

Effects of Sacubitril/Valsartan on resistant hypertension and myocardial work in hemodialysis patients

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Abstract

Growing evidences have confirmed the effect of Sacubitril/Valsartan (SV) on anti-hypertension and cardiac protection in general population. However, there was no prospective study about the effect and safety of SV on resistant hypertension and myocardial work in hemodialysis patients. In this single-center, prospective, before-after study, enrolled patients were endured with resistant hypertension for more than 6 months. Participants were initially instructed to take SV 50 mg twice daily, and the dosage was gradually increased up to 100 mg twice daily. The primary outcomes were blood pressure (BP) control, N-terminal pro-B-type natriuretic peptide (NT-proBNP), myocardial work (MW), fatigue and life quality. In addition, the adverse events were also recorded in this cohort. A total of 18 patients (34–64 years old) was finally enrolled and completed in this study. The SV-based regimen provided significantly mean sitting systolic BP (msSBP) and mean sitting diastolic BP (msDBP) reductions from baseline (-20.7/-8.3 mm Hg), respectively. The cardiac remodeling parameters were partially improved. Compared to the baseline, NT-proBNP was significantly reduced at week 4 (8119.50 [3710.75, 29300] pg/ml to 7216.50 [4124.75, 17455.00] pg/ml, $p = .046$), which was much lower at week 12 (3130.50 [2244.50, 9565.70] pg/ml, $p = .037$). Global MW index was higher at week 12 compared to the baseline ($p = .026$). MW efficiency was also improved accordingly compared to the baseline, even though the statistical difference was not significant ($p = .226$). Life quality and fatigue were improved at week 12 compared to the baseline (all $p = .000$). There was no serious adverse events were observed. SV safely and effectively controlled resistant hypertension and improved MW as well as life quality in hemodialysis patients.

KEYWORDS

hemodialysis patients, myocardial work, resistant hypertension, Sacubitril/Valsartan

1 | INTRODUCTION

Cardiovascular disease (CVD) is extremely higher in patients with chronic kidney disease (CKD), and the mortality due to CVD was 10–30 times higher in patients with end stage renal disease (ESRD)

than that in the general people.¹ Heart failure (HF) remains one of the main CVD events in hemodialysis patients.² On the basis of left ventricular ejection fraction (LVEF) cut-off points, chronic HF is defined as HF with reduced EF (HFrEF), mid-range EF (HFmrEF) and preserved HF (HFpEF).³ Myocardial work (MW) as a new parameter has recently

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been used to quantify the myocardial function beyond LVEF, especially in patients with hypertension and diastolic dysfunction.⁴

Hypertension is a core reason for the high incidence of CVD in ESRD population, and the prevalence was up to 82% among hemodialysis patients and only 38% of them had achieved blood pressure (BP) control.^{5,6} Resistant hypertension usually means BP levels persist above the therapeutic target, or reaching BP target by usage of four or more anti-hypertension drugs.⁷ The prevalence of resistant hypertension was about 30% in ESRD patients.⁸ Despite strict control of volume and dry weight in combination with the use of conventional anti-hypertensive agents such as calcium channel blocker, renin-angiotensin system inhibitors, sympathetic nervous system inhibitors, and so on, some patients with ESRD still have unsatisfactory blood pressure control.⁹

Sacubitril/Valsartan (SV), angiotensin receptor neprilysin inhibitor (ARNI), consisting of neprilysin inhibitor sacubitril and angiotensin II receptor blocker (ARB) valsartan, is much more effective than ARB in controlling hypertension and heart failure in the general population.¹⁰ Recently, growing evidence demonstrated that SV showed substantial benefits and well tolerant in patients with either HFrEF or HFpEF.^{11,12} The PRARDIGM-HF trial showed that SV is superior to angiotensin-converting enzyme inhibitor (ACEI) for patients with HFrEF.¹¹ PARAMOUNT trial further demonstrated SV greatly reduced N-terminal pro-B-type natriuretic peptide (NT-proBNP) in HFpEF patients.¹² In the general hypertensive patients, greater reduction in systolic blood pressure (SBP) was observed with SV 400 mg than with valsartan 320 mg at week 8 (-5.7 vs -3.4 mm Hg), and long-term (52-

week) use provided more significant reduction of mean sitting systolic BP (msSBP) (-24.7 mm Hg) from baseline.^{13,14}

Although lots of powerful evidence in the general population showed the advantages of SV in controlling BP and HF, there is still a lack of evidence among the patients with CKD, especially for dialysis patients. A recent retrospective study found that SV could safely improve LVEF in HFrEF patients with ESRD.¹⁵ Sadayoshi Ito and coworkers firstly demonstrated SV was generally safe in Japanese patients with hypertension and estimated glomerular filtration rate (eGFR 15 ~ 60 ml/min/1.73 m²), and achieved the mean reduction in msSBP and mean sitting diastolic BP (msDBP) 20.5 ± 11.3 and 8.3 ± 6.3 mm Hg at week 8, respectively.¹⁶ However, there was no prospective study about the effect of SV on resistant hypertension and MW in hemodialysis patients.

