# Use of Angiotensin Receptor Neprilysin Inhibitor in Patients on Maintenance Hemodialysis with Reduced Cardiac Ejection Fraction

## Real-World Experience From a Single Center

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Original Paper

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**Keywords**. hemodialysis, heart failure, angiotensin receptor neprilysin inhibitor, reduced ejection fraction

**Introduction.** Angiotensin receptor neprilysin inhibitor (ARNI) has been recommended by major guidelines as the leading therapy for heart failure with reduced ejection fraction (HFrEF). But little is known about its safety and effectiveness among maintenance hemodialysis patients with HFrEF in real-word practice.

**Methods.** An observational study was conducted among maintenance hemodialysis patients who received ARNI at our dialysis center. Enrollment commenced on June 1, 2018; and follow-up was completed on May 31, 2019.

**Results.** A total of 110 patients included in the study (age: 54.2 ± 14.8 y, 59% males). After 12 months of treatment, the average ARNI daily dose increased from 135 mg to 308 mg. The mean NT-pro-BNP concentration at baseline was 14455 pg/mL and 6435 pg/mL after 12 months of treatment ($P < .001$). The left ventricular ejection fraction improved (35.1 vs. 49.8%, $P < .001$) over the 12 months, while left ventricular end-diastolic diameter, left ventricular mass index, left ventricular end-systolic diameter, and left atrial diameter also changed significantly (167.8 vs. 154.9 g/m, $P < .001$; 52.2 vs. 51.5 mm, $P < .05$; 35.9 vs. 36.9 mm, $P < .001$; 42.2 vs. 40.3 mm, $P < .001$). Furthermore, we found the quality of life and the NYHA symptom severity class improved significantly ($P < .001$). Kaplan-Meier analysis indicated that higher dose of ARNI and less vintage of HD were associated with best survival.

**Conclusion.** In our study, ARNI appeared to be safe, relieved heart failure symptoms, and improved the scores of KCCQ physical and social activities in hemodialysis patients in real-world practice.

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## INTRODUCTION

Heart failure (HF) is a well-known frequent complication in patients undergoing maintenance hemodialysis. It has been reported that almost one-third of hemodialysis patients experienced HF after commencing dialysis treatment, recurring in 50% of them during dialysis. Additionally, even patients with no history of heart failure have a 25% probability of experiencing heart failure during dialysis.[1-4]

Recently, sacubitril/valsartan, an angiotensin receptor neprilysin inhibitor (ARNI), has been shown to effectively reduce hospitalization time and mortality in patients suffering from heart failure with reduced ejection fraction (HFrEF).[5] Due to the inhibition of neprilysin, the levels of natriuretic

peptides, bradykinin, and adrenomedullin are consistently elevated, resulting in a protective effect on cardiofunction.[33-35] However, the safety and tolerability of this new medication class in maintenance hemodialysis (HD) patients remains unclear. Furthermore, subgroup results in numerous major trials have suggested that Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs) can benefit patients with chronic kidney disease (CKD) stage 3 or higher, similar to or even better than the benefit to the general trial population.[6,7] Although current guidelines do not discuss the use of ARNI therapy in patients with CKD stage > 3, its beneficial effect may extend to patients on hemodialysis, without unwarranted nephrotoxic effects. Accordingly, our purpose was to investigate the safety and efficacy of ARNI treatment among hemodialysis patients at a single medical center in China.

## MATERIALS AND METHODS

### Patients

This single-center observational study was conducted in the 2nd Hospital of Tianjin Medical University, PR China, and attempted to investigate the safety and efficacy of sacubitril/valsartan in treating maintenance hemodialysis patients with HFrEF. The definition of HF used in this study was based on the European Society of Cardiology (ESC) guideline: presentation of typical HF symptoms accompanied by signs of a structural and/or functional cardiac abnormality.[13] An HFrEF patient was defined as a patient with New York Heart Association (NYHA) class II, III, or IV HF symptoms with a left ventricular ejection fraction (LVEF) less than 40%. The study was conducted at our hospital's dialysis center between June 1, 2018 and May 31, 2019. The inclusion criteria were patients on maintenance hemodialysis for over three months whose age > 18 years with LVEF ≤ 40% diagnosed via echocardiography and of NYHA functional class II-IV. The exclusion criteria were those who underwent hemodialysis treatment < 3 months, a previous history of heart or lung transplantation, inability or refusal to sign consent, known significant and unrepaired coronary artery or valvular disease (such as unstable angina pectoris ischemic cardiomyopathy), congenital heart disease, COPD Gold IV, history of angioedema (drug-related or otherwise), any hospital admission/discharge related to HF within two weeks prior to participating in the study, history of malignancy of any organ or system, or participation in another clinical study. This study was conducted according to the ethical standards of the institutional and national research committee alongside the 1964 Helsinki Declaration and its later amendments (No. KY2018K091). All patients included in this study provided their written informed consent.

### Follow-up

If ACEIs or ARBs were in use, these drugs were discontinued following enrollment. Patients previously on ACEIs before the study were informed to wait 36 hours from taking their last dose of ACEIs until taking their first dose of sacubitril/valsartan. All other patients were given sacubitril/valsartan without a prior clearance period. Following ARNI initiation, patients returned for study visits approximately every two weeks during hemodialysis and drug dose titration. The baseline information, including medical history, medication, residual urinary output, as well as dialysis-associated parameters were collected. The follow-up period lasted for 12 months until the end of May 2019. Patients received hemodialysis three times per week with a target Kt/v of no less than 1.2. This was calculated using the Daugirdas formula. At the time of clinical examination, all patients were at their prescribed dry weight ± 0.5 kg. Additionally, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) was tested before dialysis, at baseline, 6 months and after 12 months of the study. Furthermore, Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to evaluate quality of the lives of the patients both at baseline as well as 12 months after treatment.

