


Efficacy of angiotensin receptor neprilysin inhibitor in Asian patients with refractory hypertension

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Abstract

Sacubitril/valsartan, simultaneously inhibits neprilysin and angiotensin II receptor, showed an effect in reducing blood pressure (BP). The authors aimed to study whether it can be used as an antihypertensive agent in patients with refractory hypertension who have already been treated. A total of 66 Chinese patients with refractory hypertension were enrolled. Patients received sacubitril/valsartan 200 instead of angiotensin II receptor blocker or angiotensin converting enzyme inhibitor while other agents continued. If BP was uncontrolled after 4 weeks, sacubitril/valsartan was increased to 400 mg. The BP reduction was evaluated by office BP and ambulatory BP monitoring after 8-week treatment. The baseline office BP and mean arterial pressure (MAP) were 150.0/95.0 mmHg and 113.3 mmHg. BP and MAP reduced to 130.6/83.2 mmHg and 99.0 mmHg at week 8. Office BP and MAP reductions were 19.4/11.8 mmHg and 14.3 mmHg at endpoint (all $p < .001$). The 24-h, daytime and nighttime ambulatory BP were 146.2/89.1, 148.1/90.3, and 137.5/83.7 mmHg, respectively at baseline, and BP reduced to 129.6/79.8, 130.6/81.1, and 121.7/75.8 mmHg, respectively at week 8. The 24-h, daytime and nighttime ambulatory BP reductions were 16.6/9.3, 17.5/9.2, and 15.8/7.9 mmHg, respectively at endpoint (all $p < .001$). Sacubitril/valsartan significantly reduced office and ambulatory BP in refractory hypertension patients. Our study provided new evidence for sacubitril/valsartan in refractory hypertension.

KEYWORDS

ambulatory blood pressure monitoring, angiotensin receptor neprilysin inhibitor, Asia, refractory hypertension, sacubitril/valsartan

1 | INTRODUCTION

The prevalence of refractory hypertension is approximately 10%–20% in patients with hypertension.¹ It is clearly defined that blood

pressure (BP) control cannot be adequately achieved even though we apply three reasonable and tolerable dose of antihypertensive (including a thiazide diuretic) drugs at least 4 weeks on the basis of improved lifestyle, or at least four drugs are needed to achieve the

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BP control.² White coat hypertension and medication nonadherence must be excluded when refractory hypertension was diagnosed. Evidence has shown that refractory hypertension is related to multiple adverse cardiovascular disease outcomes, such as chronic renal failure, ischemic heart disease, stroke, or death.³ The existence of refractory hypertension suggests that some mechanisms of hypertension are not completely antagonized by the antihypertensive medications, so new drugs may be needed for refractory hypertension therapy.

Sacubitril/valsartan, a cocrystallization, which is combined with neprilysin inhibitor sacubitril and angiotensin receptor blocker valsartan. It firstly has been approved as the therapeutic drug for heart failure with reduced ejection fraction.⁴ Neprilysin, a metallopeptidase which can hydrolyze various biologically active peptides, especially natriuretic peptides including atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide.^{5,6} Natriuretic peptides exert multiple actions, most importantly, execute sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) inhibition, natriuretic, diuretic, vasodilatory, and aldosterone secretion inhibition effects by combining with natriuretic peptide receptors. And all these effects are indirectly enhanced by sacubitril which decreases natriuretic peptides degradation.^{4,6} The inhibition of RAAS by angiotensin receptor blocker leads to a reduction in BP and systemic vascular resistance. It also causes systemic arterial dilatation and renal blood flow increased.⁷ Sacubitril/valsartan, the dual inhibition of neprilysin and angiotensin type 1 receptor showed a more substantial and complementary efficacy in BP reduction than inhibition of either target alone.⁸ The unique diuretic and natriuretic effect lead to the possibility of usage in refractory hypertension.

It has demonstrated that sacubitril/valsartan provided dose-dependent BP-lowering efficacy of office and ambulatory in Caucasian patients with hypertension compared with valsartan⁹ and Asian patients who had mild-to-moderate hypertension compared with placebo.¹⁰ Kario et al.¹¹ also reported a powerful office BP-lowering efficacy with sacubitril/valsartan regimen in Japanese patients with severe hypertension. But till now, there were no evidence in refractory hypertension treatment. Thus, we intend to evaluate whether sacubitril/valsartan can be used as an effective antihypertensive agent in patients with refractory hypertension.

