

Review

Continuation of Chronic Heart Failure Therapies During Heart Failure Hospitalization - a Review

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Randomized controlled trials have demonstrated the benefits of guideline-directed medical therapy in the outpatient setting for treatment of chronic heart failure. However, the benefits of continuation (or discontinuation) of major chronic heart failure therapies when treating acute heart failure during hospitalization are less clear. Real and anticipated worsening renal function, hyperkalemia and hypotension are the three major reasons for discontinuation of renin-angiotensin-aldosterone system inhibitors during hospitalization, and a failure to resume renin-angiotensin-aldosterone system inhibitors before discharge could worsen cardiovascular outcomes. Available data, mostly observational, shows that continuation or initiation of renin-angiotensin-aldosterone system inhibitors appears efficacious, safe, and well tolerated in majority of acute heart failure patients during hospitalization. Worsening renal function portends poor prognosis only if associated with congestion in acute heart failure, and clinicians should not de-escalate diuretic therapy routinely for worsening renal function.

Keywords

Acute heart failure; cardiorenal syndrome; cardiovascular outcomes; medication continuation; medication discontinuation

1. Introduction

Pulmonary vascular congestion is the primary reason for hospitalization of patients with acute heart failure (AHF) and is the

key driver of adverse outcomes. Cardiorenal syndrome type I (CRS1) is defined as worsening renal function (WRF) because of AHF and occurs in about a third of the patients admitted with AHF (Gottlieb et al., 2002). Optimal management of CRS1 is critical since it is an independent predictor of in-hospital mortality (Damman et al., 2014). Inhibition of the renin-angiotensin-aldosterone system (RAAS) along with diuresis to relieve congestion is the cornerstone of the treatment of HF with reduced ejection fraction (HFrEF). The medications used to inhibit the RAAS include angiotensin-converting-enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRA), and ARB-neprilysin inhibitors. While the safety and benefits of these medications and diuretics are well characterized in patients with compensated HFrEF, data on the benefits (or risks) of initiation, continuation, or discontinuation of HF therapies in HFrEF patients when hospitalized with AHF, especially in patients who develop CRS1, are limited. Clinicians often discontinue HF therapies during hospitalization, especially in patients with CRS1, in an effort to preserve renal function and limit the extent of acute kidney injury (AKI). However, data suggest that a lack of RAASi in AHF independently increases mortality (Iglesias et al., 2019). Physiological benefits of RAASi and neprilysin inhibitors in AHF are shown in Fig. 1. In this article, we review the risks and benefits of continuation or discontinuation of heart failure (HF) therapies in HFrEF patients admitted for AHF, especially with CRS1.

