Role of renin–angiotensin–aldosterone system inhibitors in heart failure and chronic kidney disease

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Abstract
Renin–angiotensin–aldosterone system (RAAS) inhibitors are the key medications for patients with heart failure and chronic kidney disease. Multiple randomized controlled trials have demonstrated their benefits in an outpatient setting for the treatment of chronic heart failure. Additional advantages in acute heart failure treatment during inpatient hospitalization are less clear but a small number of non-randomized studies have favored their use. Conditions that result in stoppage of RAAS inhibitors during inpatient stay are an increase in serum creatinine, hyperkalemia, and hemodynamic instability such as hypotension. The role of RAAS inhibitors in chronic kidney disease has also been documented in multiple randomized controlled trials, with their use in hypertension and proteinuria being unambiguous. This narrative review summarizes the role of RAAS inhibitors in acute and chronic heart failure and chronic kidney disease.

Keywords: acute heart failure, chronic heart failure, chronic kidney disease, renin–angiotensin–aldosterone system inhibitors, RAAS.

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Introduction
The renin–angiotensin–aldosterone system (RAAS) plays a significant role in the mediation of cardiovascular (CV) and renal physiology and its activation is key in hypertension, heart failure (HF), kidney disease, and other pathological conditions. Angiotensinogen is cleaved by renin to produce an inactive peptide, angiotensin I, which is then converted by endothelial angiotensin-converting enzyme (ACE) to angiotensin II in lungs. Angiotensin II mediates the release of aldosterone from adrenal glands, leading to sodium retention and hypertension, followed by vascular remodeling of the heart and disease progression.1 The discovery of RAAS inhibitors was ground-breaking and has led to significant developments in the prevention and treatment of HF, chronic kidney disease (CKD), and hypertension. In this narrative review, we provide a comprehensive, objective, and critical analysis of the current knowledge on RAAS inhibitors in HF with both reduced and preserved ejection fraction, acute decompensated HF (ADHF), and CKD.

Methodology
PubMed was searched from 1990 to 2020 using the terms ‘RAAS inhibitors,’ ‘heart failure,’ ‘acute heart failure,’ ‘ACE inhibitors,’ ‘ACEIs,’ ‘angiotensin receptor blockers,’ ‘ARBs,’ ‘ARBs-neprilysin inhibitors,’ ‘ARNI,’ ‘chronic kidney disease,’ and ‘CKD’ and included all relevant major randomized controlled trials (RCTs) on the use of RAAS inhibitors in HF and CKD. The search was restricted to English-language publications. Data on rationale, design, and study outcomes were extracted and analyzed.

History of ACEIs
The RAAS has been the subject of study for many years. In 1898, Scandinavian researchers extracted a substance from the kidney that had a powerful pressor effect. In the 1950s, the substance was subsequently identified as angiotensin and found to exist in two forms, angiotensin I and angiotensin II. ACE is required for the conversion from angiotensin I to angiotensin II. In 1968, studies performed on dog lungs
demonstrated that peptides from the Brazilian viper’s venom successfully inhibited the activity of ACE. In 1975, the first ACE inhibitor (ACEI), named captopril, was discovered, and was launched in 1981. In 1982, Chatterjee et al. demonstrated an improvement in left ventricle function by increased cardiac output and stroke volume along with a decrease in pulmonary capillary wedge pressure following captopril administration. In 1985, a new longer-acting ACEI, called enalapril, was developed.

The perception of ACEIs further changed following the CONSENSUS study, which evaluated the prognosis of severe congestive heart failure (CHF) in 253 patients following administration of enalapril (2.5–40 mg per day). Patients were divided into two groups in a double-blind, randomized study to receive either placebo (n=126) or enalapril (n=127) along with basic HF treatment. This study demonstrated a 31% mortality reduction at 1 year in patients with severe HF who were treated with enalapril compared to placebo. Similarly, the SAVE trial concluded that, in patients with asymptomatic HF with reduced ejection fraction (HFrEF) after myocardial infarction (MI), the long-term administration of captopril was independently associated with a reduction in morbidity and mortality from major CV events. The SOLVD trial showed that, in patients with asymptomatic HFrEF, enalapril use significantly decreased the incidence of HF and the rate of HF-associated hospital admissions when compared to placebo. Although the prognosis for CHF remains poor, these studies heralded a new era in the treatment of HF and hypertension and provided the building blocks needed to achieve the new age of medicine for the treatment of CHF.

