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ORIGINAL RESEARCH ARTICLE

Renin–Angiotensin–Aldosterone System Optimization for Acute Decompensated Heart Failure Patients (ROAD-HF): Rationale and Design

Bhagwan Dass[1,5] · Michelle Dimza[2] · Girish Singhania[3] · Cody Schwartz[2] · Jerin George[2] · Avni Bhatt[4] · Nila Radhakrishnan[1] · Asha Bansari[1] · Shahab Bozorgmehri[5] · Rajesh Mohandas[5]

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Abstract

Introduction The long-term benefits of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) on outcomes in patients with chronic congestive heart failure are well-known, making them one of the most widely prescribed medications. However, the administration of ACEIs/ARBs in acute decompensated heart failure (ADHF) can increase the risk of morbidity and mortality secondary to worsening renal function (WRF). A decrease in estimated glomerular filtration rate (eGFR) during the treatment of ADHF has been associated with an increase in mortality proportional to the degree of WRF.

Aim The aim of our study is to determine whether withholding ACEIs/ARBs during the initial 72 h of admission in patients with ADHF will prevent WRF and allow more effective diuresis.

Methods Four hundred and thirty patients will be randomized to the intervention (withholding ACEIs/ARBs) or control (continue/start ACEIs/ARBs) arms for 72 h. Primary outcomes include rates of acute kidney injury (AKI), patient global assessment, and change in kinetic eGFR over 72 h, while secondary outcomes include change in weight, fluid balance, change in signs and symptoms of congestion, change in renal function, change in urinary biomarkers (tissue inhibitor of metalloproteinases 2 [TIMP-2] × insulin-like growth factor-binding protein 7 [IGFBP7]), patients experiencing treatment failure, hospital length of stay (LOS), cost analysis, mortality within 30 days, and hospital readmissions over 30 days and 1 year.

Conclusion This prospective clinical trial will prove if withholding ACEIs/ARBs will prevent AKI in ADHF. It will help us understand the complex interactions between the heart and kidney, and delineate the best treatment strategy for ADHF. Holding ACEIs/ARBs might help preserve renal function, and decrease hospital LOS, readmission rates, and cost of care in ADHF.

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Bhagwan Dass, Michelle Dimza, Girish Singhania, and Rajesh Mohandas contributed equally to this work.

✉ Bhagwan Dass
Bhagwan.Dass@medicine.ufl.edu

1 Division of Hospital Medicine, University of Florida, PO Box 100238, Gainesville, FL 32610, USA

2 Department of Internal Medicine, University of Florida, Gainesville, FL, USA

3 Department of Hospital Medicine, CHI St. Vincent Infirmary, Little Rock, AR, USA

4 Department of Pediatrics, Division of Hospital Medicine, University of Florida, Gainesville, FL, USA

5 Division of Nephrology, University of Florida, Gainesville, FL, USA

Key Points

Angiotensin-converting enzyme inhibitor (ACEIs) use and angiotensin receptor blocker (ARBs) use in acute decompensated heart failure (ADHF) can cause worsening renal function and prevent effective diuresis.

This study will examine the question of whether withholding ACEIs/ARBs during the initial 72 h of admission will improve clinical outcomes in patients with ADHF.

1 Introduction

While the benefits of using angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) in chronic heart failure are well-documented, their role in acute decompensated heart failure (ADHF) is less clear. The introduction of ACEIs can be associated with worsening of renal function in some patients. An initial increase in creatinine of up to 30% is considered acceptable due to the desired effect of efferent arteriole dilation, and should not result in discontinuation of the medication. However, the long-term renal and cardiac benefits are not applicable to the altered hemodynamic state of ADHF. ACEIs/ARBs impair renal autoregulation, and, in some settings, transient volume depletion or hypotension can predispose to acute kidney injury (AKI). Recent studies have found worsening renal function (WRF) during index hospitalization is strongly associated with increased mortality, hospital length of stay (LOS), readmission rates, and cost of care [1, 2]. Even small increases in creatinine can be associated with adverse consequences [3]. Furthermore, an increase in creatinine often prompts withdrawal of diuretics, regardless of intravascular volume status. This results in suboptimal volume control, a vital component of ADHF management [4–6].