2 | METHODS

2.1 | Study design

This was a multiple centers prospective study. The study comprised an initial 4-week screening period (period 1) and an 8-week treatment period (period 2, Scheme 1).

The hypertensive patients accepted an evaluation of refractory hypertension screening and a series of lab tests during screening period. Eligible patients entered the 8-week treatment period. Patients received sacubitril/valsartan 200 mg instead of angiotensin receptor blocker while other agents continued. If angiotensin converting enzyme inhibitor was used, it should be stopped for 36 h, and then

changed to sacubitril/valsartan. If the BP was still uncontrolled after 4 weeks, sacubitril/valsartan was increased to 400 mg. Ambulatory BP monitoring was evaluated at baseline, weeks 4 and 8.

The study protocol was approved by the Ethics Committee at each center and all patients provided written informed consent before screening. The trial is registered at www.Chictr.org.cn as ChiCTR2100044672.

2.2 | Subjects

Individuals aged 18–80 years with refractory hypertension were selected from the following clinic centers: The First Affiliated Hospital of Dalian Medical University, The Affiliated Zhongshan Hospital of Dalian University, The Central Hospital of Liaoyang City Affiliated China Medical University, The Affiliated Central Hospital of Shenyang Medical College, The Affiliated Shengjing Hospital of China Medical University, The Second People's Hospital of Dalian, and The First Affiliated Hospital of Jinzhou Medical University.

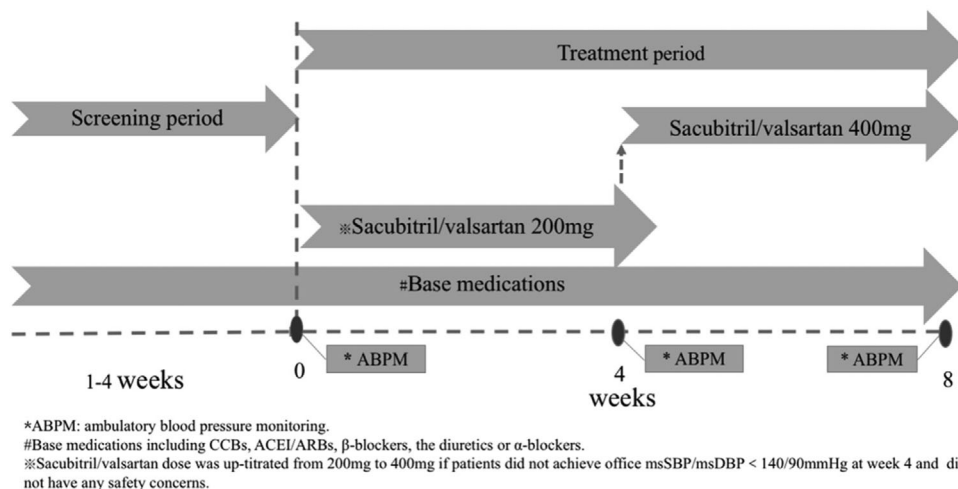
The refractory hypertension was diagnosed according to ambulatory BP in conformity to the Chinese Guidelines for Management of Hypertension.² And it was defined that BP control was not adequately achieved even though we applied three reasonable and tolerable dose of antihypertensive (including a thiazide diuretic) drugs at least 4 weeks on the basis of improved lifestyle, or at least four drugs are needed to achieve the BP control.

The exclusion criteria are as follows: white coat hypertension; history of angioedema; renal parenchymal and vascular hypertension, aortic stenosis, Cushing's syndrome, primary aldosteronism, pheochromocytoma, cystic nephropathy, drug-induced hypertension; immune system diseases; evidence of severe liver and renal impairment (blood potassium > 5.5 mmol/L, serum alanine aminotransferase and/or aspartate aminotransferase > 3.0 × Upper Limit of Normal value), evidence of severe renal impairments (required dialysis or with estimated glomerular filtration rate < 30 ml/min/1.73 m²); acute coronary syndrome, pulmonary embolism, aortic dissection, cerebral hemorrhage, massive cerebral infarction, and malignant tumor within 3 months; hemodialysis; gastrointestinal lesions or gastrointestinal surgery; pregnancy.

