

## Successful Treatment of Severe Heart Failure in Advanced Diabetic Kidney Disease Using Angiotensin–neprilysin Inhibitors (Sacubitril/valsartan) – Report of Two Cases with Review of Options in Literature

### Abstract

Patients with heart failure (HF) and advanced chronic kidney disease (CKD) constitute a special population that experience poor outcomes due to poor adherence to established therapies because of potential safety concerns. Role of newer agents like angiotensin–receptor neprilysin inhibitors (ARNI) in early stages of CKD is well elucidated. We report two cases of HF with reduced ejection fraction, who received ARNI in advanced stage of CKD (stage 5) and achieved remarkable outcomes in terms of quality of life and longevity.

**Keywords:** Advanced chronic kidney disease, ARNI, heart failure

### Introduction

The heart and kidney interact in a complex and bidirectional manner. Heart failure (HF) is one of the leading causes of emergency department visits and hospitalizations in patients with advanced stages of chronic kidney disease (CKD), more so in dialysis patients.<sup>[1]</sup> There is paucity of data on the efficacy and safety of established treatments of HF among advanced CKD population because such patients are excluded in the majority of clinical trials. Clinicians often get dissuaded from initiating standard therapy resulting in poorer outcomes. Synergistic collaboration of nephrologists and cardiologists may aid in implementing guidelines-directed strategy to improve patient outcomes. We report our experience of two such cases with follow-up observation, where the appropriate use of angiotensin receptor – neprilysin inhibitor (ARNI) (sacubitril/valsartan) in advanced CKD resulted in good quality of life and avoidance of recurrent hospitalization.

### Case 1

A 59-year-old male patient was referred by a cardiologist to CKD clinic for cardio-renal syndrome (CRS)

type 2 [Table 1]. He was initiated on sacubitril/valsartan earlier but had to be withdrawn due to hyperkalemia. He was started on peritoneal dialysis (PD) via Tenckhoff catheter with 1 exchange of 2L 2.5% dextrose per day which yielded a UF of 400–600 mL in 4 hours. He was restarted on sacubitril/valsartan with a low dose of 100 mg/day and was titrated up to 200 mg/day, which was well tolerated. He was continued on torsemide and metolazone, and eplerenone was withheld with appropriate dietary restriction for potassium. At 12 months of follow up, he did not require any hospitalization or develop hyperkalemia (potassium monitoring done weekly for 1 month and then monthly). His renal and cardiac function (LV EF) remained stable without further deterioration. His NT pro BNP and Trop I were always high at all evaluations [Table 1]. His quality of life improved significantly in the form of improvement in NYHA class 4 to class 2, weight gain of 5 kg and confidence of self-care. After 1 year, he defaulted on ARNI therapy and presented with HF as he sustained acute coronary syndrome (ACS). He underwent revascularization by CABG and mitral repair. He expired during the same admission due to sepsis.

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**Table 1: Clinical characteristics**

Variable	Case-1	Case-2
Age/Sex	59 Y Male	50 Y Male
Diagnosis	CKD-Stage 5, CAD, HFrEF/Diabetes	CKD-Stage 5, CAD, AF, HBSAG Positive (Viral Load 3284 Copies/mL), Neuropathic foot
Referral problem	CRS-2/hyperkalemia	CRS-2/pulmonary edema
BP mmHg	128/78	140/70
Pedal edema	Till ankle	Till knee
BMI kg/m <sup>2</sup>	28.2	36
Hb g%	12.4	9
UACR	176 mg/g	5600 mg/g
S. Creatinine, eGFR (mL/min)	5.1 mg/dL/11 mL/min	5.9/10 mL/min
Electrolytes Na/K/Cl (m eq/l)	131/3.5/97	131/3.74/96
NTproBNP (pg/l)	>25,000 (first reading), subsequent readings all above 15,000 done in follow up at 3-month interval	>25,000 (first reading) subsequent readings all above 15,000 done in follow up at 3-month interval
Trop I (ng/l)	113 (first admission), 2120 (last admission with ACS)	1731 (first admission), 140 (last admission)
ECG	Old AAMI with LBBB	Atrial fibrillation, diffuse ischaemic changes
Chest X-ray	Cardiomegaly, bilateral pleural effusion	Cardiomegaly, pulmonary edema
USG abdomen	Normal sized kidneys, ascites	Normal sized kidneys, fatty liver
2D-Echo	LV EF-30%, LV RWMA+, Severe MR (follow up 33%)	LVEF-38%/40% initially, global hypokinesia (follow up 42%)
Cardiac MRI	Severe LV global hypokinesia, non-transmural myocardial scar involving LCX, LAD territory	-
Number of hospitalizations in 1 y pre ARNI	3	3
Treatment received (RAS blockade/B blocker/MRA/antianginal/digoxin /others)	ARNI: 100 BD Torsemide 20 mg BD Carvedilol 10 mg BD Aspirin 75 mg OD Atorvastatin 20 mg OD Nitroglycerine 2.6 mg BD Nikorandil 10 mg BD Trimetazidine 35 mg BD Allopurinol 100 mg OD Premix Insulin 15 U BD Digoxin 0.25 mg on alternate days PD 1 EXCHANGE	ARNI: 100 BD Torsemide 20 mg BD Carvedilol 20 mg BD Aspirin 75 mg OD Atorvastatin 20 mg OD Nitroglycerine 6.4 mg BD Nikorandil 10 mg BD Trimetazidine 35 mg BD Insulin glargine 30 U OD Digoxin 0.25 mg on alternate days Apixaban 2.5 mg OD Amiodarone 200 mg OD PD 1 exchange after 2 y
Follow up	Lived for 1 y: died of sepsis No hospitalization/ No hyperkalemia	Hospitalised after 2 y: initiated on Peritoneal Dialysis: never had hyperkalemia

