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ORIGINAL ARTICLE
Hypertension and Circulatory Control

Clinical Benefit of Sacubitril/Valsartan for Hypertensive Patients in Daily Practice and Predictors of Its Antihypertensive Effect

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Background: The blood pressure (BP)-lowering effect of sacubitril/valsartan (Sac/Val) is greater than that of angiotensin II receptor blockers (ARBs) but in in real-world clinical practice, Sac/Val is used in a variety of patterns other than switching from ARBs. In the present study we investigated the effects of Sac/Val on BP and biochemical parameters when switching from or adding it to various antihypertensive drugs and examined what factors could be predictors of the antihypertensive effect of Sac/Val.

Methods and Results: In 108 hypertensive patients treated with antihypertensive agents (including 4 naïve cases), clinic BP and various biochemical parameters were assessed before and after switching to/adding Sac/Val (200 mg/day). Systolic and diastolic BPs significantly decreased after treatment with Sac/Val (P<0.0001, respectively). As for biochemical parameters, alanine aminotransferase, triglycerides, C-reactive protein, and uric acid significantly decreased after administration of Sac/Val, but renal function, B-type natriuretic peptide, and plasma renin activity (PRA) did not change before or after treatment with Sac/Val. Multiple regression analysis revealed that low PRA and high baseline systolic BP were independent determinants of systolic BP reduction after Sac/Val treatment.

Conclusions: Sac/Val is beneficial for poorly controlled hypertension in daily clinical practice and low PRA may be a predictor of the antihypertensive effect of switching to/adding Sac/Val.

Key Words: Angiotensin receptor-neprilysin inhibitor; Antihypertensive effect; Metabolic parameters; Plasma renin activity; Renal function

Sacubitril/valsartan (Sac/Val), a first-in-class angiotensin receptor-neprilysin inhibitor (ARNI) that provides simultaneous neutral endopeptidase (neprilysin) inhibition and angiotensin II receptor-1 blockade,[1–3] has been currently approved in Japan not only for the treatment of chronic heart failure,[4,5] but also as an antihypertensive drug.[6–8] Many studies have shown that the antihypertensive effect of Sac/Val is greater than that of angiotensin II receptor blockers (ARBs),[9–13] which is probably derived from the natriuretic/diuretic and direct vasodilatory effects of sacubitril enhancing the biological activity of natriuretic peptides.[1,2] In real-world clinical practice of hypertension management, Sac/Val is used not only for switching from ARBs, but also for switching from other classes of antihypertensive drugs, including combination drugs, and as an additional drug for patients whose blood pressure (BP) is not adequately controlled. To date, however, no study has investigated the antihypertensive effect of Sac/Val and its influence on laboratory parameters, comparing these effects when switching from or adding to various antihypertensive drugs. In addition, the factors that can predict the antihypertensive effect of Sac/Val after switching to/adding it have not been elucidated. Therefore, we investigated the effects of Sac/Val on BP and biochemical parameters when switching from or adding to other antihypertensive drugs and examined which factors could be predictive of the antihypertensive effect of switching to/adding Sac/Val in hypertensive patients.

Methods

Study Subjects

In this retrospective observational study, we enrolled from among patients with poorly controlled hypertension even

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under treatment with ≥1 antihypertensive agent or with untreated hypertension in the outpatient clinic during September 2021 and July 2023 a total of 108 patients who underwent switching from 1–2 antihypertensive agents (including a fixed-combination drug) to or adding (without switched drugs) Sac/Val (200 mg/day), and whose biochemical parameters including B-type natriuretic peptide (BNP) and plasma renin activity (PRA) were measured before and after treatment with Sac/Val. Poorly controlled hypertension was defined as failure to achieve the target control levels of clinic and home BP indicated in the current Guidelines for the management of hypertension from the Japanese Society of Hypertension (JSH2019),[14] and a clinic systolic BP ≥130 mmHg. Untreated hypertension was defined as a clinic systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg on repeated measurements. Subjects showing overt "white coat" phenomenon (clinic minus home systolic BP ≥20 mmHg) were excluded. The final decision of switching to/adding Sac/Val was left to the discretion of the physician in charge of the patient. None of the patients had a change in other medications or lifestyle modification throughout the study period.