2.3 | Office BP and ambulatory BP measurements

Office BP was measured by an automated BP monitor (Omron HEM-8102A, Kyoto, Japan) with appropriately size cuffs in conformity to the Chinese Guidelines for Management of Hypertension (2018).² All BP values were measured three times consecutively with a 1–2 min interval on the right arm after at least 5 min rest in a relaxed sitting position.

Ambulatory BP was measured by an ambulatory BP monitor (Standard W-BPB, Jiangsu, China) with the size-appropriate cuff fitted to the nondominant arm. BP readings were obtained every 30 min during the daytime (6:00–22:00) and every 60 min during the nighttime (22:00–6:00). A valid recording should cover at least 20 h, and include



SCHEME 1 Study design

at least 20 daytime and 7 nighttime readings. Ambulatory hypertension was defined as systolic/diastolic blood pressure (SBP/DBP) $\geq 130/80$ mmHg, $\geq 135/85$ mmHg, or $\geq 120/70$ mmHg for 24 h, daytime or nighttime, respectively. Ambulatory BP monitoring was performed with all patients enrolled at the baseline, weeks 4 and 8.

2.4 | Efficacy assessments

The primary efficacy assessments were the reductions in office BP and mean arterial pressure (MAP) at week 8 endpoint. The secondary efficacy assessments were the reductions in ambulatory BP for 24-h, daytime and nighttime, respectively at week 8 endpoint. The control rate of office BP at week 8 endpoint (< 140/90 mmHg). The control rate of ambulatory BP for 24-h (< 130/80 mmHg), daytime (< 135/85 mmHg) and nighttime (< 120/70 mmHg), respectively at week 8 endpoint.

2.5 | Statistical analyses and sample size

The target sample size was calculated based on the primary efficacy variable, change from baseline in MAP, and a standard deviation of 20 mmHg. The sample size would provide 80% power to obtain statistical significance under the alternative hypothesis that the MAP reduction would be 10 mmHg at a two-sided significance level of .05. Assuming dropout rate of 15% dropout rate during the treatment period, the total targeted sample size was 75 patients.

Normally distributed data were described as mean \pm standard deviation. Changes in BP from baseline were presented as mean \pm standard error. Non-normally distributed data was represented by median (interquartile range). Student's T-test was used to assess the average difference between groups if the data was normally distributed, otherwise, the Mann-Whitney U test was selected. $p < .05$ were considered statistically different. All data were analyzed using IBM SPSS software, version 23.0 (SPSS Inc, Chicago, IL, USA).

3 | RESULTS

3.1 | Baseline demographics and characteristics

82 patients entered the screening period. And 6 patients who achieved ambulatory BP standard but did not meet the office BP criteria discontinued the study during the screening period. A total 76 patients entered the treatment period. With a 13% dropout rate, 66 patients finished the study. 37 patients uptitrated the drug dose from 200 to 400 mg to achieve BP target. Baseline demographic characteristics were summarized in Table 1. The mean age of refractory hypertension patients was 55.1 ± 12.6 years and 27.3% were more than 65 years. Most of patients were men (78.8%). The baseline office BP was 150.0/95.0 mmHg. The baseline 24-h ambulatory BP was 146.2/89.1 mmHg, while daytime and nighttime ambulatory BP were 148.1/90.3 and 137.5/83.7 mmHg. The uncontrol rate was 68.2% for 24-h ambulatory BP, while 56.1% and 78.8% for daytime and nighttime, respectively at baseline. Blood biochemical indexes and the history of patients' medication were shown in Table 2. In our study, there were 56.1% of refractory hypertension patients used three drugs (including a thiazide diuretic) and 43.9% of refractory hypertension patients needed four drugs to control their BP.

3.2 | Effects of treatment on office BP

The baseline office BP was $150.0 \pm 19.5/95.0 \pm 18.3$ mmHg and the BP reduced to $137.0 \pm 16.0/85.1 \pm 10.9$ mmHg at week 4, and $130.6 \pm 15.1/83.2 \pm 9.9$ mmHg at week 8. The baseline MAP was 113.3 ± 16.8 mmHg and the MAP reduced to 102.4 ± 10.8 mmHg at week 4, and 99.0 ± 9.6 mmHg at week 8 (Figure 1A).