### Echocardiographic Studies

The same physician at both baseline and 12 months of treatment performed all standardized transthoracic echocardiographic evaluations. The Left ventricular end-diastolic diameter (LVDD), left ventricular end-systolic diameter (LVSD), and left atrial anteroposterior dimension (LAD) were measured by using para-sternal views. Meanwhile, biplane Simpson's method was used to calculate the LVEF on the apical 4-chamber and 2-chamber views.[8]

### Outcomes

The primary outcome of this study was defined as death from cardiovascular causes or first unplanned hospitalization for heart failure. Furthermore, information about deaths only from cardiovascular causes, deaths from any other causes, and unplanned rehospitalizations for heart failure were recorded.

### Statistical Analysis

Continuous variables were expressed as mean ± standard deviation. If the variable was not normally distributed, it was expressed as a median (range, minimum and maximum). Categorical variables were analyzed using the chi-square test and were expressed as frequencies (%). Confidence intervals (CIs) and P-values were two-sided. Statistical significance was set at $P < .05$. Statistical analysis was performed using SPSS for Windows version 20 (IBM Corp. Armonk, NY, USA).

## RESULTS

### Baseline Clinical Characteristics

A total of 165 patients with HF were assessed to participate in the ARNI treatment study between June 2018 and May 2019. Of these patients, 16 cases declined to participate, 6 patients were unable to consent, 12 patients did not have sufficient baseline data, and 21 patients did not complete their echocardiographic examination after 12 months of ARNI treatment. As a result, endpoint analysis was available for 110 patients (Figure 1).

The baseline characteristics of this study comprised of 110 patients are shown in Table 1. The average age was 54.2 ± 14.8 years, with male being predominant (59%). Main causes of end-stage renal disease were found to be glomerulonephritis (39%),

