CardioRenal Medicine

Cardiorenal Med 2020;10:69–84
DOI: 10.1159/000504167
Published online: February 14, 2020

Review Article

Benefits and Risks of Continuing Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Antagonists, and Mineralocorticoid Receptor Antagonists during Hospitalizations for Acute Heart Failure

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Keywords
Acute heart failure · Diuretics · Renin-angiotensin-aldosterone system · Ultrafiltration · Acute kidney injury · Cardiorenal syndrome · Tubular injury biomarkers

Abstract
Background: The renin-angiotensin-aldosterone axis plays a pivotal role in the pathophysiology of acute and chronic heart failure (HF) and represents an important target for guideline-directed medical therapy. ***Summary:*** The use of appropriate directed medical therapies for inhibition of the renin-angiotensin-aldosterone axis in chronic HF has been the subject of several landmark clinical trials, with high levels of adherence exhibited in the outpatient setting. However, less clarity exists with respect to the initiation, continuation, and cessation of renin-angiotensin-aldosterone system inhibitors (RAASi) in the setting of acute HF and exacerbation of HF necessitating hospitalization. In this review, we summarize relevant aspects of the physiology of the renin-angiotensin-aldosterone axis in acute HF and during decongestion. We also summarize the available evidence for the risks and benefits of initiating and continuing RAASi in acute HF. ***Key Message:*** We offer a decision-making pathway for the use of RAASi in the setting of acute HF that would help guide the cardiologist and nephrologist caring for patients with acute HF and cardiorenal syndrome.

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Introduction

The renin-angiotensin-aldosterone system (RAAS) plays a central role in the pathophysiology of acute and chronic heart failure (HF). It is extensively influenced by decongestive strategies such as diuresis and ultrafiltration for HF as well as pharmacotherapies used in guideline-directed medical therapy (GDMT) directed at RAAS inhibition. While modulation of the renin-angiotensin-aldosterone axis is well represented in landmark HF trials in the setting of chronic HF, there is less guidance on the use of RAAS inhibitors (RAASi) in the setting of acute HF. In this review, we discuss the data regarding safety and the logistics surrounding initiation, continuation, and withdrawal of RAASi in acute HF. We focus on angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), angiotensin receptor neprilysin inhibitors (ARNi)/valsartan, and mineralocorticoid receptor antagonists (MRA) as part of the RAAS-targeting GDMT portfolio for patients with HF. Finally, we outline an opinion-based decision-making pathway that will help cardiologists and nephrologists treating patients with acute HF apply best clinical practices to optimize outcomes in these vulnerable patients.

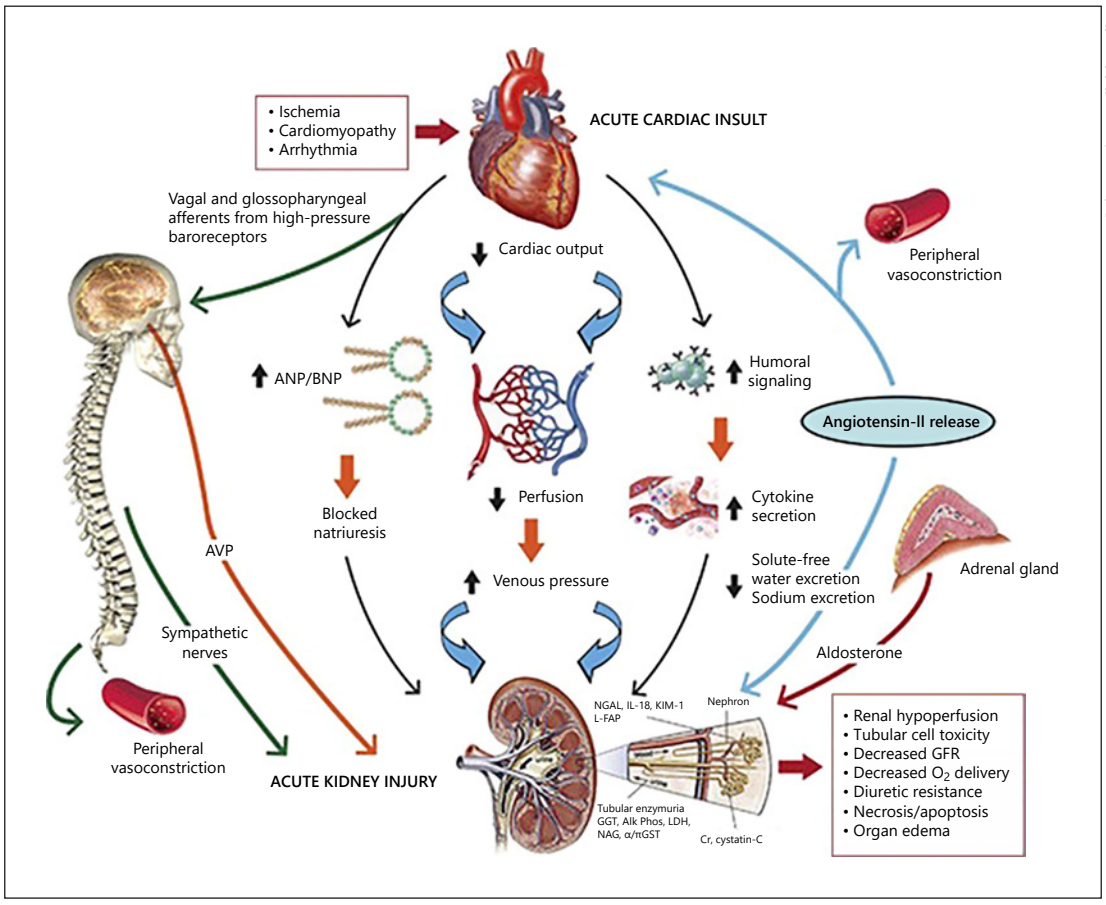
Physiology of the RAAS

Renin is an enzyme synthesized by specialized granular cells in the juxtaglomerular apparatus and released by the afferent arteriole in response to three stimuli: (1) decreased arterial blood pressure, sensed by the baroreceptor cells in the arteriolar vessel wall, (2) decreased intracellular chloride levels inside the macula densa cells, lining the renal tubules at the end of Henle's loop, a process that is potentiated by potassium depletion, and (3) sympathetic activation. Renin breaks down hepatically secreted circulating angiotensinogen, converting it into angiotensin I which is later transformed into angiotensin II by endothelial cells. Angiotensin II is a potent stimulator of aldosterone release by the adrenal glands. The purpose of the RAAS is to regulate blood pressure, fluid and electrolyte balance, and systemic vascular resistance.

Renin-Angiotensin-Aldosterone Axis in HF and Kidney Injury

Plasma renin activity (PRA) and plasma aldosterone are key mediators of HF decompensation and progression. Persistent and excessive RAAS activation causes adverse cardiac remodeling and fluid retention, with worsening congestion (Fig. 1). RAAS activation is sensitive to low cardiac output (CO)/low renal perfusion, responding even to simple postural changes. Low CO in early stages of HF prompt RAAS-activated fluid retention, which increases ventricular preload and CO until CO again meets the RAAS activation threshold. RAAS activation is kept at an increased set point to maintain the compensated CO [1]. When the ventricular stroke volume declines, the CO cannot reach the new higher RAAS activation threshold. The RAAS is stimulated to compensate for the lowering CO in a futile attempt to elevate the decreased CO. With increased salt retention accompanying this maladaptive activation of the RAAS, there is a shift of the Frank-Starling curve to the right, precipitating an ineffective, excessive, and congested state in HF [2].

The activation of the RAAS drives worsening kidney function and cardiorenal syndrome in subjects with acute HF. Additionally, decongestive therapies in acute HF (diuretics and ultrafiltration) themselves modulate the RAAS. The Diuretic Optimization Strategies in Acute Heart Failure (DOSE) and Cardiorenal Rescue Study in Acute Decompensated Heart Failure



Color version available online

Fig. 1. Pathophysiology of neurohumoral and inflammatory pathways involved in cardiorenal syndrome. Reprinted from Ismail et al. [39] with permission from Elsevier. © 2012, Elsevier.