The office BP reduction (\pm standard error) was $13.0 \pm 2.2/9.9 \pm 2.3$ mmHg at week 4, and $19.4 \pm 2.1/11.8 \pm 2.0$ mmHg at week 8 (all $p < .001$). The MAP reduction was 10.9 ± 1.9 mmHg at week 4, and 14.3 ± 1.8 mmHg at week 8 (all $p < .001$) (Figure 1B).

TABLE 1 Baseline demographic characteristics

Characteristics at study	Total (N = 66)
Age, y	55.1 ± 12.6
<65 years, No. (%)	48(72.7)
≥65 years, No. (%)	18(27.3)
Sex, No. (%)	
Male	52(78.8)
Female	14(21.2)
BMI, kg/m ²	27.2 ± 5.2
Office BP, mmHg	
SBP	150.0 ± 19.5
DBP	95.0 ± 18.3
MAP	113.3 ± 16.8
Mean ambulatory SBP, mmHg	
24-h	146.2 ± 18.1
Daytime	148.1 ± 18.8
Nighttime	137.5 ± 18.7
Mean ambulatory DBP, mmHg	
24-h	89.1 ± 13.0
Daytime	90.3 ± 13.2
Nighttime	83.7 ± 13.2

Abbreviations: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure. Data are presented as mean ± standard deviation unless otherwise indicated.

3.3 | Effects of treatment on ambulatory BP

The baseline 24-h ambulatory BP was 146.2 ± 18.1/89.1 ± 13.0 mmHg and the BP reduced to 131.0 ± 13.1/80.6 ± 8.6 mmHg at week 4, and 129.6 ± 13.6/79.8 ± 9.1 mmHg at week 8. The baseline daytime ambulatory BP was 148.1 ± 18.8/90.3 ± 13.2 mmHg and the BP reduced to 133.7 ± 14.1/81.9 ± 9.6 mmHg at week 4, and 130.6 ± 14.9/81.1 ± 8.5 mmHg at week 8. The baseline nighttime ambulatory BP was 137.5 ± 18.7/83.7 ± 13.2 mmHg and the BP reduced to 124.4 ± 14.6/77.2 ± 9.9 mmHg at week 4, and 121.7 ± 12.8/75.8 ± 9.0 mmHg at week 8 (Figure 2A and C).

The 24-h ambulatory BP reduction (± standard error) was 15.2 ± 1.8/8.5 ± 1.4 mmHg at week 4, and 16.6 ± 1.5/9.3 ± .8 mmHg at week 8 (all $p < .001$). The daytime ambulatory BP reduction was 14.4 ± 1.8/8.4 ± 1.3 mmHg at week 4, and 17.5 ± 1.6/9.2 ± .8 mmHg at week 8 (all $p < .001$). The nighttime ambulatory BP reduction was 13.1 ± 1.9/6.5 ± 1.3 mmHg at week 4, and 15.8 ± 1.8/7.9 ± 1.0 mmHg at week 8 (all $p < .001$) (Figure 2B and D).

3.4 | Control rate of office BP and ambulatory BP

The control rate of office BP was 74.2%, while control rate of office SBP and DBP were 87.9% and 84.8%, respectively at week 8 (Figure 3A).