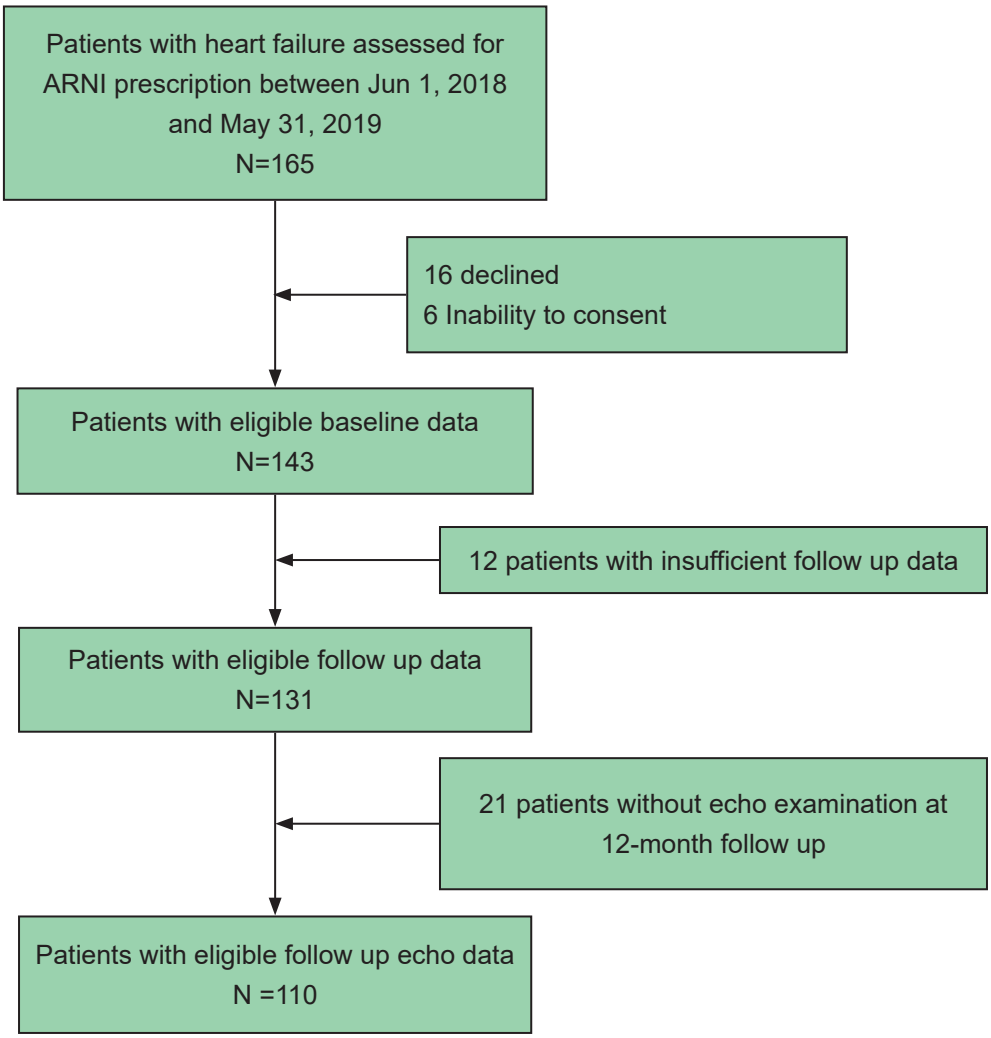


**Figure 1.** Patient Flow Chart

**Table 1.** Baseline Characteristics of the Study Patients (n = 110)

| Parameter | Sacubitril-Valsartan (number (%)) |
|---|---|
| Age, y | 54.2 (14.8) |
| Sex | |
| Male | 65 (59) |
| Female | 45 (41) |
| Body Mass Index | 24 (3.7) |
| Cause of ESRD | |
| Glomerulonephritis | 43 (39%) |
| Diabetes | 25 (23%) |
| Hypertension | 21 (19%) |
| Systematic Lupus Erythematosus | 12 (11%) |
| Unknown | 9 (8%) |
| Past Medical History | |
| Ischemic Cardiomyopathy | 13 (11.8%) |
| Old Myocardial Infarction | 6 (5.5%) |
| Stroke/TIA | 8 (7.3%) |
| Atrial Fibrillation | 9 (8.2%) |
| Medications | |
| ACEI/ARB | 102 (93%) |
| CCB | 105 (95%) |
| β-Blocker | 41 (37%) |
| Laboratory Data | |
| BUN, mg/dL | 70 (27) |
| Creatinine, mg/dL | 8.8 (3.5) |
| Potassium, mg/dL | 19 (2.7) |
| Urea Acid, mg/dL | 6.8 (1.7) |
| Urine Output, mL | 333 (262) |
| Baseline Vital Signs | |
| Systolic Blood Pressure, mmHg | 145 (20) |
| Diastolic Blood Pressure, mmHg | 84 (12) |
| Heart Rate, beats/min | 72 (9) |
| Dialysis Vintage, year | 4.7 (3.9) |

Data presented as n (%), n or mean standard ± deviation.
Abbreviations: ESRD, end stage renal disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; BUN, blood urea nitrogen.

diabetes (24%), hypertension (19%), systematic lupus erythematosus (11%), and unknown causes (7%). Ischemic cardiomyopathy was part of the medical history in 11.8% of patients, while 8.2% had atrial fibrillation, 7.3% had a stroke or TIA, and 5.5% had an old myocardial infarction. At baseline, the mean potassium level was 4.6 meq/L, and the mean NT-pro-BNP level was 14,455 pg/mL. The average dry weight was 64 kg and mean UF was 1.7 kg. The baseline mean LVEF was observed to be 35.1%, while the mean left ventricular mass index (LVMI) was 167.8 g/m, LVDD was 52.2 mm, LVSD was 35.9 mm, and LAD was 42.2 mm. Prior to commencing ARNI therapy, the prescription rates of ACEI/ARB, CCB, and beta-blocker were 92.7%, 95.4%, and 37.2%; respectively. In addition, the number of patients using diuretic, digoxin, and mineralocorticoid receptor inhibitors were 6, 12 and 4, respectively. In regard to vascular access, 64 patients had arteriovenous fistula (AVF) while 46 patients had a tunneled cuffed catheter (TCC).

## Prescription Pattern of Sacubitril/Valsartan

The mean dose of ARNI was 135 mg/d at the start of the study and 308 mg/d in the end. Based on the improvement of EF or frequency of hypotension, the dose of ARNI was reduced or increased. Figure 2 illustrates the number of patients with different doses at baseline in both the 6$^{th}$ and 12$^{th}$ months. Sixty percent of the patients received 100 mg/d as the starting dose. After 12 months, 32.7% of the patients maintained a standard dose of 400 mg/d, while 54.5% received 300 mg/d, 10% stayed at 200

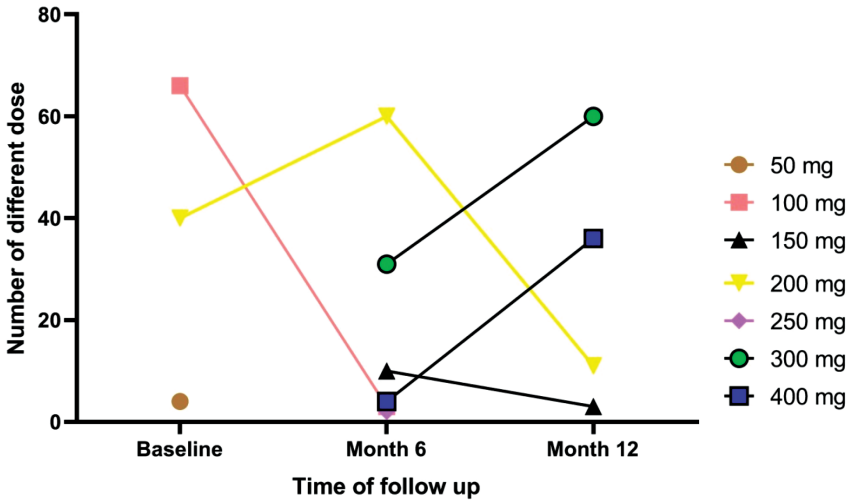


**Figure 2.** Number of Patients with Different ARNI Doses at Start, 6$^{th}$ Month, and 12$^{th}$ Month (ARNI indicates angiotensin receptor neprilysin nhibitor)

mg/d and 2.7% of the patients received less than half of the standard dose.

## Clinical Outcomes

Five patients died during the study. Among them, 3 died from heart failure, while 2 died from cerebral hemorrhage. The cumulative event rate of first unplanned hospitalization for HF was found to be 9.1% in 12 months. Table 2 shows the interval changes of echocardiographic parameters and NYHA class between baseline and the 12th month of ARNI treatment. Following 12-month treatment, a significant improvement was found in LVEF, LVDD, LVMI, LVSD, and LAD. Moreover, a significant difference was noted in a fraction of patients with NYHA II and IV when evaluating their NYHA class after 12 months of treatment (Table 2). In terms of quality of life, the mean KCCQ Scores were found to improve significantly throughout the 12 months of treatment (Table 3). However, when the KCCQ Score was evaluated at a different dose of ARNI at 12 months, no significant difference was present among the different dose within each mean KCCQ Score (Figure 3). Meanwhile, the patients' NT-pro BNP levels significantly decreased over the 12 months of treatment (Figure 4).