Diabetes mellitus was diagnosed as a fasting plasma glucose level ≥126 mg/dL (7.0 mmol/L), a nonfasting plasma glucose level ≥200 mg/dL (11.1 mmol/L), and/or a hemoglobin A1c level ≥6.5%, or when medication was taken for treatment of hyperglycemia. A diagnosis of dyslipidemia required a serum low-density lipoprotein cholesterol (LDL-C) ≥140 mg/dL (3.62 mmol/L) and/or a serum triglyceride level ≥150 mg/dL (1.69 mmol/L), or the use of lipid-lowering drugs.

All procedures in the present study were carried out in accordance with the principles outlined in the Declaration of Helsinki and national ethical guidelines for human studies. The study protocol was approved by the Ethics Committee of Ishikiriseiki Hospital (approval no. 23-2). Written informed consent was not required because of the retrospective observational study design. Instead, information about this study was available on the hospital's website and patients had the opportunity to opt out.

Clinical Parameters

The average levels of clinic BP measured on 2 occasions before (−2 and 0 months) and after (2 and 4 months) drug switching to/adding Sac/Val were assessed in the analysis. Laboratory parameters were measured just before and 2–4 months after treatment with Sac/Val. BNP and PRA were determined by chemiluminescent immunoassay and enzyme immunoassay methods, respectively. The estimated glomerular filtration rate (eGFR) was calculated, based on age, sex, and serum creatinine, using a formula taken from the Modification of Diet in Renal Disease Study and adjusted for Japanese subjects.[15]

Statistical Analysis

No statistical sample size calculations were conducted in advance, but the target sample size was calculated to be 97 (or 73) patients, based on 90% (or 80%) power and 0.05 significance level, to detect a difference in systolic BP of 10 mmHg before and after Sac/Val treatment with a standard deviation (SD) of 15 mmHg.

Values are expressed essentially as mean±SD and as median (25, 75 percentiles) for C-reactive protein (CRP), urinary protein, BNP, and PRA because of the right skew in their distributions. The significance of differences in various parameters before and after treatment with Sac/Val was evaluated with a paired t-test, but for CRP, urinary protein, BNP, and PRA, it was non-parametrically using the Wilcoxon signed-rank test. An unpaired Student's t-test was used for comparison between groups. The significance of differences among ≥3 groups was evaluated by an unpaired analysis of variance with subsequent Dunnett's post hoc test. A multiple regression analysis was performed to identify independent predictors of systolic BP reduction after treatment with Sac/Val. $P<0.05$ was accepted as statistically significant.

Table 1. Baseline Clinical Characteristics of the Study Subjects (n=108)

Variable	
Age, years	69.4±12.9
Sex, male/female	54/54
Diabetes mellitus	26 (24%)
Dyslipidemia	49 (45%)
Antihypertensive drugs (before treatment with Sac/Val)	
ARB	77[a] (71%)
CCB	75[b] (69%)
Diuretic	30[c] (28%)
β-blocker	13[d] (12%)
MR antagonist	2[e] (2%)
Switched drugs	
ARB	50 (46%)
ARB plus diuretic*	21 (19%)
CCB	9 (8%)
Diuretic	4 (4%)
ARB plus CCB*	4 (4%)
CCB plus diuretic	2 (2%)
β-blocker	1 (1%)
MR antagonist	1 (1%)
None (addition)**	16 (15%)

Values are mean±SD or number (percentage). *Several types of fixed-combination drugs are included. **Four naïve cases are included. [a]1 case with low dose, 71 with standard dose, and 5 with high dose; [b]11 cases with low dose, 48 with standard dose, and 16 with high dose; [c]all 30 cases with low dose; [d]3 cases with low dose and 10 with standard dose; [e]1 case with standard dose and 1 with high dose. ARB, angiotensin II receptor blocker; CCB, calcium-channel blocker; MR, mineralocorticoid receptor; Sac/Val, sacubitril/valsartan.

