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SHORT REPORT

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Comparative effects of valsartan plus cilnidipine or hydrochlorothiazide on nocturnal home blood pressure

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Abstract

We tested our hypothesis that, in hypertensive patients with higher nocturnal home systolic blood pressure (HSBP) at baseline, a valsartan/cilnidipine (80/10 mg) combination would reduce nocturnal HSBP more markedly than a valsartan/hydrochlorothiazide (80/12.5 mg) combination. Patients measured their nocturnal HSBP over three nights prior to study randomization and at the end of treatment. Sixty-three and 66 patients comprised the valsartan/cilnidipine and valsartan/hydrochlorothiazide groups; their respective baseline nocturnal HSBP values were 124.3 ± 15.6 and 125.8 ± 15.2 mm Hg (P = .597). Nocturnal HSBPs were significantly reduced from baseline in both groups. Although the valsartan/hydrochlorothiazide group exhibited a significantly greater reduction in nocturnal HSBP compared to the valsartan/cilnidipine group (−5.0 vs. −10.0 mm Hg, P = .035), interaction between the treatment groups and the baseline nocturnal HSBP levels for the changes in nocturnal HSBP after the treatment periods was significant (P = .047). The BP-lowering effect of valsartan/cilnidipine was more dependent on baseline nocturnal HSBP than that of valsartan/hydrochlorothiazide.

1 | INTRODUCTION

Nocturnal home blood pressure (BP) has been strongly associated with cardiovascular target organ damage and cardiovascular mortality in hypertensive patients.[1,2] A previous meta-analysis demonstrated that the nocturnal BP values measured by home BP monitoring (HBPM) were similar to those measured by ambulatory BP monitoring (ABPM) and showed a comparable relationship with target organ damage compared to those measured by ABPM,[3] which has been the gold standard for measurement of nocturnal BP levels.[4] A reduction of nocturnal ambulatory BP (ABP) has been linked to cardiovascular protection,[5] and thus, nocturnal home BP (HBP) reduction could be an important strategy for the management of hypertension.[6] However, information regarding the antihypertensive effects of reducing nocturnal HBP levels is quite limited.

Cilnidipine is an L/N-type calcium channel blocker. Generally, patients with morning hypertension or those with an abnormal BP dipping pattern exhibit increased sympathetic activity. We showed that cilnidipine significantly reduced morning systolic BP (SBP) in patients with higher baseline morning SBP[7] and restored the abnormal BP dipping status (including extreme dipping) toward a normal dipping pattern,[8] both of which were measured by ABPM. These results indicated that cilnidipine could control the ABP level of patients with increased sympathetic activity and that it does not lower the nocturnal BP levels of patients whose nocturnal BP has already

been controlled. We thus hypothesized that, in patients with higher nocturnal HBP at baseline, cilnidipine could reduce the nocturnal HBP levels more markedly than other classes of antihypertensive agents.

We tested our hypothesis in the Study on Uncontrolled Morning Surge for N-type CCB and Low Dose of HCTZ, Using the Internet Through Blood Pressure Data Transmission System (SUNLIGHT),[9] a randomized controlled trial that recruited patients with morning hypertension, using a valsartan/cilnidipine combination or a valsartan/hydrochlorothiazide (HCTZ) combination.

2 | METHODS

2.1 | Study design

The details of the SUNLIGHT trial have been published.[9] Briefly, eligible patients who showed morning SBP ≥ 135 mm Hg or diastolic BP (DBP) ≥85 mm Hg as assessed by HBPM performed more than three times during a 4-week run-in period with valsartan (80 mg) monotherapy treatment were randomized in a blind fashion to receive one of two treatments: a fixed-dose valsartan/cilnidipine combination (80 mg/10 mg) tablet (valsartan/cilnidipine group) or a fixed-dose valsartan/HCTZ combination (80 mg/12.5 mg) tablet (valsartan/HCTZ group), which are the standard dose for Japanese, over 8 weeks. The present study was a post hoc analysis of the SUNLIGHT trial.