When the patients were divided into the AVF group and TCC group, no significant differences in the dose of ARNI among baseline, 6 months and 12 months were found (Table 4). In terms of KCCQ Scores, better improvement was noted in the AVF group than in the TCC group among symptoms (71.1 vs. 67.6, $P < .05$), symptom stability (51.5 vs. 48, $P < .05$), self-efficacy (74.3 vs. 69.7, $P < .05$), and KCCQ function score (46.1 vs. 44.2, $P < .05$) at 12 months (Table 5).

**Table 3.** Changes of KCCQ Score Between the Baseline and 12-Month Follow-up

| KCCQ Score | Baseline Mean Value | 12th Month Mean Value | *P* |
|---|---|---|---|
| Physical Limitation | 19.1 ± 5.7 | 21.1 ± 4.6 | < .05 |
| Symptoms | 66.1 ± 7.6 | 69.7 ± 7.6 | < .05 |
| Symptom Stability | 48.2 ± 6.9 | 50.1 ± 6.8 | < .05 |
| Social Limitation | 65.4 ± 10 | 69.5 ± 9.6 | < .05 |
| Self-efficacy | 68.4 ± 8.9 | 72.4 ± 8.4 | < .05 |
| Quality of Life | 65.1 ± 7.8 | 70.2 ± 9.6 | < .001 |
| KCCQ Functional Status | 42.5 ± 4.6 | 45.4 ± 4.6 | < .001 |
| KCCQ Clinical Summary | 53.9 ± 5.3 | 57.6 ± 4.9 | < .001 |

KCCQ means "kansas city cardiomyopathy questionnaire".

Factors associated with echocardiographic change, cardiovascular death or unplanned hospitalization for HF.

When a regression analysis was performed on the dose of ARNI with echocardiographic changes at 12 months, the final dose was observed to be correlated with both LVEF ($r^2 = 0.341$, $P < .01$) and left atrial diameter ($r^2 = 0.114$, $P < .01$) (Figure 5). Furthermore, univariate and multivariate Cox regression analysis were performed to evaluate the predictability of factors on unplanned hospitalization for HF, as shown in Table 6. Accordingly, urine output (Hazard Ratio = 1.003, 95% CI: 1.000 to 1.006; $P < .05$), systolic blood pressure (Hazard Ratio = 1.047, 95% CI: 1.018 to 1.076; $P < .05$), and LVEF (Hazard Ratio = 1.323, 95% CI: 1.008 to 1.737; $P < .05$) were found to be associated with higher incidences of unplanned hospitalization for HF.

In regard to the survival rate from cardiac deaths, the Kaplan-Meier analysis indicated that there were significant differences among different doses of ARNI (Figure 6) as well as among different vintages

**Table 2.** Changes of Echocardiographic and Related Clinical Data Between the Baseline and 12-Month Follow-up

| Parameter | Baseline | 12th Month | *P* |
|---|---|---|---|
| Echocardiographic | | | |
| LVEF (%) | 35.1 ± 3.3 | 49.8 ± 8.7 | < .001 |
| LVMI, g/m | 167.8 ± 54.3 | 154.9 ± 46.2 | < .001 |
| LVEDD, mm | 52.2 ± 7.7 | 51.5 ± 6.3 | < .05 |
| LVESD, mm | 35.9 ± 8.7 | 36.9 ± 7.9 | < .05 |
| LAD, mm | 42.2 ± 5.9 | 40.3 ± 5.4 | < .05 |
| NYHA Symptom Severity Class | | | |
| II | 27 (24.5%) | 58 (52.7%) | < .001 |
| III | 48 (43.6%) | 46 (41.8%) | > .05 |
| IV | 35 (31.9%) | 6 (5.5%) | < .001 |

*Data presented as n (%), n or mean standard ± deviation.*
*Abbreviations: LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LAD, left atrial diameter, NYHA, New York Heart Association.*