Results

The baseline clinical characteristics of the 108 patients (mean age 69.4 years; 50% male) are summarized in **Table 1**. As the antihypertensive drug administrated before switching to/adding Sac/Val, ARB (71%) and calcium-channel blocker (CCB) (69%) were most common, followed by diuretic (28%) and β-blocker (12%). As switched drugs, ARB (46%) was the most frequent, followed by ARB plus diuretic (19%), including a fixed-combination drug, and CCB (8%). The addition of Sac/Val without switched drugs was done in 16 patients (15%), including 4 naïve (untreated hypertensive) cases. Details of antihypertensive drug patterns before treatment with Sac/Val are presented in **Supplementary Table 1**.

Individual BP changes before and after treatment with

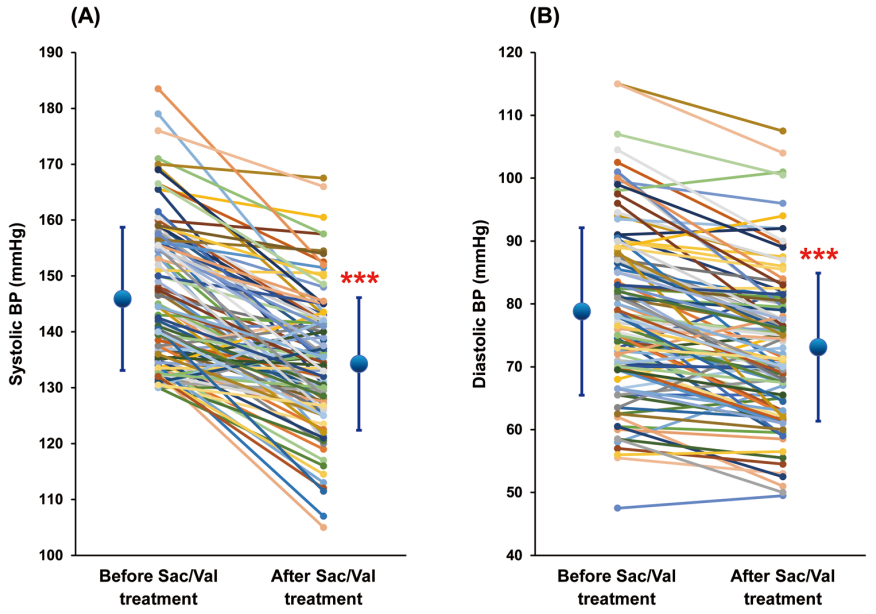

Figure 1. Changes in systolic (**A**) and diastolic (**B**) blood pressure (BP) before and after treatment with sacubitril/valsartan (Sac/Val) in all patients (n=108). Data are presented as individual plots and mean±SD. ***P<0.0001 vs. before Sac/Val treatment.

