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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.

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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 (≥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 × 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

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