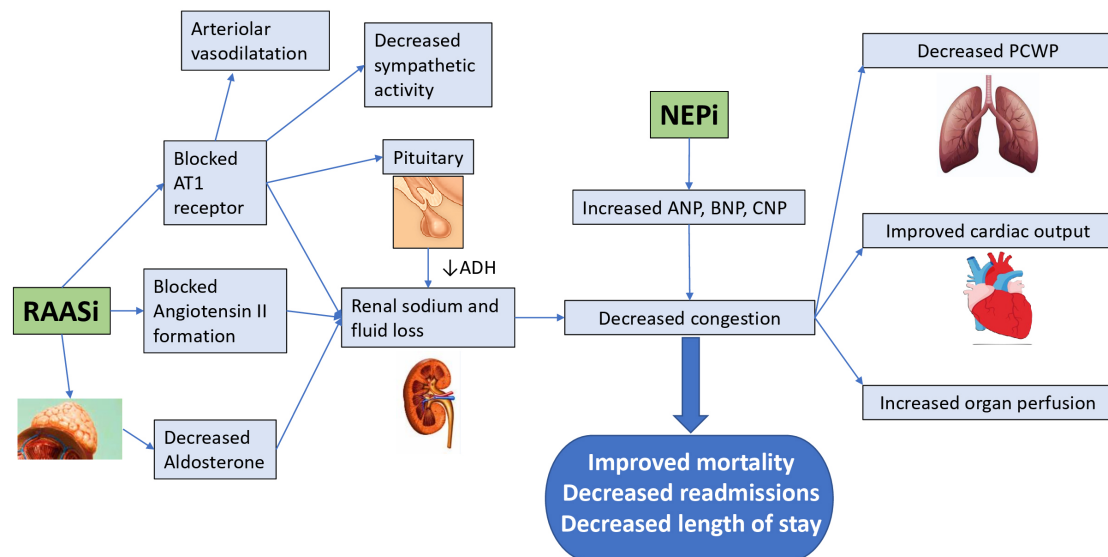


Figure 1. Physiological benefits of renin-angiotensin-aldosterone system inhibitors and neprilysin inhibitors in acute heart failure. RAASi, renin-angiotensin-aldosterone system inhibitors; AT1, angiotensin II receptor type 1; ADH, antidiuretic hormone; NEPi, neprilysin inhibitors, ANP, atrial natriuretic peptide; BNP, b-type natriuretic peptide or brain natriuretic peptide; CNP, c-type natriuretic peptide; PCWP, pulmonary capillary wedge pressure.

2. Use of angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers in acute heart failure

There is no randomized controlled trial (RCT) to our knowledge that has investigated the initiation, continuation, or discontinuation of ACEi/ARBs in HFrEF patients with AHF. However, there are several observational reports in the form of retrospective chart reviews and post hoc analyses of RCTs on this topic. We have reviewed the major publications below and in Table 1.

In a retrospective chart review, Kane et al. (2017) found ACEi/ARB dose reduction/discontinuation (r/d) in 17.2% of 174 African American patients with HFrEF admitted with AHF. Patients with ACEi/ARB dose r/d had a significantly greater median length of stay (LOS) (5.5 vs 3.0 days) versus those without dose r/d. The most common reasons for dose r/d were AKI (56.7%), hypotension (23.3%) and hyperkalemia (10%). Interestingly, of the patients who had ACEi/ARB dose r/d because of AKI, 23.5% patients did not have a rise in creatinine level during hospitalization. On reviewing the 16,052 patients in the Get With The Guideline-Heart Failure (GWTG-HF) Registry data (Gilstrap et al., 2017), discontinuation of ACE/ARB at discharge in HFrEF patients admitted for AHF was associated with a higher 30-day, 90-day and 1-year mortality compared with continuation of ACEi/ARB.

Several other observational studies have reported improved outcomes with continuation of ACEi/ARB therapy in AHF. Sanam et al. (2016) studied 1,384 hospitalized Medicare beneficiaries with HFrEF (EF < 45%) and showed that continued use of ACEi/ARB was associated with lower 30 day all-cause readmissions (hazard ratio (HR) 0.74; 95% confidence interval (CI), 0.56-0.97) and 30-day all-cause mortality (HR 0.56; 95% CI, 0.33-0.98), and that both beneficial associations remained significant at one year post discharge. A recent post hoc analysis of the REALITY-AHF trial by Yoshioka et al. (2019) analyzed the effects of early (within 48

hours) initiation of ACEi/ARB in 900 patients who were not on ACEi/ARB at admission. Compared to the no ACEi/ARB group, the ACEi/ARB group had significantly higher event-free survival at one year (HR 0.51; 95% CI, 0.32-0.82), and no significant difference was found for in-hospital mortality, WRF, or LOS between the groups.

Although there are paucity of RCT results, observational data suggest that the most common reason for discontinuation of ACEi/ARB in patients with AHF is renal insufficiency; and that HFrEF patients admitted with AHF have better outcomes with continuation of ACEi/ARB therapy. However, observational analyses can be fraught with bias, so these results should only be considered hypothesis generating. It is possible that withdrawal or dose reduction in ACEi/ARB therapy identify a particularly at-risk group of patients. Nevertheless, the above referenced data suggest that whenever clinically appropriate, clinicians should continue ACEi/ARB therapy in HFrEF patients admitted with AHF.

3. Use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers in type 1 cardiorenal syndrome

Even though it remains unclear whether the benefits of continuation of ACEi/ARB therapy in AHF persist in patients who develop CRS1, WRF is cited as the most common reason to discontinue or reduce ACEi/ARB therapy. A 2015 abstract published in Circulation suggested that continuation of ACEi/ARB in AHF with CRS1 is beneficial (Siddiqui et al., 2015). The authors found that among patients hospitalized for HF at 106 U.S. hospitals (from 1998-2001) who developed AKI (N = 2180) during hospitalization for CRS1, discharge prescription of ACEi or ARBs was associated with significant reduction in 30-day and 12-month re-admission and mortality rates. However, we need larger prospective trials to clarify this.

