$  mg of furosemide equivalent daily) and were admitted with a primary diagnosis of AHF manifested by at least 1 sign and 1 symptom. Patients with systolic blood pressures  $< 90$  mm Hg, serum creatinine concentration of  $> 3$  mg/dl, or who required vasoactive medications were excluded. A total of 308 patients were enrolled at 26 sites between March 2008 and November 2009. The study used a  $2 \times 2$  factorial design to randomize patients to a strategy of high-dose intravenous furosemide (2.5 times the previous oral dose) or low-dose furosemide (equivalent to the patient's previous oral dose) and continuous infusion or intermittent bolus furosemide administration every 12 h.

CARRESS-HF was a prospective, randomized, controlled trial that enrolled patients with AHF and evidence of cardiorenal syndrome and persistent congestion. Patients were eligible if they were admitted with a primary diagnosis of AHF regardless of LVEF. Patients also were required to have had WRF (defined as an increase in serum creatinine concentration of at least 0.3 mg/dl within 12 weeks before or 10 days after AHF admission) and persistent congestion on the basis of at least 1 of the following symptoms: peripheral edema of at least 2+, jugular venous pressure  $> 10$  cm of water, or pulmonary edema or pleural effusion on chest radiography. Patients with serum creatinine concentration  $> 3.5$  mg/dl at admission or who required vasoactive medications were excluded. A total of 188 patients were enrolled at 22 sites between June 2008 and January 2012. Patients were randomized to either a stepped pharmacologic therapy strategy or UF at a fluid removal rate of

Minnesota. The DOSE-AHF and CARRESS-HF studies were funded by the National Heart, Lung, and Blood Institute, U.S. National Institutes of Health. Gambro/CHF Solutions provided research grant funding and equipment to Duke University in support of the CARRESS-HF trial. Dr. Goldsmith has received honoraria from CHF Solutions; and grant support, consulting, and speaker fees from Otsuka America Pharmaceuticals, not directly relevant to the present work. Dr. Mentz has received research support from Bristol-Meyers Squibb, GlaxoSmithKline, Novartis, Otsuka, ResMed, Amgen, AstraZeneca, Gilead, and Thoratec. Dr. DeVore has received research support from American Heart Association, Novartis, and Thoratec. Dr. O'Connor has consulted for Cardiorentis; and has received research funding from Roche Diagnostics. Dr. Hernandez has received research support from Amgen, Bristol-Meyers Squibb, Janssen, and Novartis. Dr. Braunwald has received research grant support from Duke University to NHLBI Heart Failure Network. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. John R. Teerlink, MD, has served as Guest Editor for this paper.

200 ml/h. The algorithm for stepped pharmacologic therapy has been published previously (15). Briefly, intravenous diuretic therapy was used to manage signs and symptoms of congestion and maintain a urine output of 3 to 5 l/day. Specific recommendations were provided for the use of intravenous vasodilators and inotropic agents on the basis of blood pressure, LVEF, and right ventricular function to attain this urine output.

The DOSE-AHF and CARRESS-HF studies were approved by the Heart Failure Network Steering, Protocol Review, and Data Safety Monitoring Committees and were approved by each participating site's institutional review board. All patients provided written informed consent.

**BIOMARKERS.** Plasma samples were collected from patients enrolled in both the DOSE-AHF and the CARRESS-HF studies at baseline and at 72 h (DOSE-AHF) or 96 h (CARRESS-HF) and analyzed at a central core laboratory blinded to treatment assignment. RAAS activation was characterized by serum plasma renin activity (PRA) and aldosterone level. PRA was measured with a GammaCoat PRA iodine-125 radioimmunoassay kit (catalog no. CA-1533, Diasorin, Stillwater, Minnesota). Expected PRA values range from 0.85 to 16.34 ng/ml/h, and the interassay coefficient of variation provided by the manufacturer is <10%. Aldosterone was measured by radioimmunoassay method (catalog no. ALDOCTK-2, Diasorin). Expected values for aldosterone in healthy individuals range from 7.5 to 150 pg/ml. The interassay coefficient of variation provided by the manufacturer is <5.3%.

**STUDY POPULATION.** Patients enrolled in DOSE-AHF and CARRESS-HF studies were included in the study population if they had baseline RAAS biomarkers and follow-up for death or heart failure hospitalization at 60 days.

**OUTCOMES.** WRF was defined on the basis of an increase in serum creatinine concentration of at least 0.3 mg/dl from baseline to 72 h to 96 h. We analyzed time to composite of death or HF rehospitalization by 60 days.

**STATISTICAL METHODS.** Patients' PRA and aldosterone concentrations above the median were compared with those below the median at baseline. Continuous variables were presented as median values (25th and 75th percentiles) and were compared with Wilcoxon rank sum tests. Categorical variables were presented as percentages and compared with chi-square tests. RAAS levels in patients taking baseline angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin receptor blocker (ARB) and aldosterone antagonist therapy were compared with

those in patients not on ACE-I/ARB therapy by using Wilcoxon rank sum tests. We assessed the relationships between the changes in biomarkers of RAAS activation from baseline to 72 h (DOSE-AHF) or to 96 h (CARRESS-HF) and decongestion strategy. Comparisons were high- versus low-dose and continuous infusion versus bolus furosemide for DOSE-AHF and UF versus stepped pharmacologic care for CARRESS-HF. Treatment groups were compared with linear regression models in which the follow-up biomarker value was the outcome, the baseline biomarker value was an adjustment variable, and the treatment group was the independent variable of interest. Log base 2 transformations were used for baseline and follow-up biomarkers to account for deviations from normality (i.e., the skewed nature of the data), and models were adjusted for whether ACE-I/ARB and aldosterone antagonist were taken at randomization. Median values (25th, 75th percentiles) and mean  $\pm$  SD for each RAAS measure at baseline and the change from baseline to 72 h or 96 h were presented separately for each treatment group. In addition, we performed a similar analysis of RAAS biomarkers at baseline and following different decongestion strategies in patients with reduced LVEF (<50%) versus preserved EF ( $\geq$ 50%). We evaluated the percentage of patients who developed WRF from baseline to 72 h or 96 h stratified by baseline RAAS biomarker levels (median split). We also assessed the association between the change in RAAS biomarkers from baseline to 72 h or 96 h and WRF by using Cox proportional hazards regression models.