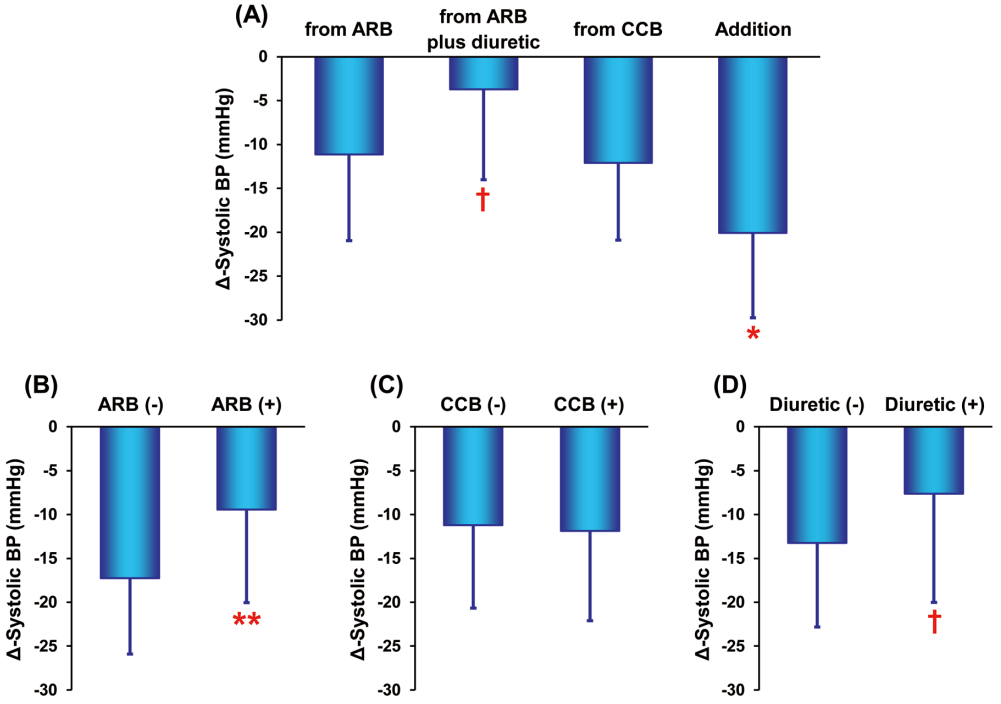

Figure 2. (**A**) Comparison of systolic blood pressure change (Δ-systolic BP) after treatment with sacubitril/valsartan (Sac/Val) between patient groups (only groups of ≥5 cases) by antihypertensive drugs switched, i.e., those with switching to Sac/Val from angiotensin II receptor blocker (ARB) (n=50), from ARB plus diuretic (n=21), and from calcium-channel blocker (CCB) (n=9), and adding Sac/Val without switched drugs (n=16, including 4 naïve cases). †P<0.05 and *P<0.01 vs. switching from ARB. (**B**–**D**) Comparison of Δ-systolic BP after treatment with Sac/Val between groups without and with ARB (**B**), CCB (**C**), or diuretic (**D**) as antihypertensive drug before treatment with Sac/Val. **P<0.001 vs. without ARB, †P<0.05 vs. without diuretic.

Table 2. Changes in Biochemical Parameters Before and After Treatment With Sac/Val in All Study Patients

	Before	After	P value
AST, IU/L	24.2±9.3	23.2±8.3	0.1404
ALT, IU/L	21.4±15.0	19.8±13.4	0.0181
Triglycerides, mg/dL	137.5±89.0	124.5±81.6	0.0317
LDL-C, mg/dL	114.1±25.9	112.1±26.6	0.2126
Glucose, mg/dL	115.1±30.8	114.0±27.3	0.5790
HbA1c, %	6.08±0.67	6.07±0.70	0.5806
CRP, mg/dL#	0.10 (0.05, 0.21)	0.08 (0.04, 0.19)	0.1273
Log CRP	−0.99±0.43	−1.05±0.44	0.0324
Creatinine, mg/dL	0.86±0.33	0.86±0.31	0.9726
eGFR, mL/min/1.73 m^2	66.1±22.2	65.2±21.2	0.2441
Uric acid, mg/dL	5.63±1.39	5.40±1.37	0.0027
Sodium, mEq/L	140.9±2.1	141.3±2.0	0.0528
Potassium, mEq/L	4.14±0.47	4.09±0.48	0.1867
Urinary protein, g/gCr#	0.10 (0.05, 0.17)	0.10 (0.04, 0.18)	0.9913
Log urinary protein	−0.98±0.39	−0.97±0.44	0.5015
BNP, pg/mL#	18.3 (8.7, 40.8)	21.2 (7.9, 46.4)	0.1232
Log BNP	1.31±0.43	1.33±0.45	0.2797
PRA, ng/mL/h#	1.55 (0.60, 3.30)	1.70 (0.70, 3.30)	0.9023
Log PRA	0.18±0.48	0.19±0.47	0.7361

Values are mean±SD or median (25, 75 percentiles). #Nonparametrically compared using Wilcoxon signed-rank test. AST, aspartate aminotransferase; ALT, alanine aminotransferase; BNP, B-type natriuretic peptide; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; PRA, plasma renin activity; Sac/Val, sacubitril/valsartan.

