Prognostic and Therapeutic Implications of Renal Insufficiency in Heart Failure

Se Yong Jang, MD, PhD^1,2,3, and Dong Heon Yang, MD, PhD^1,2,3

1 Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Korea
2 Division of Cardiology, Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Korea
3 Division of Cardiology, Department of Internal Medicine, Kyungpook National University Chilgok Hospital, Daegu, Korea

ABSTRACT

The heart and kidneys are closely related vital organs that significantly affect each other. Cardiorenal syndrome is the term depicting the various spectra of cardiorenal interaction mediated by the hemodynamic, neurohormonal, and biochemical cross-talk between these two organs. In patients with heart failure (HF), both the baseline and worsening renal function are closely related to prognosis. However, for both investigational and clinical purposes, the unified definition and classification of renal injury are still necessary. Renal insufficiency is caused by multiple factors, and categorizing them into monogenous subgroups of phenotype is difficult. Various clinical scenarios related to the chronicity of HF, progression of renal dysfunction, and issues related to pharmacologic therapies associated with the prognosis of patients with HF have been reviewed in this study.

Keywords: Heart failure; Renal insufficiency; Prognosis

INTRODUCTION

The heart and kidneys are closely related vital organs that significantly affect each other. The kidneys need blood flow to remove waste products, salt, and water. The heart also depends largely on the kidneys, since the removal of extra body water and salt allows the heart to optimally maintain pulmonary and peripheral circulation. The pathophysiology of the interaction between the heart and kidneys has been widely studied in the past few decades. The classification of cardiorenal interaction has been specified, and the importance of renal function has been emphasized in the prognosis and management of various heart diseases. However, since heart and kidney conditions are frequently comorbid and a limited number of tools are available to access failing heart and kidneys in clinical practice, evaluating the condition of the kidneys in relation to heart disease or vice versa is often challenging.

Renal function is greatly important in risk stratification, pharmacologic therapy, and the prognosis of patients with heart failure (HF).^1,3,5^ The deterioration of heart function can result in the worsening renal function (WRF) and vice versa. Besides the heart function itself, the pharmacologic treatment of HF is closely related to renal function as regards initiation, titration, and discontinuation, making the situation more complex. This review...
will summarize the definition of cardiorenal syndrome (CRS), the prognosis related to renal insufficiency and WRF, and the issues related to pharmacologic therapy in HF.

**CRS**

CRS is the term used to describe a multitude of conditions, in which the dysfunction of the heart or kidneys can induce acute or chronic dysfunction in the other organ. Various mechanisms of hemodynamics, inflammation, neurohormonal activation, cytokines, atherosclerosis, hematopoiesis, and bone metabolisms underlie the confluence of the heart–kidney interaction. Although previous research has suggested the perception of structural changes of the heart in kidney disease, 6) CRS was initially attempted by the working group of the National Heart, Lung, and Blood Institute in 2004. The most frequently used classifications were proposed in 2008, which defined 5 subtypes based on the causality and sequence of organ involvement (Table 1). 7)

From a cardiocentric perspective, more than 30% of the patients with HF have moderate-to-severe renal dysfunction. A systematic review of 16 researches, including 80,098 patients with HF, has revealed that 29% had moderate to severe renal impairment (creatinine ≥1.5 mg/dL, creatinine clearance <53 mL/min/1.73 m², or cystatin-C ≥1.56). 8) The Acute Decompensated Heart Failure National Registry (ADHERE) has reported that approximately 30% of the patients had chronic kidney disease (CKD, creatinine >2.0 mg/dL). 9) Renal dysfunction itself confers excess mortality and also can be an important hurdle for the pharmacologic treatment of HF. 8) 9) CRS classification aims to clarify the initial insult and subsequent effect in both organs, thereby facilitating the development of novel diagnostic tools and management strategies for CRS. Although the definition of CRS has outlined the type of cardiorenal interactions, more specific criteria for measuring changes in renal function are necessary to treat patients with HF.

