

## Effects of a Combination of Losartan and Hydrochlorothiazide in Patients with Hypertension and a History of Heart Failure

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**Objectives:** To evaluate the switching from an angiotensin receptor blocker (ARB) to a drug combination containing an ARB and a diuretic drug in terms of effects on hypertension, cardiac load, and cardiac function.

**Methods:** In a study conducted on 82 patients with a history of heart failure and hypertension who had been treated with an ARB but failed to reach the target blood pressure, ongoing oral ARB treatment was switched to a drug combination of losartan and hydrochlorothiazide (HCTZ). Using ambulatory blood pressure monitoring (ABPM), the variations in blood pressure and the effects on cardiac load and cardiac function were evaluated before and after treatment.

**Results:** Comparison of the ABPM findings before and after switching treatment showed significant improvements in mean systolic and diastolic blood pressure, improvements in systolic and diastolic blood pressure 1 hour before getting out of bed, and improvements in the plasma levels of human brain natriuretic peptide as an indicator of cardiac load.

**Conclusion:** The drug combination of losartan and hydrochlorothiazide showed a stronger antihypertensive effect than that of the conventional ARB and improved heart function.

**Key words:** ABPM, morning surges, BNP, adherence, salt sensitivity

### INTRODUCTION

The number of patients with hypertension in Japan is currently estimated to be about 40 million, but only approximately 20% have fully achieved a reduced blood pressure to target levels through the use of antihypertensive drugs [1]. Hypertension is the greatest risk factor for cardiovascular disease, and its prevention and treatment are matters of worldwide challenge. The guidelines for hypertension in Japan (JSH2009) recommend that the concurrent use of several antihypertensive drugs is needed rather than monotherapy to achieve a reduction of blood pressure to target levels. One of the possible options consists of the combination of an angiotensin receptor blocker (ARB) and a diuretic [2]. A decrease in the circulating blood volume induced by hydrochlorothiazide (HCTZ) causes activation of the renin-angiotensin system (RAS); therefore, the combined use of this drug with an ARB, which inhibits the RAS, is both rational and effective.

In recent years, fluctuations in blood pressure have been the focus of attention in patients with hypertension as a risk factor for developing cardiovascular events. The circadian rhythm of blood pressure has been found to be associated with hypertension-induced organ damage and allows for the accurate prediction of cardiovascular events, while excessive

morning surges are a risk factor for developing cardiovascular events. Based on these circumstances, ambulatory blood pressure monitoring (ABPM) was first approved for insurance coverage in Japan in 2008. Since then, the usefulness of ABPM in the diagnosis and treatment of hypertension has been specified by the JSH2009. The mean values found through the use of ABPM more accurately reflects organ damage than blood pressure measurement in a clinical examination room. A worldwide consensus has been reached with regard to the fact that ABPM allows for an accurate estimation of the prognosis and that there is a need for a strict and high-quality reduction in blood pressure. Therefore, in this study of patients with hypertension and a history of heart failure whose blood pressure had failed to reach target levels despite antihypertensive treatment, we switched the patients from an ongoing oral ARB treatment to a drug combination of Losartan and HCTZ. Using ABPM to compare values found before and after treatment, we evaluated blood pressure fluctuations as well as the effects of the drug combination on cardiac load.

### PATIENTS AND METHODS

This study was approved by the Tokai University Ethics Committee (authorization number: 07R039), and informed consent forms were received from all patients. The conditions for study inclusion included the

following: blood pressure that failed to reach target levels (a mean systolic blood pressure of 130 mmHg and a diastolic blood pressure of 80 mmHg measured using ABPM) despite having received antihypertensive treatment involving an ARB for at least 6 months and a history of congestive heart failure but no severe deterioration of cardiac function (left ventricular ejection fraction [LVEF] < 40%). Because the ARB that the patients were taking at the start of the study was switched to the drug combination of losartan (50 mg) and HCTZ (12.5 mg), the following items were measured before switching and 6 months later, and their fluctuations were observed: mean blood pressure, pulse rate and blood pressure 1 hour before getting out of bed, serum levels of human brain natriuretic peptide (BNP) according to data obtained from blood samples, the LVEF and left ventricular mass index according to data obtained from echocardiography, and the cardiothoracic ratio (CTR) according to plain radiographs of the chest. We used a TM-2431 portable blood pressure monitor (manufactured by A & D Co., Ltd Tokyo Japan) and TM-2430-15 analysis software. The measurements were conducted continuously during a 24-hour period starting at 10:00 a.m. until 10:00 a.m. the next day. The measured values are expressed as mean value  $\pm$  standard deviation (mean  $\pm$  SD), and the data that were collected at the beginning of the treatment and those collected at 6 months were compared using the Wilcoxon t-test. A p-value of 5% was considered the standard level of significance.