History of ARBs

After ACEIs were discovered in the late 1970s, the substantial role of angiotensin II in the regulation of blood pressure and fluid and electrolyte balance was confirmed. However, several deficiencies of ACEIs were proposed. First, it was thought that competitive blockade of ACE may cause augmentation of angiotensin I and renin levels, which can overcome the effect of the blockage. Second, blockade of ACE leads to the accrual of bradykinin. Third, the synthesis of angiotensin II can take place through pathways that are non-ACE dependent and are unaffected by ACE inhibition. Therefore, angiotensin receptor blockers (ARBs) were developed to overcome these deficiencies. ARBs provide enhanced inhibition of angiotensin II by selectively interacting at the receptor site. Armed with this knowledge and drive, angiotensin II analogues, like saralasin, were developed to have potent angiotensin II receptor-blocking capabilities yet they had poor oral bioavailability. Losartan was subsequently developed and was able to specifically block the AT1 subtype of the angiotensin II receptor. Several trials were established identifying the role of ARBs as an effective HF therapy and compared their efficacy to that of ACEIs. Initially, the ELITE trial showed a significant reduction in mortality in the losartan group compared to captopril, mainly due to a 64% decrease in the relative risk (RR) of sudden cardiac death in patients taking losartan; however, this was not the primary endpoint of the study and there was a relatively small number of events. Later, the ELITE II study did not find superiority in the use of losartan (50 mg daily) when compared to captopril (50 mg three times daily), although losartan tolerance was preferable. The dissimilarities in morbidity or mortality rates between the two were insignificant and, thus, losartan is considered to be an appropriate alternative choice for patients who are unable to tolerate ACEIs.

**ACEIs versus ARBs**

The binding of angiotensin II to its receptors exerts effects on various organs, including brain, kidney, heart, adrenal, and the vascular wall. Angiotensin II receptors have two subtypes – AT1 and AT2. Activation of AT1 results in vasoconstrictor effects and is associated with left ventricle (LV) and arterial hypertrophy. The role of AT2 is limited but has been associated with a stimulation of growth of the arterial wall. Angiotensin II can activate both the AT1 and AT2 subtypes; thus, the inhibition of angiotensin II by ACEIs will inhibit both subtypes. In contrast, ARBs will only inhibit the AT1 subtype of angiotensin II. ACE is also important in the metabolism of kinins and the inhibition of ACE will increase kinin levels. Excess kinin levels are also proposed to contribute to the hypotensive effects of ACEIs by unleashing nitric oxide from vascular endothelial cells. An increase in kinins may also improve insulin sensitivity, thus helping to lower blood glucose levels in patients with type 2 diabetes mellitus. A lack of increase in kinins by ARB use also explains the lack of cough as a symptom in these patients. The use of ACEIs does not affect the alternate pathway (involving chymase) of angiotensin II production, while ARBs will still inhibit angiotensin II from either pathway. Although it was initially thought that the combined use of ACEIs and ARBs will have synergistic effects, studies have shown that it can increase the risk of adverse effects, cancer incidence, and mortality; thus, combined therapy is not recommended.

