Perspective

Can sacubitril/valsartan become the promising drug to delay the progression of chronic kidney disease?

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1 Introduction

Chronic kidney disease (CKD) often coexists with or is a complication of cardiovascular disease. Previous studies have shown that CKD increases the risk of cardiovascular death and all-cause death and was considered to be a risk equivalent of coronary heart disease.[1,2] Adjusted for confounders, decreased glomerular filtration rate (GFR) and increased albuminuria are both independent risk factors for cardiovascular events.[3,4] The risk for cardiovascular death linearly increases with the decline of GFR in a certain range (< 70 mL/min per 1.73 m²) and the increase of albuminuria without a threshold effect.[3]

Many complicated pathophysiological mechanisms are involved in the crosstalk of kidney and heart failure (HF), i.e., renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system and natriuretic peptide system (Figure 1). Activation of RAAS causes water and sodium retention, volume overload, ventricular remodeling, and even progression of HF.[5] In contrast, the natriuretic peptide system, including atrial natriuretic peptide, B-type natriuretic peptide and C-type natriuretic peptide, has several beneficial physiological effects, such as diuresis, natriuresis, vasodilation, counteracting RAAS and sympathetic nervous system.[6]

Sacubitril/valsartan (Sac/Val) is the combination of an inhibitor of neutral endopeptidase and angiotensin I receptor blocker. Sacubitril inhibits degradation of natriuretic peptide, angiotensin, bradykinin, and other vasoactive peptides, thereby increasing their plasma concentration. Sac/Val inhibits RAAS and meanwhile regulates natriuretic peptide system, having been demonstrated beneficial in patients with mild to moderate arterial hypertension and HF[6] (Figure 1).

Given the interaction between CKD and cardiovascular disease, a hypothesis that whether Sac/Val benefits kidney as it does to heart emerges. Here, by analyzing the paper published recently, we try to summarize the impact of Sac/Val on renal function in different population: patients with established HF and patients with advanced chronic kidney disease.

2 What’s the impact of Sac/Val on renal function in chronic heart failure?

2.1 Heart failure with reduced ejection fraction

The application of RAAS inhibitor, including angiotensin converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB), has significantly improved clinical outcome in HF patients since the 1990s.[7,8] However, the mortality and hospitalization rates of HF patients remain high, leaving a heavy burden on global health and economy.[9]

The Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure (PARADIGM-HF) trial, a multicenter randomized controlled trial, showed a 20% reduction in the risk of cardiovascular death or hospitalization for HF in patients with
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Sacubitril/valsartan treatment, compared with enalapril. Therefore, American College of Cardiology/the American Heart Association/the Heart Failure Society of America (ACC/AHA/HFSA) and European Society of Cardiology (ESC) both recommended Sac/Val as first-line treatment for patients with HF with reduced ejection fraction (HFrEF).

The PARADIGM-HF trial recruited 8,442 HFrEF patients with an estimated GFR (eGFR) ≥ 30 mL/min per 1.73 m² and followed up for 27 months. The baseline eGFR was 70 mL/min per 1.73 m² (standard deviation: 20 mL/min per 1.73 m²) and the prevalence of decreased eGFR (< 60 mL/min per 1.73 m²) was 33%. During the follow-up, there was no significant difference between Sac/Val group and enalapril group in the incidence of developing acute kidney injury (AKI) and end-stage renal disease (ESRD), which was 1.8% in Sac/Val group versus 1.9% in the enalapril group for AKI, 0.2% in Sac/Val group versus 0.4% in the enalapril group for ESRD, respectively. Nevertheless, fewer patients treated with Sac/Val reached a serum creatinine level of 2.5 mg/dL, and discontinued trial drug for renal events (P-value < 0.05 for comparison). Secondary analysis found a slower rate of decline in the eGFR with Sac/Val treatment, which was 1.61 mL/min per 1.73 m² compared with 2.04 mL/min per 1.73 m² in enalapril group (P-value < 0.001 for comparison).

Heart failure with preserved ejection fraction

Epidemiology has shown that up to half of HF patients had preserved ejection fraction (HFpEF), and the proportion is on the rise. In the Prospective comparison of ARNI with ARB on Management Of heart failure with preserved ejection fraction (PARAMOUNT) trial, 149 patients with a baseline eGFR of 67 mL/min per 1.73 m² were randomly assigned to Sac/Val treatment, and 152 patients with a baseline eGFR of 64 mL/min per 1.73 m² were assigned to valsartan group. The prevalence of insufficient kidney function (eGFR < 60 mL/min per 1.73 m²) was 38% and 45% in Sac/Val and valsartan groups, respectively. After a median follow-up of 12 weeks, comparable incidence of AKI (2%) and worsening renal function (WRF) (12%) was associated with Sac/Val treatment when compared with valsartan (5% for AKI and 18% for WRF). WRF was defined by a serum creatinine level increase of > 0.3 mg/dL and/or > 25% between two time-points. In the secondary analysis, less decline of eGFR was observed in Sac/Val group, which was 1.5 mL/min per 1.73 m² compared to 5.2 mL/min per 1.73 m² in valsartan group (P-value = 0.002 for comparison).