TABLE 2 Blood biochemical indexes and the history of patients' medications

Characteristics at study	Total (N = 66)
Creatinine, μmol/L	91.7 ± 37.7
Mean eGFR, ml/min/1.73 m ²	86.9 ± 29.4
Uric acid, mmol/L	383.6 ± 92.3
Male	402.4 ± 75.2
Female	364.8 ± 110.1
Diabetes, No. (%)	17 (25.8)
Total cholesterol, mmol/L	4.1 ± 1.3
Total triglyceride, mmol/L	2.2 ± 1.3
HDL-C, mmol/L	1.1 ± .3
LDL-C, mmol/L	2.6 ± 1.0
Serum potassium, mmol/L	3.9 ± .4
Serum sodium, mmol/L	140.7 ± 3.5
Blood glucose, mmol/L	6.1 ± 1.6
Glycated hemoglobin (%)	6.2 ± 1.0
ALT, mmol/L	29.8 ± 18.0
AST, mmol/L	23.8 ± 12.9
Homocysteine, mmol/L	14.3 ± 5.9
NT-proBNP, pg/ml	133.4 ± 138.7
UACR, g/mg	115.9 ± 155.1
hs-CRP, mg/L	7.9 ± 13.5
Base medications	
ARB, No. (%)	61 (92.4)
CCB, No. (%)	56 (84.8)
β-blocker, No. (%)	39 (59.1)
Diuretic, No. (%)	37 (56.1)
α-blocker, No. (%)	29 (43.9)
ACEI, No. (%)	5 (7.6)
SGLT2i, No. (%)	7 (10.6)

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin receptor blocker; AST, aspartate aminotransferase; CCB, calcium channel blocker; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low density lipoprotein cholesterol; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SGLT2i, sodium-glucose cotransporter 2 inhibitor; UACR, urinary albumin to creatinine ratio.

Data are presented as mean ± standard deviation unless otherwise indicated.

The control rate of ambulatory BP was 53.0% for 24-h, while 68.2% and 51.5% for daytime and nighttime, respectively at week 8. SBP control rate of ambulatory were 66.7% for 24-h, while 78.8% and 74.2% for daytime and nighttime, respectively at week 8. DBP control rate of ambulatory were 60.6% for 24-h, while 74.2% and 54.5% for daytime and nighttime, respectively at week 8 (Figure 3B). The control rate of total ambulatory BP for 24-h, daytime and nighttime was 45.5% in these refractory hypertension patients.

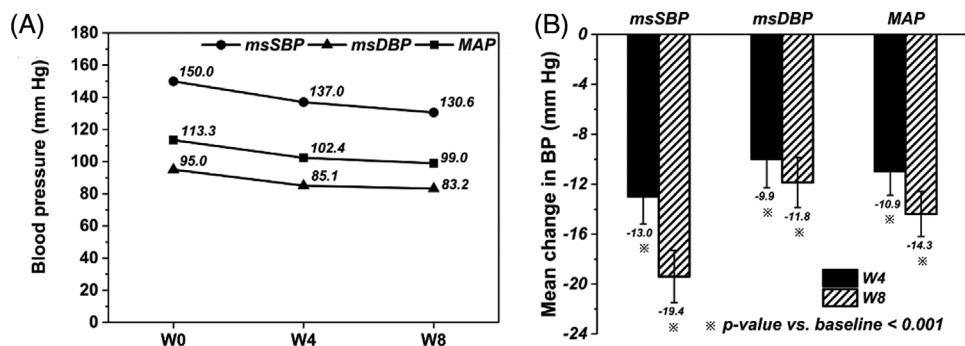


FIGURE 1 The (A) reduction and the (B) change in office msSBP, msDBP, and MAP from baseline to endpoint based on sacubitril/valsartan regimen. Error bars represent standard error. Abbreviations: msSBP, means sitting diastolic systolic blood pressure; msDBP, means sitting diastolic blood pressure; MAP, MAP