The Renin Angiotensin Aldosterone Optimization in Acute Decompensated Heart Failure (ROAD-HF) study is a randomized controlled trial (RCT) aimed at investigating the hypothesis that withholding ACEI/ARBs for the initial 72 h of ADHF hospitalization will reduce the rates of WRF, while allowing for more aggressive diuresis and clinical improvement. If the goals of this study are realized, it would assist in standardizing the treatment approach for ADHF, minimize adverse events, shorten hospital stay, and prevent readmission for patients admitted with ADHF.

2 Materials and Methods

2.1 Overview of Study Design

ROAD-HF is a randomized controlled, open-label clinical trial designed to study the effect of holding ACEIs/ARBs for the initial 72 h of hospitalization for the treatment of ADHF on kidney function and other clinical outcomes. ROAD-HF plans to recruit 430 patients presenting to the Emergency Department (ED) with an established diagnosis of congestive heart failure (CHF) or a clinical diagnosis of ADHF based on having two of the four diagnostic criteria (Table 1) and reduced left ventricular ejection fraction (EF; $<50\%$) on previous echocardiography. Participants will be enrolled within 24 h of presentation and randomized into a control or intervention group. If the control group was receiving ACEIs/ARBs prior to admission, they will be continued on the same dosage; however, if they have not previously received ACEIs/ARBs, they will be administered either the full dose of ACEIs/ARBs or a reduced dose based on the admission serum creatinine value. Creatinine values vary on renal excretion and muscular mass and it is envisaged that randomization will lead to an even distribution of muscle mass between the two treatment groups. The intervention group will not receive ACEIs/ARBs for the first 72 h of hospitalization.

The primary outcomes are rates of AKI from randomization, with AKI defined as a rise in creatinine >0.3 mg/dL over 48 h, patient global well-being assessment by modified Borg/VAS scale area under the curve (AUC) [7], change in dyspnea over 72 h assessed by modified Borg/VAS scale AUC [7], and change in kinetic estimated glomerular filtration rate (eGFR) over 72 h [8]. The kinetic eGFR uses the change in creatinine to estimate GFR and does not rely on steady-state assumptions. Secondary outcomes include change in weight, fluid balance, change in signs and symptoms of congestion, change in renal function, change in urinary biomarkers (the tissue inhibitor of metalloproteinases 2 [TIMP-2] $\times$ insulin-like growth factor-binding protein 7 [IGFBP7] biomarker that can help distinguish between change in serum creatinine due to tubular injury from that due to transient hemodynamic fluctuation), patients experiencing treatment failure, hospital LOS, cost analysis, mortality within 30 days, and hospital readmissions over 30 days and over 1 year. This extended follow-up will enable us to separate individuals with transient elevations in creatinine from those with more substantial renal injury. ROAD-HF is registered on ClinicalTrial.gov as RAAS Optimization for Acute CHF Patients (ROAD-HF; NCT03695120). Randomization began in February 2019.

2.2 Funding Announcement, Sponsor and Oversight

This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors. The study is supported by the Department of Hospital Medicine at the University of Florida, Gainesville, FL, USA.

2.3 Participant Eligibility

ROAD-HF inclusion and exclusion criteria are listed in Table 1. Briefly, participants will be eligible for randomization if they (1) have been previously treated for ADHF within the last 24 h; (2) have been newly diagnosed with ADHF based on two of four findings, including elevated

Table 1 Eligibility criteria of the ROAD-HF trial

Inclusion criteria
Being treated for ADHF within the last 24 h
or
HF based on two or more of the following four diagnostic criteria:
Elevated concentration of BNP (> 300 for sinus rhythm, > 500 for patients with AF) or N-terminal pro-BNP (> 1000 for sinus rhythm, > 1600 for AF)
Pulmonary edema on physical examination
Radiologic pulmonary congestion or edema
History of HF with an anticipated need for intravenous loop diuretics for at least 48 h
LVEF < 50%, as seen on previous transthoracic echocardiography
Willingness to provide informed consent
Exclusion criteria
End-stage renal disease
Admission serum potassium > 5.5 mmol/L
Admission serum creatinine > 3 mg/dL (only patients with creatinine above 3 mg/dL were excluded; the remainder were included)
Cardiogenic shock, ST-segment elevation myocardial infarction, ongoing acute ischemia
Sodium level < 132 mg/dL (indicative of hyponatremia)
Need for renal replacement therapy through dialysis or ultrafiltration
MI within 30 days of screening
Systolic BP < 90 mmHg
Requiring intravenous vasodilators or inotropic agents (other than digoxin) for HF
BNP < 250 ng/mL and/or proBNP < 1000 mg/mL
Pregnant women, prisoners, and institutionalized individuals
Severe stenotic valvular disease
Complex congenital heart disease
Need for mechanical hemodynamic support
Sepsis
Terminal illness (other than HF) with expected survival of < 1 year
Previous adverse reaction to the study drugs
Use of intravenous iodinated radiocontrast material in the last 72 h or planned during hospitalization
Enrollment or planned enrollment in another RCT during the current hospitalization
Inability to comply with planned study procedures
Primary admission diagnosis other than acute HF