Another larger randomised controlled trial, Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF), observed...
4,822 HFP EF patients treated with Sac/Val or valsartan. The mean eGFR was 63 mL/min per 1.73 m² and 62 mL/min per 1.73 m² at baseline in Sac/Val and valsartan groups, respectively. Compared to patients in the control group, patients treated with Sac/Val had comparable incidence of AKI (3.72% in Sac/Val group and 4.58% in valsartan group) and ESRD (1.28% in Sac/Val group and 1.21% in valsartan group) after 35 months. Interestingly, the risk of renal composite outcome, which was death from renal failure, ESRD, or a decrease in the estimated glomerular filtration rate of 50% or more from baseline, decreased 50% in Sac/Val treatment compared to valsartan treatment. Less decline in eGFR was observed with Sac/Val treatment than that with valsartan treatment (−2.0 versus −2.7 mL/min per 1.73 m² per year). After a medium follow-up of 24 weeks, less incidence of AKI (0.3%) and less decline in eGFR (−1.47 mL/min per 1.73 m²) was associated with Sac/Val when compared to standard medical therapy (0.6% and −2.57 mL/min per 1.73 m², respectively).

At the 2020 ESC Congress, outcomes of the latest PARALLAX trial were present. Its aim was to determine whether Sac/Val compared with standard medical therapy, which includes enalapril, valsartan or placebo, could benefit HF patients with ejection fraction > 40%. After a medium follow-up of 24 weeks, less incidence of AKI (0.3%) and less decline in eGFR (−1.47 mL/min per 1.73 m²) was associated with Sac/Val when compared to standard medical therapy (0.6% and −2.57 mL/min per 1.73 m², respectively).

3 What’s the impact of Sac/Val on renal function in acute decompensated heart failure?

When it comes to more severe HF, 881 patients with acute decompensated HF were 1:1 assigned to Sac/Val and enalapril groups in PIONEER-HF (Comparison of Sacubitril-Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) trial. The baseline eGFR were 58.4 and 58.9 mL/min per 1.73 m² in Sac/Val and control groups, respectively. After eight weeks, patients treated with Sac/Val had comparable incidence of AKI (8.2% versus 8.4%), and worsening renal function (13.6% versus 14.7%), which was determined as an increase in the serum creatinine level of 0.5 mg per deciliter or more and a decrease in the estimated glomerular filtration rate of 25% or more. Since relatively short duration of follow-up, the incidence of ESRD was not mentioned.

The renal effect of Sac/Val in comparison with RAAS inhibitor was summarized in Table 1. In HFrEF and HFP EF patients, less renal events and less decline in eGFR were found to relate to Sac/Val treatment with statistically significance. Small population size and relatively short follow-up duration might prevent to spotlight some differences in the PIONEER-HF trial. It is a rational hypothesis that with long-term follow-up, renal compliance with Sac/Val could be better than RAAS inhibitor in established HF patients.

4 Can sacubitril/valsartan delay the deterioration of kidney function in CKD?

Rat models of CKD and diabetic nephropathy have shown that Sac/Val could restrict the deterioration of kidney function through its anti-oxidant, anti-inflammatory, anti-fibrotic and anti-glomerulosclerosis effects. Another canine model of experimental induced cardiorenal syndrome suggests that Sac/Val could improve left ventricular systolic function, improve mitochondrial function and decrease biomarkers of heart and kidney injury despite of comparable serum creatinine level before and after the treatment. However, whether Sac/Val could counteract the deterioration of kidney function in adult CKD patients have not been exactly validated.

Haynes, et al previously reported the renal effect of Sac/Val in patients with more advanced CKD in the UK Heart and Renal Protection (HARP)-III trial (Table 1). Their inclusion criteria were: (1) an eGFR of ≥ 45 and < 60 mL/min per 1.73 m² and the urine albumin-to-creatinine ratio (uACR) > 20 mg/mmol; or (2) an eGFR of ≥ 20 and < 45 mL/min per 1.73 m² regardless of the uACR. The mean eGFR at baseline was 34.0 and 34.7 mL/min per 1.73 m² in Sac/Val group and irbesartan group. There were no differences in the eGFR variation between Sac/Val group and control group during the follow-up. Further analysis in subgroups prescribed according to age, sex, blood pressure, magnitude of proteinuria, and cause of CKD did not make any difference, either. In fact, at any time point during the 12-month study period, eGFR in the ARNI arm was not higher than that in the ARB arm. The change in uACR was not significantly different between randomized groups after 12-month follow-up (~17.8 mg/mmol in Sac/Val group versus ~16 mg/mmol in irbesartan group).