Cox proportional hazards regression models were used to evaluate the relationship between biomarkers of RAAS activation (PRA and aldosterone) and 60-day death or HF hospitalization. These models were generated from combining DOSE-AHF and CARRESS-HF into 1 dataset in which the trial was an adjustment variable. Models were fitted with the biomarker variable of interest defined as baseline RAAS greater than the median and repeated where the baseline RAAS biomarker was transformed with log base 2. We also assessed the association between baseline RAAS biomarker quartile and time to death or HF hospitalization. We analyzed the association between the change in RAAS biomarkers from baseline to 72 h or 96 h and death or HF hospitalization by using proportional hazards regression models that included baseline RAAS as an adjustment variable. All models of time to death or HF hospitalization were adjusted for baseline ACE-I/ARB and aldosterone antagonist use.

Total fluid losses were compared between decongestion strategies, using Wilcoxon rank sum tests.

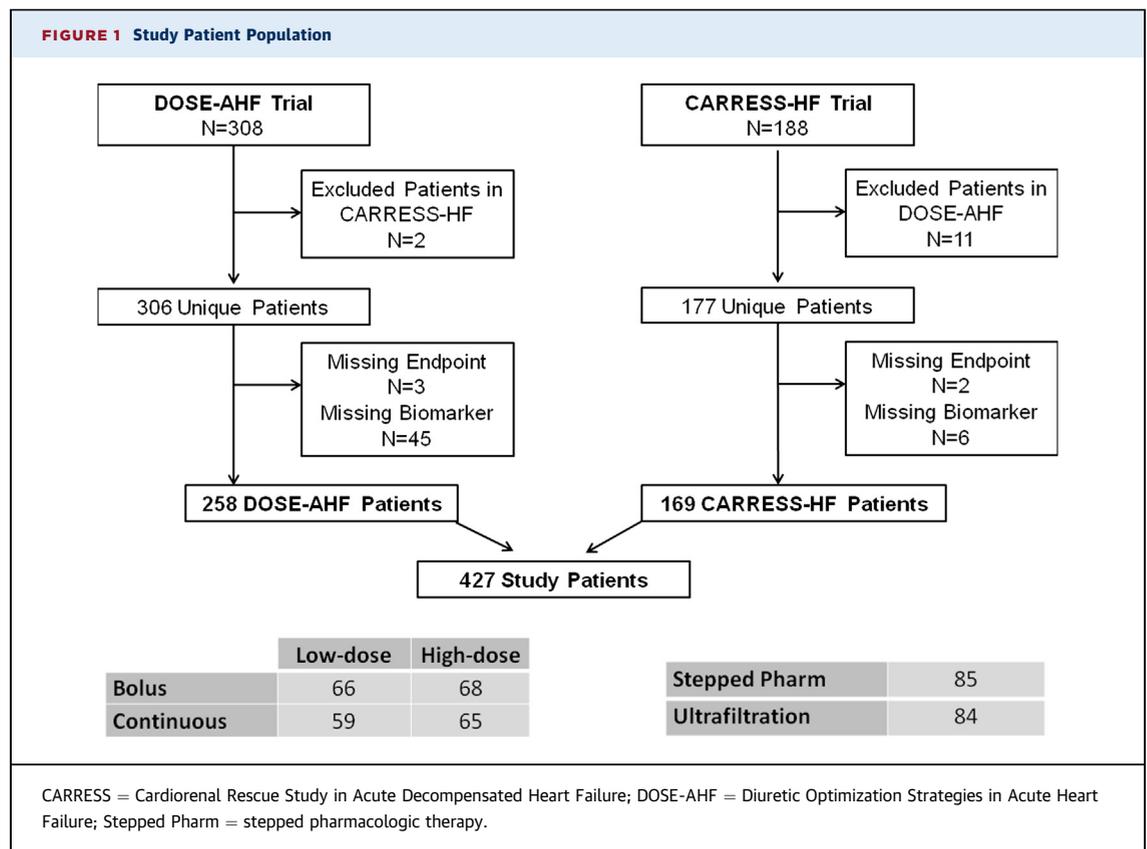
The association between total fluid loss and change in biomarkers of RAAS activation from baseline to 72 h (DOSE-AHF) or to 96 h (CARRESS-HF) is shown with scatterplots. A p value of 0.05 was considered statistically significant. SAS version 9.2 software (SAS Institute, Cary, North Carolina) was used for all analyses.

## RESULTS

Among 483 unique patients enrolled in DOSE-AHF and CARRESS-HF, 427 had complete data for baseline PRA, baseline aldosterone, and 60-day clinical outcomes (258 in DOSE and 169 in CARRESS) (Figure 1). In general, baseline characteristics of patients included in the analysis cohort were similar to those of patients who were excluded (Online Table 1). Of note, the 56 patients who were excluded tended to be nonwhite and had lower EF and better renal function than the study cohort. At baseline, the median PRA in the study population was 5 ng/ml/h, and the median aldosterone level was 210 pg/ml. Patient characteristics on the basis of the median split of baseline RAAS biomarkers are displayed in Table 1. Overall, patients with greater baseline RAAS activation had more implantable cardioverter-defibrillator

(ICD) use, lower blood pressure, lower serum sodium, and higher blood urea nitrogen (BUN) levels than those with lower baseline RAAS activation. In addition, those with higher baseline RAAS levels tended to have a higher frequency of aldosterone antagonist therapy and higher baseline doses of furosemide. Patients with higher PRA levels were more often white, had New York Heart Association functional class IV symptoms, and had lower N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels at baseline. Those with higher baseline aldosterone levels tended to have lower LVEF, were less likely to receive ACE-I/ARB, and had higher baseline creatinine levels.