2.2 | BP measurements

The patients measured their own BP values at home using an automatic information and communication technology (ICT)-based device (HEM-7252G-HP; Omron Healthcare) based on the cuff-oscillometric principle. All data obtained by the device were transmitted automatically to a cloud-based remote monitoring system,[10] and the data were managed at an independent facility, Satt Co., Ltd.

Self-measured daytime HBP and office BP values were obtained according to the JSH2014 guidelines.[11] The patients were instructed to measure their daytime HBP in a sitting position in an appropriate environment after resting for 1-2 minutes with the legs not crossed. The arm cuff position was maintained at heart level. Two home BP readings were taken at a 1-2-minutes interval in both the morning (within 1 hour of waking and before taking antihypertensive medication) and evening (before bed).

Office BP was measured at each participating medical center using the center's own validated cuff-oscillometric devices. Two consecutive measurements were taken at a 1-2 minutes interval, and the average of the two measurements was used to define office BP.

The patients' nocturnal HBP was measured during the sleep periods. The ICT-based device was preset to take three BP measurements at fixed times: 2:00, 3:00, and 4:00 AM The patients were instructed to wear the BP cuff and press the button to start the timer when they went to bed in order to measure their nocturnal HBP. Nocturnal HBPM was conducted during the run-in period, and at the end of the treatment period, and both the run-in and end-of-treatment measurements were performed over three nights (not necessarily consecutive).

2.3 | Statistical analysis

The data are presented as the mean ± standard deviation (SD). Fisher's exact test was used for categorical variables to determine background differences. For continuous variables, Welch's *t* test was used to determine any significant difference between the two groups, and a paired *t* test was used to determine intragroup differences. Interactions between treatment groups according to the baseline nocturnal home SBP (HSBP) levels and the change in nocturnal HSBP levels were evaluated by a linear regression model. All statistical analyses were performed using SAS ver. 9.4 software (SAS Institute). A P value < .05 was considered significant.

3 | RESULTS

The patient disposition of this study was shown in Figure S1. In the valsartan/cilnidipine and valsartan/HCTZ groups, 63 and 66 patients completed the treatment, respectively. Table S1 shows the demographic variables and clinical and behavioral characteristics of both groups. There were no significant differences in baseline clinical characteristics between the groups. In the cilnidipine group and the HCTZ group, the changes in nocturnal HSBP from baseline to the end of the 8-week treatment were −5.0 mm Hg and −10.0 mm Hg, respectively (both P < .001) (Table 1). The nocturnal HSBP in the HCTZ group was significantly decreased (P = .035) compared to that in the cilnidipine group.

The Figure 1 shows the scatter plots between the baseline nocturnal HSBP levels and the changes in nocturnal HSBP from baseline to the end of the treatment period in each treatment group. The interaction between the two treatment groups and the baseline nocturnal HSBP levels for the changes in nocturnal HSBP after the treatment periods was significant (P = .047).

4 | DISCUSSION

This study compared the nocturnal HSBP measured by an ICT-based HBPM device between a valsartan/cilnidipine combination group and a valsartan/HCTZ combination group of patients with morning hypertension. Although the valsartan/HCTZ group showed significantly reduced nocturnal HSBP compared to the valsartan/cilnidipine group, a significant interaction was observed between treatment groups in regard to the baseline nocturnal HSBP level and the change in nocturnal HSBP. That is, in patients with higher nocturnal HSBP at baseline, a valsartan/cilnidipine combination could

TABLE 1 Comparison of the changes in blood pressure parameters between the treatment groups