The neutral outcome may be disappointing. However, irbesartan has already proven the renoprotective and antiproteinuric effects in type 2 diabetic nephropathy and non-diabetic advanced CKD. The UK-HARP III trial showed similar effect of Sac/Val in CKD progression and antiproteinuric effects when compared with irbesartan. Besides, the trial showed the good tolerance of Sac/Val in CKD patients even when eGFR was 20 to 30 mL/min per 1.73 m². Thus, there is a suggestion of less contraindication of kidney function in the clinical use of Sac/Val.
Table 1. Renal effect of sacubitril/valsartan in randomised controlled trials.

| Studies          | Population type | Study size | Control size | TGFR mean (mL/min per 1.73 m²) | CGFR mean (mL/min per 1.73 m²) | TAKI | CAKI | TESRD** | CESRD | Definition of WRF                      | TWRF | CWRF |
|------------------|-----------------|------------|--------------|-------------------------------|--------------------------------|------|------|---------|-------|----------------------------------------|------|------|
| PARADIGM-HF      | HFrEF           | 4,187      | 4,212        | NA                            | NA                             | 74   | 79   | 8       | 18    | ESRD or a decrease in the eGFR of at least 50% or a decrease of more than 30 mL/min per 1.73 m² from randomization to less than 60 mL/min per 1.73 m² > 0.3 mg/dL increase in creatinine in combination with an increase of more than 25% in serum creatinine between two time point | 94   | 108  |
| PARAMOUNT        | HFeP            | 149        | 152          | 66.5                          | 64.3                           | 3    | 7    | NA      | NA    | > 0.3 mg/dL increase in creatinine in combination with an increase of more than 25% in serum creatinine between two time point | 16   | 25   |
| PARAGON-HF       | HFeP            | 2,419      | 2,389        | 63                            | 62                             | 90   | 110  | 31      | 29    | A sustained reduction in eGFR by 50% from baseline (randomization) as determined by 2 consecutive post-baseline central laboratory measurements separated by ≥ 30 days | 33   | 64   |
| PARALLAX         | HFeP, HFeMF     | 1,280      | 1,284        | NA                            | NA                             | 4    | 7    | NA      | NA    | An increase in the serum creatinine concentration of ≥ 0.5 mg/dL and a decrease in the estimated glomerular filtration rate of ≥ 25% | NA   | NA   |
| PIONEER-HF       | ADHF            | 440        | 441          | 58.4                          | 58.9                           | 36   | 37   | NA      | NA    | A significant decline in eGFR (defined as ≥ 25% reduction) | 60   | 65   |
| UK HARP-III      | CKD             | 207        | 207          | 35.4                          | 35.5                           | 3    | 6    | 2       | 3     | A significant decline in eGFR (defined as ≥ 25% reduction) | 71   | 67   |

Data are presented as n. *Refers to AKI was defined as increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours or increase in serum creatinine to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior seven days or urine volume < 0.5 mL/kg per hour for six hours. **Refers to ESRD was defined by reaching an eGFR of < 15 mL/min per 1.73 m² or requiring maintenance renal replacement therapy for more than three months. ADHF: acute decompenated heart failure; AKI: acute kidney injury; CAKI: acute kidney injury in control group; CESRD: end-stage renal disease in control group; CGFR: glomerular filtration rates in tested group; CKD: chronic heart failure; CWRF: worsening renal function in control group; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; HGFR: glomerular filtration rates in tested group; HDHF: heart failure with mid-range ejection fraction; HFeP: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFeMF: heart failure with preserved ejection fraction; NA: not available; TAKI: acute kidney injury in tested group; TESRD: end-stage renal disease in tested group; TGFR: glomerular filtration rates in tested group; TWRF: worsening renal function in tested group; WRF: worsening renal function.

5 Conclusions and perspectives

The CKD often coexists with heart disease and increases the risk of cardiovascular death. Sac/Val brings great benefits for HF patients and is better tolerated than RAAS inhibitor in established HF patients as to the renal effect. Animal models show the potential of Sac/Val in delaying the progression of CKD, and the randomised controlled trial showed the similar renoprotective and antiproteinuric effects of Sac/Val to irbesartan, which was approved in the clinical practice to treat hypertension with type 2 diabetic nephropathy.[28] The CKD may become a promising indication for Sac/Val, especially with cardiovascular disease. More high quality randomised controlled trials are needed to assess the issue.

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