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Updates in the management of heart failure for the chronic kidney disease patient

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Abstract

PURPOSE OF REVIEW—Heart failure (HF) is highly prevalent in patients with chronic kidney disease (CKD) and a leading cause of morbidity and mortality in this population. HF therapies proven to benefit the general population may have different risk-benefit profiles in patients with concurrent CKD, plausibly due to the unique pathophysiology of HF in this population. The present review highlights recent advances in HF treatment as they apply to patients with CKD.

RECENT FINDINGS—Several recent publications have shown possible benefits of established HF therapies to improve clinical outcomes in patients with CKD; while others conclude neutral or even harmful effects of HF therapies in CKD patients. Novel HF therapies show promise to improve outcomes in the general population and should be evaluated in future studies to further elucidate the efficacy and safety of these novel therapies specifically in patients with CKD.

SUMMARY—Knowledge of HF treatment to improve clinical outcomes in the CKD population remains limited. Future studies should focus on patients with CKD to evaluate the generalizability of HF therapies to this patient population.

Keywords

chronic kidney disease; heart failure; congestive heart failure; heart failure with reduced ejection fraction; heart failure with preserved ejection fraction

INTRODUCTION

Chronic kidney disease (CKD) affects one in seven American adults (~45 million adults) and accounts for over \$98 billion in annual Medicare costs.¹ Heart failure (HF) is highly prevalent in patients with CKD and a leading cause of morbidity, mortality and health care costs in this population.^{1,2} It is estimated that approximately 8 million patients in the U.S have HF, and of those, ~30% have CKD. Therefore, primary and secondary treatment of HF in patients with CKD is a public health priority.

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CONFLICTS OF INTERESTS

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HF can be categorized into two subtypes: HF with preserved ejection fraction (HFpEF) or with reduced ejection fraction (HFrEF). Although HFpEF has become the predominant subtype of HF in the general population and in patients with CKD, no randomized clinical trial (RCT) has convincingly showed the benefit of *any* therapy for HFpEF, even in patients with normal kidney function. There is much stronger evidence for HFrEF therapies to improve clinical outcomes, such as β -blockers and renin-angiotensin aldosterone system (RAAS) inhibitors, although few studies have been conducted in the CKD population. Therefore, there is an urgent need for novel HF therapies in the CKD population. In this article we review recent advances in the treatment of HF that may be promising for use in patients with CKD.

MINERALOCORTICOID ANTAGONISTS

Chronically increased neurohormonal activity is recognized as a major pathophysiologic mechanism in the progression of HFrEF. Medications such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) target maladaptive neurohormonal pathways like the RAAS, and are now standard-of-care therapies for HFrEF.

Mineralocorticoid antagonists (MRA) have also become mainstay neurohormonal modulatory drugs in HF treatment, particularly steroidal MRAs like spironolactone and eplerenone. The landmark RALES trial demonstrated that spironolactone reduced all-cause mortality and HF hospitalizations in patients with HFrEF both with and without CKD (mean eGFR of the CKD group was 47 mL/min/1.73 m², comprising 48% of the study population).^{3,4} TOPCAT, a trial that randomized patients with HFpEF to spironolactone vs. placebo and included 39% CKD patients (mean eGFR of all study participants was 65 mL/min/1.73 m²), did not find reduction in cardiovascular outcomes in those treated with spironolactone. Moreover, treatment with spironolactone was associated with higher rates of AKI and hyperkalemia.⁵

With the limitations of traditional MRAs, there has been interest in the study of novel, non-steroidal MRAs. Finerenone (formerly known as BAY 94–8862) is a non-steroidal MRA that is more selective for the mineralocorticoid receptor compared with spironolactone, with a lower affinity for androgen and progesterone receptors that cause side effects such as gynecomastia, impotence, and amenorrhea.⁶ A 2016 RCT of 1,066 patients with HFrEF and CKD showed that finerenone reduced albuminuria and N-terminal pro brain natriuretic peptide (NT-proBNP), a cardiac biomarker of hemodynamic stress, with lower rates of AKI and hyperkalemia when compared to spironolactone.⁷ More recently, Bonnard *et al.* characterized the effects of finerenone on cardiac complications in a mouse model of CKD.⁸ Four weeks after subtotal nephrectomies, these “CKD mice” exhibited evidence of diastolic dysfunction. The finerenone-treated CKD mice had partially corrected diastolic filling profiles as measured by echocardiography and reversal of cardiomyocyte hypertrophy on histology; however, stroke volume and cardiac output did not improve. These studies position finerenone as a potential alternative to traditional steroidal MRAs, particularly in CKD patients and possibly in HFpEF. FINESSE-HF (EUCTR2015–002168-17) is an ongoing phase 3 RCT of >3,000 patients with HFrEF and CKD that will compare the

efficacy and safety of finerenone with eplerenone and add to the knowledge of finerenone use in this population.

ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITORS

Neprilysin is an endopeptidase that degrades endogenous peptides key to counteracting the harmful effects of RAAS upregulation, but also degrades angiotensin II (ATII), a hormone with known negative effects on HF. Consequently, to both augment the endogenous natriuretic peptide system and prevent elevated levels of ATII, neprilysin inhibitors were combined with ARBs to form a novel class of drugs called angiotensin receptor-neprilysin inhibitors (ARNI).

The first agent in this class, valsartan/sacubitril, was studied in PARADIGM-HF, a landmark trial that was stopped early due to the overwhelming superior cardiovascular benefit with valsartan/sacubitril treatment compared to enalapril.⁹ While those with eGFR <30 mL/min/1.73 m² were excluded, 33% of patients in this cohort had CKD (mean eGFR 49 mL/min/1.73 m²). The trial found that the beneficial effect of valsartan/sacubitril in reducing death from cardiovascular causes or hospitalization for HF was similar among patients with vs. without CKD. Moreover, rates of elevations in serum creatinine and hyperkalemia were lower in the valsartan/sacubitril group compared with enalapril. Consequently, the ARNI may now be used in place of an ACEI or ARB in patients with HFrEF, a class 1B-R recommendation.¹⁰ In a post-hoc study published this year, Damman *et al.* compared kidney outcomes between the 8,399 patients in the PARADIGM-HF cohort randomized to either valsartan/sacubitril or enalapril.¹¹ Over a 48-month period, the valsartan/sacubitril group exhibited a lower rate of eGFR decline as compared to the enalapril group, -1.61 mL/min/1.73 m²/year compared with -2.04 mL/min/1.73 m²/year, respectively. The valsartan/sacubitril group also had lower systolic and diastolic blood pressures, and lower rates of cardiovascular and composite kidney outcomes (ESRD or 50% decrease in the baseline eGFR; hazard ratio of 0.63). This came at the expense of a small increase in urine albumin:creatinine ratio (UACR) in the valsartan/sacubitril group as compared with the enalapril group (1.20 mg/mmol vs 0.90 mg/mmol, respectively). It should be noted that the optimal strategy to model change in UACR as an outcome in trials remains an area of active discussion among clinical trialists.

Haynes *et al.* also examined outcomes associated with the use of an ARNI as compared to a more established RAAS inhibitor in patients with HFrEF and CKD. Four-hundred and fourteen patients with a mean eGFR of 35.5 mL/min/1.73 m² were randomized to either valsartan/sacubitril or irbesartan and followed over 12 months.¹² Unlike the Damman study, Haynes *et al.* found no difference in eGFR or UACR at pre-specified intervals up to 12 months between the valsartan/sacubitril group and the irbesartan group. However, the valsartan/sacubitril group did achieve lower blood pressures, troponin and NT-proBNP, all intermediate outcomes important in treatment of HF.

Altogether, existing studies suggest that compared to RAAS inhibitors alone, valsartan/sacubitril has possible beneficial effects on kidney and cardiovascular outcomes in patients with CKD. The ongoing trial PARAGON-HF ([NCT01920711](https://clinicaltrials.gov/ct2/show/study/NCT01920711)) will compare long-term

outcomes between valsartan/sacubitril with valsartan alone in 4,822 patients with HFpEF, 47% of whom have CKD (mean eGFR 63 ± 19 mL/min/1.73 m²), and will provide additional insight.

SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS

Sodium-glucose co-transporter 2 (SGLT2) inhibitors work by blocking glucose reabsorption through the eponymous channels in the proximal tubule, promoting urinary glucose excretion and thus lower blood glucose levels. As glycemic control agents, their effect is relatively modest, but their unexpected association with significantly reduced cardiovascular events, in particular HF, shows their tremendous promise as HF therapies. The landmark EMPA-REG trial demonstrated >30% relative risk reduction in death from cardiovascular causes and hospitalization with HF with empagliflozin compared with placebo¹³, while the CANVAS trial showed lower rates of death from cardiovascular causes, nonfatal myocardial infection or nonfatal stroke with canagliflozin (hazard ratio 0.86).¹⁴ Results from these trials also showed significant kidney benefits with SGLT2 inhibition as compared to placebo, including a reduction in albuminuria, eGFR decline, ESRD and kidney-associated deaths.¹⁵ Twenty-six percent of the EMPA-REG cohort had CKD, however the mean eGFRs of the study populations in EMPA-REG and CANVAS were high (83.1 and 76.5 mL/min/1.73 m², respectively) and excluded patients with eGFR <30 mL/min/1.73 m² thus limiting generalizability to patients with advanced CKD.

In a pooled analysis of 11 phase 3 clinical trials, Petrykiv *et al.* showed that the effects of dapagliflozin on cardiovascular risk factors vary based on kidney function.¹⁶ Changes in hemoglobin A1c (HbA1c), body weight, blood pressure, hematocrit and UACR over 24 weeks were assessed in 4,404 patients with type 2 diabetes according to 3 baseline eGFR subgroups (≥ 90 mL/min/1.73 m², 60 to <90 mL/min/1.73 m², and 45 to <60 mL/min/1.73 m²). While dapagliflozin consistently decreased body weight, blood pressure and UACR regardless of eGFR, its HbA1c-lowering effects decreased as kidney function declined (0.6%, 0.5%, and 0.3%, respectively, for each consecutive lower eGFR subgroup after 24 weeks of treatment). This suggests that SGLT-inhibitors may have differential effects on cardioprotection based on degree of kidney function and highlights the importance of trials with SGLT-2 inhibitors in patients with CKD.

CREDENCE ([NCT02065791](#)) is an ongoing RCT that includes 4,401 patients with CKD (mean eGFR 56.2 ± 18.2 mL/min/1.73 m²) and will provide additional evidence for canagliflozin use in CKD. Another RCT, EMPA-KIDNEY ([NCT03594110](#)), will examine the effect of empagliflozin on kidney and cardiovascular outcomes in patients with CKD and begins enrollment in November 2018.

CARDIAC IMPLANTABLE ELECTRONIC DEVICES

Permanent pacemakers, implantable cardiac defibrillators (ICD), and left ventricular assist devices (LVAD) are among a group of medical technologies collectively known as cardiac implantable electronic devices (CIED), and are being placed at higher frequencies in an aging population with high cardiovascular disease (CVD) burden. The indications for

insertion are broad, but as a group, CIEDs have improved survival in multiple primary and secondary prevention RCTs of participants largely without CKD. Despite the incidence of CVD and associated deaths being higher in patients with CKD, two recent observational studies from our group suggest that the benefits of CIEDs may not extend to the CKD and ESRD population.

In the first, we compared the mortality rate associated with LVAD placement between Medicare beneficiaries from 2003–2013 with and without ESRD and found an exceptionally higher mortality rate among patients with ESRD.¹⁷ Whereas 96% of patients without ESRD at the time of LVAD placement survived to hospital discharge with a median survival of nearly 6 years, less than half of patients with ESRD survived to discharge with a median survival of only 16 days. In another, non-interventional cohort study, we examined associations between primary prevention ICDs with risk of death and hospitalization in a community-based population of 5,877 ICD-eligible patients with HF and CKD.¹⁸ In models adjusted for demographic and CVD risk factors, no difference was found in all-cause mortality between the ICD vs non-ICD groups. ICD recipients, however, experienced higher rates of HF-related and any-cause hospitalization (adjusted relative risk 1.49 and 1.25, respectively). These studies underscore the importance of informed decision-making in the CKD and ESRD population, the latter who are already on one form of life-sustaining treatment, who may not derive the survival benefit from CIEDs as those without kidney disease.