**ACUTE HF**

**Acute kidney injury in HF**

The Kidney Disease: Improving Global Outcomes (KDIGO) 3-5) released in 2012 defined acute kidney injury (AKI) as any of the following 10):

- Increase in serum creatinine level by ≥0.3mg/dL within 48 hours
- Increase in serum creatinine level by ≥1.5 times baseline within the last 7 days
- Urine output of <0.5 mL/kg/h for 6 hours

Serum creatinine level and urine output are the most widely used clinical parameters for evaluating AKI. However, these two markers are also closely related to and affected by cardiac function. The rapid congestion of acute decompensation and decongestion by treatment can affect these parameters regardless of the changes in renal function, which complicates the assessment of AKI in patients with acute HF.

| Table 1. Classification of cardiorenal syndrome |
|-----------------------------------------------|
| Phenotype | Description                                      |
| Type 1 acute cardiorenal syndrome | Acute kidney injury due to heart failure |
| Type 2 chronic cardiorenal syndrome | Chronic kidney disease due to heart failure |
| Type 3 acute renocardiac syndrome | Acute heart failure due to acute kidney injury |
| Type 4 chronic renocardiac syndrome | Chronic heart failure due to chronic kidney disease |
| Type 5 secondary cardiorenal syndrome | Systemic condition resulting in both heart failure and kidney injury |
The abrupt decrease in the estimated glomerular filtration rate (eGFR) is frequently observed in patients with acute decompensated HF. Baseline renal function carries an important prognostic implication in patients with acute HF. The Korean Acute Heart Failure registry (KorAHF registry; 2011–2019) showed that 36.8% of patients with HF with reduced ejection fraction (HFrEF) had an eGFR below 60 mL/min/1.73 m² and 10.9% had severe renal impairment (eGFR <30 mL/min/1.73 m²). Renal perfusion is maintained by the difference between the arterial and venous outflow pressure. HF is a condition in which cardiac output is decreased. Although the great loss of forward flow can cause AKI in clinical situations, including cardiogenic shock or severe left ventricular dysfunction, the glomerular filtration rate can be preserved to some extent with decreased cardiac output. The constriction of the efferent arterioles is the key mechanism for maintaining the intraglomerular pressure in such a case. However, excessive activation of the renin–angiotensin–aldosterone system (RAAS) resulting in reduced preglomerular blood flow and elevated central venous pressure in patients can deteriorate the renal function when these effects exceed the threshold of a compensatory mechanism. In the analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, the right atrial pressure was the only parameter that correlated with baseline serum creatinine level, which indicates the importance of central venous pressure in renal perfusion among HF patients.

Changes in renal function during the treatment of acute HF

WRF is frequently observed during acute HF treatment, and its clinical course is diverse. Some patients show persistently deteriorating renal function, whereas others often present with improved renal function during hospital stay and decongestion, which is a transient form of WRF. The prevalence of renal insufficiency among Korean patients with acute HF was suggested by two large multicenter cohort registries. The Korean Heart Failure registry (KorHF registry; 2004–2009) has reported that 21.5% of patients hospitalized for acute HF has experienced WRF, which is defined by a 1.5-fold increase in serum creatinine level from the baseline. The KorAHF registry (2011–2019) has revealed that the incidence of WRF is much higher up to 55.1%, because the transient-type WRF, which had been resolved by the time of hospital discharge, has been identified and included in the statistics. Regarding the persistent-type WRF, the incidence was higher (38.1%) than that in the KorHF registry, probably because of the aged population and higher incidence of comorbidities, including diabetes and hypertension.

To date, many observational data and post hoc analyses of randomized clinical trials have reported the association between persistent WRF and the adverse outcomes in patients with acute HF (Table 2). Reports for the KorAHF registry have also demonstrated that persistent WRF was an independent risk factor for 1-year mortality presenting a 1.41- and 1.72-fold increased risk in HFrEF and HF with preserved ejection fraction (HFpEF), respectively.