(CARRESS-HF) trials are the largest contemporary datasets with data on RAAS biomarker changes (PRA and serum aldosterone) during decongestive treatment for acute HF. In these studies, PRA and plasma aldosterone were measured at baseline and after 72 and 96 h of decongestive treatment, and the relationship between RAAS activation and HF severity in the DOSE and CARESS-HF trials was described by Mentz et al. [3]. In this analysis, patients had high adherence to neurohumoral blocker therapies including ACEi, ARB, and MRA. PRA levels significantly increased with decongestive therapy in the continuous group compared to the bolus of furosemide group of the DOSE trial (median: +1.66 vs. +0.66 ng/mL/h with continuous vs. bolus infusion, respectively, $p = 0.021$), and in the ultrafiltration group compared to the stepped pharmacological care arm of CARRESS-HF (+4.05 vs. +0.56 ng/mL/h with ultrafiltration vs. stepped care, respectively, $p = 0.014$). However, there were no significant differences in PRA or plasma aldosterone levels between the high and low dose of furosemide group in the DOSE trial. Worsening renal function correlated with higher levels of RAAS biomarkers (PRA of ≥1.058 ng/mL/h and aldosterone levels of ≥0.95 pg/mL). Neither baseline PRA nor aldosterone was associated with worse mortality or HF hospitalization (hazard ratio [HR] for a doubling of 1.05; 95% confidence interval [CI]: 0.98–1.13; $p = 0.18$; and HR: 1.13; 95% CI: 0.99–1.28; $p = 0.069$, respectively). A low proportion of subjects achieved clinical decongestion in these trials (15% after 72 h in the DOSE study and 10% after 96 h in the CARRESS-HF trial). Importantly, mortality and HF readmissions after 60 days were not associated with higher levels of RAAS biomarkers at 2–96 h.

Of note, the analysis by Mentz et al. [3] clarified prior misconceptions, such as potential worsening of HF due to excessive RAAS activation with high-dose loop diuretics or ultrafiltration, when the excessive RAAS activation is actually related to HF severity [4]. The timing of the sample acquisition was key as well, since the DOSE and CARRESS-HF trials were designed to collect the data of subjects with "excess" circulating volume, and their decongestive strategies were aimed at euvolemia. Ultrafiltration results in a greater PRA increase than does stepped pharmacologic care, which may be related to transient intravascular hypovolemia, despite the stable rate fluid removal. The RAAS activation with furosemide may be related to changes in sodium flux in the macula densa and baroreceptor-related countermechanisms, renal sympathetic nerve activity, and intrarenal prostaglandins.

Aside from the worsening HF itself that can alter the RAAS and contribute to the worsening congestion and renal function in cardiorenal syndrome as discussed above, biochemical evidence of acute kidney injury (AKI) is commonly seen in the form of elevations in serum creatinine in patients with acute decompensated HF. Often this happens in the setting of the use of RAASi medications. These elevations in serum creatinine do not necessarily reflect actual kidney tubular damage. In fact, in a subanalysis of two large studies of intensive blood pressure lowering, the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD-BP) trial and the Systolic Blood Pressure Intervention Trial (SPRINT), even though there were a noted elevation of serum creatinine and lower estimated glomerular filtration rates (eGFRs) in the intensive blood pressure lowering groups, there was no associated elevation of kidney injury biomarker levels [5, 6]. This suggests that these serum creatinine elevations and decreases in eGFR could result from hemodynamic changes and may not necessarily indicate actual kidney tubular damage [5, 6]. Thus, discontinuation of RAASi in the setting of elevations in serum creatinine may actually represent missed opportunities to improve clinical outcomes in patients with acute HF. We therefore proceed to discuss the current evidence on initiation, maintenance, and discontinuation of RAASi in patients with HF, including the use of urinary biomarkers to help identify actual kidney tubular damage to help maximize the use of these RAASi in these patients.

RAASi in Acute HF

Initiation and Maintenance of RAASi

Goal-directed medical therapies in HF involve inhibition of the RAAS as one of the key targets for treatment in HF, with high-quality data available on the benefits of RAASi in chronic HF. ACEi reduce morbidity, mortality, and hospitalization in cases of HF with reduced ejection fraction (HFrEF) [7]. Comparable findings have been described with ARB [8]. Prescribing an ACEi at hospital discharge may impact adherence in the outpatient setting [9]. There is evidence of protective benefits with upward titration of ACEi even with elevations in serum creatinine during HF hospitalization [10]. The initiation of therapy with ACEi, ARB, and ARNi is a class I indication in the management of patients with HFrEF [11]. However, there are no high-quality clinical outcome data to guide the initiation of in-hospital ACEi/ARB in acute HF. Tables 1 and 2 include the studies that support the initiation of RAASi in acute HF, which will be discussed in this section [12–19]. A large observational study from the Get with the Guidelines Heart Failure (GWTG-HF) registry by Gilstrap et al. [13] found that in a cohort of 16,052 patients, those who were initiated on ACEi/ARB before the time of discharge after a hospitalization for acute HF had lower death and readmission rates at 1 year. Another observational cohort of HF patients found that individuals initiated on an ACEi/ARB had lower 30-day all-cause readmissions (18 vs. 24%; HR: 0.74; 95% CI: 0.56–0.97; $p = 0.030$) and all-cause mortality (7 vs. 14%; HR: 0.56; 95% CI: 0.33–0.98), both

Table 1. Summary of studies on initiation or continuation of ACEi/ARB in acute HF

Therapy, reference	Design, population (*n*)	Findings
GWTG-HF Sanam et al. [12]	observational: patients without prior ACEi/ARB use and discharge on ACEi/ARB; prescription vs. no prescription; *n* = 954	30 days after discharge, ACEi/ARB was associated with significantly lower propensity-adjusted all-cause readmission (HR: 0.74; 95% CI: 0.56–0.97; $p = 0.030$); lower 30-day all-cause mortality (HR: 0.56; 95% CI: 0.33–0.98; $p = 0.041$); associations remained significant at 1 year
GWTG-HF (Medicare claims data) Gilstrap et al. [13]	observational: ACEi/ARB withdrawal vs. continuation; *n* = 16,052	1-year after discharge, in-hospital ACEi/ARB withdrawal was associated with higher adjusted mortality risk compared with continuation (HR: 1.35; 95% CI: 1.13–1.61; $p < 0.001$); 30-day mortality started or continued ACEi 540/14,535 vs. 117/1,517 (HR: 0.48) stopped or discontinued; 30-day readmission on ACEi 2,679/14,535 vs. 369/1,517 discontinued (HR: 0.76)
PIONEER-HF Velazquez et al. [14]	randomized clinical trial: patients randomized to in-hospital initiation of sacubitril/valsartan vs. enalapril with 12-week follow-up; *n* = 881	the time-averaged reduction in the NT-proBNP concentration was significantly greater in the sacubitril-valsartan group than in the enalapril group; the greater reduction was evident as early as week 1 (ratio of change: 0.76; 95% CI: 0.69–0.85); the rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly between the two groups
PARADIGM-HF McMurray et al. [15]	randomized clinical trial: patients were randomized to angiotensin receptor-neprilysin (LCZ696) inhibitor vs. enalapril; means follow-up 27 months; *n* = 8,442	angiotensin receptor-neprilysin inhibitor was superior to enalapril in reducing the risks of death HR for death from any cause (HR: 0.84; 95% CI: 0.76–0.93; $p < 0.001$) and reduced hospitalization for HF (HR: 0.79; 95% CI: 0.71–0.89; $p < 0.001$)

GWTG-HF, Get With the Guidelines Heart Failure; PARADIGM-HF, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure; PIONEER-HF, Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure.

of which remained significant 30 days and 1 year after discharge [12]. A large Medicare population analysis showed that in patients with changes in serum creatinine values that met the criteria for AKI that developed during hospitalization for HF, 54% had received ACEi/ARB prescriptions at discharge, and the benefits of these therapies were accrued with significantly lower 30-day all-cause readmission, 30-day HF readmission, and 30-day all-cause mortality [20]. Notably, these effects were still present 1 year after discharge post HF hospitalization. This observation underscores the importance of distinguishing functional causes of fluctuations in biomarkers of glomerular filtration from true intrinsic kidney injury, for which the clinical use of biomarkers of renal tubular injury may play an important role [13]. This concept is further discussed in the section on urinary biomarkers of kidney injury. Caution should be used in truly hypovolemic patients because RAAS activation is appropriately high in this context, and ACEi/ARB may cause excessive blood pressure lowering and exacerbation of a prerenal state. The barriers towards starting these medications in acute HF identified in these different analyses were presence of azotemia, hypotension, worsening serum creatinine, cost, and adverse side effects such as angioedema and hyperkalemia [21].