Table 3. Changes in Metabolic and Renal Function Parameters Before and After Treatment With Sac/Val: Subgroup Analysis

	Group A (n=27)		Group B (n=81)	
	Before	After	Before	After
AST, IU/L	24.3±8.6	22.9±8.2	24.2±9.6	23.3±8.4
ALT, IU/L	21.6±12.7	19.1±10.6†	21.3±15.7	20.0±14.3
Triglycerides, mg/dL	147.6±82.7	134.7±69.9	134.1±91.3	121.1±85.3
LDL-C, mg/dL	113.3±31.3	107.9±28.9	114.3±24.0	113.5±25.8
Glucose, mg/dL	123.1±36.1	115.5±27.4	112.5±28.5	113.6±27.5
HbA1c, %	6.21±0.56	6.14±0.59	6.04±0.70	6.04±0.73
Creatinine, mg/dL	1.01±0.31	0.95±0.28†	0.81±0.32	0.83±0.32†
eGFR, mL/min/1.73 m^2	52.7±18.4	55.4±16.6	70.6±21.7	68.4±21.7†
Uric acid, mg/dL	6.28±1.44	5.70±1.55**	5.42±1.31	5.31±1.30
Sodium, mEq/L	140.9±2.4	141.6±2.1	140.8±2.0	141.1±2.0
Potassium, mEq/L	4.18±0.48	4.17±0.40	4.13±0.47	4.07±0.50

Values are mean±SD. Patients switched from antihypertensive drugs containing diuretics (n=27) were placed in Group A, and all other patients (n=81) were placed in Group B. †P<0.05 and **P<0.001 vs. before (treatment with Sac/Val). Abbreviations as in Table 2.

Sac/Val in all patients are shown in **Figure 1**. Systolic (145.9±12.8 to 134.2±11.9 mmHg) and diastolic BP (78.8±13.3 to 73.1±11.8 mmHg) significantly decreased after switching to/adding Sac/Val (P<0.0001, respectively). The degree of change in systolic BP after treatment with Sac/Val was compared between patient groups (only groups of ≥5 cases) by antihypertensive drugs switched (i.e., those with switching to Sac/Val from ARB, from ARB plus diuretic, and from CCB, and adding Sac/Val without switched drugs (including 4 naïve cases)). Compared with the group switching from ARB, the systolic BP reduction in the group switching from ARB plus diuretic was significantly smaller (P=0.0137) and that in the group adding Sac/Val without switched drugs was significantly greater (P=0.0061) (**Figure 2A**). Systolic BP changes after treatment with Sac/Val were also compared between groups without and with ARB, CCB, or diuretic as the antihypertensive drugs before switching to/adding Sac/Val. The fall in systolic BP in the patient group with ARB or diuretic before treatment with Sac/Val was significantly smaller than that in the group without each drug (P=0.0004 for ARB, P=0.0139 for diuretic) (**Figure 2B–D**).

Changes in biochemical parameters before and after treatment with Sac/Val in all patients are shown in **Table 2**.

Table 4. Independent Predictors of Systolic BP Reduction After Treatment With Sac/Val in the Multiple Regression Analysis

Baseline parameter	Univariate		Multivariate	
	β	P value	β	P value
Age	−0.0532	0.5848	0.0268	0.8014
Diabetes mellitus, yes	−0.0863	0.3744	0.0135	0.8707
ARB, yes	−0.3334	0.0004	−0.1131	0.2219
CCB, yes	0.0291	0.7651	0.0369	0.6715
Diuretic, yes	−0.2361	0.0139	−0.0521	0.5627
Systolic BP	0.5010	<0.0001	0.3787	<0.0001
eGFR	0.2148	0.0256	0.1017	0.2894
Log BNP	0.0308	0.7521	0.0786	0.4200
Log PRA	−0.3984	<0.0001	−0.2381	0.0113

The degree of systolic BP reduction, as the objective variable in this analysis, represents the difference in systolic BP before minus after drug switching to/adding Sac/Val. BP, blood pressure. Other abbreviations as in Tables 1,2.