However, a few concerns should be considered regarding this plausible association between WRF and the poor prognosis of patients with acute HF. First, studies investigating the adverse impact of WRF on prognosis had various definitions of AKI with increased serum creatinine level from baseline or decreased eGFR with different cutoffs. Second, serum creatinine level itself may be convenient to use in clinical practice. However, an increase in serum creatinine level is not always associated with tubular injury, and kidney function derived from novel biomarkers may reflect the prognosis of patients with acute HF more accurately than creatinine. Post hoc analysis of Renal Optimization Strategies Evaluation–Acute Heart Failure (ROSE-AHF) trial has presented that WRF developing during the
decongestion was not associated with renal tubular injury as assessed using the urine tubular injury biomarkers. The elevation of serum creatinine level during acute HF treatment also can occur due to aggressive diuresis, RAAS antagonism, and a decrease in blood pressure level, in which cases we hardly differentiate the true kidney injury (CRS type I) from a mere decrease of eGFR without kidney injury. In the same context, WRF is rather correlated with the severity of HF itself compared with kidney injury in a considerable number of patients with acute HF. Because the eGFR by serum creatinine is largely affected by the complexity of the patient’s clinical conditions, the association between WRF by serum creatinine and prognosis can hardly be considered as a simple linear relationship. For example, Testani et al. have presented that patients with evidence of hemoconcentration evaluated by the changes of serum hematocrit, albumin, or total protein levels showed more fluid loss and greater reduction of filling pressure. Patients with hemoconcentration showed a five-fold higher incidence of WRF but also had significantly better survival in 6 months. Similarly, data from the Diuretic Strategies in Patients with Acute Decompensated Heart Failure (DOSE) trial have demonstrated the paradoxical relationship between eGFR and prognosis, indicating that increased serum creatinine was associated with a lower risk of composite events of death, hospitalization for HF, or emergency department visits.

According to previous studies, the prognosis of patients experiencing transient WRF during acute HF was inconsistent. Aronson and Burger studied 467 patients with acute HF defining persistent and transient WRF based on the changes in serum creatinine level for a 30-day period. Persistent WRF was associated with increased 6-month mortality, but the prognosis of the patients with transient WRF was similar to that of those without WRF. Data from the KorAHF registry and Krishnamoorthy et al. have presented the significant association between transient WRF and poor prognosis together with persistent WRF. Conversely, data from Ruocco et al. have demonstrated that patients with transient WRF showed a greater decrease of natriuretic peptide and better responses to diuretics, which seemed to be a positive sign in the prognosis after acute HF. This inconsistency between the studies may be attributable to the lack of consensus in the definition of persistent and transient WRF. Furthermore, more complex mechanisms, including status of congestion, hemoconcentration, and renal perfusion, may be considered rather than the simple fluctuation of serum creatinine level.

| Study (trial)         | Year | Study design | No.  | Definition of WRF                                                                 | Findings                                                                 |
|-----------------------|------|--------------|------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Krumholz et al.       | 2000 | Registry     | 1,681| >0.3 mg/dL increase of serum creatinine                                          | 2.72-fold increased risk of in-hospital mortality                         |
| Forman et al.         | 2004 | Cohort       | 1,004| >0.3 mg/dL increase of serum creatinine                                          | 7.5-fold increased risk of in-hospital mortality                         |
| Owatin et al.         | 2006 | Registry     | 6,052| >25% increase or >0.3 mg/dL increase of serum creatinine                           | 1.39-fold increased risk of 1-month mortality                             |
| Chittineni et al.     | 2007 | Cohort       | 509  | >0.5 mg/dL increase of serum creatinine                                          | 2.21-fold increased risk of in-hospital mortality                         |
| Kociol et al.         | 2010 | Registry     | 20,063| >0.3 mg/dL increase of serum creatinine                                           | 1.12-fold increased risk of 1-year mortality                             |
| Testani et al.        | 2010 | Cohort       | 993  | >0.3 mg/dL increase of serum creatinine                                           | WRF by creatinine and GFR were related to a 2.1- and 2.3-fold increased risk of 30-day mortality |
| Breidthardt et al.    | 2011 | Cohort       | 657  | >0.3 mg/dL increase of serum creatinine                                           | 1.92-fold increased risk of 1-year mortality                             |
| Lanear et al.         | 2011 | Cohort       | 2,465| >0.3 mg/dL increase of serum creatinine                                           | 1.12-fold increased risk of death and rehospitalization (median of 2.1 years of follow-up) |
| Kang et al. (KorAHF)  | 2018 | Cohort       | 5,625| >0.3 mg/dL increase of serum creatinine                                           | 2.75-fold and 9.48-fold increased risk of 1-year mortality for HFrEF and HFpEF, respectively |