Table 2. Summary of studies on the use of MRA in acute HF

Therapy, reference	Design, population (*n*)	Findings
MRA in ADCHF Ferreira et al. [16]	nonrandomized clinical trial, single-blind: patients assigned to short in-hospital course of spironolactone 50–100 mg/day plus standard care vs. standard care alone; *n* = 100	worsening renal function was more frequent in the control group (20 vs. 4%; *p* = 0.038); greater proportions of patients receiving spironolactone were congestion free (less edema, rales, jugular venous pressure, and orthopnea) at day 3 (32 vs. 66%; *p* = 0.001) (all *p* < 0.05)
ATHENA-HF Butler et al. [17]	randomized clinical trial: high-dose spironolactone 100 mg/day for 4 days plus standard care vs. standard care alone; *n* = 360	spironolactone not associated with excess in-hospital worsening renal function or hyperkalemia in 51 of 182 patients (28%) taking high-dose spironolactone and 57 of 178 patients (32%) receiving usual care (*p* = 0.42); spironolactone therapy improved clinical markers of congestion compared with standard care
Alabama HF Project Lam et al. [18]	observational propensity-matched cohort: patient without MRA use at admission, discharged with MRA prescription vs. no prescription; *n* = 648	30 days after discharge, MRA therapy was not associated with propensity-adjusted risk of all-cause readmission (HR: 0.92; 95% CI: 0.64–1.32; *p* = 0.650), all-cause mortality (HR: 0.84; 95% CI: 0.38–1.88; *p* = 0.678), or HF readmission (HR: 0.74; 95% CI: 0.41–1.31; *p* = 0.301); associations remained consistent at 1 year
JCARE-CARD registry Hamaguchi et al. [52]	observational: use of spironolactone at discharge vs. no use; *n* = 946	mean post-discharge follow-up of 2.2 years, use of spironolactone associated with lower adjusted risk of all-cause mortality (HR: 0.62; 95% CI: 0.41–0.93; *p* = 0.020), and lower cardiovascular death (HR: 0.52; 95% CI: 0.32–0.87; *p* = 0.013); spironolactone not associated with adjusted risk of all-cause hospitalization (HR: 0.79; 95% CI: 0.59–1.05; *p* = 0.101)
GWTG-HF Hernandez et al. [19]	observational: among patients eligible for therapy, discharge MRA prescription vs. no prescription; *n* = 5,887	3 years after discharge, MRA therapy was not associated with adjusted risk of mortality (HR: 1.04; 95% CI: 0.96–1.14; *p* = 0.32); cardiovascular rehospitalization (HR: 1.00; 95% CI: 0.91–1.09; *p* = 0.94); MRA therapy associated with lower adjusted risk of HF rehospitalization (HR: 0.87; 95% CI: 0.77–0.98; *p* = 0.02); MRA therapy associated with higher adjusted risk of hospitalization for hyperkalemia at 30 days (HR: 2.54; 95% CI: 1.51–4.29; *p* < 0.001) and 1 year (HR: 1.50; 95% CI: 1.23–1.84; *p* < 0.001)

ADCHF, acutely decompensated chronic heart failure; ATHENA-HF, Aldosterone Targeted Neurohormonal Combined with Natriuresis in Heart Failure; GWTG-HF, Get With the Guidelines Heart Failure.

There are limited data to support the continuation of RAASi in the hemodynamically stable hospitalized patient. Serial hemodynamic measurements by Packer et al. [22] demonstrated that ACEi (captopril and enalapril) acutely lower right and left ventricular filling pressures, mean arterial pressure, heart rate, and systemic and pulmonary vascular resistance, and also increase cardiac, stroke volume, and stroke work index. The interpretation of the hemodynamic measurements provided by right heart catheterization assist the clinician in understanding the filling pressures of the patient and help with the clinical dilemma of diuresis and volume status assessment. If the patient is showing signs of elevated filling pressures such as elevated right atrial pressures and elevated pulmonary capillary wedge pressure, this may suggest volume overload and need for diuresis. Continuation of diuresis and RAASi in this

setting may be feasible. The use of biomarkers may also guide for the RAASi decision-making. Solomon et al. [23] reported on a recent meta-analysis that included data from the Inhibition of Metallo-Protease by Omapatrilat in a Randomized Exercise and Symptoms Study of Heart Failure (IMPRESS), Omapatrilat versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE), and Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trials. The composite outcome of death or HF was reduced numerically in patients receiving combined neprilysin/ARB in all three trials, with a pooled HR of 0.86 (95% CI: 0.76–0.97). Combined ARNi/ARB compared to ACEi were associated with more hypotension, less renal dysfunction, and hyperkalemia.

In the Prospective Comparison of ARNI versus ARB on Management of Heart Failure with Preserved Ejection Fraction (PARAMOUNT) trial [24], LCZ696 decreased N-terminal prohormone of brain natriuretic peptide (NT-proBNP), blood pressure, and atrial size to a greater extent while preserving eGFR to a greater extent (36-week decline of eGFR, 1.6 mL/min/1.73 m^2 in the LCZ696 group vs. 5.2 mL/min/1.73 m^2 in the valsartan group; $p = 0.007$) [24]. The evidence generated by the PARAMOUNT trial led to the Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure (PIONEER-HF) trial. This was a prospective, multicenter, double-blind, randomized controlled trial that showed the benefits of in-hospital initiation of ARNi (sacubitril) combined with valsartan versus enalapril in appropriately stabilized patients. PIONEER-HF also demonstrated reductions of NT-proBNP with ARNi versus enalapril as early as after 1 week of use in acute HF [25]. There were clinical exploratory outcomes as well that demonstrated that HF readmissions were significantly reduced at 8 weeks after initiation of ARNi in acute HF. This was likely due to the diuretic effect of sacubitril. Neprilysin inhibitors used together with an ARB in this case which is a classic RAASi seem to point again to the potential benefits of starting and continuing RAASi in the acute phase of decompensated HF.

When added to an ACEi/ARB, MRA provide more effective blockade of the RAAS with well-proven long-term benefits in subjects with HFrEF. The decrease in mortality and cardiovascular events with HFrEF was seen in landmark trials such as The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure (RALES) [26] and Eplerenone, a Selective Aldosterone Blocker, in Patients with Left Ventricular Dysfunction after Myocardial Infarction (EPHESUS) [27]. However, there are limited high-quality data on the optimal use of MRA in the setting of acute HF. The Aldosterone Targeted Neurohormonal Combined with Natriuresis in Heart Failure (ATHENA-HF) trial compared initiation of high-dose spironolactone 100 mg daily plus usual care versus usual care alone among patients hospitalized for HF and found no significant difference between 30-day all-cause mortality/HF hospitalization rates [15]. Recently, a pilot study on the use of spironolactone in subjects with diuretic resistant acute HF reported clinically significant weight loss and reduced dyspnea without associated worsening hyperkalemia or renal function [28]. There is a need to validate this observation in larger randomized clinical trials. Finally, there is a paucity of data with the use of MRA in HFrEF and chronic kidney disease (CKD). A synopsis of the available data on MRA in HF with impaired kidney function is available in the Scientific Statement on Cardiorenal Syndrome by the American Heart Association [5]. The initiation of RAASi during HF hospitalization up to hospital discharge and follow-up is associated with good clinical outcomes. There is less available evidence with the actual initiation of MRA in the setting of acute HF.