**Role in HF**

**Role of ACEIs/ARBs in chronic HFrEF**

The goals of treatment of HF are an improvement in symptoms and survival along with a promotion of favorable remodeling of the LV. Initial therapy with diuretics, ACEIs, ARBs, ARBs–neprilysin inhibitors (ARNIs), and beta-blockers has shown benefits in both symptoms and survival. ACEIs improve survival in patients with LV systolic dysfunction (LVEF ≤40%) as shown in multiple large prospective RCTs. ACEIs demonstrated significant mortality reduction as well as an improvement in clinical state and symptoms. A meta-analysis of five trials (three started during the first 1–3 weeks post-MI) involving 12,763 patients with LVEF ≤35% or <40% and/or clinical HF compared ACEI use to placebo and showed a lower total mortality for ACEI use (23% versus 27% for placebo, odds ratio (OR) 0.80, 95% CI 0.74–0.87). This benefit of treatment was apparent soon after the commencement of treatment and continued to increase for >4 years. ACEIs also...
showed a lower rate of readmission for HF (14% versus 19% for placebo, OR 0.67, 95% CI 0.61–0.74) and a lower incidence of MI (9% versus 11% for placebo, OR 0.79, 95% CI 0.70–0.89).

The CHARM-Alternative trial assessed ARB use in 2028 patients with chronic HF who were intolerant to ACEIs and found a significant improvement in CV-related death or hospital admissions for CHF in patients on candesartan compared to placebo (adjusted HR 0.70, 95% CI 0.60–0.81).14 A systematic review of 9 randomized trials with a total of 4643 patients compared ARB therapy (without background ACEI therapy) to placebo and found a mildly overall reduced mortality (RR 0.87, 95% CI 0.76–1.00).15 The review noted that ARBs are better tolerated than ACEIs but did not recommend the use of combination ACEI and ARB therapy due to an increased risk of adverse effects. Similarly, another analysis of 7 clinical trials found a smaller reduction in mortality (RR 0.91, 95% CI 0.79–1.04) with no significant variance in rates of hospitalization compared to placebo (RR 1.00, 95% CI 0.92–1.08).16

Role of ACEIs/ARBs in chronic HFrEF

The pathophysiology of HF with preserved ejection fraction (HFrEF) is considerably different from HFrEF. Most of the medications showing a benefit on morbidity and mortality in HFrEF also improve LV dilation and cause favorable remodeling. In contrast, there is no or minimal LV dilation in HFrEF; thus, the benefits are also minimal. The current therapies for HFrEF are tailored toward treating clinical symptoms and other major clinical conditions, such as hypertension, lung disease, coronary artery disease, atrial fibrillation, and kidney disease. Certainly, there is a lack of RCTs showing the benefits of RAAS inhibitors in mortality in patients with HFrEF, with most being related to their antihypertensive effects. RAAS inhibitors have been proposed to prevent LV hypertrophy by controlling blood pressure, which in turn can improve diastolic function.17 A randomized, double-blind trial, the PEP-CHF study, enrolled 850 patients with a mean age of 76 years after the exclusion of patients with substantial HFrEF and valvular disease, and compared placebo with an ACEI (perindopril) for an effect on the composite of all-cause mortality.18 Although the results were not significant for all-cause mortality, there was a trend towards a benefit from treatment with ACEIs at 1 year (HR 0.692, 95% CI 0.474–1.010; p=0.055).

The CHARM-Preserved trial evaluated 3023 symptomatic HFrEF with LVEF ≥40% and controlled blood pressure and assigned them randomly to either daily candesartan or placebo;19 of note, 19% of patients were also on ACEIs. At a median follow-up of 36.6 months, there was a trend toward a decrease in incidence of the primary endpoint of CV death or hospitalization for HF (adjusted HR 0.86, 95% CI 0.74–1.00; p=0.051), with a significant decrease in the number of hospital admissions for HF (16% versus 18%; p=0.017). Unfortunately, more patients could not continue candesartan because of acute kidney injury, high potassium levels, or hypotension. Similarly, in the I-PRESERVE trial, 4128 patients with symptomatic HF, controlled blood pressure, and an LVEF ≥45% were randomly assigned to either receive irbesartan daily or placebo daily.20 At a follow-up of 49.5 months (mean), no significant differences were observed in death or hospitalization for HF, mortality from any cause, hospital admission from a CV cause, and quality of life. These studies suggest that the direct effect of RAAS inhibitors on HFrEF in CV mortality is minimal and the focus should be on controlling blood pressure and other comorbidities.