Table 1. Studies showing the effects of angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers and/or diuretics in patients with acute heart failure.

First Author/ Year/ Reference	Study Design	N	Intervention	Outcomes			Major findings/comments
				Renal outcomes	Hypotension	Hyperkalemia (HK)	
Iglesias et al., 2019	Retrospective Age ≥ 65 years patients	2,361	Role of ACEi/ARB on mortality in CRS1	CRS1 occurred in 637 patients	NA	NA	In-hospital mortality decreased significantly in patients receiving ACEi/ARB (6.8% vs 32.8%, OR 0.34, 95% CI 0.25–0.49). Development of CRS1 was significantly associated with increased in-hospital mortality (6.0% vs 3.9%, OR 1.54, 95% CI 1.03–2.3)
Kane et al., 2017	Retrospective chart review	174	30 patients reduced/Discontinued (r/d) ACEi/ARB	13 patients had WRF	4 patients had SBP less than 100	3 patients had HK	ACEi/ARB dose r/d group had a significantly greater median LOS (5.5 vs 3.0 days) versus those without dose r/d
Gilstrap et al., 2017	Analysis of (GWTG-HF) registry	16,052	90.5% patients continued and started ACEi/ARB	Incidence of WRF in each group: Continued ACEi/ARB: 11.84% Discontinued ACEi/ARB: 11.38% Not started ACEi/ARB: 15.58% Not started ACEi/ARB: 13.23%	Incidence of SBP < 90: Continued: 2.80%, Started: 2.42%, Discontinued: 3.90%, Not started 1.82%	Incidence of HK Continued: 2.37%, Started: 1.59%, Discontinued: 3.90%, Not started 2.40%	30-day mortality higher on discontinued group HR: 1.92; (1.32–2.81) versus continued group 30-day mortality higher on not started group HR 1.50; (1.12–2.00) vs started. 1-year mortality on discontinued group HR 1.35 (1.13–1.61), and not started group HR of 1.28 (1.14–1.43) was higher compared to continued and started group respectively.
Sanam et al., 2016	Retrospective chart review	1,384	734 patients were initiated on ACEi/ARB	NA	NA	NA	Patients on ACEi/ARB had lower risk of 30-day all-cause readmission HR 0.74 (0.56–0.97)
Yoshioka et al., 2019	Post hoc analysis of the REALITY-AHF trial	900	ACEi/ARB initiation within 48 hour of admission vs no ACEi/ARB	148 patients had WRF within 5 days.	NA	NA	The ACEi/ARB group had significantly higher event-free survival HR 0.51 (0.32–0.82)
Siddiqui et al., 2015	Retrospective	8,049	Studied medicare beneficiaries hospitalized for HF	2,180 patients had WRF	NA	NA	30-day all-cause readmission occurred in 21% and 27% of patients receiving ACEi or ARB, respectively HR 0.89 (0.79–1.00). Benefit persisted at 1-year and not receiving ACEi or ARB, respectively HR 0.77 (0.62–0.95)