ADHF acute decompensated heart failure, *AF* atrial fibrillation, *BNP* B-type natriuretic peptide, *BP* blood pressure, *HF* heart failure, *LVEF* left ventricular ejection fraction, *MI* myocardial infarction, *RCT* randomized controlled trial, *ROAD-HF* Renin Angiotensin Aldosterone Optimization in Acute Decompensated Heart Failure

B-type natriuretic peptide (BNP) or pro-BNP, signs of pulmonary edema on physical examination, radiographic evidence of congestion, or a history of heart failure with an anticipated need for intravenous loop diuretics for 48 h; (3) had reduced EF on previous transthoracic echocardiography (EF < 50%); and (4) showed a willingness to provide informed consent.

2.4 Targeted Recruitment

Patients presenting to the ED with suspected ADHF will initially be evaluated by ED physicians. Patients being admitted will be evaluated by either the ED physician or the admitting officer of the day (AOD) for eligibility for the ROAD-HF study based on the above criteria. The AOD, principal investigator (PI), co-investigators, and study coordinator will be the primary contacts with the participants. A Health Insurance Portability and Accountability Act of 1996 (HIPAA) waiver has been granted to allow study staff to identify eligible patients. Participants will be consented in accordance with the study protocol; ensuring understanding of the purpose of the study, interventions, potential risk, benefits, and the option of not participating. They will be required to sign an informed consent form prior to enrollment. Eligible participants will be selected and added to the research team in the ED or on the hospital floor. Additionally, direct admissions from other centers and clinics will undergo the same evaluation for eligibility.

2.5 Study Data Collection

A participant's electronic medical record will be used to record markers, including serum creatinine, kinetic eGFR, N-terminal pro-BNP, and weight, at 24, 48 and 72 h. Additionally, ED visits, readmission, and death within 30 days after discharge will be monitored. Data will be collected by study staff and stored in RedCap.

2.6 Intervention and Treatment Group Assignment

Participants will be randomized to a control or a variable group using a block randomization strategy with varying blocks of 8–10 for a total of 430 subjects. Allocation concealment will be ensured using RedCap software. The control group will consist of subjects receiving ACEIs/ARBs, and this group will either be continued on their home dose or on a full dose of ACEIs/ARBs. Full-dose ACEIs/ARBs will be defined as lisinopril 40 mg daily or losartan 100 mg daily in patients with serum creatinine levels < 1.6 mg/dL, and lisinopril 20 mg or losartan 50 mg in patients with serum creatinine levels ≥ 1.6 mg/dL but ≤ 3.0 mg/dL. The intervention group will consist of subjects who will not receive ACEIs/ARBs during the first 72 h of admission.

All participants will receive a baseline medical evaluation at the time of enrollment into the study. This will include a detailed history and physical examination, with particular attention to symptoms of heart failure, such as edema, shortness of breath, orthopnea, change in weight, and history of hospitalization for heart failure in the last 12 months. We will also record the list of home medications, including dose of ACEIs/ARBs, β-blockers, and furosemide or equivalent. Laboratory data will include BNP or Pro-BNP, renal function panel, kinetic eGFR, and [TIMP-2] × [IGFBP7] biomarker.

All subjects will be started on intravenous furosemide or its equivalent, at a conversion rate of three times their oral home dose every 12 h if serum creatinine is > 2.5 mg/dL or 2.5 times their home dose every 12 h if serum creatinine is < 2.0 mg/dL.

Standard of care laboratory and clinical data will be evaluated again at 24, 48, and 72 h, and on the day of discharge. These data include (1) weight; (2) vital signs; (3) volume status, i.e. (a) fluid balance (net intake minus output), (b) crackles on auscultation, (c) lower extremity edema on physical examination, (d) freedom from signs and symptoms of congestion (yes/no), (e) dyspnea assessment by modified Borg/VAS scale, and (f) global well-being score; (4) cardiac function parameters, including left ventricular EF, jugular venous pressure, BNP, and/or pro-BNP; (5) renal function panel; (6) change in cardiovascular medications; and (7) any other unanticipated adverse events.