	Valsartan/cilnidipine (n = 63)			Valsartan/HCTZ (n = 66)			Comparison between groups
BP variable	Baseline	Change	*P* value	Baseline	Change	*P* value	*P* value
Nocturnal SBP, mm Hg	124.3 ± 15.6	−5.0 ± 12.3	<.001	125.8 ± 15.2	−10.0 ± 10.5	<.001	.035
Nocturnal DBP, mm Hg	76.4 ± 9.4	−2.3 ± 7.7	.067	76.2 ± 10.2	−4.6 ± 5.5	<.001	.092
Nocturnal HR, bpm	63.1 ± 8.4	0.2 ± 5.3	.888	60.3 ± 7.9	−1.2 ± 3.9	.022	.137
Morning SBP, mm Hg	142.4 ± 14.5	−10.7 ± 11.7	<.001	142.4 ± 15.7	−13.6 ± 10.7	<.001	.142
Morning DBP, mm Hg	87.0 ± 10.3	−4.5 ± 5.4	<.001	87.7 ± 10.9	−6.5 ± 5.6	<.001	.042
Morning HR, bpm	68.4 ± 8.2	1.1 ± 6.6	.378	65.5 ± 8.3	0.9 ± 4.3	.115	.844
Evening SBP, mm Hg	133.3 ± 14.2	−9.3 ± 9.8	<.001	132.7 ± 14.0	−13.1 ± 10.7	<.001	.042
Evening DBP, mm Hg	80.6 ± 10.8	−4.8 ± 6.2	<.001	79.7 ± 9.3	−5.6 ± 5.6	<.001	.411
Evening HR, bpm	71.8 ± 10.5	0.3 ± 6.4	.479	70.6 ± 10.3	0.4 ± 5.5	.549	.913
Office SBP, mm Hg	143.9 ± 17.7	−11.8 ± 15.9	<.001	144.2 ± 18.1	−13.8 ± 16.4	<.001	.490
Office DBP, mm Hg	82.9 ± 13.3	−5.6 ± 10.4	<.001	85.2 ± 11.6	−8.3 ± 9.5	<.001	.124
Office HR, mm Hg	75.9 ± 9.0	−1.3 ± 6.9	.085	72.5 ± 10.2	0.5 ± 9.4	.725	.212

Note: Abbreviations: BP, indicates blood pressure; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.
Data are mean ± SD. The changes from baseline in each treatment group are compared.

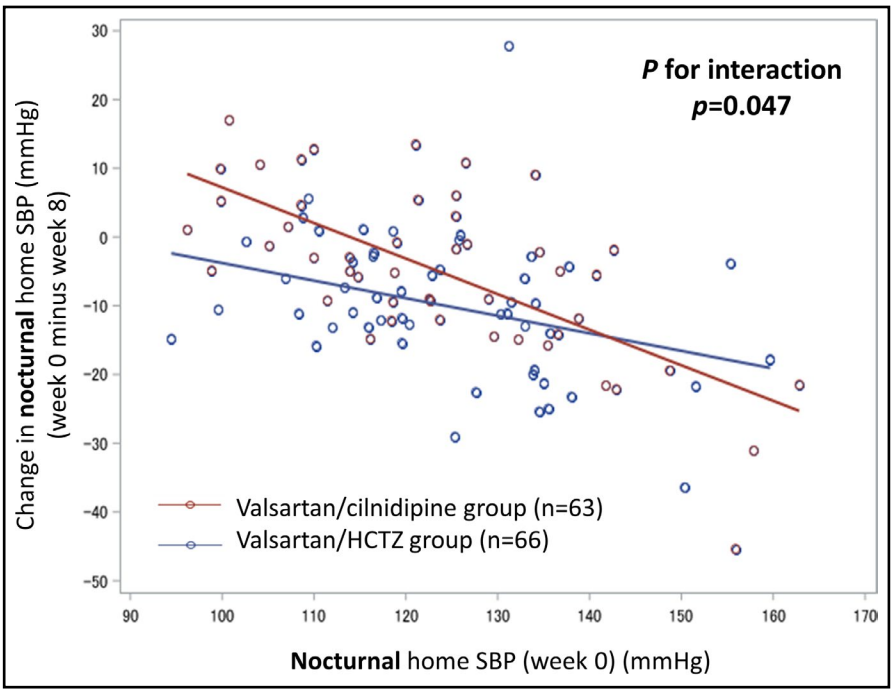

FIGURE 1 Scatter plots of the baseline nocturnal home SBP levels and the changes in nocturnal home SBP from baseline to the end of the treatment period in the total group of patients. HCTZ, hydrochlorothiazide; SBP, systolic BP

reduce nocturnal HSBP more markedly than a valsartan/HCTZ combination.