Table 1. Continued

First Author/ Year/ Reference	Study Design	N	Intervention	Outcomes			Major findings/comments
				Renal outcomes	Hypotension	Hyperkalemia (HK)	
Fudim et al., 2018	Post hoc analysis of ESCAPE trial	433	AHF (EF \leq 30%) therapy guided by measures of decongestion	68 patients had temporary WRF, 67 had persistent WRF	NA	NA	Persistent congestion with concomitant WRF at discharge was associated with increased mortality HR 3.46 (1.89-6.31) compared to no WRF + no congestion. WRF was not significantly associated with 180-day all-cause death among decongested HR: 0.52 (0.20-1.35)
Aronson and Burger, 2010	Post hoc analysis VMAC trial	467	Comparing the hemodynamic and clinical effects of Nesiritide to nitroglycerin	WRF occurred in 115 patients (24.2%) Persistent in 76 patients, Transient WRF in 39 patients	NA	NA	Increased mortality in patients with persistent WRF HR 3.2 (2.1-5.0). Mortality of patients with transient WRF was similar to that of patients without WRF HR 0.8 (0.4-1.7)
Metra et al., 2018	A Post Hoc Analysis of the PROTECT Data	1,684	Rolofylline for AHF to Assess effect on Congestion and Renal Function	Only studied patients with WRF	NA	NA	WRF + congestion has higher 30-day mortality or HF hospitalization HR 1.49 (1.06-2.09) in congested patients. Congestion score \leq 2 with WRF was not associated with worse outcomes HR 0.98 (0.76-1.27)
Metra et al., 2012	Prospective	599	Patients were subdivided into 4 groups according to development or not of WRF and the persistence of congestion at discharge	WRF + congestion: 45 patients. WRF + no congestion: 253 patients	NA	NA	LOS because of WRF was 3.51 (1.29-5.73) more days
Ahmad et al., 2018	Post hoc analysis of ROSE-AHF trial	283	High dose diuretics therapy and study of renal biomarkers	60 patients had WRF	NA	NA	WRF alone is not an independent determinant of outcomes in patients with AHF
							WRF in the setting of aggressive diuresis was not associated with renal tubular injury

N, number of patients; HK, Hyperkalemia; CV, cardiovascular; ACEi, Angiotensin-converting-enzyme inhibitors; ARB, Angiotensin II receptor blockers; CRS1, Cardiorenal syndrome type 1; OR, odds ratio; CI, confidence interval; WRF, Worsening renal function; SBP, Systolic blood pressure; LOS, length of stay; GWTG-HF, Get With The Guideline-Heart Failure; HR, Hazard ratio; REALITY-AHF, Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure; ; HF, heart failure; ESCAPE, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness; AHF, Acute heart failure; VMAC, Vasodilation in the Management of Acute Congestive Heart Failure study; PROTECT, Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function; ROSE-AHF, Renal Optimization Strategies Evaluation-Acute Heart Failure.

Gayat et al. (2018) studied the association between ACEi/ARB and 1-year mortality rate in 1,551 patients discharged from 21 European ICUs and found that in patients with AKI (N = 611, 39%), 1-year mortality rates were lower in patients treated with ACEi/ARB at ICU discharge (HR 0.55, 95% CI, 0.35-0.89). Note that this was an AKI study and therefore did not study AHF or CRS1. Regardless, it does suggest the importance of ACEi/ARB at discharge even in those who developed AKI during hospital admission. Iglesias et al. (2019) retrospectively examined the effects of ACEi/ARB usage and CRS1 development among elderly (aged ≥ 65 years) AHF patients and found that lack of ACEi/ARB usage and CRS1 were both independent predictors of increased in-hospital mortality. However, this analysis was not designed to study the effects of ACEi/ARB use specifically in CRS1.

Considering the paucity of clear results, clinicians will need to continue individualized care in CRS1. It may be reasonable to hold ACEi/ARB therapy in patients with CRS1 for bona fide hemodynamic instability and significant hyperkalemia; however, it remains unclear whether there is a threshold increase in azotemia alone above which continuation of ACEi/ARB therapy would be detrimental. The study by Edner et al. (2015) showed that in HFrEF patients with creatinine clearance less than 30 mL/min, use of RAAS inhibitors are associated with lower HR (0.76; 95% CI, 0.67-0.86) for mortality. Thus far, the data suggest continuation of ACEi/ARB is beneficial.