Patients receiving ACE-I/ARB therapy had similar baseline PRA and lower baseline aldosterone levels than those not receiving these agents (median PRA: 4.4 ng/ml/h vs. 5.4 ng/ml/h, respectively;  $p = 0.18$ ; and median aldosterone: 168 pg/ml vs. 283 pg/ml, respectively;  $p < 0.0001$ ) (Online Table 2). Patients receiving aldosterone antagonists had significantly higher PRA and aldosterone levels compared with those not receiving aldosterone antagonists (median: 10.0 ng/ml/h vs. 3.2 ng/ml/h and 327 pg/ml vs. 175 pg/ml, respectively; both:  $p < 0.001$ ). Between randomization and discharge, ACE-I/ARB therapy



**TABLE 1 Patient Characteristics by Baseline RAAS Biomarkers (Median Split)**

	Entire Cohort (N = 427)	PRA		p Value	Aldosterone		p Value
		<5 ng/ml/h (n = 214)	≥5 ng/ml/h (n = 213)		<210 pg/ml (n = 213)	≥210 pg/ml (n = 214)	
Age, yrs	68 (58-78)	69 (58-78)	68 (59-77)	0.47	69 (59-78)	68 (58-77)	0.21
% of males	75%	71%	79%	0.061	73%	77%	0.42
% of whites	76%	70%	83%	0.002	72%	80%	0.065
Ejection fraction, %	32 (20-55)	31 (20-55)	32 (20-53)	0.75	35 (20-55)	29 (20-50)	0.023
Ejection fraction <50%	69%	66%	72%	0.16	64%	74%	0.021
New York Heart Association functional class IV	35%	29%	41%	0.014	34%	37%	0.44
Hospitalization for HF in the previous year	74%	74%	73%	0.87	75%	73%	0.74
Ischemic cause	60%	59%	61%	0.72	57%	63%	0.22
Atrial fibrillation/flutter	54%	50%	57%	0.16	53%	55%	0.60
Diabetes mellitus	57%	57%	57%	0.88	55%	58%	0.53
Implantable cardioverter defibrillator	34%	26%	42%	<0.001	26%	42%	<0.001
Baseline medications (at randomization)							
ACE-I or ARB	56%	58%	53%	0.26	69%	42%	<0.001
Beta-blocker	82%	85%	79%	0.13	81%	82%	0.78
Aldosterone antagonist	25%	16%	35%	<0.001	16%	35%	<0.001
Nitrates	31%	34%	29%	0.31	31%	32%	0.70
Nitrates and hydralazine	11%	13%	10%	0.30	10%	13%	0.46
Furosemide equivalent dose, mg/day	120 (80-160)	80 (80-160)	160 (80-180)	<0.001	80 (80-160)	160 (80-200)	<0.001
Physical examination							
Weight, lbs	209 (179-257)	206 (182-254)	215 (174-261)	0.46	205 (176-254)	213 (181-261)	0.29
BMI, kg/m <sup>2</sup>	31.9 (26.9-38.4)	31.6 (27.2-37.8)	32.5 (26.7-39.3)	0.83	31.3 (26.6-38.4)	32.3 (27.6-38.5)	0.43
Systolic blood pressure, mm Hg	114 (104-129)	121 (111-135)	110 (100-121)	<0.001	116 (105-132)	113 (103-125)	0.038
Heart rate, beats/min	76 (68-85)	75 (68-85)	77 (66-84)	0.68	75 (65-83)	77 (68-85)	0.21
JVP ≥8 cm water	93%	95%	91%	0.19	95%	91%	0.085
Orthopnea	91%	88%	95%	0.030	90%	93%	0.24
Peripheral edema grade ≥2+	83%	85%	81%	0.30	85%	81%	0.32
Laboratory results							
PRA, ng/ml/h	13.3 ± 23.1	1.5 ± 1.4	25.1 ± 28.2	<0.001	10.1 ± 21.4	16.4 ± 24.4	<0.001
Aldosterone, pg/ml	331 ± 400	205 ± 206	457 ± 497	<0.001	111 ± 53	549 ± 470	<0.001
Sodium, mg/l	138 (135-141)	139 (137-141)	137 (134-139)	<0.001	139 (136-141)	138 (134-140)	<0.001
Blood-urea-nitrogen, mg/dl	40 (26-57)	35 (22-53)	46 (29-61)	<0.001	38 (22-56)	43 (29-59)	0.002
Creatinine, mg/dl	1.7 (1.2-2.2)	1.6 (1.2-2.1)	1.7 (1.3-2.2)	0.089	1.5 (1.1-2.1)	1.8 (1.4-2.2)	0.001
Estimate of GFR, ml/min/1.73 m <sup>2</sup>	40.0 (29.4-56.6)	41.3 (30.1-60.3)	38.7 (28.9-51.3)	0.051	44.1 (30.3-62.8)	38.2 (28.2-47.4)	<0.001
NT-proBNP, pg/ml	4307 (2273-9823)	5076 (2480-11701)	3874 (1849-8285)	0.005	4205 (2350-9388)	4399 (2193-11227)	0.64

Values are n (range), %, or mean ± SD.

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; HF = heart failure; JVP = jugular venous pressure; NT-proBNP = N-terminal pro brain natriuretic peptide; PRA = plasma renin activity; RAAS = renin-angiotensin-aldosterone system.

was discontinued for 10.9% of patients and initiated for 8% of patients. Also, aldosterone therapy was discontinued for 6.1% of patients and initiated for 9.2% of patients between randomization and discharge.