The aims of this study were as follows: (i) To evaluate the effect of SV on resistant hypertension in hemodialysis patients; (ii) To measure the effect of SV on cardiac remodeling and MW in hemodialysis patients; and (iii) To observe the safety of SV in hemodialysis patients.

2 | MATERIALS AND METHODS

2.1 | Study design

This was a 12-week, single-center, prospective, before-after study (Figure 1A). 360 hemodialysis patients from the Institute of Blood Purification Center, Zhongda Hospital, Southeast University, China

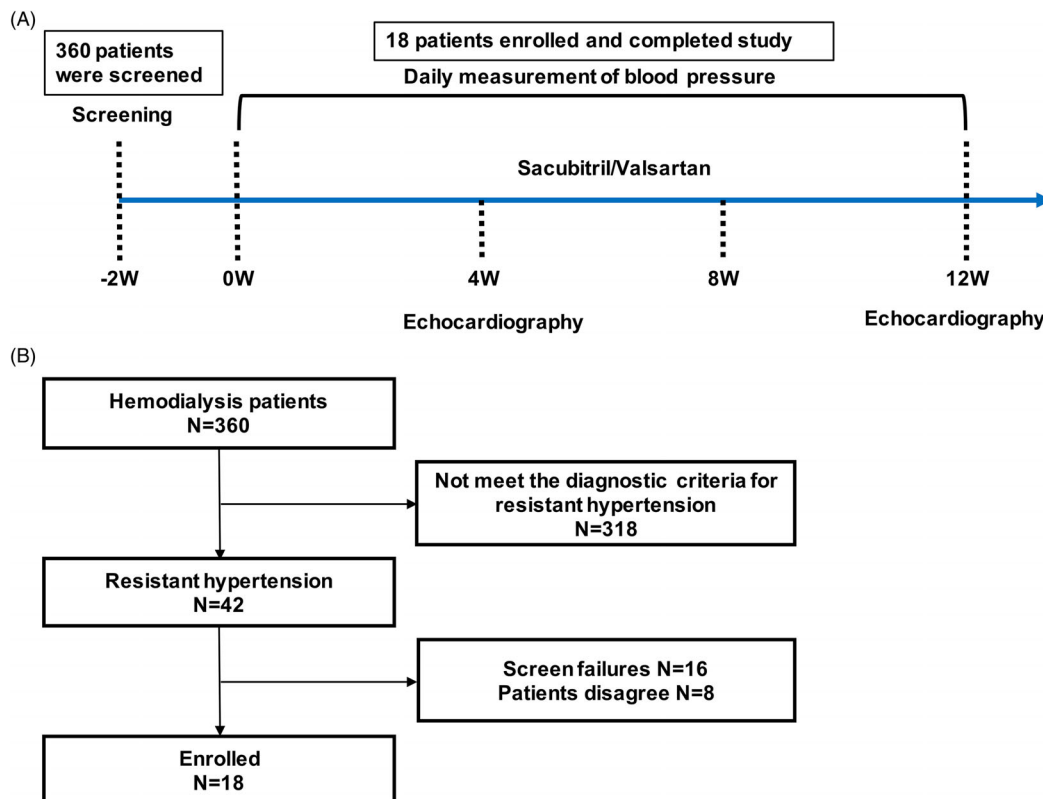


FIGURE 1 Chart of the study. (A) Study design. (B) Patient disposition

were initially screened. The inclusion criteria were as following: 18–75 years old, maintenance hemodialysis for more than 6 months, resistant hypertension which means home msSBP \geq 140 mm Hg even though taking more than three antihypertensive drugs, or $<$ 140 mm Hg with use of \geq 4 antihypertensive drugs. Patients were excluded if they had severe hypertension (home msSBP \geq 180 mm Hg), acute coronary syndrome or stroke within 3 months prior to the study, chronic liver disease even liver cirrhosis, respiratory failure, malignancy or patients with expected survival period of less than 3 months, suffering from mental disease, active tuberculosis, pregnancy or lactation.

Enrolled patients who took ACEI or ARB previously should stop the drug for more than 72 hours before SV (49/51 mg per tablet) were prescribed. Participants were initially instructed to take SV 50 mg twice daily and the dosage of SV was gradually increased up to 100 mg twice daily after 1 week who did not achieve a home msSBP $<$ 140 mm Hg and had no safety concern. On the contrary, if the patients with hypotension (msSBP $<$ 100 mm Hg at any time during the study), the dosage of SV was decreased. The study protocol reviewed by the ethical committee of Zhongda Hospital. All enrolled patients provided written informed consent prior to the study (2020ZDSYLL210-P01).