Among the various parameters, alanine aminotransferase (ALT), triglycerides, log-transformed CRP, and uric acid (UA) were significantly decreased after Sac/Val administration. BNP, PRA, and parameters of glucose metabolism and renal function including urinary protein did not significantly change before or after treatment with Sac/Val. When examining changes in biochemical parameters in the subgroup switched to Sac/Val from other drugs (n=92), similar results were obtained, except for slight but significant increases in sodium and BNP after switching to Sac/Val (**Supplementary Table 2**).

Because diuretics can affect metabolic parameters and renal function, we re-examined the changes in such parameters before and after treatment with Sac/Val by divided into 2 groups: patients switched from antihypertensive drugs containing diuretics (Group A, n=27) and all other patients (Group B, n=81). Significant decreases in ALT and UA after treatment with Sac/Val were observed only in Group A (**Table 3**), and a significant decrease in creatinine was also found in Group A. In Group B, creatinine was slightly but significantly increased and eGFR was significantly decreased after treatment with Sac/Val. However, when examining only the subjects switching from ARB to Sac/Val (n=50), neither creatinine nor eGFR significantly changed before or after treatment with Sac/Val (creatinine, 0.82±0.33 to 0.83±0.33 mg/dL, P=0.5475; eGFR, 69.9±22.7 to 68.8±22.6 mL/min/1.73 m^2, P=0.3370).

Finally, independent predictors of systolic BP lowering by drug switching to/adding Sac/Val were examined by multiple regression analysis. In the univariate analysis, systolic BP, eGFR, PRA (log-transformed value), and the use of ARB or diuretic before drug switching/adding were significantly associated with a reduction in systolic BP after treatment with Sac/Val (**Table 4**). In the multivariate analysis, among these possible determinants, low PRA as well as high baseline systolic BP independently predicted systolic BP reduction after treatment with Sac/Val. Although the use of ARBs clearly increases the PRA level, low PRA was still an independent determinant of systolic BP reduction after treatment with Sac/Val, even when limited to only patients with antihypertensive drugs including ARB before Sac/Val treatment (**Supplementary Table 3**).

Discussion

In Japan, Sac/Val is currently used not only as a therapeutic agent for heart failure,[4,5] but also as an antihypertensive drug.[6–8] In particular, the BP-lowering effect of sacubitril through its neprilysin-inhibitory action is unique and not found in any other antihypertensive drug to date.[1–3] Most studies of the antihypertensive effect of Sac/Val have compared it with the antihypertensive effect of ARBs[9–13] or only examined the effects of switching from ARBs.[8,16,17] In the real-world clinical setting, however, Sac/Val is used not only for switching from ARBs, but also for switching from other classes/patterns of antihypertensive drugs, and as an additional drug for patients whose BP is not adequately controlled. In the present study, we clearly showed that the addition of Sac/Val in switching from or adding to various antihypertensive drugs was useful for additional BP-lowering in poorly controlled or untreated hypertensive patients.

We also investigated the changes in various biochemical parameters before and after treatment with Sac/Val, and of them ALT, triglycerides, log CRP, and UA were significantly decreased after Sac/Val treatment. Ye et al reported greater decreases in UA and inflammatory factors, including high-sensitive CRP, in hypertensive patients treated with Sac/Val than in those treated with losartan,[18] which is compatible with our results. As for the effect of Sac/Val on the parameters of glucose metabolism, inconsistent findings have been reported. Sazawa et al showed that treatment with Sac/Val improved glycemic control (decreased HbA1c) in patients with heart failure and/or hypertension, especially in those with concomitant diabetes,[7] but Zhang et al showed that in hypertensive patients with diabetes, favorable effects on HbA1c and LDL-C did not differ between Sac/Val and olmesartan.[19] Further studies are needed to determine whether Sac/Val has a more favorable effect on glucose metabolism than other antihypertensive drugs.