4. Use of diuretics in type 1 cardiorenal syndrome

Use of diuretics to treat volume overload in patients with AHF can be associated with WRF. Clinicians often face the dilemma of whether to continue diuresis in patients with CRS1. A post hoc analysis of the Evaluation Study of Congestive HF and Pulmonary Artery Catheterization Effectiveness (ESCAPE) (Fudim et al., 2018), a multicenter RCT, analyzed the association between congestion/decongestion and WRF (creatinine increase of ≥ 0.3 mg/dL) in 433 patients with HFrEF (ejection fraction (EF) $\leq 30\%$), and with at least one sign and one symptom of congestion. This study showed that WRF in patients with resolved symptoms of congestion at discharge did not increase the risk of 180-day all-cause death, while inadequate decongestion and persistent (> 30 days) renal dysfunction was associated with increased risk of all-cause death. The authors cautioned against use of WRF as a routine justification for de-escalation of diuretic therapy. Aronson and Burger (2010) in an analysis of the Vasodilation in the Management of Acute Congestive HF study showed that mortality in patients with persistent WRF (serum creatinine ≥ 0.5 mg/dL above baseline at day 30) was higher (HR 3.2; 95% CI, 2.1-5.0) and those with transient WRF (Serum creatinine ≤ 0.5 mg/dL from baseline at day 30) was similar (HR 0.8; 95% CI, 0.4-1.7) compared to patients without WRF. Metra et al. (2012) also showed that WRF leads to adverse outcomes only in patients with persistent signs of congestion. In a post hoc analysis of the PROTECT study (Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With AHF and Volume Overload to Assess Treatment Effect on Congestion and Renal Function), Metra et al. (2018) showed that worse outcomes with WRF were driven by patients with congestion at the time of renal function assessment. The HR for WRF

on 30-day death or heart failure hospitalization was 1.49 (95% CI, 1.06-2.09) times higher in significantly congested compared to nonsignificantly congested patients

Ahmad et al. (2018) analyzed data from the ROSE-AHF (Renal Optimization Strategies Evaluation-AHF) trial and found that WRF (defined as a $\geq 20\%$ decrease in glomerular filtration rate estimated with cystatin C) in patients treated with aggressive diuresis was not associated with tubular injury. This was suggested by an absence of increase in the tubular injury markers: neutrophil gelatinase-associated lipocalin, N-acetyl- β -D-glycosaminidase and kidney injury molecule 1. The study also demonstrated that increases in tubular injury biomarkers were paradoxically associated with improved survival (adjusted HR 0.80 per 10-percentile increase; 95% CI, 0.69-0.91). Authors hypothesized that this increase in tubular biomarker could be in the setting of aggressive diuresis in the patients with AHF and the change is usually clinically benign.

Again, as with ACEi/ARB, there is no clear result from RCT's indicating an optimal strategy for the use of diuretics in CRS1. The observational studies in the form of post hoc analyses suggest that worse outcomes with WRF may be a result of vascular congestion and neurohumoral dysregulation, rather than WRF due to traditional causes. This could imply that clinicians should not routinely de-escalate diuretic therapy for mild to moderate WRF alone.

5. Use of Mineralocorticoid Receptor Antagonist in Acute Heart Failure

MRAs (spironolactone & eplerenone) have been well known to reduce mortality, decrease readmissions and improve HF symptoms in patients with severe HFrEF (Pitt et al., 1999). Some studies have shown the clinical benefit and safety of MRAs in hospitalized AHF patients, but this is not well defined. A single-center prospective single-blinded study of 100 patients divided equally between standard therapy (control) and treatment (standard therapy plus 50-100 mg/day spironolactone) groups demonstrated that a significantly greater proportion of patients in the treatment group were congestion free, while WRF was more likely in the control group (Ferreira et al., 2014).

A post hoc secondary analysis of the multicenter COACH (Coordinating Study Evaluating Outcomes of Advising and Counseling in HF) trial involving 534 AHF patients showed that spironolactone was prescribed to about 55% patients at discharge and that spironolactone use was associated with a significant reduction in 30-day mortality and readmissions (HR 0.538; 95% CI, 0.299-0.968; $P = 0.039$) (Maisel et al., 2014). Another study by Hamaguchi et al. (2010) in 946 AHF patients showed similar results; 46% were prescribed spironolactone at discharge and its use was associated with significant reduction in all-cause (HR 0.619; 95% CI, 0.413-0.928) and cardiac death (HR 0.524; 95% CI, 0.315-0.873) over the 2.2 years of follow-up. A study by Hernandez et al. (2012) that used clinical registry data linked to Medicare claims from 2005 to 2010 to study the association between MRA therapy and mortality/readmission risk in 5,887 patients admitted with HFrEF did not find a significant difference in cardiac mortality. However, the 3-year HF readmission rate was lower among patients on MRA therapy at discharge (HR, 0.87; 95% CI, 0.77-0.98).