At 48 h, the treating physician will have the option to adjust the diuretic strategy based on clinical response. The physician could increase the dose by 50%, maintain the same strategy, or discontinue intravenous treatment and change to oral diuretics. After 72 h, all treatment will be at the discretion of the treating physician. At approximately 30 days postdischarge, data will be collected for readmissions, adverse events, and death. These data will be collected solely from chart review and will not require contact with the participant.

At approximately 1-year postdischarge, follow-up will consist of a chart review to determine (1) whether the patient had been hospitalized since the last visit, and the reasons for admission; (2) LOS in subsequent hospitalizations; (3) has the patient experienced adverse events in the past year; and (4) has the patient passed away, and, if so, the cause of death.

2.7 Outcomes

2.7.1 Primary Outcomes

(a) WRF will be compared from admission to 72 h and defined as a serum creatinine rise > 0.3 mg/dL over 48 h.
(b) Patient global assessment (PGA) over 72 h, by modified scale (based on Borg and VAS) AUC [7]. Patients will rate their general well-being using a scale that ranges from 'best I've ever felt' to 'worst I've ever felt'. Patients will self-assess at randomization (start of the trial), and at approximately 24, 48, and 72 h.
(c) Clinical change in dyspnea over 72 h assessed by modified scale (based on Borg and VAS) AUC [7]. Patients will rate their shortness of breath using a scale that ranges from 'no shortness of breath at all' to 'I can't breathe!'. Patients will self-assess at randomization (start of the trial), and at approximately 24, 48, and 72 h.
(d) Change in kinetic eGFR (calculated as the change from baseline at 24, 48, and 72 h).

2.7.2 Secondary Outcomes

Secondary outcomes for ROAD-HF will include (a) change in weight; (b) net fluid balance; (c) freedom from signs and symptoms of congestion; (d) [TIMP-2] × [IGFBP7] biomarker (baseline level for all patients and reassessment at 48 h for the first 100 patients); (e) persistent or worsening heart failure; (f) treatment failure; (g) hospital LOS; (h) cost analysis of hospital stay; (i) death at 30 days; (j) readmission, or ED visit within 30 days; and (k) readmission rates at 1 year.

[TIMP-2] × [IGFBP7] is a biomarker that predicts the risk of moderate or severe AKI within 12 h, in patients

hospitalized to intensive care units [9]. All patients enrolled in the trial will receive at least one [TIMP-2]×[IGFBP7]. This test is used for AKI risk score ranging from 0.04 to 10.0. Patients whose score exceeds 0.3 are considered to be at risk of developing AKI. The first 100 patients will also receive the test twice, at 0 and 48 h. Re-agents for the test will be provided by Astute Pharmaceuticals free of charge. This company has waived access or input into the study design and data.

2.8 Safety

The overall design and nature of the study uses therapies that are considered standard of care and are thus considered relatively low risk. Withholding the ACEIs/ARBs poses minimal risks. We will exclude patients who may be at high risk of adverse events as outlined in the exclusion criteria. The health and safety of the patients will be our foremost priority. The treating physician will have the freedom to adjust therapy for heart failure as clinically appropriate, and, if necessary, deviate from the research protocol or withdraw the patient from the study. If the physician feels the patient would benefit from restarting ACEIs/ARBs, they will promptly be restarted. One concern is that ACEIs/ARBs may not be restarted prior to discharge. For this purpose, a Data Safety Monitoring Board (DSMB), comprised of members outside of the study staff, will specifically focus on ensuring that all patients enrolled in the trial are restarted on their home ACEIs/ARBs after 72 h and prior to discharge from the hospital. The DSMB will monitor any adverse events throughout the study and will have the power to stop enrollments or shut down the study if there are concerns for patient safety.

2.9 Sample Size/Power Analysis

All analyses will be performed according to the 'intention-to-treat' principle. The primary objective is to assess the incidence of AKI in patients randomized to receive ACEIs/ARBs versus those who are not exposed to high-dose ACEIs/ARBs, and determine whether this difference is significantly different from a statistical perspective.