Role of ACEIs/ARBs in ADHF

ADHF is a common and key driver of acute respiratory failure. It can occur due to systolic and/or diastolic HF. Treatment is mainly focused on improvement of symptoms, oxygenation, identifying the precipitating factors, and management of comorbidities like atrial fibrillation and cardioselective syndrome. In a meta-analysis of 98,496 patients derived from 4 RCTs, 30-day mortality was significantly better in patients who received ACEIs (initiated within 36 hours of MI) compared to placebo (7.1% versus 7.6%, RR 0.93, 95% CI 0.89–0.98).21 These results support the use of ACEIs early in the treatment of patients post MI. As mentioned earlier, the benefits were more significant in patient with reduced EF. It is recommended to start therapy prior to hospital discharge in stable patients with MI and usually within the first 24 hours in hemodynamically stable patients with large anterior ST-elevation MI.22,23 ADHF can also lead to worsening of renal function (WRF), defined as cardioselective syndrome type 1 (CRS1), and is an independent predictor of increased inpatient mortality. Although the data on RAAS inhibitors in chronic HF are strong, randomized trials are lacking in the continuation of these medications in patients admitted for ADHF or in those who develop CRS1. Clinicians often discontinue these medications to preserve renal function and avoid hypotension. In a review of currently available studies, the most common reason of discontinuation of RAAS inhibitors was WRF.24 Many patients were discontinued from ACEI therapy during hospitalization, and treatment was not resumed at the time of hospital discharge. In a post hoc analysis of a multicenter RCT of patients with HFrEF and congestion (ESCAPE trial), an increase in serum creatinine in patients with adequate decongestion at the time of discharge did not increase the risk of 180-day all-cause mortality, while suboptimal decongestion and persistently elevated creatinine (>30 days) were correlated with an increased risk of all-cause mortality.25 Thus, transient WRF alone should not be considered as a casual reason for de-escalation of diuretic therapy. In patients with CRS, it may be reasonable to hold the administration of RAAS inhibitors due to risk of hemodynamic instability or severe refractory hyperkalemia.

Role of MRAs in HF

Mineralocorticoid receptor blockers (MRAs), such as spironolactone and eplerenone, have been widely studied...
in patients with chronic severe HFrEF with EF <35%. In 1999, a study by Pitt et al. showed that, in addition to standard HF therapy, MRAs (spironolactone 25 mg daily) were associated with a significant reduction in morbidity and mortality (35% versus 46% in placebo, RR 0.70, 95% CI 0.60–0.82; p<0.001) in patients with chronic severe HFrEF (EF <35%) compared to placebo.26 Similar results were shown in another randomized, double-blind trial of 2737 patients with chronic HFrEF (EF <35%), where MRAs (epironoletone, up to 50 mg daily) were found to lower the composite of mortality from CV causes or hospitalization due to HF (HR 0.63, 95% CI 0.54–0.74; p<0.001) although the risk of hyperkalemia was higher in patients on MRAs.27 Currently, evidence is unsupported for the role of MRAs in patients with HFpEF with EF >45% as seen in data from the TOPCAT trial, although regional variability was seen in the trial and a subgroup of patients from the Americas showed benefit.28,29 Multiple trials are being undertaken to study the effects of MRAs in HFpEF. The FINEARTS-HF trial is currently recruiting patients with HFpEF (EF ≥40%) and studying the safety and efficacy of finerenone, an MRA, on morbidity and mortality.30 Similarly, the SPIRIT trial is testing the hypothesis that spironolactone plus standard of care compared to standard of care alone reduces the composite of CV mortality and HF hospitalization.31