Table 2. Studies showing the effects of mineralocorticoid receptor blockers and angiotensin II receptor blockers-neprilysin inhibitors in patients with acute heart failure.

First Author/ Year/ Reference	Study Design	N	Intervention	Outcomes			Major findings/comments
				Renal outcomes	Hypotension	Hyperkalemia (HK)	
Ferreira et al., 2014	Prospective single center single blind	100	Standard therapy + spironolactone (treatment group) vs standard (control group)	WRF was more frequent in control group 20% (10 patients) vs. 4% (2 patients); $P = 0.038$.	NA	Serum potassium did not differ significantly between groups	Greater proportion of patients in the treatment group were free of congestion at day 3
Maisel et al., 2014	Secondary analysis of COACH study	534	30-day outcome between patients treated with spironolactone vs not	Spironolactone treatment was significantly beneficial in groups with elevated SCr ($P = 0.009$)	NA	NA	Patients discharged on spironolactone had significantly less 30-day event (death or rehospitalization) HR 0.538 (0.299-0.968)
Hamaguchi et al., 2010	Prospective	946	Prescription of Spironolactone at discharge	NA	NA	NA	All cause and cardiac death in spironolactone group was significantly reduced vs other HR 0.619 (0.413-0.928) and HR 0.524 (0.315-0.873) respectively
Hernandez et al., 2012	Retrospective. Medicare registry data	5,887	Studied patients who got MRA therapy (treated group) at discharge	NA	NA	30-day Incidence of HK was 2.9% vs 1.2% ($P < .001$) between treated vs not. 1-year (8.9% vs 6.3%)	No significant differences in mortality at 3-year between two groups HR 1.05 (0.97-1.15). 3-year HF readmission rate was lower among patients on MRA therapy at discharge HR 0.87 (0.77-0.98)
Tromp et al., 2017	Post hoc analysis of PROTECT trial	1,867	Studied association between HK at admission and mortality	NA	NA	176 patients (9%) had HK	Potassium levels at admission or its change during hospitalization are not associated with mortality after multivariate adjustment.
Rossignol et al., 2012	Post hoc analysis of EPHEBUS trial	5,792	Post-acute MI patients were given Eplerenone vs placebo	914 patients had WRF (16.9% in eplerenone and 14.7% in placebo). More frequent early decline in eGFR with Eplerenone	NA	Potassium level > 6 in 1 patient	Eplerenone is safe and beneficial in patients with HF after myocardial infarction with a SCr < 2.5 mg/dL and a serum potassium < 5.0 mmol/L

Table 2. Continued

First Author/ Year/ Reference	Study Design	N	Intervention	Outcomes			Major findings/comments
				Renal outcomes	Hypotension	Hyperkalemia (HK)	Mortality/CV outcomes
Greene et al., 2019	Post hoc analysis of ATHENA- HF	360	High dose Spironolactone (100mg) vs standard care (25mg or placebo)	WRF from baseline to 96 hours/discharge were similar in 2 groups	NA	HK from baseline to 96 hours and 30-day were similar in 2 groups	eGFR \leq 50 is associated with higher risk for mortality HR 12.11 (1.37-107.22) High-dose spironolactone did not improve congestion more than usual care, irrespective of renal function
Oh et al., 2015	Retrospective	1,035	Studied MRA use in CKD	Patient with severe CKD 4-5 may not benefit from spironolactone	NA	Incidence of HK was 11.9% at admission, 3.6% at discharge, and 10.3% at 1 month after discharge	Spirolactone use was not an independent predictor of all-cause mortality after adjusting other HF risk factors HR 0.974 (0.681-1.392) Spirolactone may not benefit AHF patients with severe renal dysfunction (eGFR < 45 mL/min per 1.73 m ²)
Velazquez et al., 2018	Randomized	881	ARNI vs enalapril group	No change in renal function between two groups RR 0.93 (0.67 -1.28)	No change in BP between two groups RR 1.18 (0.85-1.64)	No change in potassium between two groups RR 1.23 (0.84-1.84)	No change in mortality between two groups. 0.66 (0.3-1.48) Greater reduction in NT-proBNP level in ANI group