Power Analysis We chose a pragmatic sample size of 430 patients (215 in each group). Since the study intervention is only for a short period of 3 days, we expect most patients to complete the study. We factored a dropout rate of 7.5%, to account for patient's crossing over or stopping the study due to patient or physician preference. Hence, we expect 200 patients per group will complete the study and be included in the final analysis. For the purpose of the power analysis, we used an estimate of 28% for the incidence of AKI among controls (i.e. patients with ACEI/ARB use). Our review of the literature showed an average incidence of AKI of 28% in patients admitted with ADHF (Table 2). Since our study is primarily confined to patients with left ventricular systolic dysfunction, and we are using a change in creatinine of 0.3 mg/dL as the definition of AKI, we expect our study population to have a significantly larger incidence of AKI. We have also provided power analysis for estimates of 30% and 35% incidence in AKI.

Our power analysis shows that a sample size of 400 patients achieves 87% power to detect a 45% reduction in the incidence of AKI using a Chi-square test with a significance level (alpha; type I error rate) of 0.05. Table 3 presents our power analysis for a range of numbers for the AKI incidence rate (28%, 30%, and 35%) and the percentage reduction (30%, 35%, 40%, and 45%) in the

Table 2 Studies with an incidence of worsening renal function during acute decompensated heart failure [18–27]

Authors	PMID	Total number of patients	Incidence of AKI [*n* (%)]
Breidthardt et al. [18]	21247523	657	136 (21)
Cioffi et al. [19]	17502758	79	16 (20)
Damman et al. [20]	19696057	1023	112 (11)
Forman et al. [21]	14715185	1004	273 (27)
Gottlieb et al. [22]	12140805	1002	200 (20)
Hata et al. [23]	20023042	251	150 (60)
Krumholz et al. [24]	10781761	1681	470 (28)
Smith et al. [25]	12612868	412	101 (24)
Wang et al. [26]	23607443	1709	550 (32.2)
Weinfeld et al. [27]	10426840	48	10 (21)

AKI acute kidney injury, *PMID* PubMed identifier number

Table 3 Power analysis for a sample size of 200 patients in each group (a total of 400 patients) according to different rates for acute kidney injury incidence and percentage reduction in acute kidney injury incidence in the intervention group compared with controls

Incidence of AKI in controls (%)	Percentage reduction in AKI rate compared with controls	Power (%)
28	30	51
28	35	64
28	40	77
28	45	87
30	30	54
30	35	68
30	40	81
30	45	90
35	30	63
35	35	77
35	40	88
35	45	95

AKI acute kidney injury

AKI incidence rate compared with the control group (i.e. patients who receive ACEIs/ARBs).

Statistical Analysis Baseline demographics and clinical characteristics will be examined using one-way analysis of variance (ANOVA) and Kruskal–Wallis tests for normally and non-normally distributed continuous variables, respectively, and the Chi-square test for categorical variables. This will help us evaluate whether there is any difference between the intervention (i.e. patients without ACEIs/ARBs) and control (i.e. patients with ACEI/ARB use) groups, although one of the goals of randomization is to make the two groups comparable with respect to the baseline characteristics.

For the primary outcome (the occurrence of AKI), we will use the Chi-square test to investigate the difference in the proportion of AKI occurrence between patients with and without ACEI/ARB use. We will use a multivariate logistic regression model to assess the association between ACEI/ARB use and AKI occurrence after controlling for potentially confounding variables such as age, sex, race, body mass index, baseline eGFR, diabetes mellitus, and left ventricular EF (in case the two treatment groups are statistically different with respect to clinically important variables impacting the primary outcome). We will compare the patient global well-being and dyspnea VAS scores at 24, 48, and 72 h from admission, between the intervention and control groups, using repeated measures ANOVA. For each patient, a plot of the respective global well-being and dyspnea VAS scores over time will be constructed, with points existing for each of the VAS measurements at baseline, 24, 48, and 72 h from admission. For each patient, we will calculate the AUC for the respective global well-being and dyspnea VAS scores using the sum of the areas of each of the individual trapezoids. The mean AUCs of global well-being and dyspnea VAS scores will be compared between the intervention and control groups using ANOVA. We will use a multivariate generalized linear regression model to assess the association between ACEI/ARB use and the AUCs of global well-being and dyspnea VAS scores after adjusting for potentially confounding variables. For analyzing secondary outcomes, which include change in weight, net fluid loss, freedom from signs and symptoms of congestion, persistent or worsening heart failure, treatment failure, hospitalization LOS, 30-day mortality, and 30-day and 1-year readmission rates, we will use repeated measures ANOVA, mixed-effects, generalized linear, or logistic regression models when appropriate. We will also stratify outcomes by the degree of AKI and by urinary biomarkers. All significant tests will be two-sided, with a p value < 0.05 considered statistically significant. Statistical analyses will be performed using Statistical Analysis Software (SAS) version 9.4 (SAS Institute Inc, Cary, NC, USA).