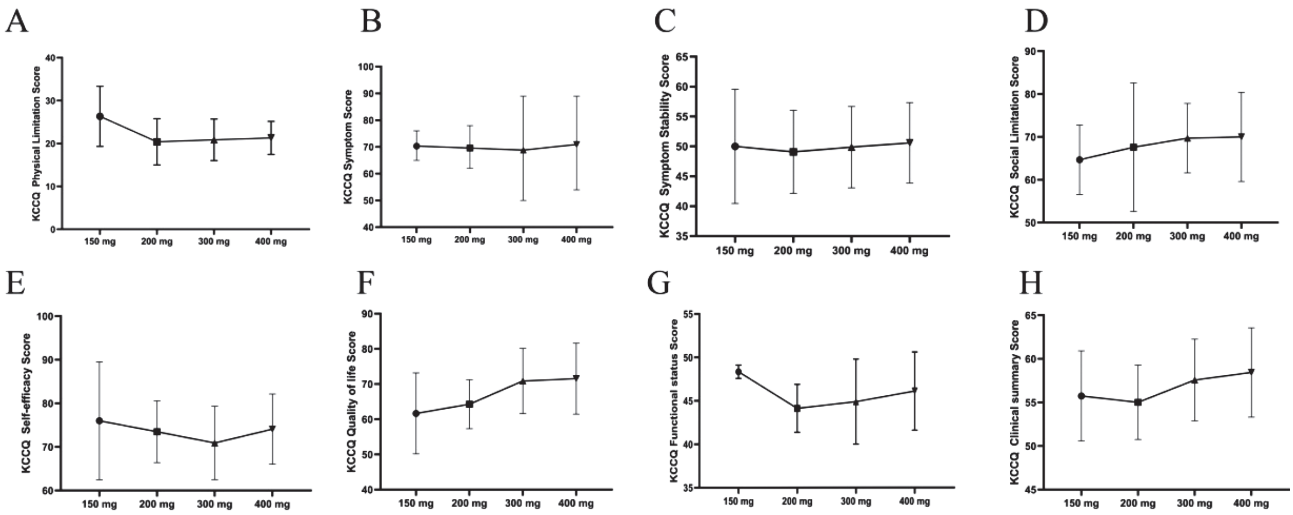


**Figure 3.** Mean KCCQ Score with different dose of ARNI at 12th month (A: Mean KCCQ Physical Limitation Score Among Different Dose of ARNI, B: Mean KCCQ Symptoms Score Among Different Dose of ARNI, C: Mean KCCQ Symptom Stability Score Among Different Dose of ARNI, D: Mean KCCQ Social Limitation Score Among Different Dose of ARNI, E: Mean KCCQ Self-efficacy Score Among Different Dose of ARNI, F: Mean KCCQ Quality of Life Score Among Different Dose of ARNI, G: Mean KCCQ Functional Status Score Among Different Dose of ARNI, and H: Mean KCCQ Clinical Summary Score Among Different Dose of ARNI)

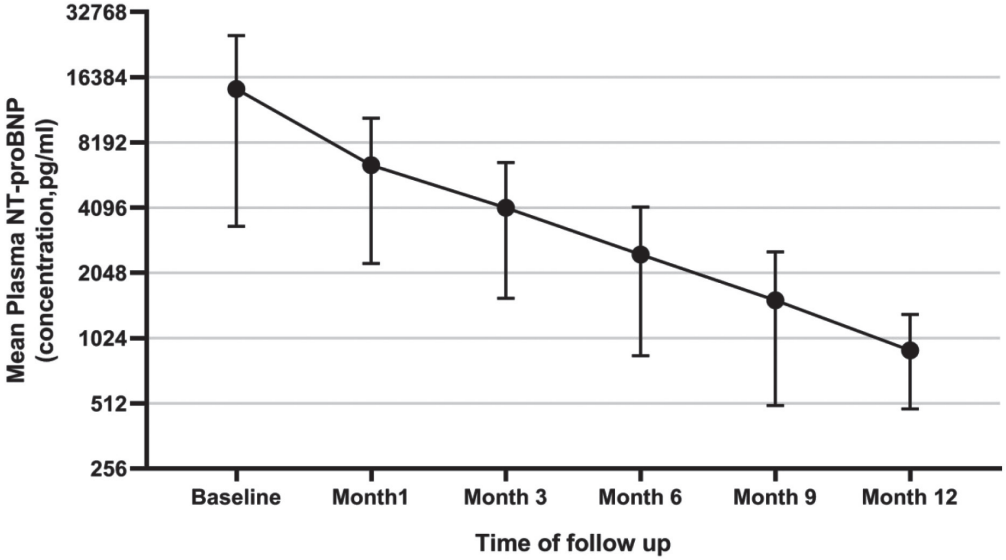


**Figure 4.** The Mean NT-pro BNP Level at Baseline, 1st Month, 3rd Month, 6th Month, 9th month, and 12th Month During the Follow-up of 12th Months

**Table 4.** Changes of Dose of ARNI Between the AVF Group and TCC Group

| Time | AVF Group Mean Dose | TCC Group Mean Dose | *P* |
|---|---|---|---|
| Baseline | 132.8 ± 49.7 | 136.9 ± 52.1 | > .05 |
| 6th Month | 235.1 ± 65.2 | 220.7 ± 60.2 | > .05 |
| 12th Month | 315.6 ± 77 | 297.8 ± 69.9 | > .05 |

Abbreviations: AVF, arteriovenous fistula; TCC, tunneled cuffed catheter

**Table 5.** Changes of KCCQ Score Between the AVF group and TCC group at 12-Month

| KCCQ Score | AVF Group (Mean Value) | TCC Group (Mean Value) | *P* |
|---|---|---|---|
| Physical Limitation | 21.3 ± 4.6 | 20.8 ± 4.7 | > .05 |
| Symptoms | 71.1 ± 8 | 67.6 ± 6.6 | < .05 |
| Symptom Stability | 51.5 ± 6.9 | 48 ± 6 | < .05 |
| Social Limitation | 70.6 ± 11 | 69.7 ± 6.8 | > .05 |
| Self-Efficacy | 74.3 ± 8.9 | 69.7 ± 6.8 | < .05 |
| Quality of Life | 70.6 ± 9.6 | 69.8 ± 9.7 | > .05 |
| KCCQ Functional Status | 46.1 ± 4.6 | 44.2 ± 4.3 | < .05 |
| KCCQ Clinical Summary | 58.3 ± 4.8 | 56.6 ± 4.7 | > .05 |

Abbreviation: KCCQ, kansas city cardiomyopathy questionnaire.