## RESULTS

The study included a total of 86 patients (54 men, 32 women). The mean age was  $68 \pm 8.2$  years. None of the patients dropped out due to adverse events. However, 4 patients were eliminated for either changing their medication or added other medications, so the evaluations were ultimately conducted in 82 patients.

The mean body mass index was  $24 \pm 3.4$  kg/m<sup>2</sup>. 58 patients (70.7%) had a family history of high blood pressure. Complications included dyslipidemia in 36 patients (43.9%), diabetes in 24 patients (29.3%), cerebrovascular disorders in 21 patients (25.6%), and chronic kidney disease (stage 3 or higher) in 53 patients (64.6%).

The ARB that the patients had been taking prior to switching treatment consisted of losartan 50 mg (27 patients, 32.9%), olmesartan 40 mg (20 patients, 24.4%), olmesartan 20 mg (15 patients, 18.3%), telmisartan 40 mg (9 patients, 11.0%), candesartan 8 mg (3 patients, 3.7%), valsartan 80 mg (3 patients, 3.7%), losartan 100 mg (2 patients, 2.4%), telmisartan 80 mg (2 patients, 2.4%), and candesartan 12 mg (1 patient, 1.2%). The combination drugs (including overlapping duplicates) included  $\beta$ -blockers (51 patients, 62.2%), calcium channel blockers (45 patients, 54.9%), diuretics (22 patients, 26.8%), angiotensin-converting enzyme (ACE) inhibitors (16 patients, 19.5%), nitrites (15 patients, 18.3%), and  $\alpha$ -blockers (1 patient, 1.2%).

The changes in blood pressure after administration of the drug combination of losartan and HCTZ are shown in Table. According to the ABPM, the mean systolic blood pressure changed from  $139 \pm 15.3$  mmHg

before switching treatment to  $124 \pm 12.5$  mmHg ( $P < 0.01$ ) 6 months after switching treatment; the mean diastolic blood pressure changed from  $81 \pm 9.8$  mmHg to  $72 \pm 7.2$  mmHg ( $P < 0.01$ ), showing improvement. The systolic blood pressure 1 hour before getting out of bed changed from  $154 \pm 15.7$  mmHg to  $137 \pm 16.0$  mmHg ( $P < 0.01$ ), while the diastolic blood pressure changed from  $89 \pm 9.7$  mmHg to  $79 \pm 10.5$  mmHg ( $P < 0.01$ ). The average pulse rate also decreased from  $69 \pm 10.3$  beats/min to  $67 \pm 9.7$  beats/min ( $P = 0.03$ ). In addition, the mean change in body weight was from  $62 \pm 11.4$  kg to  $62 \pm 11.3$  kg, with no significant difference.

The changes in each parameter after switching treatment are shown below. The plasma levels of BNP changed from  $90 \pm 86$  pg/mL to  $38 \pm 45$  pg/mL ( $P < 0.01$ ). In addition, echocardiography showed that the LVEF had changed from  $64 \pm 13\%$  to  $69 \pm 9.8\%$  ( $P < 0.01$ ) and that the left ventricular mass index had changed from  $150 \pm 40.0$  g/m<sup>2</sup> to  $136 \pm 39.9$  g/m<sup>2</sup> ( $P < 0.01$ ). Finally, plain chest radiographs showed that the CTR had changed from  $52 \pm 5.4\%$  to  $49 \pm 5.2\%$  ( $P < 0.01$ ).