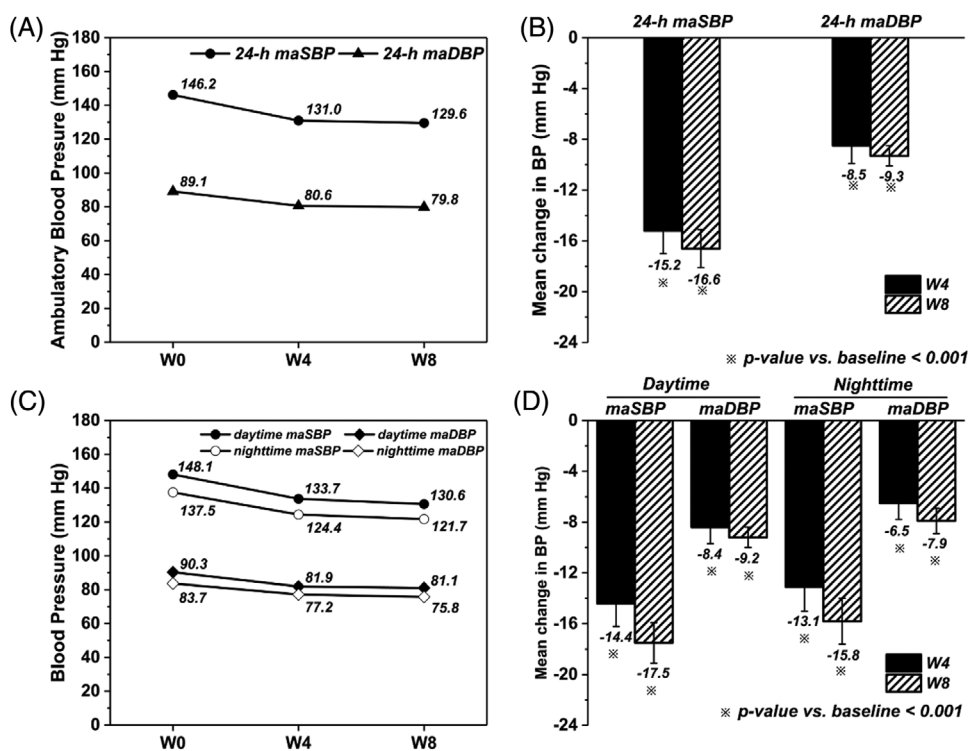


FIGURE 2 The reduction in (A) 24-h and (C) daytime, nighttime and the change in (B) 24-h and (D) daytime, nighttime maSBP and maDBP from baseline to endpoint based on sacubitril/valsartan regimen. Error bars represent standard error. Abbreviations: maSBP, means ambulatory systolic blood pressure; maDBP, means ambulatory diastolic blood pressure

4 | DISCUSSION

Our study demonstrated that office BP reduction was 19.4/11.8 mmHg with sacubitril/valsartan during the 8-week therapy for refractory hypertension patients. The finding in this trial was in line with the result of BP reduction efficacy of sacubitril/valsartan conducted in a Japanese study.¹² They found office BP reduction was 20.5/8.3 mmHg in hypertension accompanying chronic kidney disease (CKD). Actually, hypertension secondary to CKD was also belonging to refractory

hypertension. Thus, we considered the BP reduction was comparable in two groups because there was an overlap between enrolled patients. Another study showed the BP reduction was 13.3/6.2 mmHg in salt-sensitive hypertension patients compared with valsartan, which was lower than our results.¹³ It may be because the baseline BP of 147.0/90.2 mmHg in their study was lower and the treatment duration was 4 weeks shorter. In our study, BP reduction was observed when angiotensin converting enzyme inhibitor or angiotensin receptor blocker was replaced by sacubitril/valsartan while other