**Table 6.** Multivariate Analysis for Factors Associated with Fisrt Unplanned Hospitalization

| Baseline Characteristics | Univariate Analysis | | | Multivariate Analysis | |
|---|---|---|---|---|---|
| | Unplanned Hospitalization for HF (+) | Unplanned Hospitalization for HF (-) | *P* | HR (95% CI) | *P* |
| Age, y | 59.2 ± 15.4 | 53.7 ± 14.8 | > .05 | - | NS |
| Body Mass Index | 23.6 ± 2.36 | 24.1 ± 3.8 | > .05 | - | NS |
| Cause of ESRD | | | | | |
| Glomerulonephritis | 4 (9.3%) | 39 (90.7%) | > .05 | - | NS |
| Diabetes | 1 (4%) | 24 (96%) | > .05 | - | NS |
| Hypertension | 3 (14.3%) | 18 (85.7%) | > .05 | - | NS |
| Systematic Lupus Erythematosus | 2 (16.7%) | 10 (83.3%) | > .05 | - | NS |
| Unknown | | 8 (100%) | > .05 | - | NS |
| Past Medical History | | | | | |
| Ischemic Cardiomyopathy | 4 (30.8%) | 9 (69.2%) | > .05 | - | NS |
| Old Myocardial Infarction | 1 (16.7%) | 5 (83.3%) | > .05 | - | NS |
| Stroke/TIA | 2 (25%) | 6 (75%) | > .05 | - | NS |
| Atrial Fibrillation | 3 (33.3%) | 6 (66.7%) | > .05 | - | NS |
| Medications | | | | | |
| ACEI/ARB | 8 (7.8%) | 94 (92.2%) | > .05 | - | NS |
| CCB | 9 (8.6%) | 96 (91.4%) | > .05 | - | NS |
| β-Blocker | 3 (7.3%) | 38 (92.7%) | > .05 | - | NS |
| Urine Output, mL | 430 ± 211 | 323 ± 265 | < .05 | 1.003 (1.000 to 1.006) | < .05 |
| Baseline Vital Signs | | | | | |
| Systolic Blood Pressure, mmHg | 165 ± 19 | 142 ± 18 | < .001 | 1.047 (1.018 to 1.076) | < .05 |
| Diastolic Blood Pressure, mmHg | 82 ± 12 | 84 ± 11 | > .05 | - | NS |
| Heart Rate, beats/min | 72 ± 8 | 72 ± 9 | > .05 | - | NS |
| Dialysis Vintage, mo | 67 ± 56 | 56 ± 46 | > .05 | - | NS |
| Baseline Echocardiographic Parameters | | | | | |
| LVEF, % | 35.9 ± 2.6 | 34.9 ± 3.4 | < .05 | 1.323 (1.008 to 1.737) | < .05 |
| LVEDD, mm | 37.4 ± 9.3 | 35.9 ± 8.6 | > .05 | - | NS |
| LVMI, g/m | 164.3 ± 63.6 | 168.1 ± 53.6 | > .05 | - | NS |
| LVESD, mm | 37.4 ± 9.4 | 35.9 ± 8.6 | > .05 | - | NS |
| LAD, mm | 43.6 ± 7.2 | 42.1 ± 5.8 | > .05 | - | NS |
| Baseline NYHA Symptom Severity Class | | | | | |
| II | 2 (7.7%) | 24 (92.3%) | > .05 | - | NS |
| III | 6 (12.5%) | 42 (87.5%) | > .05 | - | NS |
| IV | 2 (6.1%) | 31 (93.9%) | > .05 | - | NS |
| Baseline NT-pro-BNP | 19569.5 ± 12505.5 | 13944.4 ± 10887.3 | > .05 | - | NS |
| Baseline Dose of ARNI | | | | | |
| 50 mg | 0 | 4 (100%) | > .05 | - | NS |
| 100 mg | 8 (12.1%) | 58 (87.9%) | > .05 | - | NS |
| 200 mg | 2 (5%) | 38 (95%) | > .05 | - | NS |

*Abbreviation: ESRD, end stage renal disease; TIA, transient ischemic attack; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; BUN, blood urea nitrogen; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LAD, left atrial diameter; NYHA, New York Heart Association; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; ARNI, angiotensin receptor neprilysin inhibitor.*

of HD (Figure 7). A higher dose of ARNI and less vintage of HD were found to be associated with best survival. However, no significant difference was found between the two vascular access groups (Figure 8).

## DISCUSSION

Similar to some studies where ARNI was used, including in CKD patients, improvements were noted in left ventricular remodeling. However, the patients in the present study were on hemodialysis for an average of five years, signifying that left ventricular remodeling occurred long before the start of the study. Moreover, ESRD is a strong risk factor in regard to cardiovascular disease.[9-11] This is further complicated by a variety of

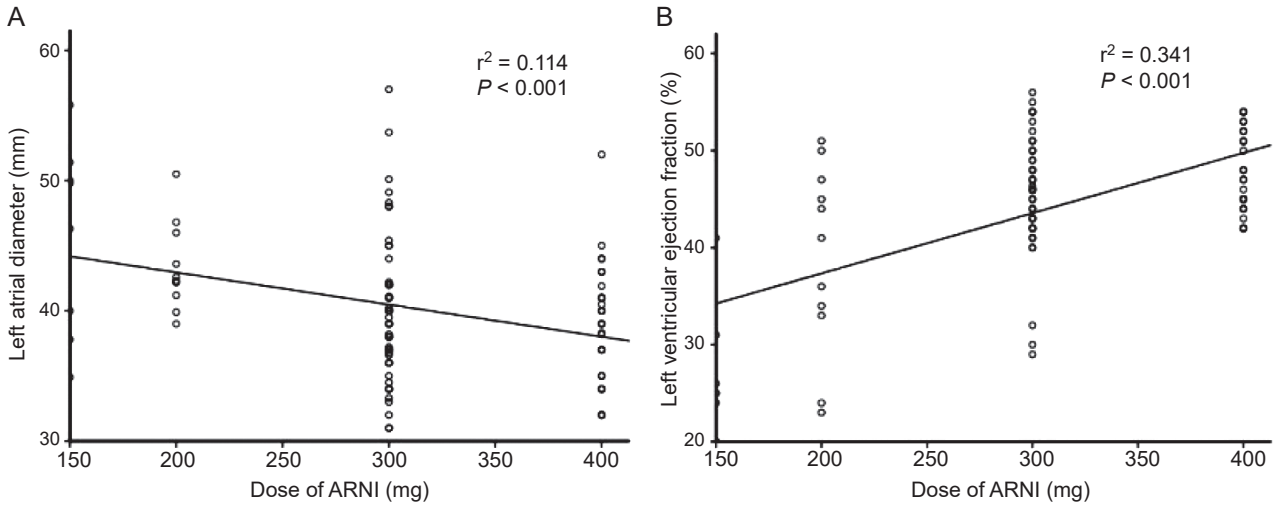


**Figure 5.** Regression Analysis of the Dose of ARNI with Echo Cardiograhic Change at 12th Month. The dose was correlated with both LVEF($r^2$ = 0.341, *P* < .01) and left atrial diameter ($r^2$ = 0.114, *P* < .01)