**BIOMARKER CHANGE BY DECONGESTION STRATEGY.**

Table 2 displays baseline RAAS values and changes from baseline to 72 h and 96 h by decongestion strategy. Median changes in PRA and aldosterone on the basis of decongestion strategy is presented in Figures 2 and 3, respectively. Continuous infusion and UF were associated with greater increases in PRA than bolus furosemide and stepped pharmacologic therapy, respectively (both: p < 0.05). There were no

significant differences between RAAS biomarker changes with high-dose diuretic therapy and those with low-dose diuretics (both: p > 0.5). At the time of follow-up biomarker assessment, 84% of patients in the high-dose diuretic arm and 90% of patients in the low-dose diuretic arm remained on diuretic therapy, and the median furosemide daily doses on the day of follow-up biomarker assessments were 200 mg and 120 mg, respectively.

Online Table 3 displays baseline RAAS values and the changes from baseline to 72 h and 96 h by decongestion strategy in those with reduced and preserved LVEF. Overall, patients with preserved EF tended to have lower baseline aldosterone levels than

**TABLE 2** Changes in PRA and Aldosterone From Baseline Based on Decongestion Strategy

Treatment	PRA (ng/ml/h)			p Value	Aldosterone (pg/ml)			p Value
	Log <sub>2</sub> (Baseline)	Log <sub>2</sub> (72 h)	Change at 72 h (Untransformed)		Log <sub>2</sub> (Baseline)	Log <sub>2</sub> (72 h)	Change at 72 h (Untransformed)	
<b>DOSE trial</b>								
<b>Bolus</b>								
N	112	112	112		114	114	114	
Mean ± SD	1.96 ± 2.60	2.41 ± 2.41	2.4 ± 30.7		7.54 ± 1.45	7.54 ± 1.39	-7 ± 263	
Median (25th, 75th percentile)	2.04 (-0.09, 4.08)	2.69 (1.03, 4.29)	0.66 (-0.46, 5.50)		7.72 (6.70, 8.46)	7.50 (6.73, 8.39)	-5 (-91, 43)	
Continuous infusion				0.021				0.50
N	97	97	97		103	103	103	
Mean ± SD	1.64 ± 2.53	2.72 ± 2.43	10.5 ± 53.8		7.56 ± 1.26	7.67 ± 1.23	6 ± 285	
Median (25th, 75th percentile)	1.93 (-0.55, 3.57)	3.02 (1.48, 4.30)	1.66 (-0.19, 9.96)		7.42 (6.67, 8.44)	7.61 (6.86, 8.51)	3 (-83, 106)	
<b>Low dose</b>								
N	96	96	96		103	103	103	
Mean ± SD	1.87 ± 2.51	2.60 ± 2.34	3.2 ± 28.1		7.48 ± 1.34	7.62 ± 1.40	32 ± 259	
Median (25th, 75th percentile)	2.06 (-0.30, 3.89)	2.78 (1.40, 4.07)	1.58 (-0.52, 6.75)		7.64 (6.64, 8.36)	7.59 (6.80, 8.51)	12 (-58, 106)	
High dose				0.89				0.51
N	113	113	113		114	114	114	
Mean ± SD	1.76 ± 2.62	2.51 ± 2.49	8.6 ± 52.6		7.62 ± 1.38	7.59 ± 1.24	-30 ± 284	
Median (25th, 75th percentile)	1.93 (-0.39, 3.94)	2.86 (1.02, 4.30)	1.03 (-0.25, 6.12)		7.60 (6.71, 8.48)	7.50 (6.76, 8.33)	-7 (-102, 47)	
	<b>Baseline</b>	<b>96 h</b>	<b>Change at 96 h</b>		<b>Baseline</b>	<b>96 h</b>	<b>Change at 96 h</b>	
<b>CARRESS trial</b>								
<b>Ultrafiltration</b>								
N	76	76	76		76	76	76	
Mean ± SD	2.42 ± 2.19	3.40 ± 2.07	13.1 ± 32.3		7.83 ± 1.61	7.69 ± 1.70	-9 ± 497	
Median (25th, 75th percentile)	2.53 (1.34, 4.08)	3.70 (2.29, 4.65)	4.0 (-0.2, 14.1)	0.014	7.74 (7.06, 8.65)	7.73 (6.73, 8.65)	-12 (-95, 62)	0.89
<b>Stepped pharmacological care</b>								
N	78	78	78		79	79	79	
Mean ± SD	1.67 ± 3.05	2.37 ± 2.50	3.8 ± 44.3		7.82 ± 1.61	7.70 ± 1.50	-70 ± 404	
Median (25th, 75th percentile)	1.84 (-0.14, 3.89)	2.47 (0.79, 4.12)	0.56 (-1.5, 4.48)		7.97 (6.86, 8.55)	7.77 (6.76, 8.76)	7 (-101, 102)	

p Values correspond to the treatment effect in linear regression models for 72- or 96-h RAAS, adjusted for baseline RAAS, use of baseline ACE-I/ARB, and use of baseline aldosterone antagonist where a log base 2 transformation was applied to both the baseline and the follow-up RAAS measure.  
CARRESS = Cardiorenal Rescue Study in Acute Decompensated Heart Failure; DOSE = Diuretic Optimization Strategies in Acute Heart Failure; other abbreviations as in Table 1.

those with reduced EF. For PRA values, the treatment differences observed for continuous infusion and UF remained after adjusting for preserved or reduced LVEF. There was evidence of a differential association between UF versus stepped pharmacological care for PRA change on the basis of baseline LVEF. The increase in PRA with UF compared with stepped pharmacologic care was more pronounced in the preserved EF patients than in the reduced EF patients (median: 4.6 vs. 0.09 ng/ml/h, respectively, in those with preserved EF and 3.0 vs. 0.72 ng/ml/h, respectively, in those with reduced EF; interaction  $p = 0.019$ ).