2.2 | Basic data collection

Basic data for the enrolled patients were collected in terms of age, sex, body mass index, smoking, duration of hemodialysis, complications (such as diabetes, stroke, atrial fibrillation, coronary artery disease). Additionally, other data such as hemoglobin levels, serum potassium, dry weight, and hospitalization rates for cardiovascular events were also collected before and after the study.

2.3 | BP measurement

BP was recorded at home (three times per day), pre-dialysis and intra-dialysis. Blood pressure monitor was used for home BP measurement. Changes of the home msSBP and home msDBP from the baseline was assessed every week. The reductions of in msSBP and msDBP from baseline to 12 weeks were also assessed at the endpoint.

2.4 | NT-proBNP measurement

Serum samples were collected for the measurements of NT-proBNP, at baseline (week 0), week 4 and week 12. NT-proBNP was measured using automatic chemiluminescence immunoassay analyzer cobas 8000 e 801.

2.5 | Echocardiography assessment of cardiac structure and function

Comprehensive transthoracic echocardiography was performed by experienced sonographers using a Vivid E95 ultrasound system at

week 0, week 4, and week 12, respectively. The parameters to evaluate the cardiac function and structure were as follows: left ventricular diastolic diameter (LVDd), left ventricular systolic diameter (LVDs); inter-ventricular septal thickness at diastole (IVSd), left ventricular mass (LVM), LVM index, left ventricle end-diastolic Volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (LVEF), global longitudinal strain of left ventricle (LVGLS), peak velocities of trans-mitral early (E), septal and lateral peak early diastolic velocity (E'), trans-mitral to mitral annular early diastolic velocity (E/E'). The method for measuring cardiac structure was according to current recommendations, and LVEF was calculated using the Simpson biplane method.¹⁷

Besides the above routine parameters, MW was also taken into account, including left ventricular pressure-strain loop (LV PSL), global MW index (GWI), global constructive work, global wasted work, global MW efficiency (GWE).⁴ Assuming that the peak LV systolic blood pressure is equal to the peak arterial pressure, the brachial cuff SBP was record immediately before the echocardiography measurement.

2.6 | Fatigue and life quality assessment

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item, Health-related Quality of Life (HRQL) instrument that has been widely used for heart failure.¹⁸ Multidimensional Fatigue Index (MFI-20) consists of 20 statements to assess fatigue.¹⁹

2.7 | Safety assessment

The safety and tolerability of SV in hemodialysis patients were also recorded, such as hypotension, dizziness, hyperkalemia, etc. Serum electrolytes potassium were measured before and after the study.

2.8 | Statistical analysis

Categorical variables are expressed as percentages. Numerical variables passing normality test are reported as the mean \pm Standard Error of Mean (SEM), and medians (P25, P75) are used for those fail to pass normality test. Comparisons of the data before and after the study were analyzed using paired t-test or the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. $p < .05$ was considered statistically significant. All the analyses were performed with SPSS 23.0 and GraphPad Prism 9.0.

3 | RESULTS

3.1 | Baseline characteristics and exposure of enrolled patients

As shown in Figure 1B, a total of 18 patients (34–64 years old) was finally enrolled and completed the study. Baseline characteristics

TABLE 1 Demographics and baseline characteristics

Parameter	N = 18
Age, years	53.6 ± 14.5
Male, n, (%)	15 (83.3%)
BMI (kg/m ²)	24.5 ± 5.2
Smoking n, (%)	5 (27.8%)
Etiology of ESRD n, (%)	
Diabetes	8 (44.4%)
Chronic glomerulonephritis	8 (44.4%)
Essential hypertension	2 (11.1%)
Stroke n, (%)	2 (11.1%)
Atrial fibrillation n	0
Coronary artery disease n, (%)	2 (5.6%)
Duration of dialysis (months)	36 (16, 69)
Antihypertensive drugs n, (%)	
Beta-blocker	18 (100%)
ACEI/ARB	18 (100%)
Calcium channel blocker	16 (88.9%)
Diuretic	4 (22.2%)
sympathetic nervous system inhibitor	3 (16.7%)
Alpha-blocker	9 (50%)
Vasodilator	4 (22.2%)
Baseline LVEF n, (%)	
< 40%	1 (5.5%)
40–49%	3 (16.7%)
≥ 50%	14 (77.8%)
Hemoglobin (g/L)	
Week 0	104.5 ± 10.4
Week 12	106.4 ± 9.2
p value	0.539
Dry-weight (kg)	
Week 0	70.7 ± 17.3
Week 12	70.5 ± 16.9
p value	0.976
spKt/V	
Week 0	1.22 ± 0.16
Week 12	1.24 ± 0.11
p value	0.612