GFR = glomerular filtration rate; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; WRF = worsening renal function.
**CHRONIC HF**

**Baseline renal function and prognosis**
Renal insufficiency has been shown to have an adverse impact on the prognosis of patients with HF. Patients with renal disease are often found to be more hypertensive and commonly have diabetes, lipid disorder, vascular calcifications, and high inflammatory status, which explains the high incidence of cardiovascular disease as a leading cause of death in patients with chronic renal disease. Renal insufficiency per se is a risk factor and can also be a problem in using RAAS antagonists. Concerns over renal insufficiency may prevent physicians from prescribing medications, which may be beneficial to the patients in the long term. An individualized approach is needed evaluating the risk and benefits considering the responses to the drugs and tolerability. Patients with renal insufficiency also have a higher incidence of poor diuretic response and diuretic resistance, making the management more complex and difficult.

**Worsening renal function and prognosis in chronic HF**
The deterioration of renal function in chronic HF (CRS type 2) can also be associated with a poor prognosis (Table 3). However, defining WRF in chronic HF has been inconsistent in the previous clinical trials because of the ambiguousness of the interval between the measurement of eGFR and the varying cutoff level of creatinine. De Silva et al. have investigated the impact of WRF in 1,216 patients with chronic HF, and WRF was defined as an increase of more than 0.3 mg/dL of serum creatinine level during a 6-month period. They have demonstrated that both baseline renal function and WRF are related to higher mortality. Khan et al. have evaluated the WRF differently. They have classified 6,640 patients from the Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fractions and Congestive Heart Failure (SOLVD) trial as the group with 5 mL/min/year decrease in eGFR. The patients presenting with a rapid deterioration of eGFR (>15 mL/min/year) were related to a significant increase in mortality (hazard ratio [HR], 5.63; 95% confidence interval [CI], 4.90–6.46), compared with those with a minimal decrease in eGFR (<5 mL/min/year). Another study by Damman et al. has investigated the prognostic impact of WRF that occurred during 0–6 months and 6–12 months after the discharge from the admission for acute HF. WRF that occurred during early and late 6 months has been associated with 2.06- and 5.03-fold increased risk of the composite event of all-cause mortality and HF readmission, respectively.

In chronic HF, the gradual deterioration of renal function even without any interventions can be observed and related to poor prognosis. However, the titration of RAAS antagonists, the use of aggressive diuretics, and hypotension, whether it is drug-induced or HF-related, are

| Study (trial) | Year | Study design | No. | Definition of WRF | Findings |
|---------------|------|--------------|-----|-------------------|----------|
| de Silva et al. | 2006 | Cohort | 1,216 | >0.3 mg/dL increase of serum creatinine over a 6-month period | WRF and baseline renal disease were associated with higher mortality |
| Khan et al. (SOLVD) | 2006 | Substudy RCT 6,640 | | Grouped with every 5 mL/min/year decrease in eGFR | Patients with rapid worsening of eGFR (>15 mL/min/year) were related to a 5.63-fold increase of mortality compared with those with slow worsening (<15 mL/min/year) |
| Iglesias et al. | 2008 | Cohort | 682 | ≥0.5 mg/dL increase of serum creatinine | 13.2-fold increased risk of mortality |
| Damman et al. (COACH) | 2010 | Substudy RCT 1,049 | | >0.3 mg/dL absolute increase of serum creatinine with >25% increase from baseline | 2.06-fold and 5.03-fold increased risk of the composite events of cardiovascular death or hospitalization for HF and all-cause death for WRF that occurred during 0–6 and 6–12 months after discharge from admission |

eGFR = estimated glomerular filtration rate; HF = heart failure; RCT = randomized clinical trial; WRF = worsening renal function.
closely related to the decrease in GFR. Developing an effective pharmacologic therapy for patients with WRF and HF is more difficult due to inconsistent results from clinical trials.