The role of MRAs in ADHF is not well defined. There are no RCTs demonstrating the effect of MRAs in ADHF. In a post hoc analysis of the COACH trial, 534 patients with acute HF (55% were discharged on MRAs) showed a 30-day significant reduction in mortality and rehospitalization (HR 0.58, 95% CI 0.39–0.86; p=0.039).32 Another study of 946 patients showed a significant reduction in CV (HR 0.524, 95% CI 0.315–0.873) and all-cause mortality (HR 0.619, 95% CI 0.413–0.928) in 46% of the patients who were prescribed MRAs at discharge and were followed up for 2.2 years.33 Similarly, an analysis of a Medicare registry of 5887 patients showed a decrease in HF-related hospitalizations at 3 years when MRAs were prescribed at discharge (HR 0.87, 95% CI 0.77–0.98), although this analysis did not show significant benefit in CV mortality.34 As congestion is one of the worse prognostic factors for patients with ADHF, one study evaluated the use of MRAs and congestion and demonstrated that the use of MRAs was associated with a significantly higher proportion of ADHF patients without congestion.35

There are multiple trials currently ongoing assessing the effects of MRAs in heart disease. The CLEAR SYNERGY trial will study the long-term effects of treatments (colchicine versus placebo and spironolactone versus placebo) following percutaneous coronary intervention to treat MI.36 There are multiple reports of hyperkalemia and decline in renal function in patients on MRAs, but some studies showed that the variability in potassium levels or renal function is transient and, in most cases, it does not affect the benefit of MRAs in reducing mortality and HF-related readmissions in patients with ADHF.34,37–39 However, it is still unclear at what level of decline in glomerular filtration rate or hyperkalemia MRAs should not be initiated or discontinued; further RCTs are needed for this.

Role of ARNI in HF
Neprilysin is a neutral endopeptidase, the inhibition of which results in natriuretic and vasodilatory effects. Neprilysin inhibitors along with ARBs have been widely used in the treatment of HFrEF following multiple RCTs showing their benefit. The beneficial effects of ARNIs were shown in 8442 patients in the PARADIGM--HF trial, a double-blind RCT.40 ARNI was significantly superior to enalapril in reducing the composite of CV mortality or HF hospitalizations (HR in the ARNI group 0.80, 95% CI 0.73–0.87; p<0.001) in stable patients with HFrEF. ARNI also significantly reduced the risk of HF-related hospital admissions by 21% (p<0.001) and 30-day readmission from any cause (OR 0.74, 95% CI 0.56–0.97; p=0.031).41 In patients with HFrEF, the benefits of ARNI in reducing HF–related hospitalizations and mortality from CV causes were not significant based on the PARAGON--HF trial.42

The earlier-mentioned study was on patients with stable chronic HF. Despite the significant benefit of ARNI in HFrEF, a GWTG-HF registry analysis demonstrated that, among 21,078 patients hospitalized for HFrEF, only 2.3% were discharged on ARNIs,43 highlighting provider hesitancy in starting ARNIs in patients with ADHF. Later, PIONEER–HF, a double-blind RCT, enrolled 881 patients hospitalized for HFrEF.44 Although this study did not assess mortality benefit, it demonstrated a better reduction in the concentration of N-terminal pro-B-type natriuretic peptide in patients on ARNI than in those on enalapril alone at the 8-week follow-up. The difference in incidence of WRF or hyperkalemia between the two groups was not significant. Some clinical trials, such as the EntrestoTM (LCS696) in Advanced HF trial (ClinicalTrials.gov Identifier: NCT02816736), are currently also registering advanced HFrEF patients who are asymptomatic. Authors are hopeful that growing evidence on ARNIs will show their safety profile and prove their efficaciousness and that providers will feel more confident in initiating ARNIs in patients with acute or chronic HFrEF as a standard therapy.