Abbreviations: BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction, spKt/V, single pool Kt/V. The results represent the mean the mean ± SEM or medians (P25, P75). P, Week 12 vs. Week 0.

are presented in Table 1. The median dialysis age was 36 months. The kinds of antihypertensive drugs that patients took were as follows: ACEI/ARB (18, 100%), Beta-blocker (18, 100%), Calcium channel blocker (16, 88.9%), Diuretic (4, 22.2%), sympathetic nervous system inhibitor (3, 16.7%), Alpha-blocker (9, 50%), Vasodilator (4,

22.2%). Among the enrolled patients, only one patient had the baseline LVEF < 40%, 14 patients had LVEF ≥ 50%, the remaining three ones were 40–49%. All the patients maintained the same ultrafiltration volume and dry weight as before ($p = .976$). The levels of hemoglobin were not significantly different before and after the study (104.5 ± 10.4 vs. 106.4 ± 9.2 , $p = .539$). Dialysis adequacy measured by single pool Kt/V (spKt/V) stayed the same (1.22 ± 0.16 vs. 1.24 ± 0.11 , $p = .612$).

3.2 | Effects of SV on BP

The 12-week treatment with SV 100–200 mg per day resulted in significantly reductions in msSBP (-22.4 mm Hg) and msDBP (-8.3 mm Hg) from baseline, respectively (Figure 2A). The msSBP was reduced from 161.6 ± 10.6 mm Hg at baseline to 146.8 ± 8.7 mm Hg at the end of week 4 ($p = .001$), which maintained stable at week 12 (138.8 ± 7.0 mm Hg, $p = .001$) (Figure 2B). The mean msDBP was reduced from 83.9 ± 8.2 mm Hg at baseline to 77.0 ± 9.2 mm Hg at the end of week 4 ($p = .045$), which maintained stable at week 12 (74.8 ± 9.7 mm Hg, $p = .015$) (Figure 2C). During the follow-up period, eight patients were up-titrated to SV 100 mg twice daily. Patients were either taking fewer or as many types of antihypertensive drugs as before (Table 2).

3.3 | Effects of SV on cardiac structure and function

The parameters of cardiac remodeling were detailed exhibited in Table 3. Both LV mass and LV mass index were reduced but not statistically significant ($p = .203$, $p = .198$). Using of SV also lessened the EDV and ESV from baseline (133.2 ± 25.9 ml to 122.6 ± 26.1 ml and 62.8 ± 15.2 ml to 53.3 ± 11.0 ml, respectively). The E value was significantly decreased 12-weeks after the initiation of SV ($p = .026$), and the ratio of E/E' was also improved although not statistically different (14.9 ± 5.8 to 12.9 ± 4.2 , $p = .221$). Meanwhile, the percentage of LVGLS was remarkably reduced ($p = .042$), and LVEF also had a trend of improvement ($53.2 \pm 5.9\%$ to $56.3 \pm 4.7\%$, $p = .125$).

3.4 | Effects of SV on NT-proBNP and MW

As shown in Figure 3, NT-proBNP was significantly reduced at week 4 ($8119.50 [3710.75, 29300]$ pg/ml) compared to the baseline ($7216.50 [4124.75, 17455.00]$ pg/ml) ($p = .046$), which was much lower at the end of week 12 ($3130.50 [2244.50, 9565.70]$ pg/ml) relative to the value at week 4 ($p = .037$). Marked improvement of MW was observed after SV treatment. The details of two representative patients were graphically displayed in Figure 4A and 4B using seventeen-segment bull's-eye representation of GWI and GWE, which made an intuitive demonstration. Quantitative examination of global and regional MW is based upon the left ventricular PSL. GWI was higher at week 12 compared to the baseline (2185.69 ± 117 to 2045.31 ± 133.32 mm Hg%, $p = .026$, Figure 4C). Constructive MW was elevated