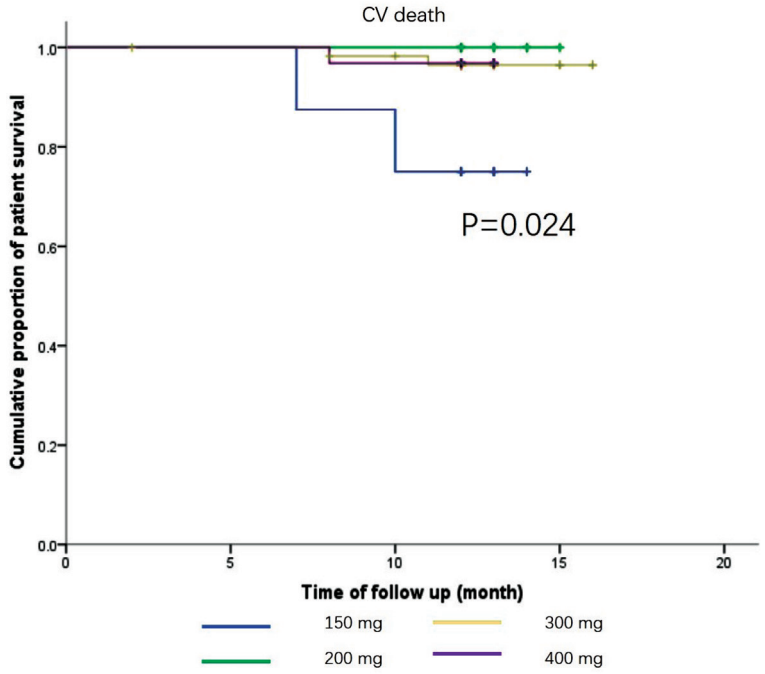


**Figure 6.** Kaplan-Meier Analysis of Patients Survival from Cardio Death Among Diferent Dose of ARNI at 12th Month (There was significant difference among patients with different dose of ARNI (*P* < .05)). The survival proprotin of patients with dose of 150 mg at 12th month was lower than the other patients with three different dose of ARNI.

pathophysiological mechanisms, including volume overload,[12] activation of the sympathetic nervous system,[13] hyperparathyroidism,[14] and oxidative stress.[15] All such factors continuously influence cardiac function, which could not be completely resolved by one year of ARNI treatment alone.

Furthermore, remodeling of the myocardium is an important step in progression towards HFrEF[17-19] and occurs in response to injury, hemodynamic changes, or neurohormonal activation. Many aspects of myocardium remodeling, including changes in cardiac geometry, function, or both, embody the reduction of LVEF.[20] In the present study, LVEF improved by the end of the study. Meanwhile, EF was found to be correlated with the dose of ARNI, suggesting that the improvement in heart function was according to a dose dependent manner.

NT-pro-BNP levels were high at the start of

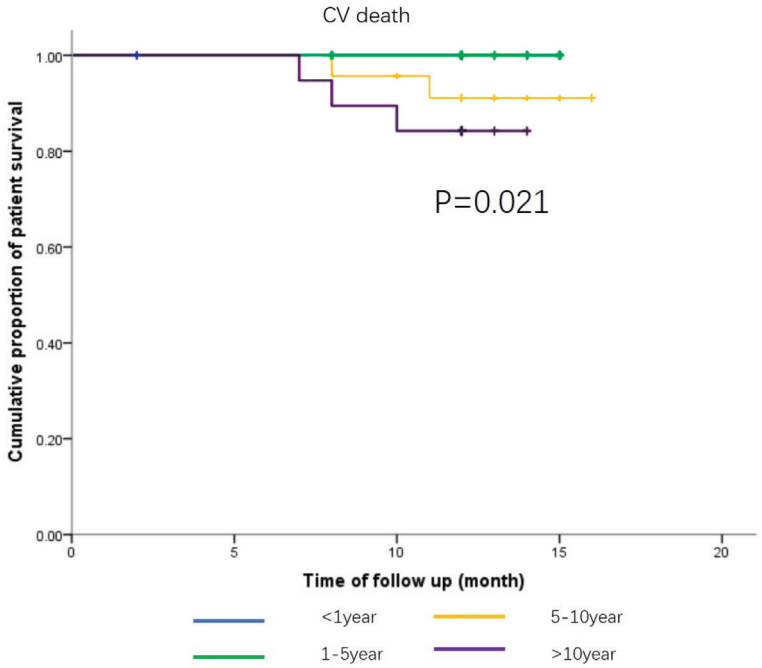


**Figure 7.** Kaplan-Meier Analysis of Patients Survival from Cardio Death Among Diferent Vintage of HD (There was significant difference among patients with different vintage of ARNI ($P < .05$)). The survival proprotin of patients with dialysis vintage > 10 years at 12th month was lower than the other patients with three different vintage of HD.