When comparing the systolic BP-lowering effect after treatment with Sac/Val among the patient groups by antihypertensive drugs switched, its effect was the smallest in the group switching from ARB plus diuretic. In addition, the degree of systolic BP reduction was obviously attenuated in the patient group with diuretic before treatment with Sac/Val. These results may be due to an overlap in the mechanism of the BP-lowering effect of sacubitril and diuretics (mostly thiazide diuretics in this study), because a natriuretic/diuretic action of sacubitril through enhancement of the biological activity of natriuretic peptides by

neprilysin inhibition is thought to be responsible, at least in part, for the antihypertensive effect of this agent.[20,21] Thiazide diuretics can have unfavorable effects on metabolic factors and renal function, and in fact, our observations indicated that in patients switched from antihypertensive drugs containing diuretics, significant improvements in metabolic and renal functional parameters such as ALT, UA, and creatinine were observed after treatment with Sac/Val. Our findings on metabolic factors and renal function were generally consistent with those in a recent study comparing the effects of ARNI (Sac/Val) therapy and thiazide diuretic/renin–angiotensin system inhibitor combination therapy.[8] Therefore, switching to Sac/Val from antihypertensive agents such as ARB plus diuretic is likely to have favorable effects on metabolic factors and renal function, even if the BP reduction after drug switching remains minimal.

Although we speculated that plasma levels of BNP might be related to the BP-lowering effect after treatment with Sac/Val, baseline BNP levels were not associated with systolic BP change after switching to/adding Sac/Val in the present subjects, a finding that suggests, at least in hypertensive patients without overt heart failure, the antihypertensive effect of Sac/Val probably does not depend on the subject's plasma BNP level. On the other hand, lower levels of PRA before administration of Sac/Val were significantly associated with systolic BP change after switching to/adding Sac/Val and further low PRA levels were an independent predictor of the reduction of systolic BP by Sac/Val. Low PRA is considered to reflect not only increased intravascular volume but also roughly having salt sensitivity and a high salt intake,[22] and furthermore, patients become more salt sensitive under treatment with ARBs. Therefore, it may be reasonable that patients with lower PRA even under antihypertensive therapy including ARBs are more likely to benefit from the BP-lowering effect of Sac/Val through natriuretic/diuretic actions via enhanced sodium excretion.[20,21] Unfortunately, we did not evaluate indices of fluid volume, such as inferior vena cava diameter and urinary sodium excretion, or these changes after treatment with Sac/Val in the present subjects, but obtaining these data may help to better clarify the mechanism of the antihypertensive effect of switching to/adding Sac/Val.

Study Limitations

First, the present findings were derived from observation without control arms carried out in a single center with a relatively small sample size. Second, the antihypertensive effect of Sac/Val was evaluated only by clinic BP, although cases of overt "white coat" hypertension were excluded. Third, variability in the classes, types, and doses of baseline antihypertensive drugs switched to Sac/Val may have affected the results of the study. Fourth, PRA levels were measured under antihypertensive medications, and some classes of antihypertensive agents significantly influence PRA. Fifth, to evaluate the change in natriuretic peptide levels before and after treatment with Sac/Val, it might have been more appropriate to use N-terminal pro-BNP, which is less sensitive to neutral endopeptidase inhibition.[23]

Conclusions

The present study results indicated that the use of Sac/Val in a variety of patterns such as switching from or adding to several classes of antihypertensive drugs is beneficial for poorly controlled or untreated hypertension and also suggest that low PRA may be a predictor of the antihypertensive effect of switching to/adding Sac/Val in real-world clinical hypertension treatment. However, our conclusions from this study should be verified by a prospective study using control groups not receiving Sac/Val. In addition, further studies, such as assessing home BP, will be required to confirm the clinical benefit of Sac/Val for hypertensive patients in daily practice.

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Disclosures

T. Horio received personal fees for lectures from Novartis Pharma and Otsuka Pharmaceutical. D.F. received personal fees for lectures from Novartis Pharma and Otsuka Pharmaceutical, and received a scholarship grant from Otsuka Pharmaceutical. M.Y. is a member of *Circulation Reports*' Editorial Team. The other authors have no conflicts of interest to disclose.

IRB Information

The study protocol was approved by the Ethics Committee of Ishikiriseiki Hospital (approval no. 23-2).

Data Availability

The identified participant data will not be shared.

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Supplementary Files

Please find supplementary file(s);
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