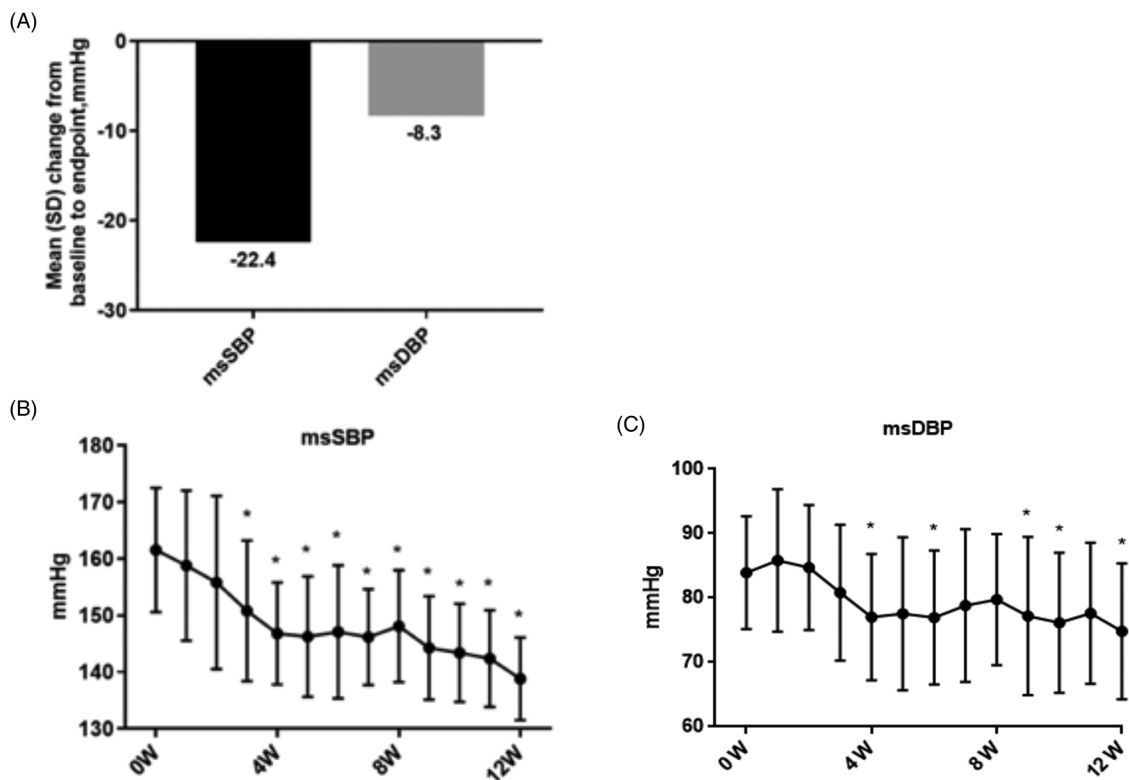


FIGURE 2 Effects of SV on BP. (A) Reductions of msSBP and msDBP from baseline to 12 weeks. (B) and (C) msSBP and msDBP over time, respectively. msSBP, mean sitting systolic blood pressure; msDBP, mean sitting diastolic blood pressure. 0W, week 0; 4W, week 4; 12W, week 12. The results represent the mean the mean \pm SEM. *, $p < .05$ compared to 0W

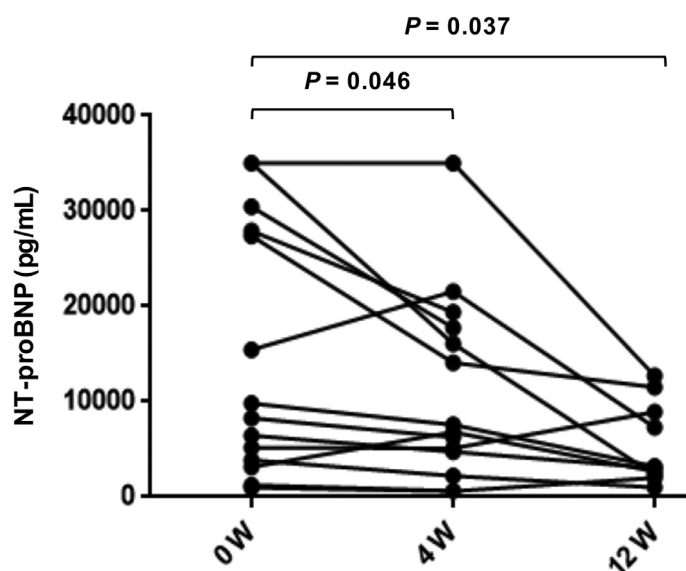
TABLE 2 Kinds of antihypertensive drugs and dose of SV for each patients

Patients	Kinds of antihypertensive drugs (before)	Kinds of antihypertensive drugs (after)	Dose of SV (mg/d)
Patient 1	4	3	100
Patient 2	4	4	200
Patient 3	6	3	200
Patient 4	4	3	200
Patient 5	3	2	100
Patient 6	4	4	200
Patient 7	3	3	200
Patient 8	3	2	100
Patient 9	3	3	200
Patient 10	4	3	100
Patient 11	3	3	150
Patient 12	3	3	100
Patient 13	6	4	200
Patient 14	3	3	100
Patient 15	4	3	100
Patient 16	4	4	150
Patient 17	3	3	100
Patient 18	5	4	200