Online Table 4 presents the net fluid losses at 72 h and 96 h by decongestion strategy. High-dose furosemide was associated with greater net fluid loss at 72 h than low-dose furosemide (median: 4,452 ml vs. 2,912 ml, respectively;  $p = 0.005$ ). Net fluid loss was not significantly different between bolus and continuous infusion furosemide and between

ultrafiltration versus stepped pharmacologic therapy (both:  $p > 0.2$ ). Figure 4 presents scatterplots of the association between net fluid loss and change in biomarkers of RAAS activation from baseline to 72 h (DOSE-AHF) or 96 h (CARRESS-HF). Most patients had modest biomarker changes, and there was no clear relationship between greater volume loss and the change in either biomarker.

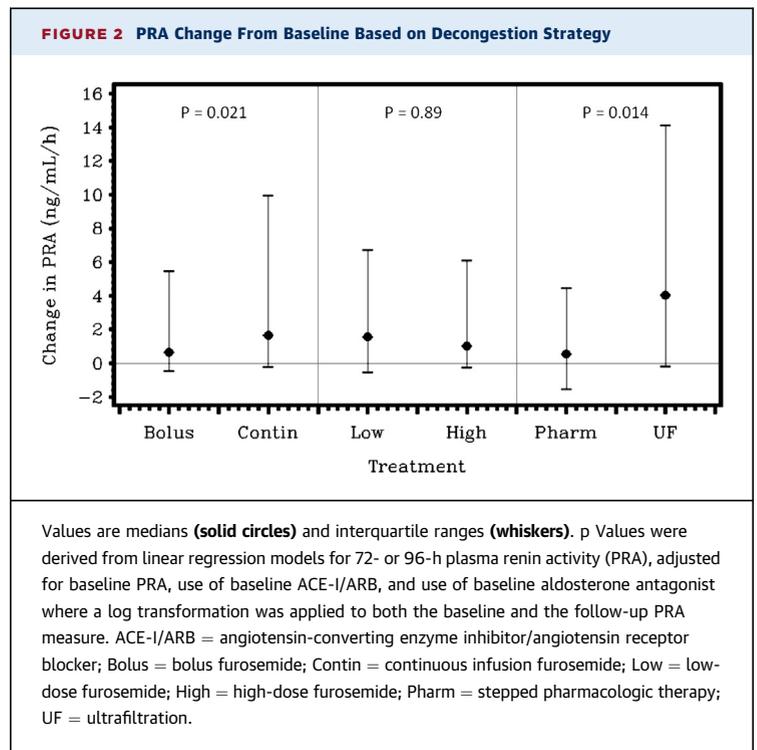
**RELATIONSHIP BETWEEN RAAS BIOMARKERS AND CLINICAL OUTCOMES.** Baseline PRA and an aldosterone level greater than or equal to the median were not associated with a greater incidence of WRF from baseline to 72 h or 96 h than RAAS biomarker levels less than the median (19% vs. 21%, respectively, for PRA and 21% vs. 19%, respectively, for aldosterone). Approximately 20% of patients developed WRF in each of the groups. However, the change in RAAS biomarkers from baseline to 72 h or 96 h was associated with an increase in WRF (Table 3). Specifically,

a 10-unit increase in PRA was associated with an 80% increase in WRF, and a 100-U increase in aldosterone was associated with a 13% increase in WRF.

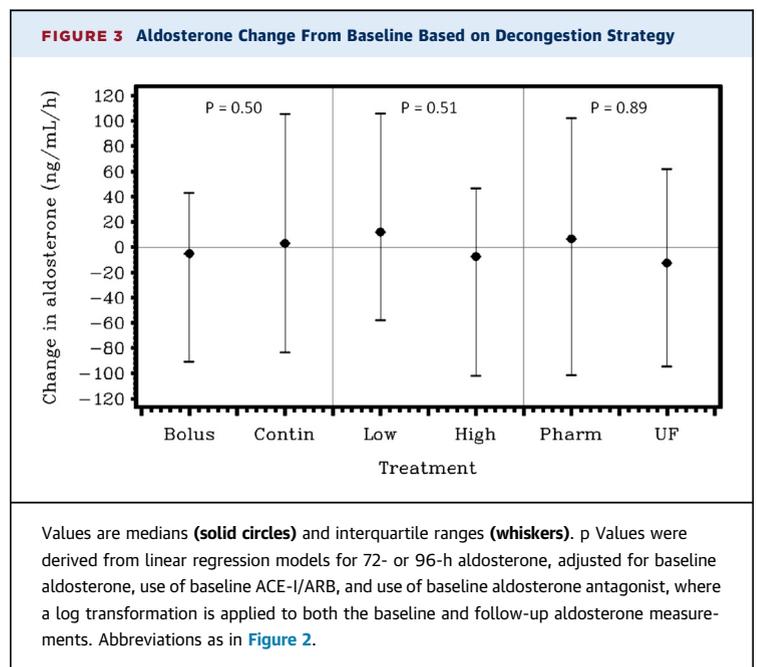
Over a follow-up period of up to 127 days, 134 patients (31.4%) died or were rehospitalized for HF. There was a total of 52 deaths (12.2%). **Table 4** presents the association between baseline and change in RAAS biomarkers and time to death or HF hospitalization. The hazard ratios (HRs) and 95% confidence intervals (CIs) for baseline PRA or aldosterone greater than or equal to the median were HR of 1.28 (95% CI: 0.91 to 1.82) and 1.39 (95% CI: 0.96 to 2.01), respectively, compared with a value less than the median. Neither baseline log PRA nor log aldosterone was significantly associated with increased death or HF hospitalization (HR: 1.05, 95% CI: 0.98 to 1.13;  $p = 0.18$ ; and HR: 1.13, 95% CI: 0.99 to 1.28;  $p = 0.069$ , respectively). These findings were concordant across both trials (data not shown). The proportional hazards assumption was met for the trial effect in the regression models for death or HF hospitalization. In general, lower quartiles of baseline RAAS activation were associated with lower rates of death or HF rehospitalization than quartile 4, but these differences were not statistically significant (**Online Table 5**). The change in RAAS biomarkers from baseline to 72 h or 96 h was not associated with outcomes (both:  $p > 0.5$ ).