Reduction of RAASi

As the severity of HF progresses, patients may not be able to tolerate higher doses of medications for GDMT due to concerns of hypoperfusion and hypotension, which would also increase the risk for worsening renal function. Fluctuations in renal function and hyperka-

lemia during the treatment of acute HF are common triggers for withdrawal of RAASi in clinical practice. However, results from the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) trial showed a marked reduction in HF-related death and symptom burden, despite an increased serum creatinine in 11% of subjects taking enalapril compared to placebo [29]. There was an early increase from baseline and return to values within 30% of the initial creatinine after the subjects continued the ACEi in the backdrop of continued diuretic usage. The Study of Left Ventricular Dysfunction (SOLVD) trial reiterated the benefits of enalapril for HF symptoms and hospitalization rate decrease in a larger population compared with CONSENSUS [30, 31]. The enalapril group in SOLVD showed a 33% higher likelihood of a serum creatinine rise >0.5 mg/dL, but there was a lack of data on progression of CKD, end-stage renal disease, or doubling of creatinine. A post-hoc analysis of SOLVD demonstrated mortality benefits even in subjects with higher degrees of CKD [32]. Using the GWTG-HF registry, it was demonstrated that 1-year mortality was 28.2% for patients who continued RAASi therapy, 29.7% for patients newly started on RAASi, and 41.6% for patients who had RAASi discontinued (adjusted HR: 1.35; 95% CI: 1.13–1.61) and 41.7% (adjusted HR: 0.28; 95% CI: 1.14–1.43) for patients who did not begin RAASi therapy [13] (Fig. 2). A more recent large retrospective analysis of the Stockholm Creatinine Measurements (SCREAM) registry studied patients newly initiated on ACEi/ARB. It found that increases in serum creatinine of ≥10% after initiation of ACEi/ARB were associated with an incremental increased risk of death, cardiovascular events (myocardial infarction and HF), and development of end-stage renal disease, depending on the degree of creatinine elevation [33]. It was interesting to note that the patients with ≥30% early increase in serum creatinine were older, had more comorbidities including HF, and used more medications compared to patients with less serum creatinine increase [33]. Acute decreases in renal function after initiation of ACEi/ARB are usually hemodynamic in origin and do not necessarily reflect structural injury to the kidneys, including in subjects with decompensated HF undergoing aggressive decongestion with high-dose loop diuretics [34, 35]. This suggests that the degree of serum creatinine elevation after ACEi/ARB initiation described in the SCREAM registry might be a reflection of the severity of patient illness and comorbidities wherein RAASi may be deleterious in sicker patients with borderline hemodynamic profiles and not cause a direct adverse effect with the use of these drugs per se. This is underscored by data from a recent analysis of the SOLVD trial dataset by McCallum et al. [36] using a conservative estimate using 0% eGFR decline in the placebo arm as the reference, where up to a 10% decline with enalapril was associated with mortality benefit (HR: 0.87; 95% CI: 0.77–0.99), while up to a 35% decline was associated with decreased risk of HF hospitalization (HR: 0.78; 95% CI: 0.61–0.98). There was no eGFR decline, including up to 40%, in any models at either 2 or 6 weeks in this trial where enalapril was associated with higher mortality risk. Thus, the critical need to ensure optimal delivery of RAASi, especially during and after the vulnerable period of HF hospitalization, reiterates the need to incorporate the use of biomarkers of tubular injury to interpret the significance of minor fluctuations in serum creatinine levels in the setting of ACEi/ARB treatment in acute HF.

In African American patients with HFrEF, ACEi/ARB dose reduction or discontinuation tend to occur more frequently than for beta-blockers (17.2 vs. 7%) [37]. Reduction or discontinuation of RAASi tends to take place because of AKI (56.7%), hypotension (23.3%), and hyperkalemia (10%) [37]. Nearly one-fourth of patients on ACEi/ARB with dose reduction or discontinuation had concerns for azotemia, although their creatinine levels did not significantly change throughout hospitalization. Interestingly, there was a trend for a higher median length of stay (5.5 vs. 3 days) and a shorter time to HF readmission in patients with discontinued versus continued ACEi/ARB therapy [32]. It appears that renal function is a main driver of decisions about medication regimen in the setting of acute HF. Additionally, there

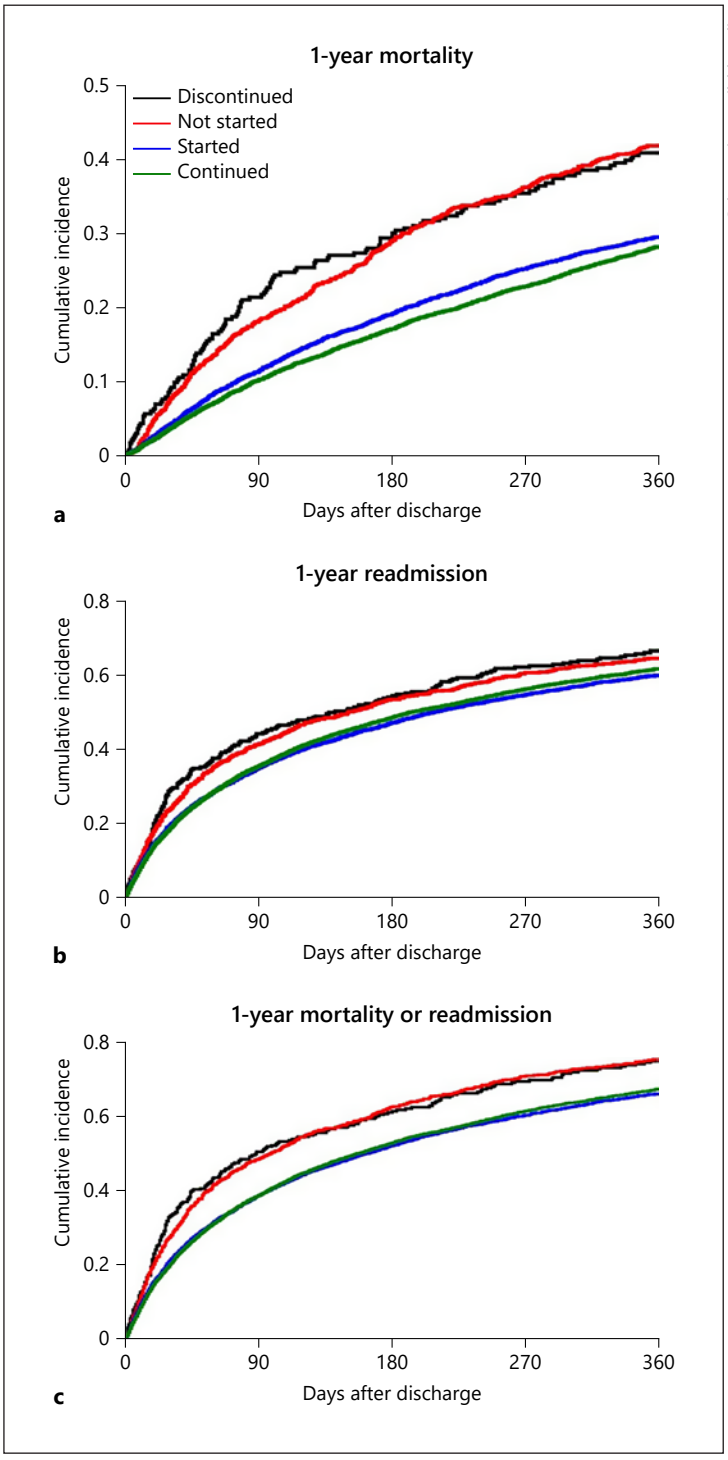


Fig. 2. Post-HF discharge outcomes by ACEi treatment groups. **a** One-year mortality. **b** One-year readmission rates. **c** One-year composite endpoint (readmissions and mortality) rates. Data as reported in and reproduced with permission from Gilstrap et al. [13].

may be racial/ethnic differences in practice patterns with the use of GDMT in HF, with higher rates of drug cessation in African-American and Afro-Caribbean patients [38, 39]. However, it should be noted that other nonphysiologic factors such as potential prescriber discrimination/biases and socioeconomic factors could account for differences in RAASi use. Simple social differences such as limited disease awareness, inadequate access to health care, and

noncompliance with clinic appointments may influence HF management and outcomes, including medication use [40]. These findings merit investigation in future dedicated trials addressing the optimal usage of GDMT in acute HF.