TABLE 3 Changes in echocardiographic indexes

Variables	0W	4W	p	12W	p
LVDd (mm)	58.0 (56.0-60.5)	54.6 ± 6.7	.168	55.1 ± 4.7	.209
LVDs (mm)	35.1 ± 6.2	34.3 ± 7.8	.395	33.7 ± 6.4	.306
IVSd (mm)	14.3 ± 2.1	14.3 ± 1.7	.541	14.0 ± 1.4	.952
LVM (g)	416.5 ± 107.3	401.3 ± 143.4	.300	390.0 ± 106.8	.137
LVM index (g/m ²)	206.2 ± 30.4	194.6 ± 48.4	.135	192.0 ± 39.6	.198
LVEDV (ml)	133.2 ± 25.9	138.7 ± 27.9	.437	122.6 ± 26.1	.251
LVEDV index (ml/m ²)	72.5 ± 16.5	75.7 ± 16.9	.387	66.6 ± 14.9	.231
LVESV (ml)	62.8 ± 15.2	65.9 ± 14.8	.361	53.3 ± 11.0	.139
LVEF (%)	53.2 ± 5.9	52.5 ± 4.6	.457	56.3 ± 4.7	.125
LVGLS (%)	-14.9 ± 3.0	-15.1 ± 3.0	.300	-15.9 ± 1.7	.042*
E average (cm/s)	81.8 ± 30.6	68.8 ± 22.2	.057	66.4 ± 17.6	.026*
Et' average (cm/s)	6.0(4.5-7.0)	4.6 ± 1.2	.110	5.4 ± 1.5	.458
E/E' ratio	14.9 ± 5.8	15.6 ± 5.4	.957	12.9 ± 4.2	.221

Abbreviations: LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; IVSd, inter-ventricular septal thickness at diastole; LVM, left ventricular mass; LVEDV, left ventricle end-diastolic Volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; LVGLS, global longitudinal strain of left ventricle; E, peak velocities of trans-mitral early; E', septal and lateral peak early diastolic velocity; E/E', trans-mitral to mitral annular early diastolic velocity. 0W, week0; 4W, week4; 12W, week12. The results represent the mean the mean ± SEM or medians (P25, P75). *, $p < .05$, 12W compared with 0W.

FIGURE 3 NT-proBNP levels at each time-point in hemodialysis patients receiving SV treatment. 0W, week 0; 4W, week 4; 12W, week 12

(2349.69 ± 103.89 to 2042.92 ± 177.23 mm Hg%, $p = .027$, Figure 4D), while wasted MW was declined even though did not reach significant levels (277.50 ± 23.47 to 316.79 ± 40.43 mm Hg%, $p = .383$, Figure 4E). The ratio of GWE was improved accordingly compared to the baseline, but the statistical different was not significant (86.07 ± 4.71% to 83.24 ± 7.28 %, $p = .443$, Figure 4F).

3.5 | Effects of SV on life quality and fatigue

Symptom improvement was quantified using KCCQ and MFI-20. Figure 5A showed that the average score of KCCQ was significantly higher

in these patients compared with their baseline data at the end of week 4 (75.4 ± 1.0 to 73.5 ± 5.1, $p = .000$), and the scores were much higher until the end of the observation (77.1 ± 4.1 to 73.5 ± 5.1, $p = .000$). Meanwhile, the change of MFI-20 score was opposite (58.0 ± 12.9 to 67.8 ± 14.1, $p = .000$, Figure 5B). This suggests that the treatment of SV improved their quality of life.

3.6 | Safety and tolerability

SV was safe and well-tolerant in hemodialysis patients during the 12-week treatment (Table 4). There were two patients endured with