This is the first study to show that a valsartan/cilnidipine combination could reduce nocturnal HSBP levels relative to those at baseline. In the ACHIEVE-ONE trial, we observed that cilnidipine greatly reduced nocturnal SBP assessed by ABPM in patients with riser and non-dipper circadian BP rhythms, whereas it did not reduce nocturnal SBP in those with the extreme dipper circadian BP rhythm.[8] It has been suggested that extreme dipping may provoke cerebral and cardiac ischemia caused by an excessive lowering of nocturnal BP, leading to hypoperfusion in elderly patients or in patients receiving antihypertensive treatment. The results of our present study and the ACHIEVE-ONE trial indicated that cilnidipine would not worsen organ damage risk in patients with already controlled nocturnal HSBP, but it would be likely to reduce cardiovascular risk, especially in those with increased nocturnal HSBP.

In the present investigation, the changes in nocturnal HSBP level from baseline to the end of the treatment period were greater in the

valsartan/HCTZ group compared to the valsartan/cilnidipine group. We reported in the NOCTURNE study[12] that an ARB/CCB combination (irbesartan 100 mg/amlodipine 5 mg) achieved a significantly greater reduction in the nocturnal HSBP level than an ARB/diuretic combination (irbesartan 100 mg/trichlormethiazide 1 mg); those results were the opposite of our present findings.

We speculate that the differences in these results might have been due to the differences in the antihypertensive drug characteristics between cilnidipine and amlodipine. Amlodipine blocks L-type calcium channels in vascular smooth muscle and induces blood flow-independent vasodilation in hypertensive patients.[13] On the other hand, cilnidipine blocks both L-type and N-type calcium channels.

With the blocking of N-type calcium channels, cilnidipine can suppress increased sympathetic activity.[14] The ACIEVE-ONE trial showed that cilnidipine did not reduce the nocturnal BP level in patients with the extreme dipper pattern, which indicated that cilnidipine could restore an abnormal nocturnal dipping status by blocking N-type calcium channels.[8] Sakata et al directly showed that cilnidipine suppressed cardiac sympathetic overactivity, whereas amlodipine had only a slight suppressive effect.[15] Their results indicated that the effects of cilnidipine and amlodipine on the reduction of nocturnal BP may be different and that cilnidipine may restore nocturnal HBP levels by blocking N-type calcium channels. Cilnidipine should thus be one of the appropriate options for the 24-h management of hypertension.

This study has some limitations. The sample size was small. In addition, since we did not use 24-h ABPM, it is possible that the nadir of nocturnal BP levels was not measured. Moreover, we did not set criteria for the timing of antihypertensive administration. Nighttime dosing of antihypertensive medications might have affected the decrease of nocturnal HSBP. Lastly, our results might not be generalizable to other hypertensive patients, since this study was originally designed to examine patients with morning hypertension.

5 | CONCLUSION

The valsartan/cilnidipine combination provided less reduction in nocturnal HSBP levels compared to the valsartan/HCTZ combination, while a significant interaction was observed between the two treatment groups and the baseline nocturnal HSBP levels for the changes in nocturnal HSBP after the treatment periods. Compared to that of valsartan/HCTZ, the BP-lowering effect of valsartan/cilnidipine is more dependent on the nocturnal HSBP value at baseline. Since nocturnal BP has been strongly associated with cardiovascular mortality and is easily assessed by HBPM, nocturnal HBPM has the potential to be generalized and to become a therapeutic target in clinical practice.

CONFLICT OF INTEREST

The authors state that they have no potential conflicts of interest.

AUTHOR CONTRIBUTION

Kario K takes primary responsibility for this paper. Fujiwara T wrote the manuscript.Kario K, Hoshide S, and Fujiwara T collected patients data. Tomitani N and Kanegae H did statistical analysis. Kario K, Hoshide S, and Tomitani N reviewed/edited the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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