

# The Influence of a Direct Renin Inhibitor on the Central Blood Pressure

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## Abstract

**Background:** Central blood pressure (CBP) is superior to brachial blood pressure as a predictor of cardiovascular risk in patients with hypertension. There is currently no consensus regarding whether a direct renin inhibitor (DRI) selectively acts on CBP.

**Methods:** Thirty subjects with essential hypertension who showed a CBP of 140 mm Hg or higher after 12 weeks of treatment with a standard dose of a DRI (150 mg) were analyzed. The patients were randomly divided into 2 groups: the high-dose DRI group (n=15) received 300 mg of DRI per day, and the combination group (n=15) received both the standard dose of the DRI and a diuretic (12.5 mg of hydrochlorothiazide). The systolic blood pressure (SBP), CBP, and the augmentation index (AI) were determined before treatment and after 12 and 24 weeks of treatment.

**Results:** The SBP, CBP and AI were significantly decreased after 12 weeks of treatment with standard dose of the DRI ( $p < 0.05$ ). From 12 to 24 weeks after assignment the SBP and CBP were also significantly decreased in both the high-dose DRI group and the combination group. The high-dose DRI group showed a greater decrease in the CBP, but not in the SBP, than did the combination group ( $p < 0.05$ ). The AI decreased significantly from 12 to 24 weeks in the high-dose DRI group ( $p < 0.05$ ) but not in the combination group ( $p = 0.14$ ).

**Conclusions:** Treatment with a DRI contributes to a decrease in the CBP and AI, and high-dose DRI therapy leads to a further decrease in the CBP and AI.

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**Key words:** central blood pressure, direct renin inhibitor, augmentation index

## Introduction

The number of patients with hypertension in Japan is estimated to be 40 million and will increase further as the population ages. Central blood pressure (CBP), the blood pressure at the origin of the aorta, increases with the age-associated progression of atherosclerosis. The latest large-scale

Anglo-Scandinavian Cardiac Outcomes Trial-Conduit Artery Function Evaluation study showed that CBP is a prognostic factor for cardiovascular events, and its effects are independent of brachial blood pressure<sup>1</sup>. Therefore, during the treatment of hypertension, evaluation and treatment based on CBP, as well as on peripheral blood pressure, are considered important. Previous studies have measured the CBP invasively. However, the CBP

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can now be estimated on the basis of the augmentation index (AI) of peripheral vessels<sup>2,3</sup>. The AI is a ratio calculated from the blood pressure waveform and is a surrogate measure of arterial stiffness. The AI has been shown in a variety of patient populations to be a predictor of adverse cardiovascular events, and a higher AI is associated with target organ damage<sup>4</sup>. The radial AI is also considered a useful variable for screening for left ventricular hypertrophy (LVH)<sup>5,6</sup>. The Sokolow-Lyon index, which is used to evaluate LVH in electrocardiograms (ECGs), is used to evaluate the effects of drug therapy.

Although many antihypertensive drugs available for clinical use, there is no consensus on which drug selectively acts on central arteries. The inhibitory effects of antihypertensive drugs on cardiovascular events are not always the same, even when their antihypertensive effects are equivalent. Angiotensin II receptor blockers (ARBs) and calcium channel blockers are more useful than  $\beta$ -blockers or diuretics for reducing the central arterial blood pressure<sup>7,8</sup>. In addition, a combination of 2 vasodilators can reportedly reduce the CBP more than a single agent can<sup>9</sup>. Patients with diabetes mellitus, chronic kidney disease, and a history of myocardial infarction, and nonelderly patients (less than 65 years) were the aggressive use of antihypertensive agents, especially diuretics<sup>10</sup>.

On the other hand, to our knowledge, no study has examined the effects of aliskiren fumarate, a new antihypertensive agent (a direct renin inhibitor, DRI), which acts on the CBP. To investigate the effects of aliskiren fumarate on CBP, this study divided patients who did not respond to a standard dose of DRI into 2 groups: a group that received a high dose of the DRI, and a group that received both the standard dose of the DRI and a diuretic. The aim of this study was to investigate the effects of DRI on CBP and the AI and to compare these effects between a high-dose DRI and combination therapy with a standard-dose DRI and a diuretic.