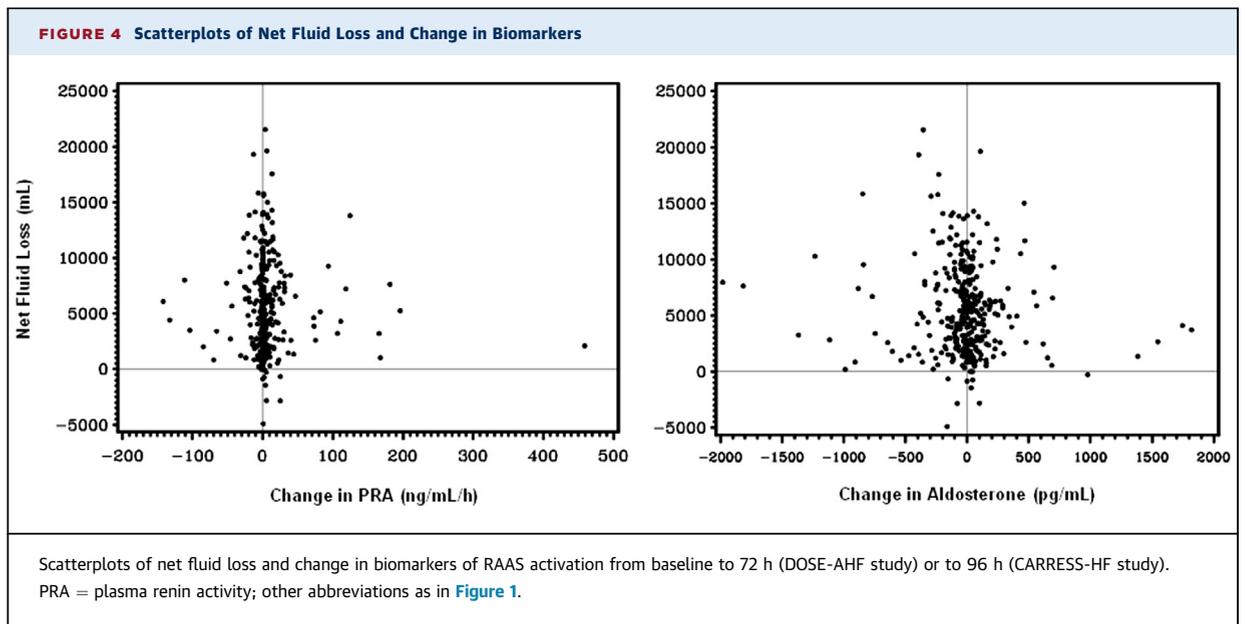
## DISCUSSION

Data from both the DOSE-AHF and CARRESS-HF populations provide a unique opportunity to examine RAAS activation across a spectrum of patients with AHF. Additionally, the fact that patients were randomly assigned to specific decongestion strategies eliminates a major potential confounder of observational data, in that sicker patients tended to be treated with more intensive therapy. We found that patients with baseline RAAS biomarker levels greater than the median had features of more severe disease, including lower blood pressure and serum sodium, higher BUN levels, and higher baseline outpatient loop diuretic doses. Contrary to our hypothesis and previous report findings, we found no evidence that higher doses of loop diuretics led to greater activation of RAAS from baseline to 72 h. In addition, UF, which is hypothesized to mitigate the RAAS activation seen with diuretics, was associated with greater PRA increases than diuretic-intensive stepped pharmacologic therapy. Despite previous suggestions linking RAAS activation and cardiorenal syndrome, we found that WRF occurred in a similar percentage of patients with baseline RAAS



biomarkers above or below the median values. However, the change in RAAS biomarkers was significantly associated with an increase in WRF. PRA and aldosterone levels at baseline and the change following decongestive therapy were not significantly associated with 60-day outcomes. These data are





different from those of previous reports regarding the relationship between specific decongestion strategies, RAAS activation, and clinical outcomes and should encourage further research to inform the understanding of these fundamental concepts in heart failure pathophysiology.

Our primary finding was that high-dose loop diuretic therapy did not result in greater RAAS activation than low-dose loop diuretic therapy. It has been suggested that loop diuretics in heart failure, especially at high doses, may cause RAAS activation (5,6). However, data supporting this concept largely predate current pharmacotherapy (10,11,16). A retrospective substudy of the SOLVD (Studies of Left Ventricular Dysfunction) study (n = 232) demonstrated that PRA was significantly elevated in heart failure patients receiving diuretics compared with those not receiving diuretics (11).