N, number of patients; HK, hyperkalemia; CV, cardiovascular; WRF, worsening renal function; COACH, Co-ordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure; SCr, serum creatinine; HR, Hazard ratio; MRA, Mineralocorticoid receptor blockers; PROTECT, Patients Hospitalized with acute heart failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; ATHENA-HF, Aldosterone Targeted Neurohormonal Combined with Natriuresis Therapy in Heart Failure; CKD, Chronic kidney disease; AHF, acute heart failure; ARNI, angiotensin II receptor blockers - neprilysin inhibitors; RR, relative risk; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

The most common reasons for in-hospital discontinuation of MRA appear to be related to the risks of hyperkalemia and WRF. The previously referenced study by [Hernandez et al. \(2012\)](#) did find higher rates of readmission associated with hyperkalemia with aldosterone antagonist therapy at 30 days (HR 2.54; 95% CI, 1.51-4.29; $P < .001$) and 1 year (HR 1.50; 95% CI, 1.23-1.84; $P < .001$). However, a study by [Tromp et al. \(2017\)](#) that analyzed data from the Patients Hospitalized with AHF and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial found that high potassium levels at admission or changes in potassium levels during hospitalization in patients with HF was not associated with 180-day mortality.

A post hoc analysis from the Eplerenone Post-Acute Myocardial Infarction HF Efficacy and Survival Study (EPHESUS) ([Rossignol et al., 2012](#)) evaluated the effect of eplerenone on renal function and the interaction between changes in renal function and subsequent CV outcomes in 5,792 patients with AHF after an acute myocardial infarction. The authors found that eplerenone induced a moderately more frequent early decline in estimated glomerular filtration rate (eGFR; $> 20\%$ decline), however this eGFR decline did not affect eplerenone's clinical benefit on CV outcomes. This trial evaluated early initiation of the MRA eplerenone in patients with acute MI and AHF. Another HF study (not AHF) similarly showed that WRF and hyperkalemia were more frequent when eplerenone was added to optimal therapy, but their occurrence did not eliminate the survival benefit of eplerenone ([Rossignol et al., 2014](#)). [Cooper et al. \(2017\)](#) studied clinical registry data linked to Medicare claims and found lower odds of MRA use in HF patients (odds ratio, 0.66; 95% CI, 0.61-0.71) when the serum creatinine was higher. Similar results were seen in another single-center study ([Chamsi-Pasha et al., 2014](#)) showing lower utilization of MRA in WRF.

These data suggest that clinicians indeed reduce MRA use in patients with WRF and hyperkalemia; and that the risk of WRF and hyperkalemia increases with MRA use, however this increased risk does not seem to affect the benefits of MRAs. These and other studies ([Greene et al., 2019](#)) indicate that it is generally safe to use MRAs in AHF. However, it is not clear if there is a threshold eGFR below which there is unacceptable risk or absence of benefit of using MRAs in AHF or CRS1. A retrospective study of a Korean HF registry ([Oh et al., 2015](#)) demonstrated that spironolactone therapy was not beneficial in AHF patients with severe renal dysfunction defined as $eGFR < 45 \text{ mL/min per } 1.73 \text{ m}^2$. Larger prospective trials are needed to clarify this. Also, most of these studies did not evaluate primary renal endpoints like doubling of serum creatinine or time to initiation of renal replacement therapy.

6. Use of angiotensin II receptor blockers - neprilysin inhibitor in acute heart failure

Neprilysin, also known as membrane metallo-endopeptidase, is a neutral endopeptidase and its inhibition increases natriuretic peptide bioavailability resulting in natriuretic and vasodilatory effects. The beneficial effects of angiotensin II receptor blockers - neprilysin inhibitor (ARNI or sacubitril/valsartan) were shown in the Prospective Comparison of ARNI With an ACE Inhibitor to Determine Impact on Global Mortality and Morbidity in HF (PARADIGM-HF) double blind RCT ($n = 8,442$ patients) ([Mc-](#)

[murray et al., 2014](#)). The study clearly showed the superiority of ARNI over enalapril in reducing CV events (composite of mortality from CV causes or hospitalization for HF, HR in the ARNI group, 0.80; 95% CI, 0.73-0.87; $P < 0.001$) in stable patients with HFrEF. ARNI also reduced the risk of HF hospitalization by 21% ($P < 0.001$). A further analysis of the PARADIGM-HF study ([De-sai et al., 2016](#)) demonstrated that the rates of 30-day readmission from any cause were significantly lower in patients who received ARNI than enalapril alone (odds ratio: 0.74; 95% CI, 0.56 to 0.97; $P = 0.031$).