**RAAS ANTAGONISM AND WORSENING RENAL FUNCTION**

RAAS inhibition has renal protection attributable to both antihypertensive and antiproteinuric effects. In HF, decreased cardiac output and vasoconstriction by subsequent sympathetic activation result in a decreased GFR. RAAS activation can cause glomerular vasoconstriction. Subsequently, renal blood flow decreases, but the constriction of the efferent arterioles maintains the intraglomerular pressure and GFR. The administration of RAAS antagonists induces vasodilatation and the decrease in hydraulic pressure and GFR. In this setting, a small decrease in systemic arteriolar pressure can go beyond the autoregulatory capacity and induce AKI. Although RAAS antagonism can decrease GFR pathophysiologically, whether WRF is related to RAAS antagonism or how much of it is related to poor prognosis is unclear.

Clark et al. have investigated the impact of RAAS inhibition-related WRF on the prognosis of patients with left ventricular systolic dysfunction using a meta-analysis including 5 randomized clinical trials (RCT) of HFrEF. The included studies used the unified definition of a decrease in GFR of 20–30% or an increase in creatinine level of >0.3 mg/dL from baseline at 2 weeks. WRF occurs more frequently in patients with RAAS inhibition and is related to higher mortality in both the RAAS inhibition group and the control group. However, mortality benefits from RAAS inhibition were greater in patients with WRF than in those without WRF, indicating that clinicians should not defer the administration of RAAS inhibitors unconditionally even in the setting of WRF. One important limitation of the investigation of the impact of RAAS inhibition-related WRF on prognosis is that WRF frequently occurs in patients with HF even without RAAS inhibitors, and the WRF related to RAAS inhibition cannot be differentiated from WRF resulting from HF itself. In patients with HFrEF, the HF guidelines have recommended initiating RAAS inhibitors as soon as possible and emphasizing the pre-discharge optimization of pharmacologic therapy in patients with acute HF. Although major clinical trials of RAAS inhibition have excluded patients with moderate to severe renal insufficiency, results from observational data have suggested the benefits of RAAS inhibition in patients with HFrEF and moderate to severe renal insufficiency.

RAAS antagonism had significant survival benefits in patients with HFrEF, whereas only a modest effect has been observed in patients with HFpEF without any proven advantage in the overall survival. In that context, WRF related to RAAS antagonism in patients with HFpEF should be dealt with more cautiously. Beldhuis et al. have investigated the difference in RAAS-antagonism-related WRF between the patients with HFrEF and those with HFpEF including the eight RCTs. Results showed that a greater risk of mortality from RAAS-antagonism-related WRF has been observed in patients with HFpEF than in those with HFrEF. However, the benefits of RAAS antagonism may offset the effect of WRF in patients with HFrEF.

**ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITORS AND RENAL OUTCOME**

The Prospective Comparison of ARNi with ACE-I to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial has demonstrated that angiotensin
receptor-neprilysin inhibitors (ARNI) have a more superior effect than angiotensin receptor blockers (ARB) in patients with HFrEF.\(^{51}\) No significant difference has been observed in the incidence of significant WRF (end-stage renal disease, ≥50% decrease in eGFR from baseline or decrease in the eGFR between 30 and <60 mL/min/1.73 m\(^2\)) between both groups administered with ARNI and angiotensin-converting enzyme inhibitors (ACEI). However, the ARNI group showed a lesser degree of eGFR decrease than that of those in the ACEI group (−1.61 vs. −2.04 mL/min/1.73 m\(^2\)/year, \(p<0.001\)). Conversely, urine albumin to creatinine ratio increased significantly in patients administered with ARNI compared with those administered with ACEI.\(^{52}\) The underlying mechanism would be dilatation of the afferent arteriole and increased renal perfusion, which can explain the occurrence of both preserved eGFR and increased proteinuria. These paradoxical responses have also been observed in the Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) trial, which tested the effect of ARNI in patients with HFpEF.\(^{53}\) In the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON) trial including 4,822 patients with HFpEF (left ventricular ejection fraction [LVEF] ≥45%), a significant renal adverse event (death from renal failure, end-stage renal disease, or decrease in eGFR by ≥50% from baseline) has been observed less in patients administered with ARNI than in those administered with ARB (1.4% vs. 2.7%, \(p<0.001\)), indicating that the renal protective effect was clearly seen in patients with HFpEF.\(^{49}\)