These observations are likely confounded by disease severity, which limits the ability to establish a causal relationship between diuretics and RAAS activation. In a study by Francis et al. (10), acute dosing with intravenous furosemide resulted in rapid PRA elevation in heart failure patients treated long-term with digoxin, and this was associated with systemic vasoconstriction. Other supportive data for the hypothesis of adverse effects of loop diuretics in heart failure come primarily from animal studies (17-19). Of note, in the present study, RAAS activation was assessed at a single time point, either 72 h or 96 h after randomized decongestion therapy in contrast to earlier studies where RAAS biomarkers were measured within hours of therapy (10) or in the outpatient setting (11,16). Thus, our findings in contrast to those of earlier studies may be partly related to the timing of sample acquisition. Our findings may also be different than those expected from previous experience, in part because the DOSE and CARRESS studies were designed to identify patients with evidence of excess circulating volume, and therapy was adjusted specifically to return patients to euvolemia. Notably, a recent small study of UF versus diuretic therapy in 30 AHF patients also demonstrated that fairly high-dose diuretics did not stimulate aldosterone levels (20). Therefore, these data should allay concerns for adverse effects on RAAS activation with higher-dose diuretics in volume-overloaded AHF patients receiving contemporary RAAS inhibitors. Interestingly, high-dose loop diuretics were not associated with more RAAS

**TABLE 3 Association Between the Change in RAAS Biomarkers (Baseline to 72 h or 96 h) With Development of WRF**

RAAS Marker	n	Events	Median Split*		Continuous Variable†	
			Odds Ratio (95% CI)	p Value	Odds Ratio (95% CI)	p Value
PRA	358	72	2.83 (1.61-4.99)	0.0003	1.80 (1.40-2.31)	<0.0001
Aldosterone	369	74	2.33 (1.30-4.16)	0.0045	1.13 (1.03-1.24)	0.0098

\*HR for change in RAAS activation measure  $\geq$  median versus  $<$  median (PRA median = 1.058 ng/mL/h; aldosterone median = -0.95 pg/mL) from proportional hazards regression model adjusted for trial, baseline RAAS activation, and baseline ACE-I/ARB and aldosterone antagonist use. †OR for 10-U increase in PRA and 100-U increase in aldosterone. Proportional hazards regression models were adjusted for trial, baseline RAAS activation, and ACE-I/ARB and aldosterone antagonist use.

WRF = worsening renal function; other abbreviations as in Table 1.

activation despite significantly greater net fluid loss compared with low-dose diuretics. These observations have important clinical applications because the DOSE-AHF trial demonstrated that high-dose loop diuretics have more favorable effects on decongestion (13), which is itself associated with improved long-term outcomes (21).

There are several potential explanations for the lack of greater RAAS activation with high-dose diuretics. Previous data suggest that the mechanisms for RAAS activation with furosemide involve direct diuretic effects caused by changes in sodium flux in the area of the macula densa in addition to nondiuretic mechanisms via baroreceptors, renal sympathetic nerves, and renal prostaglandins (10). It may be that these direct diuretic effects are not dose-related but, rather, are due to a “threshold effect.” Continuous infusion of furosemide might allow these changes to persist without relation to diuretic dose. These hypotheses may partly explain why continuous infusion furosemide was associated with a greater change in PRA than bolus dosing regardless of the magnitude of furosemide dose. Second, because study patients underwent diuresis to a normal volume level and presumably not below optimal volume, other potential causes of RAAS activation, such as overdiuresis with engagement of baroreflex mechanisms or imbalances in intravascular/extravascular volume, may have been less prominent. Third, the timing of sample acquisition may have limited the ability to detect different biomarker trajectories between decongestion strategies.

We found that UF was associated with greater PRA elevation than stepped pharmacologic therapy. This finding is in contrast to those of previous reports suggesting a favorable association between UF and markers of RAAS activation. For instance, a small, randomized study by Agostoni et al. (4) found that 16 heart failure patients treated with either UF or intravenous furosemide bolus had acutely increased RAAS activation from both therapies, but RAAS biomarkers decreased within the first 48 h in the UF group in contrast to persistent elevation in the diuretic group (4). Notably, this study differed from the CARRESS trial because the population was not acutely hospitalized and volume removal was rapid in the context of a single UF session to achieve a matched reduction in central venous pressure. That study was also performed before the use of beta-blockers or contemporary ACE-I. Importantly, the follow-up RAAS biomarker collection in CARRESS occurred at 96 h, which should have allowed for the detection of any beneficial effect of UF on RAAS levels on the basis of this previous study.

**TABLE 4 Association of Baseline RAAS Biomarkers and Change in RAAS Biomarkers (Baseline to 72 h or 96 h) With Time to Death or HF Hospitalization**

RAAS Marker	n	Events	Median Split*		Log <sub>2</sub> Transformation	
			HR (95% CI)	p Value	HR (95% CI)	p Value
PRA	427	134	1.28 (0.91-1.82)	0.16	1.05 (0.98-1.13)†	0.18
Aldosterone	427	134	1.39 (0.96-2.01)	0.080	1.13 (0.99-1.28)†	0.069
PRA change (HR for 10-U increase)	363	117			0.99 (0.92-1.06)‡	0.70
Aldosterone change (HR for 100-U increase)	372	119			1.00 (0.94-1.06)‡	0.90

\*Hazard ratio (HR) for RAAS activation measure  $\geq$  median versus  $<$  median (PRA median = 5 ng/ml/h; aldosterone median = 210 pg/ml) from proportional hazards regression model adjusted for trial, and baseline ACE-I/ARB and aldosterone antagonist use. †Hazard ratio for doubling of RAAS activation measurement from proportional hazards regression model adjusted for trial and baseline ACE-I/ARB and aldosterone antagonist use. ‡Proportional hazards regression models for change in RAAS activation from baseline to 72 h or 96 h, adjusted for trial, baseline RAAS activation, and ACE-I/ARB and aldosterone antagonist use.  
 Abbreviations as in Table 2.