Abbreviation: ARNI = Angiotensin receptor neprilysin inhibitor, AF = atrial fibrillation, CAD = coronary artery disease, LAD = left anterior descending territory, LCX = left circumflex, PD = peritoneal dialysis, disease RWMA = regional wall motion abnormality, LVEF = left ventricular ejection fraction

## Case 2

A 52-year-old male patient was referred by a cardiologist for CRS type 2 [Table 1] with orthopnoea due to pulmonary edema (LV EF 38%/40%). He was stabilized with two sessions of hemodialysis (HD) and then started on Sacubitril/Valsartan 100 mg/day, which was titrated to 200 mg/day and diuretics (potassium monitoring done weekly for 1 month and then monthly) with dietary restriction for potassium. His clinical condition improved

and had functional status of class 3 NYHA. He did not need any hospitalization for next 2 years and LV EF remained stable at 42%. His renal function was also stable with change in eGFR from 13 to 10 mL/min/1.73m<sup>2</sup>. He had a weight gain of 20 kg (BMI-43) during this period with worsening obstructive sleep apnoea (OSA). He was readmitted after 2 years with NYHA class 4 breathlessness and found to have serum creatinine of 8.8 mg/dL, serum potassium of 3.9mEq/L, high NTproBNP, and TropI [Table 1]. He was also diagnosed to have

hypothyroidism (TSH-133 micro iu/l) possibly related to amiodarone use. His 2D echo showed stable LV EF of 42% with regional wall motion abnormality. He was initiated on HD and later was shifted to single exchange of PD after treatment of anemia, hypothyroidism and OSA.

## Discussion

Patients with CKD are at increased risk of cardiovascular disease and often present with HF (two to three times higher risk, incidence around 15% in late stage).<sup>[1,2]</sup> The risk of HF increases with worsening proteinuria and declining GFR independently.<sup>[3]</sup> Conversely, patients with HF frequently have reduced kidney function (approx. 40%).<sup>[4]</sup> Regardless of whether HF begets CKD or vice versa or both developing and progressing simultaneously, prognosis of patient with HF and CKD stage 4–5 is poor.<sup>[5]</sup> It is estimated that the survival rates in CKD stages 4–5 with HF are below 40% at second year<sup>[4,5]</sup> and are far worse in a small subset of CKD population with heart failure with reduced ejection fraction (HFrEF).

HF in CKD is often underdiagnosed and could be confused with fluid overload, anemic symptoms, or uremic manifestation as there is lot of overlap in symptoms. To compound the problem, around 50–75% of CKD patients have structural heart disease as LVH on 2D echo, which may or may not be related to symptoms of dyspnea. Biomarkers like N terminal brain natriuretic peptide (NT-BNP) and Troponin I are more prognostic than diagnostic though serum ST2 could be a tool to assess HF better in CKD.<sup>[1]</sup>

Treatment for HF in CKD is based on two broad principles: (i) to target pathophysiological links between CKD and HF to prevent HF and (ii) to improve overall prognosis in established HF.<sup>[6]</sup> The main objectives of HF therapy in CKD (as well as in non-CKD) patients are to decrease the preload and after load and to reduce LVH, treat myocardial ischemia, and inhibit neurohumoral hyperactivity, especially the sympathetic nervous system and RAS (renin angiotensin system). The anatomical substrates of HF (LVH, vascular calcification, etc.) develop early in CKD and strategies to prevent it have not been rigorously tested in the CKD populations. RAS inhibition is the cornerstone of HFrEF treatment. The fear of deterioration of renal function and hyperkalemia results in reluctance to contemplate its use in advanced CKD among physicians, cardiologists, and even nephrologists and is often associated with treatment discontinuation of RAS inhibition. This decision to discontinue RAS blockade is especially disadvantageous in HFrEF patients with CKD, who are at particularly high risk of adverse cardiac and renal outcomes. These patients also have the greatest absolute risk reduction with RAS inhibition.<sup>[7,8]</sup> A trend of stable serum creatinine is a far better predictor of a good outcome than a single value even if there is initial rise of serum creatinine not exceeding 20% from baseline.