It is important to note that the PARADIGM-HF study enrolled stable chronic HF patients and did not comment much on patients with AHF or continuation/discontinuation of ARNI during hospitalization. Due to limited RCTs studying use of ARNI in AHF patients, there is some resistance to initiation of ARNI before or at discharge in this group. A GWTHG-HF registry analysis ([Luo et al., 2017](#)) found that out of 21,078 patients hospitalized for HFrEF, only 2.3% were discharged on ARNI. To address this issue, a double blind RCT, Rationale and design of the comParlson Of sacubitril/valsartaN versus Enalapril on Effect on nt-pRo-bnp in patients stabilized from an AHF episode (PIONEER-HF) was recently published ([Velazquez et al., 2018](#)). It enrolled 881 patients who were hospitalized for HFrEF in two arms (sacubitril/Valsartan vs. enalapril alone) and assessed the safety, tolerability, and efficacy of ARNI. The results showed that at 8-week follow up, the initiation of ARNI therapy led to a greater reduction in the N-terminal pro-B-type natriuretic peptide concentration than enalapril therapy. 13.6% of patients in the ARNI group experienced WRF vs. 14.7% in the Enalapril group, but this difference was not significant. However, hyperkalemia was more common in ARNI group (11.6%) compared to the Enalapril group (9.3%) though this difference was also not significant. [Table 2](#) summarizes the above mentioned studies showing the effects of MRA and ARNI in patients with AHF.

The Entresto™ (LCZ696) In Advanced HF (HFN-LIFE Study; ClinicalTrials.gov Identifier: NCT02816736) trial is currently enrolling all patients with symptomatic advanced HFrEF (not specific to AHF) who are naïve to ARNI and randomizing to ARNI plus placebo vs. valsartan plus placebo. This study will report mortality, readmission and tolerability in terms of blood pressure, renal function and potassium level. We hope that the growing body of evidence on the safety and efficacy of ARNI will make providers more confident in initiating/continuing this medication as a standard therapy in hospitalized patients with AHF.

7. Conclusion

The lack of RCTs on initiation vs. continuation vs. discontinuation of RAASi in AHF complicates clinical decision making in patients with AHF. However, several studies have shown that early initiation of RAASi is associated with significantly higher event-free 1-year survival. Discharge prescription of RAASi is associated with significant reduction in 30-day and 12-month readmission and mortality rates while the opposite is true when RAASi were discontinued. Additionally, lack of RAASi usage is an independent predictor of increased in-hospital mortality. Despite these findings, RAASi are often withheld due to WRF, hyperkalemia and hypotension and sometimes in anticipation of

the WRF. Most WRF in AHF seems to be a transient renal hypoperfusion-related decline in eGFR. Available data show that WRF leads to adverse outcomes only in patients with persistent signs of congestion, suggesting that WRF should not be a routine justification for de-escalation or discontinuation of therapy.

Hyperkalemia is a manageable problem that can be effectively controlled with the novel potassium binders (Packham et al., 2015; Weir et al., 2015). However, clinicians treat individual patients, and in certain clinical settings, it may be reasonable to hold RAASi therapy in patients with CRS1 for hemodynamic instability or hyperkalemia. In the treatment of AHF, withholding RAASi or diuretics for minor biochemical abnormalities may not be prudent in the interest of the greater good of the patient. Although most studies included in this review studied only HFREF, some did not clearly define HF based on ejection fraction and this can be considered a limitation of this review. Further prospective randomized studies are warranted to clarify this.

Author Contributions

GS contributed to acquisition, interpretation of data and drafting of manuscript. PAM contributed to the conception and revision of the manuscript. AAE, PAM, AYK, SB, BD, NS and AA contributed to the critical revision of the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

All the authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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