Studies have suggested that if fluid removal with UF does not exceed the plasma refill rate, then intravascular volume can be maintained without adverse effects on neurohormone activation (3). Given the greater elevation in PRA with UF in the present study, there may have been some degree of transient intravascular volume depletion in the UF-treated patients despite a similar rate of fluid removal from patients receiving stepped pharmacologic therapy. Interestingly, UF was not associated with a larger increase in aldosterone compared with pharmacologic therapy. This observation highlights the complexity of the relationship between decongestion strategies and RAAS biomarkers and suggests a potential uncoupling of renin and aldosterone under certain circumstances. A previous study of UF versus diuretics in 30 AHF patients also demonstrated that UF did not stimulate aldosterone levels (PRA was not measured) (20). In that previous analysis, the rates of UF were carefully titrated, which may have reduced the potential for RAAS activation due to intravascular volume depletion. The present study demonstrates that use of UF in the context of cardiorenal syndrome and contemporary heart failure pharmacotherapy is associated with larger increases in PRA than stepped pharmacologic therapy. Future studies are needed to investigate the neurohormonal effects of stepped pharmacologic care if this strategy is incorporated into clinical practice.

Several observations with these data should be highlighted when considering the clinical applications. First, although the change in these RAAS biomarkers on the basis of decongestion strategy may be modest in some instances, there are patients who experience a much greater increase or decrease in biomarker values. For instance, the mean change in

aldosterone with UF was  $-9$  pg/ml, but the standard deviation was nearly 500 pg/ml. Thus, some patients are outliers with a marked neurohormonal response to different decongestion therapies. Future studies are needed to identify the characteristics and outcomes of these patient subgroups. Furthermore, although there was no differential increase in RAAS activation between high- and low-dose diuretics, the PRA increase with either approach was fairly high (median increase: 1.58 ng/ml/h with low-dose and 1.03 ng/ml/h with high-dose). Given the high morbidity and mortality rates in both arms in DOSE, the possible implications of this RAAS change requires further study. Second, the absolute degree of RAAS activation in this cohort was markedly elevated even following completion of the randomized inpatient therapy for decompensation. Specifically, the median PRA following randomized decongestion therapy ranged from 5.7 to 13.0 ng/ml/h for the different strategies compared with a prior SOLVD analysis where median PRA values in health controls and symptomatic chronic LV dysfunction were 0.6 and 1.4 ng/ml/h, respectively (11).

Additionally, RAAS activation is frequently cited as a primary driver of WRF in AHF patients, as highlighted in a recent comprehensive review of the topic (12). We found that patients with higher baseline PRA or aldosterone levels had a similar incidence of WRF compared with patients with lower baseline RAAS values. Previous data demonstrate the complexity of predicting WRF in AHF patients (22) and highlight the role of venous congestion (23). However, there was a significant association between the change in RAAS biomarkers from baseline and the development of WRF. Thus, we provide specific data to support an association between RAAS activation and WRF in AHF patients treated with contemporary medical therapy focused on RAAS inhibition.

We did not observe a significant association between RAAS biomarkers and 60-day post-discharge outcomes. There are several possible explanations for this finding. First, multiple factors in addition to disease severity may influence the level of these biomarkers, thereby reducing their utility for prognostic stratification. For instance, we confirm prior findings that RAAS inhibitor medication use was associated with different PRA and aldosterone levels. Second, the present analysis may have been underpowered to detect an association between these biomarkers and outcomes. The point estimates for hazard associated with PRA and aldosterone levels greater than or equal to the median were 1.28 and 1.39, respectively, but these did not reach statistical significance ( $p = 0.16$  and

$p = 0.080$ , respectively). The analysis based on RAAS biomarker quartiles also suggested reduced event rates in the lower quartiles. In addition, because biomarkers were sampled only at baseline and at 72 h or 96 h, we were unable to explore the trajectory of biomarkers with further granularity (e.g., peak, nadir, and rate of change over several time points). The dynamic nature of these biomarkers may have limited our ability to observe an association with outcomes due to bias related to the timing of sample acquisition. Importantly, these findings should not be interpreted to indicate that elevation in RAAS biomarkers at baseline is benign, since the event rate was quite high in these patients (i.e.,  $>30\%$  were rehospitalized or dead within 60 days).

**STUDY LIMITATIONS.** This was a post-hoc, retrospective analysis of 2 clinical trials with specific entry criteria and may not be fully representative of the overall AHF population. The status of activation of the infrarenal RAAS may not be reflected in plasma biomarker levels. The study was likely underpowered for the analysis of the association of biomarker levels and 60-day outcomes particularly given the multiple comparison groups. Other measured and unmeasured factors may have influenced these findings. For instance, we did not adjust for different doses of RAAS inhibitor medications or medication changes during hospitalization given the lack of data on medication dose and the limited number of patients with medication changes. Also, biomarker data were available at 2 time points during hospitalization and post-discharge changes could not be explored. It was also not possible to determine peak neurohormonal activity as we assessed RAAS activation only at baseline and at 72 h and 96 h. Nonetheless, the present analysis represents that largest study to date examining RAAS activation in AHF.

## CONCLUSIONS

This study investigated the relationships between treatment strategy and biomarkers of RAAS activation (PRA and aldosterone), WRF, and outcomes in a contemporary population of AHF patients enrolled in the DOSE-AHF and CARRESS-HF trials. For several decades, there has been evidence from both observational and interventional studies demonstrating that greater disease-induced RAAS activation is associated with poorer prognosis in patients with chronic HF (24). Similarly, clinicians have hypothesized for many years that diuretic-induced exacerbation of RAAS promotes worse outcomes.

We provide contemporary evidence that is in contrast to previous data and hypotheses regarding RAAS activation, AHF therapy, and post-discharge clinical outcomes. High-dose loop diuretics did not result in greater RAAS activation than low-dose diuretics. However, UF resulted in greater PRA increase than stepped pharmacologic care. An increase in RAAS biomarkers from baseline was associated with

WRF. PRA and aldosterone were not significantly associated with short-term post-discharge outcomes in this AHF cohort.

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**KEY WORDS** acute heart failure, cardiorenal syndrome, decongestion, diuretics, outcomes, RAAS activation, ultrafiltration

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**APPENDIX** For supplemental tables, please see the online version of this article.