Discontinuation of RAASi

The GWTG-HF registry found that the rate of medication discontinuation during HF for ACEi/ARB was as high as 8.8% [41]. The Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF) registry found that ACEi/ARB discontinuation was 28%, compared to 7% for beta-blockers [42]. An analysis from the GWTG-HF registry showed that continuation of ACEi/ARB in hospitalized patients was associated with significantly lower 30-day, 90-day, and 1-year mortality and 30-day readmission compared to ACEi/ARB discontinuation. A meta-analysis of five placebo-controlled randomized clinical trials of ACEi in HF [43] showed that drug cessation was rarely necessary despite higher rates of AKI in the treatment versus placebo arms in most cases. However, in real-world experience, hyperkalemia (potassium >5 mEq/L) can be a limiting factor in the use and titration of RAASi agents in the backdrop of acute HF with underlying CKD. In an analysis of the SCREAM project, among those patients with newly initiated ACEi/ARB, the rates of potassium >5.0 and >5.5 mEq/L were 51 and 29%, respectively, for those with eGFR <30 mL/min/1.73 m^2 [44]. In a meta-analysis of clinical trials (16,065 subjects) with baseline hyperkalemia and clinical risks for hyperkalemia as exclusion criteria, the rate of MRA-associated hyperkalemia (9.5%) was approximately two-fold that of controls and, among hyperkalemic subjects, 54% were truly due to the MRA agent [45]. Collins et al. [46] recently demonstrated in a nationwide electronic medical record study (n = 1,716,141 with ≥2 potassium values) that the presence of HF appears to considerably elevate the fatal risks of hyperkalemia in patients treated with RAASi. They found that all-cause mortality was 25.7% at potassium values of 4.0–<5.0 mEq/L and 45.5% at potassium values >5.0 mEq/L. The overall death rate was 35.7% in those with hyperkalemia with HF, CKD, and diabetes mellitus, versus a death rate of 2.7% in controls at the high end of potassium values. Thus, while the benefits of RAASi maintenance in acute HF are tangible, there is a legitimate concern for the complications of hyperkalemia with the use of RAASi in patients with CKD or chronic cardiorenal syndrome [46]. The Evaluation of Patiromer in Heart Failure Patients (PEARL-HF) trial showed that among patients with HF and CKD or with a history of hyperkalemia leading to discontinuation of RAASi, patiromer combined with spironolactone had a lower incidence of hyperkalemia and the dose of spironolactone was successfully titrated up in more patients [47]. On the other hand, in the Hyperkalaemia Randomized Intervention Multidose SZC Maintenance (HARMONIZE) trial, a subgroup analysis in patients with HF and hyperkalemia showed that use of sodium zirconium cyclosilicate achieved normokalemia in 93% of patients within 48 h without the need to adjust the RAASi doses [48]. In this context, the use of novel oral antihyperkalemic agents such as patiromer acetate and sodium zirconium cyclosilicate represent valuable tools in allowing optimal dosing of goal-directed RAASi in patients with HF and CKD, in the inpatient as well as the outpatient setting [49, 50].

Summary of Clinical Outcomes with Studies of RAASi in Acute HF

To better estimate the effects of ACEi/ARB on post-HF hospitalization outcomes based on available data, we analyzed and derived the HRs for two large observational registries by deriving the ratios of the exposed over total population for both treatment and control groups. Relative risk reductions (RRRs) were then computed from these HRs by subtracting the HRs from 1 (RRR = 1 – HR) for each available outcome using a methodology similar to that reported

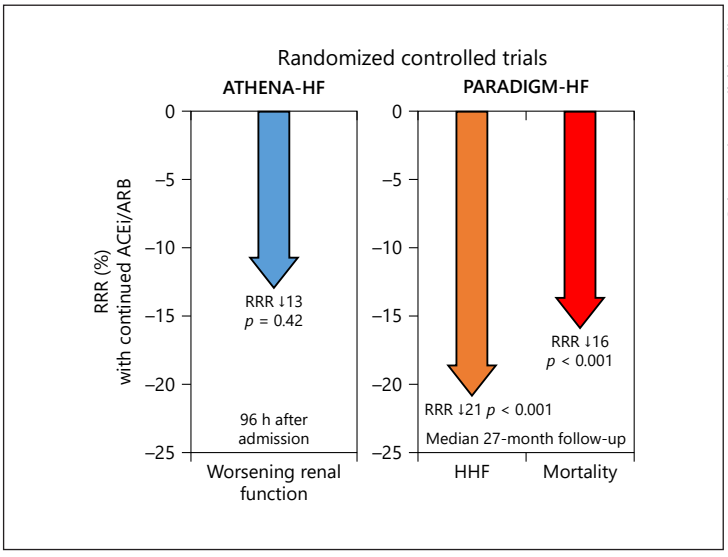


Fig. 3. RRRs and *p* values for outcomes in ACEi/ARB randomized controlled trials. RRRs were calculated from HRs. ATHENA-HF, Aldosterone Targeted Neurohormonal Combined with Natriuresis in Heart Failure; HHF, heart failure hospitalization; PARADIGM-HF, Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure.

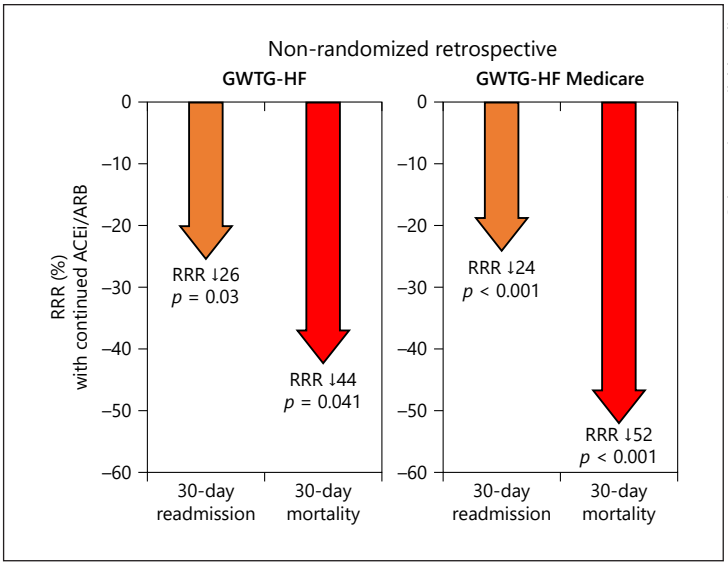


Fig. 4. RRRs and *p* values for outcomes in ACEi/ARB nonrandomized studies based on the GWTG-HF cohort. RRRs were calculated from HRs. GWTG-HF, Get With the Guidelines Heart Failure.

in other studies [15, 17, 51]. Using this method to derive RRR, the computed RRR for 30-day mortality was 44 and 52% for the GWTG-HF and GWTG-HF Medicare cohorts, respectively. This translates to roughly a 40–50% reduction in 30-day mortality overall in patients started on ACEi/ARB compared to those without ACEi/ARB. On the other hand, the RRR for 30-day readmissions was 26 and 24% for the GWTG-HF and GWTG-HF Medicare cohorts, respectively. This in turn translates to an approximate 25% reduction in 30-day readmissions in patients started on ACEi/ARB compared to those without (Fig. 3, 4). Thus, the treatment effect for the continuation of RAASi in acute HF appeared to be larger for observational studies as compared to randomized trials.