CONSIDERATIONS IN HF TREATMENT SPECIFIC TO CKD

IRON DEFICIENCY

Anemia and iron deficiency are common in CKD and independently associated with mortality in patients with HFrEF. Anker *et al.* demonstrated in 2009 that patients with HF with or without anemia treated with intravenous (IV) ferric carboxymaltose had improvements in self-reported symptoms and New York Heart Association functional class compared with placebo, which held true in their subgroup analysis for patients with CKD.¹⁹ In a recent meta-analysis, Anker *et al.* examined four RCTs totaling 839 patients with HFrEF and iron deficiency (mean ferritin 56.8 ng/mL), and showed that intravenous ferric carboxymaltose significantly reduced recurrent cardiovascular hospitalizations and associated mortality.²⁰ The mean eGFR of the combined study participants was 63 mL/min/1.73 m², with 43% with eGFR <60 mL/min/1.73 m². Thus, IV iron may be a promising therapy to improve HF outcomes in patients with mild to moderate CKD.

BONE MINERAL DISORDER

Secondary hyperparathyroidism (SHPT) and other mineral bone disorders common in patients with CKD are associated with increased HF risk, and often treated with vitamin D analogs (i.e. paricalcitol) and/or cinacalcet, a calcium-mimetic that decreases parathyroid hormone (PTH) levels. While RCTs have not shown paricalcitol to be effective in reducing cardiac remodeling or HFpEF in patients with CKD,^{21,22} there is more promise with cinacalcet. The EVOLVE trial randomized 3883 patients with SHPT on maintenance dialysis to cinacalcet vs. placebo and found no difference in risk of death or major CVD events;²³

however, two post-hoc analyses of this trial showed that cinacalcet reduced rates of non-atherosclerotic events such as HF and sudden cardiac death (hazard ratio 0.84), and cinacalcet-induced reductions in serum fibroblast growth factor 23 were associated lower rates of CVD mortality and HF.^{24,25} Evans *et al.* expanded on these findings in a large RCT of 3,526 Swedish patients with CKD stages 3–5 (median eGFR 18.6 mL/min/1.73 m²) and SHPT (median PTH 636 ng/L).²⁶ Compared to placebo, patients on cinacalcet experienced lower composite cardiovascular outcome rates as well as mortality (adjusted odds ratio 0.67 and 0.79, respectively), adding support to the treatment of SHPT with cinacalcet in patients with CKD.

MEDICATION-ASSOCIATED HYPERKALEMIA

Hyperkalemia is considered a major barrier in initiation and uptitration of key HF therapies such as MRAs and RAAS inhibitors in patients with CKD and ESRD. Given the low tolerability and poor safety profile of traditional hyperkalemia therapies, there has been active investigation of novel therapies. In a recent open-label trial, Pitt *et al.* found that prescribing patiomer, a non-absorbed potassium-binding polymer, followed by an individualized titration regimen maintained normokalemia in 63 patients on spironolactone with chronic HF and CKD stages 3–5 (mean eGFR 46.2 mL/min/1.73 m²).²⁷ A major limitation of this trial was the lack of a control group. However, the ongoing AMBER study ([NCT03071263](#)) will randomize approximately 290 patients with CKD on spironolactone to either patiomer or placebo and may be valuable in the effort to expand MRA use in CKD.

Sodium zirconium cyclosilicate (ZS-9) is also a non-absorbed, potassium-binding compound, and maintained normokalemia better than placebo in HARMONIZE, a 2014 RCT with a majority of patients with CKD, many concurrently on RAAS inhibitors. This year, preliminary data from an extension of HARMONIZE showed that after 11 months on ZS-9, the average serum potassium of patients was 4.7 mmol/L with 88% of them maintaining normokalemia,²⁸ making ZS-9 a promising long-term therapy for hyperkalemia management in CKD patients.

CONCLUSION

HF and CKD are highly prevalent in the United States, co-exist in a substantial number of the American adults, and are linked with poor clinical outcomes. There is limited knowledge of HF therapies specifically in the CKD population, where the pathophysiology of HF is likely different and thus these patients may respond differently to “standard” HF therapies. Given the introduction of numerous novel HF therapies, dedicated studies in the CKD population should be conducted to fill a critical knowledge gap to improve clinical outcomes in this large and vulnerable population.

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KEY POINTS

- HF and CKD are highly prevalent in the United States, co-exist in a substantial number of the American adults, and are linked with poor clinical outcomes.
- Novel heart failure therapies show promise in improve outcomes associated with heart failure in the general population and in small studies of patients with CKD.
- There is a need for dedicated studies of novel HF therapies in patients with HF and CKD.