The renal protective effect in patients with only CKD without HF should be investigated further. The United Kingdom Heart and Renal Protection-III (UK HARP-III) trial tested the effect of ARNI on kidney function, albuminuria, blood pressure, and N-terminal pro B-type natriuretic peptide (NT-proBNP) level compared with ACEI in patients with CKD (eGFR 20–60 mL/min/1.73 m\(^2\)) and without HF.\(^{54}\) ARNI showed a similar effect on renal function and albuminuria to irbesartan over a 12-month period. However, patients administered with ARNI showed lower blood pressure and NT-proBNP levels compared to those administered with ACEI. The reason why ARNI had not shown distinct renal protection in patients with CKD and no HF is unclear. The negative results in this trial may be attributed to the relatively short follow-up duration, and further investigation on the effect of ARNI in patients with CKD is needed.

**SODIUM-GLUCOSE CotRANSPORTER-2 INHIBITORS IN HF AND KIDNEY DISEASE**

The sodium-glucose cotransporter-2 (SLT2) inhibitors, which were developed as an anti-hyperglycemic drug, showed a reduction in major cardiovascular events and the progression of renal dysfunction in high-risk patients with type 2 diabetes mellitus (DM).\(^{55-58}\) The major benefit from the SGLT2 inhibitors in those clinical trials was the reduced hospitalization rate for HF. Subsequent clinical studies, which included patients with HF with or without DM, have revealed that SGLT2 inhibitors can significantly reduce hospitalization for HF and cardiovascular death and have shown favorable renal outcomes to slow the progression of renal dysfunction (Table 4).\(^{59-65}\) The mechanism of renal protection by SGLT2 inhibitors is thought to decrease sodium reabsorption in the proximal tubule and reduce intraglomerular pressure through the vasoconstriction of the afferent arterioles.\(^{66-67}\)

The use of SLGT2 inhibitors has become an important pharmacologic treatment for patients with HFrEF and has also shown a favorable renal effect on these populations. The Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) trial has enrolled
4,744 patients with HFrEF with or without DM. 89) Dapagliflozin showed a 26% reduction in the relative risk for the composite of worsening HF and cardiovascular death. The DAPA-HF trial has included patients with an eGFR of >30 mL/min/1.73 m², and dapagliflozin was also associated with the slow progression of renal dysfunction compared with those with placebo (decline in eGFR, −1.09 vs. −2.85 mL/min/1.73 m², p<0.01). 61) The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction (EMPEROR-Reduced) trial has tested another SGLT2 inhibitor, empagliflozin, in patients with HFrEF and an eGFR as low as 20 mL/min/1.73 m². 40) Empagliflozin was found to reduce the composite event of cardiovascular death and hospitalization for HF by the relative risk of 25%. The effect of the drug on renal function has been analyzed based on the composite kidney outcome of chronic dialysis, kidney transplantation, reduction in eGFR of ≥40%, and sustained eGFR of <15 mL/min/1.73 m² (in the case of a baseline eGFR of >30 mL/min/1.73 m²) or sustained eGFR of <10 mL/min/1.73 m² (in the case of a baseline eGFR of <30 mL/min/1.73 m²). Empagliflozin reduced the composite renal events by half (HR, 0.5; 95% CI, 0.32–0.77) compared with placebo, and the decline in the eGFR was also significantly lower in patients administered with empagliflozin (eGFR change per year: −0.55±0.23 vs. −2.28±0.23 mL/min/1.73 m², p<0.001).
The recently published results from the Empagliflozin in Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) trial have revealed that empagliflozin had clear benefits of reducing the composite events of cardiovascular death and hospitalization for HF (HR, 0.79; 95% CI, 0.61–0.88) in patients with HFrEF (LVEF >40%). Unlike HFrEF, no significant difference in the incidence of adverse renal events has been observed between patients with empagliflozin and placebo, although the decline in eGFR was low in patients with empagliflozin (eGFR change per year: −1.25±0.11 vs. −2.62±0.11 mL/min/1.73 m², p<0.001). Why the benefit of empagliflozin on renal function, which has been proven in the trials of HFrEF and CKD, was attenuated in patients with HFpEF is unclear. Packer et al. have reported a new analysis of renal outcomes with the revised definition that used a 50% drop in eGFR instead of 40% and included renal death to exclude transient and rather mild forms of renal insufficiency. The reduction in renal adverse events was changed from 5% to 22% but was not significant. Interestingly, in the patients with an ejection fraction (EF) of ≥60%, empagliflozin was rather associated with the 24% increased risk of adverse renal events, while the biggest advantage was observed in patients with an EF between 40% and 50%. The effect of empagliflozin on cardiovascular outcome was observed to be blunted as the EF increases in the EMPEROR-Preserved study, and adverse renal events were also suggested to affect the cardiovascular outcome in patients with high EF. Further investigation on the associations among cardiovascular outcomes, renal outcomes, and EF in patients with HFpEF is needed.