The evidence for the use of MRA in the setting of acute HF using the same method was mixed as prospective observational nonrandomized studies found statistically significant effects, while retrospective studies were mostly negative. First, the study by Ferreira et al. [16] demonstrated statistically significant benefits in terms of RRR of 80% for worsening renal function and a 52% RRR for worsening congestion [16]. The JCARE-CARD registry

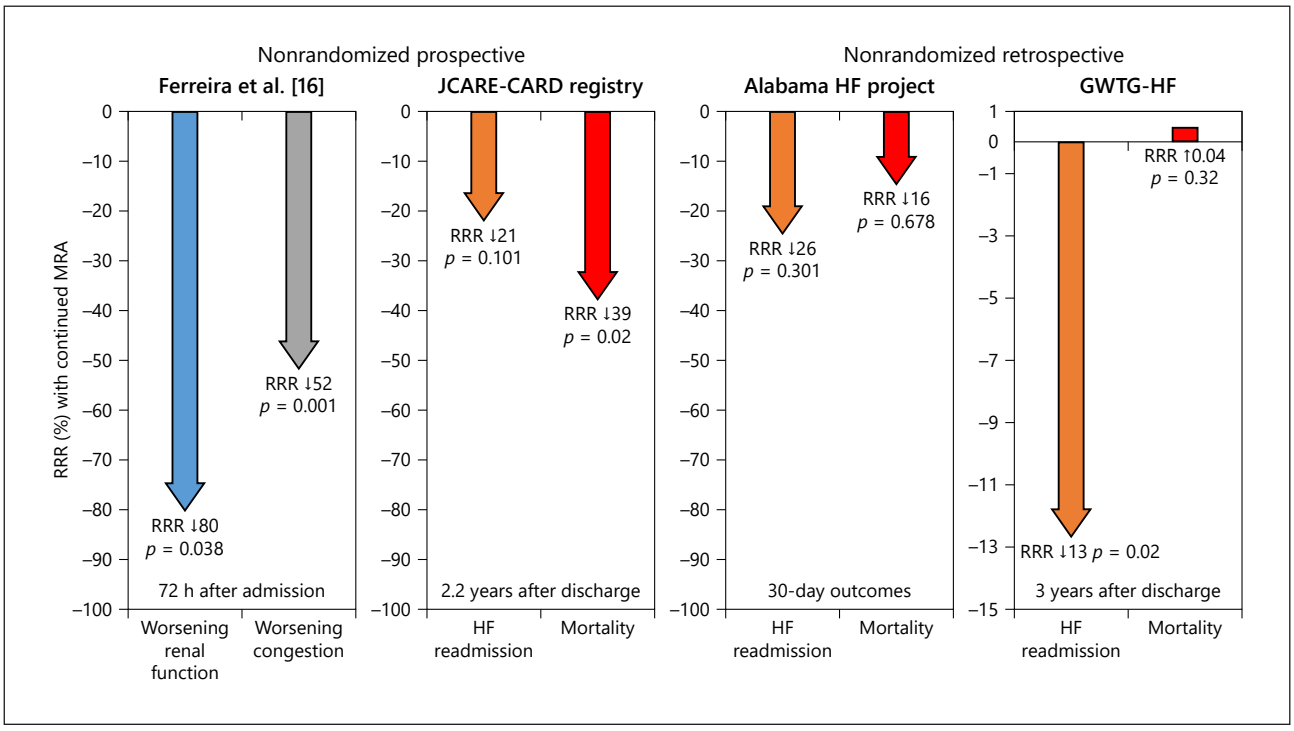


Fig. 5. RRRs and *p* values for outcomes in MRA nonrandomized studies. RRRs were calculated from HRs. GWTG-HF, Get With the Guidelines Heart Failure; JCARE-CARD, spironolactone use at discharge was associated with improved survival in hospitalized patients with systolic heart failure.

showed a significant RRR for overall mortality of 39% [52], while ATHENA-HF also found a RRR of 13% for worsening renal function [17]. In contrast, several retrospective studies showed no statistically significant differences in clinical outcomes except for HF readmissions in the GWTG-HF cohort with a RRR of 13% (Fig. 5). As of now, the data associated with the continuation of MRA in acute HF are not externally consistent.

Biomarkers

Biomarkers of kidney injury are valuable in clinical practice when RAASi may be withheld due to concerns for worsening renal function. Urine microscopy and evaluation of urine sediment represent a simple, readily available and inexpensive initial test that can differentiate an intrinsic cause of AKI from functional changes in serum creatinine. This is helpful when interpreting fluctuations in serum creatinine levels in the setting of high-dose loop diuretics or escalation of RAASi in acute HF. Currently used markers of glomerular filtration rate (GFR) such as serum creatinine levels may have a 24- to 48-h time lag to institute corrective measures. In the case of advanced HF and low CO states there may be hemodynamic consequences that lead to hypoperfusion of the kidney tissue. AKI is an effective marker of advanced HF and its presence has been linked to worse prognosis. The use of RAASi that increase creatinine values may mask the utilization of serum creatinine as a biomarker of disease. Therefore, the clinician should use other tools to interpret how much increase in the serum creatinine is caused by the RAASi or by disease progression. The availability of biomarkers of tubular injury, such as neutrophil gelatinase-associated lipocalin [53], and the combination of tissue inhibitor