Role of RAAS inhibitors in CKD
CKD is the progressive loss of kidney function due to nephron loss from a multitude of systemic and non-systemic renal insults that sets in motion a self-perpetuating vicious cycle of glomerular hyperfiltration, proteinuria, and glomerular and tubulointerstitial fibrosis.45 The loss of microvasculature due to inflammation, extracellular matrix accumulation, tubular atrophy, and rarefaction of peritubular capillaries is associated with a hypoxic milieu and production of superoxide, leading to mitochondrial and cytosolic oxidative stress, structural damage, and fibrotic response.46 Angiotensin II has a central role in CKD progression through the activation of signaling cascades, gene expression, inflammation, oxidative stress, apoptosis, and fibrosis. Angiotensin II has preferential vasoconstrictor effects in the efferent arterioles, resulting in increased intraglomerular pressure and proteinuria that can cause tubular injury and activate pro-inflammatory and fibrotic chemokines and
cytokines. Angiotensin II causes endothelial dysfunction via a complex interplay of pathways that includes increased NADPH oxidase activity and superoxide production, altered endothelial nitric oxide synthase function, and inactivation of kinases regulated by extracellular signals. Angiotensin II induces vascular smooth muscle cell proliferation and migration. Therefore, the blocking of angiotensin II, that is, RAAS inhibition, has become the main target of renal protection in CKD. It is uncertain whether RAAS inhibition induces regression of glomerulosclerosis; nevertheless, it has consistently demonstrated a reduction or prevention of progressive decline in renal function. Table 1 exhibits some of the pivotal trials that have shaped the use of RAAS inhibitors in clinical practice. The renoprotective effects of RAAS inhibitors are additive to their blood pressure-lowering effects. The FIDELIO-DKD trial, which studied the effects of finerenone in patients with CKD and type 2 diabetes (finerenone 10 or 20 mg orally once daily, or placebo when added to standard of care, including a maximum tolerated dose of ACEIs/ARBs), reported a delayed progression of CKD by reducing the combined risk of time to first occurrence of renal failure, a sustained decrease of estimated glomerular filtration rate ≥40% from baseline over at least 4 weeks, or renal death. It also reduced the composite of time to first occurrence of CV death, non-fatal MI, non-fatal stroke, or HF-related hospitalization. Although this study used both MRA and ACEIs/ARBs in the treatment arm, previous studies showed that dual blockade with ACEIs and ARBs is usually not recommended due to hyperkalemia-related adverse events and a lack of significant benefits. Data are limited on the role of RAAS inhibition in advanced CKD. It is also important to note that many patients with HF have concomitant CKD and the use of RAAS inhibitors has consistently shown benefits in lowering the number of CV events in these patients. Conclusion RAAS inhibitors have undoubtedly established themselves as key medications in standard and guideline-directed treatment of chronic HF. Their role is well defined in patients with HFrEF based on multiple RCTs, but their benefits are lacking in patients with HfPEF. Similarly, in ADHF, multiple non-randomized trials have consistently shown benefits of these medications, although well-structured RCTs are lacking. We recommend to clinicians not to de-escalate RAAS inhibitors or diuretic therapy routinely for transient WRF of
<30 days. Persistent WRF (>30 days) and persistent congestion portend poor prognosis. Although based on provider’s clinical judgment, in cases where WRF is significant, such as a decrease in estimated glomerular filtration rate of >30% from baseline, transient withholding of RAAS inhibitors may be reasonable but there should be a plan to restart these before discharge. Refractory hyperkalemia and hypotension could be a justifiable reason to temporarily withhold ACEIs in patients with ADHF but there should be a dedicated plan to restart them before discharge as suggested by their long-term clinical benefits. ARNIs have recently been established as an effective treatment in patients with HFrEF; more studies are currently enrolling patients to establish their role in ADHF. The benefits of RAAS inhibition in the treatment of CKD are unambiguous, with the effects on decreasing proteinuria and blood pressure being unquestionable. All patients with early CKD and proteinuria should be administered RAAS inhibitors unless there is an obvious contraindication. Data on advanced CKD are limited.

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7 of 9

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