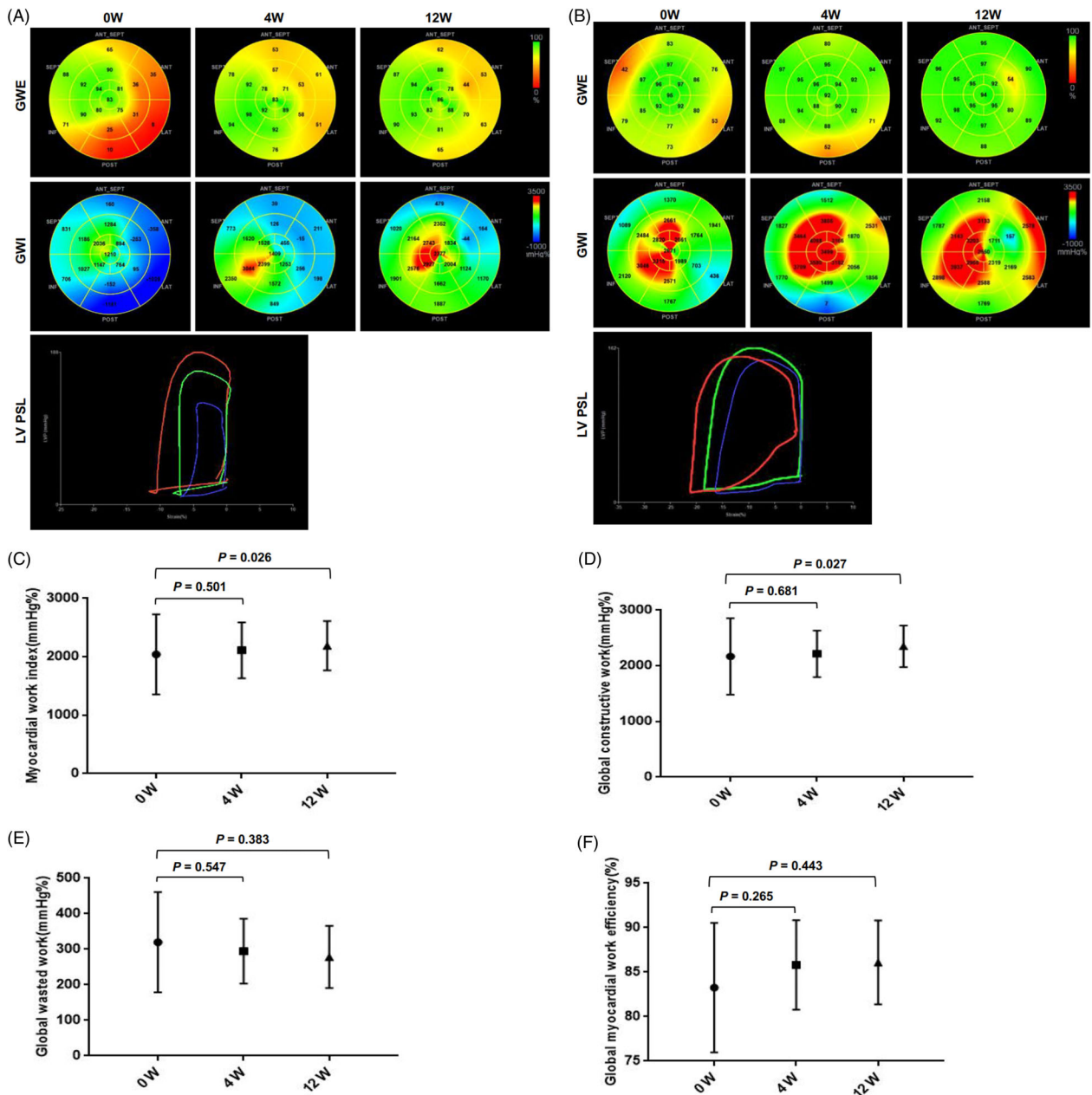


FIGURE 4 Indexes of MW at each time-point. (A) and (B) Seventeen-segment bull’s-eye representation of MW in two examples of the involved patients. GWE showed low efficiency in red and high areas in green. GWI showed areas of negative work in blue, normal in green, and high in red. LV PSL showed 0W in blue, 4W in green, and 12W in red. (C) GWI; (D) Global constructive work; (E) Global wasted work; (F) GWE. GWI, global myocardial work index; GWE, global myocardial work efficiency; LV PSL, left ventricular pressure–strain loop; 0W, week 0; 4W, week 4; 12W, week 12. The results represent the mean the mean ± SEM

symptomatic hypotension and dizziness during or after finishing hemodialysis. There was no occurrence of hyperkalemia pre-dialysis in all the patients. No death or serious adverse events (SAE) were reported in this study.

4 | DISCUSSION

In the present study, we found that SV effectively controlled resistant hypertension and improved cardiac structure and function, as well

as enhanced MW in hemodialysis patients. In addition, SV was well-tolerant in hemodialysis patients.

Recently, several trials have confirmed the favorable effect of SV on BP control relative to ARB in patients with or without CKD. In 2018, Cheung and coworkers have verified the effectiveness of SV monotherapy in patients with hypertension uncontrolled by Olmesartan.²⁰ Beside, SV/amlodipine add-on to amlodipine was effective for patients with systolic hypertension resistant to amlodipine monotherapy.²¹ The UK HARP-III trial firstly observed its additional effect of BP control in CKD patients with estimated glomerular filtration rate (GFR)