Sotagliflozin has stronger SGLT1 inhibitory properties than other SGLT2 inhibitors. Its effect was investigated in the Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure (SOLOIST-WHF) and Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease (SCORED) trials. SOLOIST-WHF enrolled patients who were hospitalized for HF and had a previous history of type 2 DM. Sotagliflozin showed a 33% reduction in the composite outcome of cardiovascular (CV) death, hospitalization for HF, and urgent visits for HF but did not present any differences in the renal outcomes. The SCORED trial targeted patients with type 2 DM and CKD (eGFR, 20–60 mL/min/1.73 m²). It also failed to show the superior renal outcome, presenting no difference in the composite events of ≥50% decline in eGFR from baseline or an eGFR of <15, long-term dialysis, and renal transplantation (HR, 0.71; 95% CI, 0.46–1.08). Unlike the previous trials of SGLT2 in patients with CKD and no HF investigating renal outcome as a primary endpoint, the primary endpoint in SCORED was defined as CV outcome (the composite cardiovascular outcome of CV deaths, hospitalizations for HF, and urgent visits for HF), which was reduced by 26% with sotagliflozin versus placebo. Because both trials of sotagliflozin were terminated early due to loss of funding, they could not complete the intended follow-up duration. Thus, no clear benefit in renal outcome from the two studies of sotagliflozin was found, which may not be conclusive; further research is needed.

SGLT2 inhibitors often induced an acute and reversible decrease in eGFR in clinical trials, which is often referred to as “initial dip.” This initial dip usually occurred within several weeks from the initiation and return to baseline over time. Long-term trajectory of eGFR and AKI was not different regardless of the presence of the initial dip and its magnitude. The analysis of the Efficacy of Ertugliflozin on Cardiovascular and Kidney Outcomes (VERTIS-CV) trial showed that the tertile with the largest initial dip at 6 months presented the lowest subsequent eGFR slope over time in patients with type 2 DM and CV disease, indicating that the initial dip of eGFR may reflect their protective mechanism of action. The initial dip after the initiation of the SGLT2 inhibitor should not be considered as a barrier for the wide utilization of the drug.
RENNAL PROTECTION IN THE PHARMACOLOGIC TREATMENT OF HF

Improvement in cardiac function itself helps in the preservation and improvement of renal function in patients with HF. Data from the Interagency Registry for Mechanically Assisted Circulatory Support (IMTHERMACS) showed improved renal function determined based on serum creatinine and blood urea nitrogen levels in patients who used left ventricular assist device and in those with moderate-to-severe renal function. Improvement of renal function occurred within 1 month and persisted for over 2 years.\(^2\) Data from cardiac resynchronization therapy have also demonstrated improved LVEF and eGFR in patients with moderate renal insufficiency (eGFR, 30–59 mL/min/1.73 m\(^2\)).\(^{73}\)