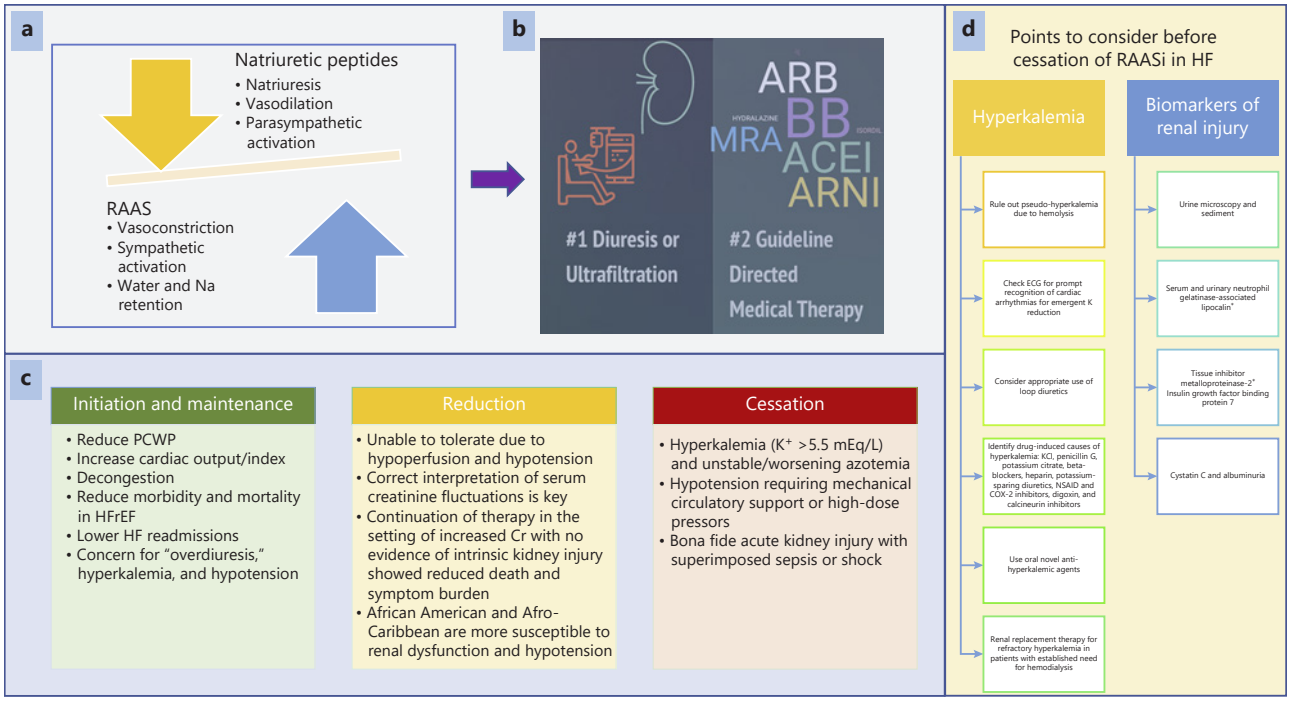


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Fig. 6. Central illustration summarizing the key points in the setting of initiation, maintenance, and discontinuation of RAASi in acute HF. **a** RAAS and natriuretic peptide pathways work simultaneously to activate natriuresis as well as water and sodium retention. **b** In the setting of acute HF the clinician had two routes to alleviate congestion: diuresis/ultrafiltration or GDMT. **c** When using RAASi in HF there are three scenarios: initiation and maintenance, reduction, or cessation. **d** Key points to consider before cessation. * Biomarkers that are commercially available for clinical use.

of metalloproteinase-2 and insulin-like growth factor-binding protein 7 (Nephrocheck™) represent valuable tools in affording early detection of intrinsic tubular injury and are able to predict progression to overt AKI with very high sensitivity [54]. These urine biomarkers also have strong negative predictive value during AKI, which would allow escalation of RAASi doses during acute HF despite small fluctuations in serum creatinine levels.

Ahmad et al. [35] showed that biomarkers of tubular injury did not correlate with worsening kidney function as measured with markers of GFR such as serum cystatin C and serum creatinine in patients undergoing high-dose loop diuretic-based decongestion in an analysis of the Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE-HF) trial. On similar lines, a post-hoc analysis of the CARRESS-HF trial compared biomarkers of renal tubular injury between the arms of stepped-up diuretic therapy and ultrafiltration in subjects with type 1 cardiorenal syndrome [55]. In this analysis, while biomarkers of tubular injury correlated strongly with worsening renal function after randomization into the CARRESS-HF trial (OR: 12.6; $p = 0.004$), increase in renal tubular injury biomarkers was associated with a higher incidence of hemoconcentration (OR: 3.1; $p = 0.015$) and, paradoxically, better recovery of creatinine at 60 days ($p = 0.01$). No differences were noted in levels of tubular injury biomarkers between the stepped-up diuretic arm and the ultrafiltration arm. Hence, fluctuations in the markers of GFR with current clinically available biomarkers (i.e., serum creatinine) in the context of aggressive diuresis in HF may have different prognostic value when compared to other scenarios of AKI such as sepsis or drug-induced nephrotoxicity [5]. Incorporation of the clinical use of biomarkers of tubular injury may afford the opportunity to

initiate and up-titrate RAASi in the context of acute HF without concern of causing intrinsic renal injury, thus providing the benefit of RAASi during an episode of acute HF to reduce the deleterious impact of unabated RAAS activation and minimize HF-related hospitalizations. A practical approach to considerations when initiating, maintaining, or reducing RAASi in the setting of acute HF is summarized in Figure 6.

Conclusions

There is strong evidence supporting the benefits of RAASi in the setting of acute HF with respect to reduction in mortality, readmission, and rehospitalization. Premature discontinuation of such therapies based on anticipated risk of hemodynamic and renal complications may be causing the HF population to lose the advantages of RAAS inactivation. Azotemia alone in the absence of hemodynamic deterioration or severe hyperkalemia does not appear to be an appropriate trigger for RAASi withdrawal. Data from our review are congruous in the finding that RAASi withdrawal is associated with harm. In contradistinction, the continuation of MRA during acute HF was not consistently associated with benefit. Future randomized clinical trials addressing the question of titration of RAASi in patients with HF and kidney disease will help elucidate the best clinical practice strategy to deliver optimal RAASi in patients with HF, thereby reducing its deleterious consequences.

Disclosure Statement

The authors have no conflicts of interest to disclose.

Funding Sources

None.

References

1 Brown MJ. Renin: friend or foe? Heart. 2007 Sep;93(9):1026–33.
2 Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. Nat Rev Cardiol. 2017 Jan;14(1):30–8.
3 Mentz RJ, Stevens SR, DeVore AD, Lala A, Vader JM, AbouEzzeddine OF, et al. Decongestion strategies and renin-angiotensin-aldosterone system activation in acute heart failure. JACC Heart Fail. 2015 Feb;3(2):97–107.
4 Francis GS, Benedict C, Johnstone DE, Kirlin PC, Nicklas J, Liang CS, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the Studies of Left Ventricular Dysfunction (SOLVD). Circulation. 1990 Nov;82(5):1724–9.
5 Malhotra R, Craven T, Ambrosius WT, Killeen AA, Haley WE, Cheung AK, et al.; SPRINT Research Group. Effects of Intensive Blood Pressure Lowering on Kidney Tubule Injury in CKD: A Longitudinal Subgroup Analysis in SPRINT. Am J Kidney Dis. 2019 Jan;73(1):21–30.
6 Nadkarni GN, Chauhan K, Rao V, Ix JH, Shlipak MG, Parikh CR, et al. Effect of Intensive Blood Pressure Lowering on Kidney Tubule Injury: Findings From the ACCORD Trial Study Participants. Am J Kidney Dis. 2019 Jan;73(1):31–8.
7 Rangaswami J, Bhalla V, Blair JE, Chang TI, Costa S, Lentine KL, et al.; American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Clinical Cardiology. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. Circulation. 2019 Apr;139(16):e840–78.
8 Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, et al.; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003 Sep;362(9386):772–6.