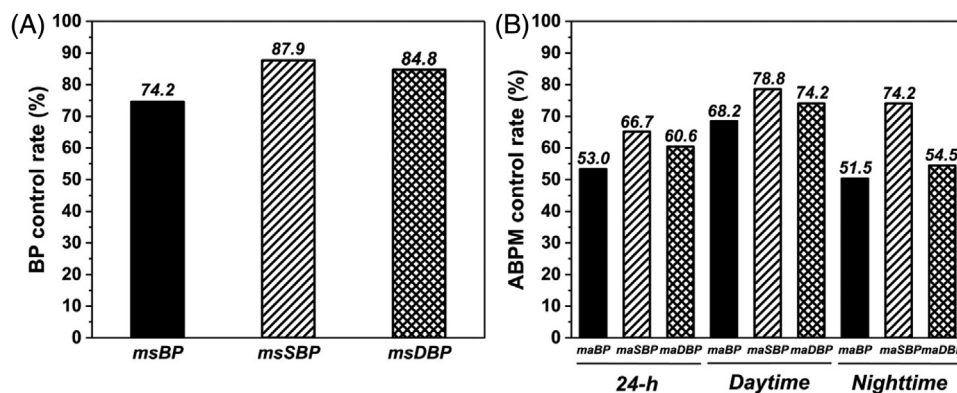


FIGURE 3 The control rate of (A) office msBP (< 140/90 mmHg), msSBP (< 140 mmHg) and msDBP (< 90 mmHg) and the control rate of (B) maBP (24-h maSBP/maDBP < 130/80 mmHg, daytime maSBP/maDBP < 135/85 mmHg, nighttime maSBP/maDBP < 120/70 mmHg), 24-h maSBP (< 130 mmHg), 24-h maDBP (< 80 mmHg), daytime maSBP (< 135 mmHg), daytime maDBP (< 85 mmHg), nighttime maSBP (< 120 mmHg) and nighttime maDBP (< 70 mmHg) based on sacubitril/valsartan regimen. Abbreviations: msBP, mean sitting blood pressure; msSBP, mean sitting systolic blood pressure; msDBP, mean sitting diastolic blood pressure; maBP, mean ambulatory blood pressure; maSBP, mean ambulatory systolic blood pressure; maDBP, mean ambulatory diastolic blood pressure

antihypertensive agents were continued. This new combination further demonstrated the powerful antihypertensive efficacy of sacubitril/valsartan in refractory hypertension patients.

Ambulatory BP monitoring was improved to be more informative than a single office BP measurement and we evaluated the efficacy of sacubitril/valsartan by ambulatory BP monitoring.¹⁴ We found 24-h ambulatory BP reduction was 16.6/9.3 mmHg by the end of the study. Moreover, the consistently greater reduction of 15.8/7.9 mmHg in nighttime ambulatory BP with sacubitril/valsartan was noteworthy. Increased nighttime BP and nondipping status were closely related to cardiovascular disease morbidity and mortality in hypertension patients.¹⁵ Studies showed restricting sodium ingestion or decreasing the circulating volume by a diuretic were effective methods to lower nighttime BP.^{15,16} A research demonstrated that BP reduction induced by sodium restriction was more obvious in refractory hypertension compared with general hypertension.¹⁷ Wang et al.¹³ demonstrated sacubitril/valsartan offered a significant nighttime BP reduction of 14.2/8.5 mmHg in patients with salt-sensitive hypertension. They explained the mechanism may be the natriuresis and diuresis in the 6-h after the first administration was significantly increased. All of the evidence further demonstrated greater nighttime BP reduction may be due to the sodium excretion caused by sacubitril. The effect of bedtime chronotherapy on sleeptime BP is controversial. A study showed ingestion angiotensin receptor blocker or angiotensin converting enzyme inhibitor once daily in the evening led to a significant sleeptime BP decline compared with the morning.¹⁸ Moreover, some studies have demonstrated that ingesting at least one antihypertensive drug at bedtime improved BP control rate and had a powerful sleeptime BP reduction compared with using multiple antihypertensive drugs upon awakening.^{19,20} In our study, 69.7% patients followed twice-daily ingestion of the sacubitril/valsartan. This may partly explain the apparently effect of higher nighttime reduction. Meanwhile, SBP is a powerful predictor for heart failure and stroke among middle-aged and elderly populations and is more difficult to control than DBP.^{21,22}

In our study, sacubitril/valsartan showed a 16.6 mmHg reduction in ambulatory SBP. The finding in our study was favorable and comparable with a previous study, which offered a greater ambulatory SBP reduction of 14.2 mmHg with sacubitril/valsartan in Asians with systolic hypertension.²² These results further revealed that sacubitril/valsartan had a strong and effective BP reduction efficacy.

Pulse pressure was a strong predictor of cardiovascular diseases such as stroke and myocardial infarction.²³ In our study, we demonstrated office pulse pressure reduction was 7.6 mmHg and 24-h ambulatory pulse pressure reduction was 7.3 mmHg. Our findings were consistent with the results of the pulse pressure-lowering efficacy of sacubitril/valsartan in Asian patients who had mild-to-moderate hypertension.¹⁰ It demonstrated significant reductions of 7.82 mmHg in office pulse pressure and 6.31 mmHg in 24-h ambulatory pulse pressure with sacubitril/valsartan compared with placebo. The reason may be the enrolled patients were all Asians in two studies. Taking the result of previous study together with our current finding, sacubitril/valsartan thereby provided significant improvements in pulse pressure and thus long-term use of it may decrease the onset of cardiovascular events.