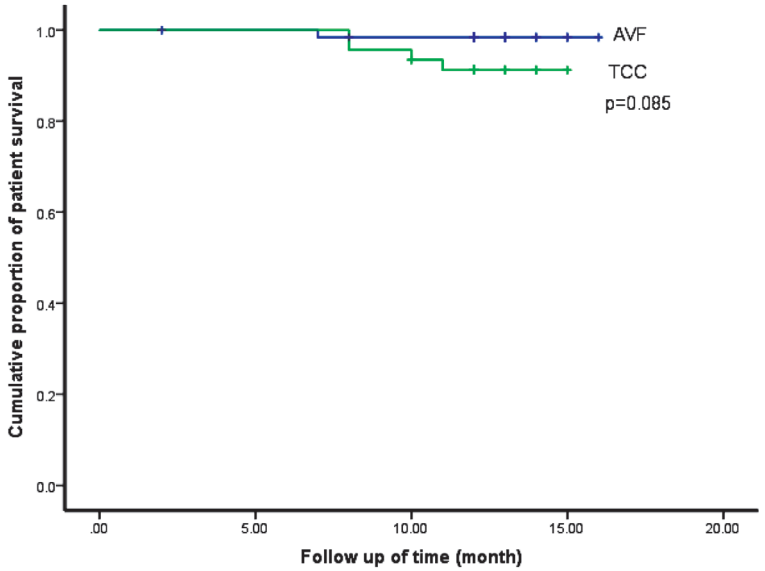


**Figure 8.** Kaplan-Meier Analysis of Patients Survival from Cardio Death Among Diferent Vascular Access (There was no significant difference among patients with different vascular access ($P > .05$))
Abbreviations: AVF, ateriovenous fistula; TCC, tunneled cuffed catheter

this study. It has been demonstrated that BNP is markedly elevated in most ESRD patients due to decreased renal excretion.[21] Several studies have also found that BNP/NT-pro-BNP ratio has an independent and strong direct correlation with left ventricular (LV) mass[22-25] as well as with cardiac diastolic,[26,27] and systolic[23,25,28,29] dysfunction in dialysis patients. Similar to patients with HF in other studies, the patients' NT-pro-BNP levels in this study dropped significantly when measured after 12 months of treatment. This drop and improvement in LVEF indicate that patients were likely experiencing improvement in cardiac function.

It is known that cardiac function affects the quality of life. In order to investigate cardiac-related quality of life parameters in the enrolled patients, the Kansas City Cardiomyopathy Questionnaire (KCCQ) we used, which was shown to be markedly reduced in patients suffering from HF,[30] even when compared with typical HRQL patients with other chronic diseases.[31] In the PARADIGM-HF trial, the overall HRQL, as determined by the KCCQ, improved in surviving patients.[32] In our study, consistent with the PARADIGM-HF trial, the KCCQ-Score has improved significantly following the 12-month treatment, as did the NYHA class. Furthermore, patients with AVF experienced better improvement than patients with TCC. Similar to other studies, ARNI reduced the degree of right ventricular hypertrophy. Therefore, it may have the same effect of reducing the cardio remodeling caused by arteriovenous fistulae [16], which is evident in echocardiography. However, no survival difference was present between the two groups of vascular access, which may be due to confounding factors such as dialysis vintage, combined complications, coronary artery disease, inflammation, and medications, all of which may have had direct effects on patient survival.

In this study, the average ARNI dose in the 12$^{th}$ month was also much lower than that in the PARADIGM-HF trial. Due to the lack of a prescription protocol for hemodialysis patients, sacubitril/valsartan is usually initiated at a low dose in order to reduce the risk of symptomatic hypotension at our practice. The enrolled patients also took other medications, such as CCB, β-blockers, and MRA, which would have put them at a higher risk of hypotension had the ARNI dose been increased. However, compared to patients with a similar body size and improvement in KCCQ score in the PARADIGM-HF trial, the actual efficient dose of ARNI in Chinese patients may be lower than that in Western patients. Furthermore, in our study, a higher dose of ARNI was found to be correlated with better survival from cardiac deaths, as well as a reduction of LAD and LVEF, which all indicate benefits to cardio function. This speculation would need to be confirmed in large randomized trials.

This study has several limitations. First, it is an observational, single-center study with a small number of patients and has no control group or unexposed patients. Therefore, the results should be interpreted with caution. Second, some parameters, such as dry weight and kt/v, were not compared before and after starting the medication. Finally, cardiac dysfunctions are common complications among patients with maintenance HD. Better control of anemia, hyperphosphatemia, and hyperparathyroidism could also contribute in improving cardio function. Due to the short follow-up duration, it may be difficult to assess the effect of ARNI and the magnitude of reverse remodeling, which may have been substantially underestimated. However, this study emphasizes the benefits of ARNI in hemodialysis patients with HFrEF. The participants of this study differ from other patients with HFrEF, and the PARADIGM-HF trial did not specifically report about such a population. Patients with a higher dose of ARNI had better survival. The corresponding data in this study provides practical experience in this population who may benefit from ARNI. The underlying mechanism of ARNI that would help achieve an additional risk reduction in these patients merits further investigation.

## CONCLUSION

The dose of ARNI from hemodialysis patients with HFrEF in the current study was lower compared to the PARADIGM-HF trial population, while the NT-pro-BNP level was higher at baseline. Angiotensin receptor neprilysin inhibitor appeared to be safe and was found to relieve the severity of heart failure symptoms in hemodialysis patients in actual practice. This treatment has also improved scores for KCCQ physical and social activities, though they differed in vascular access type.

## STATEMENT OF ETHICS

Patients have given their written informed consent and that the study protocol was approved by the institute's committee on human research.

## DISCLOSURE STATEMENT

The authors declare no conflict of interest.

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## AUTHOR'S CONTRIBUTIONS

Lihua Wang: study design, drafting the article. Lin Cheng: data collection. Haiyan Chen: data collection, interpretation of the data, analysis. Fang Wei: critical revision of the paper. Aili Jiang: Supervision. Lihua Wang and Haiyan Chen contribute equally to this work and should be taken as co-first authors. All authors read and approved the final manuscript.

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