Pharmacologic treatments of HF are closely related to renal function. ACEI and ARB have been shown to reduce proteinuria and delay the progression of renal dysfunction in patients with CKD, and they also have unequivocal evidence of improving survival of the patients with HFrEF.\(^{42,43}\) Premature discontinuation of the drug due to renal insufficiency is one of the pitfalls in managing patients with HFrEF. Obviously, patients with baseline renal insufficiency are prone to experience WRF during the initiation and titration of RAAS inhibitors, but these high-risk patients also can gain greater benefits from RAAS inhibitors.\(^{41}\) Furthermore, WRF after the initiation of RAAS inhibitors occurs during the early period, and renal function tended to stabilize after a few weeks.\(^{76}\) The threshold of the acceptable decline of eGFR after RAAS inhibition is still challenging in patients with HFrEF. An analysis of the SOLVD trial has revealed that enalapril showed a significant mortality benefit with up to a 15% of eGFR decline and protection against hospitalization for HF with eGFR decline of up to 40%.\(^{77}\)

Based on the results of the PARADIGM-HF trial and subsequent studies, ARNI became the first-line therapy in treating patients with HFrEF.\(^{42,43,51}\) In addition to the benefits in CV mortality and symptom of HF, ARNI presented incremental benefits of delaying the deterioration of renal function over ACEI (or ARB) in patients with HFrEF. In the PARAGON-HF trial, ARNI was not statistically superior to ARB regarding CV outcomes in patients with HFrEF, but the renal protective effect was also observed despite the higher incidence of hypotension in the ARNI group.\(^{49}\) The PARAGON-HF trial has enrolled patients with LVEF ≥45%, and ARNI may provide a therapeutic option in renal protection among these patients. Further study will be necessary.

The benefits of SGLT2 inhibitors are not only limited to patients with DM. With the growing evidence, the utility of SGLT2 inhibitors is a potential pharmacologic therapy for patients with HFrEF, HFP EF, CKD, and CRS.\(^{32,43,78,79}\) In patients with HFrEF, SGLT2 inhibitors became the first-line therapy according to the guidelines from major societies of HF.\(^{42,43}\) A recent clinical trial of HFP EF has proven the benefit of empagliflozin on both cardiac and renal functions in patients with HFP EF.\(^{65}\) The upcoming studies, including the Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure (DELIVER) trial and the potential for improving cardiorenal outcomes by sodium-glucose cotransporter-2 inhibition in people with chronic kidney disease (EMPA-CKD) trial, will give us a more clear understanding of the cardiorenal protective effects of SGLT2 inhibitors.\(^{80,81}\)
CONCLUSIONS

The hemodynamic, neurohormonal, and biochemical interactions between the heart and the kidneys make these two organs closely related. Baseline renal function is an important risk predictor for the prognosis of patients with HF regardless of their LVEF. WRF is one of the most commonly encountered problems in treating patients with HF. WRF can occur according to the deterioration of heart function as well as the fundamental pharmacologic therapies of HF, including ACEI, ARB, or ARNI. Data from previous studies have indicated that WRF is related to poor prognosis in patients with HF. However, not all WRF is related to poor prognosis, and various clinical scenarios can be possible. WRF related to RAAS inhibitors is frequently observed in patients with HF, and modification of pharmacologic therapy in these cases should be made along with the assessment of risk and benefits, especially in patients with HFrEF. SGLT2 inhibitors, a recently validated therapy in HF, showed a favorable effect on both the heart and kidneys. Upcoming data may guarantee a wider utilization of this drug in patients with HF as regards cardiorenal protection.

Renal insufficiency is frequently observed in patients with HF and is related to poor prognosis across all ranges of LVEF. The effort to define an actual renal injury in patients with HF will facilitate the clinical investigations of CRS to determine the area of uncertainty and to accurately predict the patients' renal outcomes. Improving heart function can be important in preserving renal function but is not enough regarding the unsatisfactory prognosis of patients with HF. The evidence from recent clinical trials, including ARNI and SGLT2 inhibitors, provides us with more effective treatment options and clinical insight into cardiorenal protection in patients with HF.

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