In addition, during the period of administration of the drug combination of losartan and HCTZ, there were no subjective or objective symptoms suggestive of any clinical difficulties. In terms of renal function, the serum creatinine level changed from  $1.1 \pm 0.5$  mg/dL to  $1.0 \pm 0.5$  mg/dL ( $P < 0.01$ ), and the estimated Glomerular filtration rate (GFR) value changed from  $54 \pm 17$  mL/min/1.73 m<sup>2</sup> to  $58 \pm 12$  mL/min/1.73 m<sup>2</sup> ( $P < 0.01$ ).

## DISCUSSION

### The use of ABPM

The aim of antihypertensive treatment is to actively reduce blood pressure; from the perspective of organ preservation, RAS inhibitors are considered the treatment of choice. The worst disadvantages of RAS inhibitors are that they cause the blood pressure to become salt sensitive and increase serum potassium levels, which could potentially put the patient at risk of developing acidosis. The combination use of diuretics is considered preferable to compensate for these 2 disadvantages [3, 4]. Reports have also shown that the addition of diuretics to ongoing ARB treatment resulted in effects that were stronger than simple additive effects [5].

In our study, the treatment was switched from ongoing ARB therapy to drug combination of Losartan and HCTZ and the evaluations were conducted using ABPM. Random blood pressure measurements taken at home or during hospital visits were not used as tools to evaluate antihypertensive effects. The mean blood pressure obtained from numerous measurements conducted during a 24-hour period is believed to better reflect an individual's specific blood pressure levels. In addition, ABPM values have been reported to better predict the damage in each patient's cardiovascular organs and better predict prognosis.

In this study, the fact that the switching of treatment from an ARB to a drug combination of Losartan and HCTZ resulted in a significant improvement in blood pressure values measured using ABPM, which

**Table** variation of each parameters before and 6 months after administration of Losartan + Hydrochlorothiazide combination

	before	6 months after	P value
mean systolic blood pressure of ABPM (mmHg)	139 ± 15.3	124 ± 12.5	< 0.01
mean diastolic blood pressure of ABPM (mmHg)	81 ± 9.8	72 ± 7.2	< 0.01
The systolic blood pressure 1 hour before getting out of bed (mmHg)	154 ± 15.7	137 ± 16.0	< 0.01
The diastolic blood pressure 1 hour before getting out of bed (mmHg)	89 ± 9.7	79 ± 10.5	< 0.01
The plasma levels of BNP (pg/ml)	90 ± 86	38 ± 45	< 0.01
Left Ventricular Ejection Fraction (%)	64 ± 13	69 ± 9.8	< 0.01
Left Ventricular mass index (g/m <sup>2</sup> )	150 ± 40.0	136 ± 39.9	< 0.01
CTR of Chest X-ray (%)	52 ± 5.4	49 ± 5.2	< 0.01

showed that the combined treatment provided a rigorous antihypertensive effect. The achievement of an antihypertensive effect that exceeded expectations (mean systolic blood pressure, 14.9 mmHg; diastolic blood pressure, ≤ 8.7 mmHg) was believed to be due to a synergistic effect resulting from the combination of an ARB and a diuretic drug.

#### Suppression of morning surges

Performing rigorous and high-quality antihypertensive control using ABPM, namely conducting an antihypertensive treatment aimed to keep the 24-hour blood pressure levels at < 130/80 mmHg, ensure a suitable circadian rhythm (dipper type), and suppress excessive blood pressure surges (variability), has often been reported to lead to further inhibition of cardiovascular events. The timing of early morning hypertension has been reported to coincide with the predilection time of the occurrence of stroke, myocardial infarction, and sudden death from cardiac causes [6]. Patients who have well controlled nighttime blood pressure and good 24-hour blood pressure control have been reported to have a lower risk of dying of cardiovascular diseases [7]. Those reports suggest that, to prevent cardiovascular events, there seems to be a need to observe and evaluate the 24-hour variations in blood pressure using ABPM. In this study, switching treatment from an ARB to a drug combination of Losartan and HCTZ resulted in a significantly improved blood pressure 1 hour before patients got out of bed; this finding suggested that suppression of the morning blood pressure surge may potentially reduce the risk of the occurrence of cardiovascular events.