3 Discussion

According to epidemiological studies, the lifetime risk for developing heart failure in Americans ≥ 40 years of age is about 20% [10]. The incidence of heart failure increases with age, from approximately 20 per 1000 individuals between 65 and 69 years of age, to > 80 per 1000 individuals among those ≥ 85 years of age [11]. The prevalence continues to increase and, per reports, approximately 5.1 million persons in the United States have clinically manifest heart failure [12]. It is predicted that by the year 2030, > 8 million Americans will have a diagnosis of heart failure, and the direct healthcare cost will exceed $70 billion [13]. Although several therapies have been developed for heart failure, the overall mortality and adverse cardiovascular outcomes has not significantly improved over time. The long-term treatment of heart failure involves the use of ACEIs/ARBs as well as β-blockers to inhibit the maladaptive upregulation of the renin–angiotensin–aldosterone system (RAAS) and sympathetic nervous system that accompanies chronic heart failure. Diuretics result in the greatest relief of symptoms by reducing pulmonary congestion caused by elevated cardiac pressures. There is also evidence that diuretics benefit mortality, slow progression of heart failure, and improve exercise capacity for patients with heart failure [14]. However, one major limiting factor to aggressive diuresis is WRF, or cardiorenal syndrome (CRS).

A 2008 review article in the *Journal of the American College of Cardiology* defined CRS as "the pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of one organ induces acute or chronic dysfunction of the other" [15]. During the treatment of ADHF, decongestant therapy results in decreased ventricular filling pressures and a drop in systemic blood pressure. The low blood pressure activates the RAAS and sympathetic nervous system to maintain eGFR. Observational data suggest that the use of RAAS inhibitors may be associated with a risk of WRF. The use of ACEIs/ARBs during aggressive diuresis and hemodynamic instability blunts RAAS autoregulation and may result in WRF. Recently, several studies have shown that WRF is an independent risk factor for increased adverse outcomes, hospitalization, and mortality, suggesting it is more than just a marker for disease severity [16, 17]. In general, this acute worsening occurs within 3–4 days of hospitalization, and is associated with electrolyte abnormalities, increased LOS, higher in-hospital costs, and increasing incidence of chronic kidney disease [3]. The ROAD-HF study will formally test the hypothesis that WRF can be mitigated by withholding ACEIs/ARBs during the initial phase of inpatient treatment, when aggressive diuresis is often attempted.

4 Conclusion

In summary, the ROAD-HF study is an RCT aimed at assessing the impact of holding ACEI/ARB medication early in the treatment of ADHF. Specifically, the study will compare two treatment strategies during aggressive diuresis—one group with continued ACEIs/ARBs and the other group without this therapy for the initial 72 h. Holding ACEIs/ARBs should mitigate the significant hemodynamic consequences on the RAAS during the aggressive diuresis phase of therapy. By allowing natural autoregulation to take place, the kidneys will be able to compensate more appropriately. We hope to find a way to reduce the incidence of WRF and the downstream implications associated with this outcome. These data can be used to help standardize therapy for a diagnosis associated with such high morbidity and mortality.

Author Contributions BD designed the study; BD, MD, GS, and RM undertook the literature review, wrote the manuscript and contributed equally to this manuscript; CS, JG, ABh, NR, and ABa undertook critical revision; and SB helped with the statistical analysis and reviewed the manuscript. All authors read and approved the final version submitted for publication.

Compliance with Ethical Standards

Funding This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest Bhagwan Dass, Michelle Dimza, Girish Singhania, Cody Schwartz, Jerin George, Avni Bhatt, Nila Radhakrishnan, Asha Bansari, Shahab Bozorgmehri, and Rajesh Mohandas declare no potential conflicts of interest that may be relevant to this work.

Ethical approval This study has been approved by the University of Florida Institutional Review Board (IRB) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in this study.

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