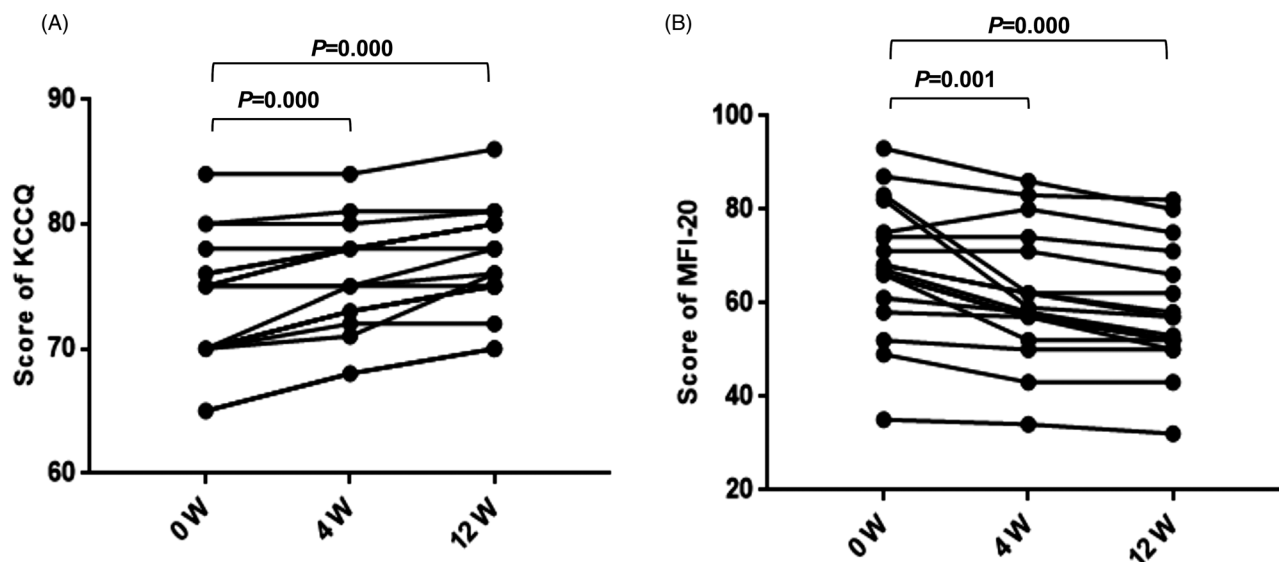


FIGURE 5 Scores of KCCQ and MFI-20 at each time-point

TABLE 4 Adverse events

	N = 18
Any serious adverse events	0
Any adverse events	4
Symptomatic hypotension	2
Dizziness	2
Hyperkalemia	0

20–60 ml/min/1.73m².²² However, all the previous studies excluded ESRD patients. In the current study, we firstly demonstrated that SV reduced the msSBP and msDBP in hemodialysis patients with resistant hypertension. Of note, the reduction of msSBP achieved at the end of week 1, which is in accordance with patients with CKD2-4.¹⁶ It is very gratifying to see that the kinds of antihypertensive drugs decreased, which also might enhance adherence to a large extent.

Beyond its antihypertensive effect, SV has been confirmed cardiovascular protection. Although the baseline LVEF of hemodialysis patients in our study were almost above 40% except one patient. SV treatment still made the tune of enhancement of LVEF. Seonhwa Lee and coworkers¹⁵ report retrospectively observed the cardiac protection in ESRD on dialysis, whereas all those patients endured with HFREF. That is the reason why we adopted MW to more precisely evaluate the effectiveness of SV in our study. Half of the patients had significant improvement in GWI through 12-week usage of SV. GWE also got well as indicated by the increased constructive MW and the decreased wasted MW. The change of the MW was partially due to the beneficial effect of SV on LV wall strain, which was further supported by the decreased NT-proBNP, E/E' ratio, and GLS at the end-points of our study. Our results got consistent with a prospective study which has proved the effectiveness of SV in MW for patients without CKD.²³ In the respect of LV remodeling, LVM, EDV and ESV were all

improved. LVMi decreased numerically without significance because of the short observation period. A meta-analysis concluded that SV was superior to ACEI/ARB on improving LV size and hypertrophy for non-CKD patients.²⁴ Thus, this study may verify the beneficial effects of SV not only via partially improving cardiac function and structure, but also through elevating MW and in hemodialysis patients.

HF is one of the most common cause for reduced healthy-related quality of life, and these patients were reported feeling of great fatigue.²⁵ In the current study, usage of SV increased the score of KCCQ and decreased MFI-20, which improved their physical and social activity.

The most common AE was symptomatic hypotension during or just after hemodialysis which was resolved by decreasing the dose of SV before dialysis. There was no incidence of SAE. The safety was in consistent with the SV study in non-dialysis patients.²⁶

There is no denying that there are limitations in the current study. Firstly, this was a single-center study. Secondly, there was limited number of patients, for the reason that SV in these patients was still off-label use although ethics and patient's informed consent were passed. Thirdly, the enrolled patients had different history of coronary heart disease or diabetes. Fourthly, 44 hour ambulatory blood pressure measurement may be more convincing, and the observation period was short. Therefore, further RCT studies on larger population and long-term outcome are needed to confirm our results.

5 | CONCLUSIONS

SV can effectively control resistant hypertension, enhance MW and partially improve cardiac structure in hemodialysis patients, which is independent of dry-weight, anemia and dialysis adequacy. The use of SV in this population is generally safe and enhances the quality of their life.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

B.W., G.H.W., and X.L.Z. designed the study; X.X.D performed the Echocardiography; G.H.W., B.W., H.X.T., J.Z. performed the study, analyzed data and created figures, G.H.W and B.W. wrote paper. B.C.L. provided valuable suggestions.

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