In our study, office BP control rate was 74.2% in refractory hypertension patients. We also observed that 24-h ambulatory BP control rate was 53.0%, while daytime and nighttime BP control rate were 68.2% and 51.5% in refractory hypertension patients. Previous studies showed that office BP control rate was 40% in severe hypertension patients¹¹ and 54.2% in mild-to-moderate hypertension in Asia.¹⁰ And our BP control rate was higher compared with these studies. The enrolled patients in our study were refractory hypertension patients and there were many mechanisms involved in refractory hypertension, including over activations of sympathetic nervous system and RAAS, excessed aldosterone levels, and an increased sodium intake and sodium retention.²⁴ The sympathetic nervous system and RAAS activations were essential in refractory hypertension pathogenesis. A study showed that sympathetic nervous system and RAAS were

inhibited by ANP, which could modulate the baroreceptors activity and stimulate vagal afferent fibers²⁵ and angiotensin receptor blocker inhibited the activation of RAAS by inhibiting the binding of angiotensin II to type I receptor, thereby decreasing peripheral vascular resistance and reducing BP.²⁵ Excess aldosterone also played an essential part in exacerbating hypertension particularly in patients with refractory hypertension. BNP reduced aldosterone production by combining with type A natriuretic peptide receptor in the adrenals.²⁵ In addition, ANP decreased plasma renin concentrations and thus inhibited angiotensin II-stimulated aldosterone secretion by calcium-independent effects of cyclic guanosine monophosphate acting on the juxtaglomerular apparatus.²⁶ So the inhibition of aldosterone maybe another reason for the improvement of refractory hypertension. Sodium retention and consequent volume expansion and vascular remodeling also play a central role in refractory hypertension. ANP induced natriuresis by inhibiting cyclic guanosine monophosphate-induced sodium reabsorption in the inner medullary collecting ducts.²⁶ These effects were exerted by inhibiting amiloride-sensitive sodium channels located on apical membrane and sodium-potassium-adenosine triphosphatase located on basolateral membrane.²⁶ In addition, there were some other mechanisms for reducing BP by sacubitril/valsartan. For example, ANP induced systemic vasodilation by endothelial nitric oxide production.^{25,27} ANP also stimulated afferent renal arterioles dilatation, resulting in pressure within the glomerular capillaries increased. Then, increased glomerular filtration and diuretic actions benefited to reduce BP.²⁵ As a result, the synergistic effects posed by sacubitril/valsartan are diuresis, natriuresis, systemic vasodilation, sympathetic nervous system and RAAS inhibition, and aldosterone secretion decrease.^{6,7} The presence of refractory hypertension suggested that the antihypertensive drug which could antagonize various mechanisms are needed by populations. Sacubitril/valsartan is a first-rate angiotensin receptor neprilysin inhibitor. The effect of natriuretic peptides enhanced by sacubitril was a new target for antihypertensive therapy, which is different from other traditional antihypertensive drugs. Thus, the combination of other antihypertensive drugs maybe a favorable therapeutic strategy for refractory hypertension patients.

There were several limitations in our study. The trial had a short follow-up period. If refractory hypertension patients did not achieve BP control using a low dose (200 mg) during 4-week treatment period, then they would receive increased doses (400 mg) of sacubitril/valsartan. Therefore, we could not compare the BP reduction efficacy of different doses sacubitril/valsartan.

5 | CONCLUSIONS

Sacubitril/valsartan significantly reduced office and ambulatory BP in refractory hypertension patients. Our study provided new evidence for the treatment of sacubitril/valsartan in refractory hypertension.

ACKNOWLEDGEMENTS

The current article was not supported by any source and only represents the effort of the authors.

CONFLICTS OF INTEREST

There are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Wanjing Li, Wei Song, and Yinong Jiang wrote the first version of the manuscript; Minghui Gong, Qin Yu, Rihui Liu, Kaiming Chen, Wei Lv, Fumei Yao, and Zhaolong Xu participated in data collection, analysis, and interpretation of results; Yi Xu and Wanjing Li conceptualization; Wei Song and Yinong Jiang supervision; All authors contributed comments and approved the final version and are accountable for the for all aspects of the work.

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How to cite this article: Li W, Gong M, Yu Q, et al. Efficacy of angiotensin receptor neprilysin inhibitor in Asian patients with refractory hypertension. *J Clin Hypertens.* 2022;24:449-456. <https://doi.org/10.1111/jch.14454>