9 Tsai JP, Rochon PA, Raptis S, Bronskill SE, Bell CM, Saposnik G. A prescription at discharge improves long-term adherence for secondary stroke prevention. J Stroke Cerebrovasc Dis. 2014 Oct;23(9):2308–15.
10 Ahmed A, Centor RM, Weaver MT, Perry GJ. A propensity score analysis of the impact of angiotensin-converting enzyme inhibitors on long-term survival of older adults with heart failure and perceived contraindications. Am Heart J. 2005 Apr;149(4):737–43.
11 Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017 Aug;136(6):e137–61.
12 Sanam K, Bhatia V, Bajaj NS, Gaba S, Morgan CJ, Fonarow GC, et al. Renin-Angiotensin System Inhibition and Lower 30-Day All-Cause Readmission in Medicare Beneficiaries with Heart Failure. Am J Med. 2016 Oct;129(10):1067–73.
13 Gilstrap LG, Fonarow GC, Desai AS, Liang L, Matsouaka R, DeVore AD, et al. Initiation, Continuation, or Withdrawal of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers and Outcomes in Patients Hospitalized With Heart Failure With Reduced Ejection Fraction. J Am Heart Assoc. 2017 Feb;6(2):e004675.
14 Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, et al.; PIONEER-HF Investigators. Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure. N Engl J Med. 2019 Feb;380(6):539–48.
15 McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al.; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014 Sep;371(11):993–1004.
16 Ferreira JP, Santos M, Almeida S, Marques I, Bettencourt P, Carvalho H. Mineralocorticoid receptor antagonism in acutely decompensated chronic heart failure. Eur J Intern Med. 2014 Jan;25(1):67–72.
17 Butler J, Anstrom KJ, Felker GM, Givertz MM, Kalogeropoulos AP, Konstam MA, et al.; National Heart Lung and Blood Institute Heart Failure Clinical Research Network. Efficacy and Safety of Spironolactone in Acute Heart Failure: The ATHENA-HF Randomized Clinical Trial. JAMA Cardiol. 2017 Sep;2(9):950–8.
18 Lam PH, Dooley DJ, Inampudi C, Arundel C, Fonarow GC, Butler J, et al. Lack of evidence of lower 30-day all-cause readmission in Medicare beneficiaries with heart failure and reduced ejection fraction discharged on spironolactone. Int J Cardiol. 2017 Jan;227:462–6.
19 Hernandez AF, Mi X, Hammill BG, Hammill SC, Heidenreich PA, Masoudi FA, et al. Associations between aldosterone antagonist therapy and risks of mortality and readmission among patients with heart failure and reduced ejection fraction. JAMA. 2012 Nov;308(20):2097–107.
20 Ratka A. Integration as a paramount educational strategy in academic pharmacy. Am J Pharm Educ. 2012 Mar;76(2):19.
21 Palazzuoli A, Ruocco G, Ronco C, McCullough PA. Loop diuretics in acute heart failure: beyond the decongestive relief for the kidney. Crit Care. 2015 Sep;19(1):296.
22 Packer M, Lee WH, Yushak M, Medina N. Comparison of captopril and enalapril in patients with severe chronic heart failure. N Engl J Med. 1986 Oct;315(14):847–53.
23 Solomon SD, Claggett B, McMurray JJ, Hernandez AF, Fonarow GC. Combined neprilysin and renin-angiotensin system inhibition in heart failure with reduced ejection fraction: a meta-analysis. Eur J Heart Fail. 2016 Oct;18(10):1238–43.
24 Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al.; Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 2012 Oct;380(9851):1387–95.
25 Morrow DA, Velazquez EJ, DeVore AD, Prescott MF, Duffy CI, Gurmu Y, et al. Cardiovascular biomarkers in patients with acute decompensated heart failure randomized to sacubitril-valsartan or enalapril in the PIONEER-HF trial. Eur Heart J. 2019 Oct;40(40):3345–52.
26 Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al.; Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999 Sep;341(10):709–17.
27 Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al.; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003 Apr;348(14):1309–21.
28 Bansal S, Munoz K, Brune S, Bailey S, Prasad A, Velagapudi C. High-Dose Spironolactone When Patients With Acute Decompensated Heart Failure Are Resistant to Loop Diuretics: A Pilot Study. Ann Intern Med. 2019 Jul;171(6):443.
29 Group CT; CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med. 1987 Jun;316(23):1429–35.
30 SOLVD Investigators, Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991 Aug;325(5):293–302.
31 Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. Lancet. 2003 May;361(9372):1843–8.

32 Khan NA, Ma I, Thompson CR, Humphries K, Salem DN, Sarnak MJ, et al. Kidney function and mortality among patients with left ventricular systolic dysfunction. J Am Soc Nephrol. 2006 Jan;17(1):244–53.
33 Fu EL, Trevisan M, Clase CM, Evans M, Lindholm B, Rotmans JI, et al. Association of Acute Increases in Plasma Creatinine after Renin-Angiotensin Blockade with Subsequent Outcomes. Clin J Am Soc Nephrol. 2019 Sep;14(9):1336–45.
34 Palmer BF. Renal dysfunction complicating the treatment of hypertension. N Engl J Med. 2002 Oct;347(16):1256–61.
35 Ahmad T, Jackson K, Rao VS, Tang WHW, Brisco-Bacik MA, Chen HH, et al. Worsening renal function in patients with acute heart failure undergoing aggressive diuresis is not associated with tubular injury. Circulation. 2018 May;137(19):2016–28.
36 McCallum W, Tighiouart H, Ku E, Salem D, Sarnak MJ. Acute declines in estimated glomerular filtration rate on enalapril and mortality and cardiovascular outcomes in patients with heart failure with reduced ejection fraction. Kidney Int. 2019 Nov;96(5):1185–94.
37 Kane JA, Kim JK, Haidry SA, Salciccioli L, Lazar J. Discontinuation/Dose Reduction of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers during Acute Decompensated Heart Failure in African-American Patients with Reduced Left-Ventricular Ejection Fraction. Cardiology. 2017;137(2):121–5.
38 Exner DV, Dries DL, Domanski MJ, Cohn JN. Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. N Engl J Med. 2001 May;344(18):1351–7.
39 Ismail Y, Kasmikha Z, Green HL, McCullough PA. Cardio-renal syndrome type 1: epidemiology, pathophysiology, and treatment. Semin Nephrol. 2012 Jan;32(1):18–25.
40 Sharma A, Colvin-Adams M, Yancy CW. Heart failure in African Americans: disparities can be overcome. Cleve Clin J Med. 2014 May;81(5):301–11.
41 Krantz MJ, Ambardekar AV, Kaltenbach L, Hernandez AF, Heidenreich PA, Fonarow GC; Get With the Guidelines Steering Committee and Hospitals. Patterns and predictors of evidence-based medication continuation among hospitalized heart failure patients (from Get With the Guidelines-Heart Failure). Am J Cardiol. 2011 Jun;107(12):1818–23.
42 Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al.; OPTIMIZE-HF Investigators and Coordinators. Prospective evaluation of beta-blocker use at the time of hospital discharge as a heart failure performance measure: results from OPTIMIZE-HF. J Card Fail. 2007 Nov;13(9):722–31.
43 Flather MD, Yusuf S, Køber L, Pfeffer M, Hall A, Murray G, et al.; ACE-Inhibitor Myocardial Infarction Collaborative Group. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. Lancet. 2000 May;355(9215):1575–81.
44 Bandak G, Sang Y, Gasparini A, Chang AR, Ballew SH, Evans M, et al. Hyperkalemia After Initiating Renin-Angiotensin System Blockade: The Stockholm Creatinine Measurements (SCREAM) Project. J Am Heart Assoc. 2017 Jul;6(7):e005428.
45 Vukadinović D, Lavall D, Vukadinović AN, Pitt B, Wagenpfeil S, Böhm M. True rate of mineralocorticoid receptor antagonists-related hyperkalemia in placebo-controlled trials: a meta-analysis. Am Heart J. 2017 Jun;188:99–108.
46 Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, et al. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. Am J Nephrol. 2017;46(3):213–21.
47 Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ; PEARL-HF Investigators. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur Heart J. 2011 Apr;32(7):820–8.
48 Anker SD, Kosiborod M, Zannad F, Piña IL, McCullough PA, Filippatos G, et al. Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized, double-blind, placebo-controlled trial. Eur J Heart Fail. 2015 Oct;17(10):1050–6.
49 Kosiborod M, Peacock WF, Packham DK. Sodium zirconium cyclosilicate for urgent therapy of severe hyperkalemia. N Engl J Med. 2015 Apr;372(16):1577–8.
50 Beccari MV, Meaney CJ. Clinical utility of patiromer, sodium zirconium cyclosilicate, and sodium polystyrene sulfonate for the treatment of hyperkalemia: an evidence-based review. Core Evid. 2017 Mar;12:11–24.
51 Kluger AY, Tecson KM, Lee AY, Lerma EV, Rangaswami J, Lepor NE, et al. Class effects of SGLT2 inhibitors on cardiorenal outcomes. Cardiovasc Diabetol. 2019 Aug;18(1):99.
52 Hamaguchi S, Kinugawa S, Tsuchihashi-Makaya M, Goto K, Goto D, Yokota T, et al. Spironolactone use at discharge was associated with improved survival in hospitalized patients with systolic heart failure. Am Heart J. 2010 Dec;160(6):1156–62.
53 Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A; NGAL Meta-analysis Investigator Group. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis. 2009 Dec;54(6):1012–24.
54 Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care. 2013 Feb;17(1):R25.
55 Rao VS, Ahmad T, Brisco-Bacik MA, Bonventre JV, Wilson FP, Siew ED, et al. Renal Effects of Intensive Volume Removal in Heart Failure Patients With Preexisting Worsening Renal Function. Circ Heart Fail. 2019 Jun;12(6):e005552.