Nepriylsin inhibition with ARNI is the most recent treatment that plays a key role in not only improving outcomes in HF but also favorably impacting CKD progression<sup>[9,10]</sup> Switching therapy in an eligible HFrEF patient from a RAS-blocker to ARNI has been reported to induce beneficial reverse remodeling of metrics of systolic and diastolic function (rise of EF 10%) and renal function stabilization (reversal of type 2 CRS), which makes it the most preferred drug in this setting. Even overtly proteinuric CKD patients on neprilysin inhibition had reduced cardiac biomarkers levels more than in patients on irbesartan.<sup>[11]</sup> Experiments using 5/6 nephrectomy models suggested that NEPI reduces proteinuria and histological markers of kidney damage more than ACE inhibition alone.<sup>[12]</sup> ARNI has additional BP lowering properties, which is a common problem in CKD population and may play a role in reducing the progression of CKD. Hence, ARNI is not only cardioprotective but also renoprotective.

The pathophysiologic mechanisms responsible for benefits of ARNI remain unclear. The benefit analysis of ARNI is done at three spheres: effect on biomarkers, cardiac reverse remodeling, and effect on functional capacity. Nepriylsin inhibition enhances circulating levels of biologically active natriuretic peptides and other vasoactive peptides that may have favorable vasodilatory, antifibrotic, and antihypertrophic effects. Favorable effects of neprilysin inhibition are also due to improvement in myocardial remodeling (assessed by focused echocardiographic end points like left ventricular end-diastolic and end-systolic volumes, left atrial volume, mitral E/e' ratio) and wall stress though one may fail to demonstrate significant difference in contractile properties as assessed (left ventricular ejection fraction and global longitudinal strain) or ventricular–vascular coupling (Ea/Ees ratio) as was the case in our patients.<sup>[13]</sup>

It is well known fact that one-third of HF patients die within 1 year after diagnosis with greatest risk of mortality in first three months.<sup>[14]</sup> Similarly, nearly 30% patients of HF patients need hospital readmission in 1 year. Such high mortality and readmission rates are favorably influenced by goal directed therapy with use of ARNI.<sup>[8]</sup> ARNI minimizes functional deterioration and positively impacts NYHA functional class.

As majority of patients in late stages of CKD are resistant to diuretics for volume control, fluid removal is better achieved with either HD or PD.<sup>[15]</sup> Patients in this advanced stage of CKD benefit more with frequent dialysis (slow long nocturnal HD) or PD for mitigating HF. Several studies have shown that PD in HF significantly improves NYHA Class and reduces the number of days hospitalized for HF.<sup>[16]</sup> Myocardial stunning during HD as assessed by cardiac PET scans is linked to further decline in LVEF of almost 10% a year increasing risk of CV death further. Ultrafiltration by PD in this context is found to be safer.

Patients with HF tend to do better with PD compared to HD in long term. Such approach can be utilized to supplement slow ultrafiltration, prevention of hyperkalemia, improving or stabilizing LV function, and preserving residual renal function.

Usage of ARNI is promoted as a grade 1a recommendation in recent guidelines for treating HF<sub>r</sub>EF among patients with eGFR >30 ml/min.<sup>[8,9,17]</sup> It is suggested in advanced kidney disease to initiate with low dose (50 mg twice) and titrate up to 100 mg twice daily in the maintenance phase, though one may use even 200 mg twice daily if tolerated.<sup>[18]</sup> We noted similar results in both our patients who were at highest risk for death and hospitalization due to diabetic status, triple vessel disease, reduced EF, and advanced CKD. ARNI positively impacted the quality of life in both of our patients (first returned to his outdoor business activity and the second was independent for his daily self-care).

## Conclusion

HF with CKD is riddled with diagnostic dilemmas and poses multidimensional challenges like hyperkalemia, deterioration of renal function, and diuretic resistance. Multipronged strategy including PD, newer agents for potassium control like patiomer or sodium zirconium silicate may allow the use of agents like RAS inhibitors, ARNI, MRA (mineralocorticoid receptor antagonist) in these patients. ARNI looks promising as a treatment option that could reduce the risk of HF safely even among patients with CKD stage V. Our limitation is to draw inference from only these two well-followed patients. However, the utility of such therapy has to be scrutinized carefully by real world experience involving a sizeable number of patients in a multicentric-pooled data having long-term follow-up for reliable assessment of such therapeutic intervention. Our report suggests that one should not deprive these high-risk patients the benefits of ARNI by contemplating its use even in late stages of advanced CKD with close monitoring.

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## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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