#### Reduction of a cardiac load/ Effect of organ-preservation

A number of large-scale clinical trials have shown and confirmed that losartan has an effect of organ-preservation [8]. In addition, reports of clinical trials on hypertension have shown that HCTZ reduces cardiovascular risk. A total of 72% of patients in the LIFE study and 84% of patients in the RENAAL study concurrently used diuretics. It would not be an exaggeration to say that the aforementioned large-scale clinical trials have demonstrated an effect of organ-preservation of the concurrent use of an ARB and a diuretic. In this study, we measured the plasma levels of BNP as a way to evaluate the differences between values before and after the switching of treatment to

the drug combination of Losartan and HCTZ. The plasma concentrations of BNP have been used to determine the degree of heart failure severity, show elevated values even in hypertensive patients, and predict the occurrence of cardiovascular events [9]. Regarding the existing ARB treatment, reports have shown that in patients whose antihypertensive treatment had failed to achieve the JSH criteria, the switching of treatment to a drug combination of Losartan and HCTZ resulted in significant antihypertensive effects and significant improvements in the plasma concentrations of BNP. Other reports have also shown that the use of a drug combination of Losartan and HCTZ resulted in an antihypertensive effect accompanied by decreased concentrations of BNP [10]. The variations in BNP concentrations showed no correlation with the decrease in blood pressure, suggesting that the cardio-preservation effect was independent of the decrease in blood pressure [11]. In our study as well, we found that the combination of an ARB and a diuretic resulted in an antihypertensive effect, an improvement in the plasma levels of BNP, and an improvement in left ventricular mass. A decrease in the CTR was also confirmed. This might have been a cardioprotective effect independent of the decrease in blood pressure.

#### Switching of treatment to a combined drug resulted in improved adherence

From the perspective of adherence, the treatment was switched from an ARB to a drug combination of Losartan and HCTZ without increasing the number of tablets ingested by the patients. Reports have shown that the use of combination drugs that do not increase (or that reduce) the number of tablets to be ingested by patients was associated with a favorable (1.29 ×) increase in adherence, which improved the reduction in blood pressure [12]. In addition, the rate of achievement of target blood pressure levels among patients with hypertension is currently as low as 42%; consequently [13], the oral intake of 2 or more antihypertensive agents is needed in most cases. Therefore, the rate of achievement of target blood pressure levels can be increased by improving adherence through the use of combination drugs [14]. Regarding the occurrence of cardiovascular events, a very important issue in antihypertensive treatment, the hazard ratio of cardiovascular diseases under high adherence conditions associated with adherence to a low number of orally ingested drugs is as low as 0.62, suggesting that

this may lead to a preventive effect against cardiovascular events [15]. Therefore, the use of combination drugs in cases of insufficient antihypertensive effects of ongoing treatments using ARBs may be extremely meaningful.

### Salt sensitivity

Salt sensitivity is a condition characterized by large fluctuations in blood pressure with change in salt intake [16]. Japanese individuals are genetically and physically (tendency toward obesity) predisposed to enhanced salt sensitivity, and > 40% of hypertensive patients in Japan are estimated to have salt-sensitive hypertension. There is no standard definition of salt sensitivity, and it differs depending on the researcher. Although there is no simple or easy method to clinically distinguish between the various types of salt sensitivity, they are generally classified based on age, family medical history, and presence of diabetes, chronic kidney disease, and obesity [17]. In this study, the mean estimated GFR was  $55.1 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^2$ , the proportion of patients with CKD stage 3 was as high as 61.6%, and the mean BMI was  $24 \pm 3.4 \text{ kg/m}^2$ . A tendency toward obesity was noted in this study population. In addition, patients with a family history of hypertension accounted for 67.4% of the total number of patients, suggesting that most patients have salt-sensitive hypertension.

Furthermore, administration of 12.5 mg of HCTZ has been reported to reduce the salt intake by 5–6 g [18]. In other words, addition of HCTZ may also be effective in lowering blood pressure in patients with salt-sensitive hypertension who respond to a reduction in the salt intake. Thus, this study showed that the combination of an ARB and a diuretic agent had a stronger antihypertensive effects and inhibitory effect on the renin-angiotensin system (RAS) than ARB alone.

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