## Materials and Patients

### Subjects

Hypertension was defined as a systolic blood pressure (SBP)  $\geq 140$  mm Hg, a diastolic blood pressure (DBP)  $\geq 90$  mm Hg, or current use of antihypertensive agents. A total of 36 consecutive subjects 20 years or older with hypertension evaluated at the Department of Cardiology, Nippon Medical School, were initially enrolled in this study. Subjects were excluded if they had secondary hypertension or bilateral or unilateral renal artery stenosis or were undergoing hemodialysis or peritoneal dialysis. Two patients declined to participate in this study. Four patients were excluded because they had achieved a good SBP and CBP after 12 weeks of treatment with 150 mg/day of the DRI (standard dose). The subjects analyzed were 30 patients with hypertension who showed a CBP of 140 mm Hg or higher after 12 weeks of treatment with a standard dose of DRI (150 mg). This study employed the prospective randomized open-label blinded-endpoint method, randomization with a random number table, and assignment by a third party. The patients were randomly assigned to 1 of 2 groups; the high-dose DRI group (15 patients) received a high dose (300 mg/day) of the DRI, and the combination group (15 patients) received combination therapy with the standard dose of the DRI (150 mg/day) and a diuretic (12.5 mg/day of hydrochlorothiazide; **Fig. 1**). All patients were instructed to continue diet and exercise therapy during the study. The study protocol was approved by the ethics committee of Nippon Medical School. All 30 subjects provided written informed consent before enrollment. This study has been registered in the University Hospital Medical Information Network Clinical Trials Registry System as trial ID UMIN000005281.

### Follow-up

The treatment period was 24 weeks. All patients were scheduled for monthly visits to measure blood pressures and to evaluate treatment compliance. Clinical assessments, blood sampling, and evaluations

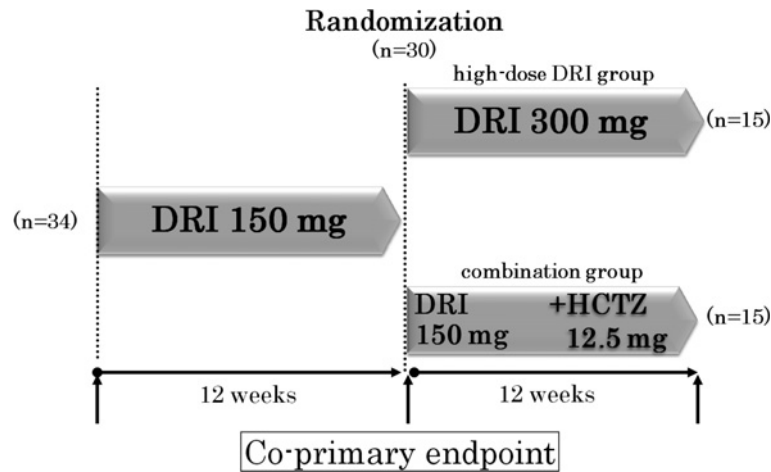


Fig. 1 Study design

A total of 34 subjects were initially enrolled. Four patients were excluded because they had achieved a good SBP and CBP after 12 weeks of treatment with a standard dose of the DRI (150 mg/day). The study analyzed 15 patients receiving the high dose of the DRI alone (high-dose DRI group) and 15 patients receiving both the standard dose of the DRI and a diuretic (combination group). SBP, systolic blood pressure; CBP, central blood pressure; DRI, direct renin inhibitor; HCTZ, hydrochlorothiazide.

of the CBP, AI, and Sokolow-Lyon index in ECGs, as indicator of the LVH, were performed before treatment with the DRI and 12 and 24 weeks after the start of treatment. After randomization at 12 weeks, all patients received regular outpatient treatment until 24 weeks.

#### Evaluation of the Effectiveness of the DRI

The primary endpoints were the effects of DRI on the CBP and aortic AI to compare these effects between the high-dose DRI group and the combination group. The secondary endpoints were the effects of the DRI on SBP, DBP, the Sokolow-Lyon index, the urinary albumin-to-creatinine ratio (ACR), and the high-sensitivity C-reactive protein (hs-CRP) level, as a marker of inflammation.

#### Measurement of Physiological Parameters

##### Blood sampling and measurements

Blood samples were obtained from the antecubital vein after an overnight fast of at least 12 hours. The hs-CRP level was measured with a validated, high-sensitivity assay (Denka-Seiken, Tokyo, Japan). Urinary albumin excretion was estimated from a morning fasting spot urine sample with the ACR (milligrams of albumin per gram of creatinine). The

urinary concentrations of albumin and creatinine were determined with a turbidimetric immunoassay (Superior-Microalbumin kit, DPC, Tokyo, Japan) and with the Jaffe' reaction by means of an autoanalyzer. Microalbuminuria was defined using standard criteria as an ACR of 30 to 300 mg/day.

##### The CBP and AI

A newly developed testing device for blood pressure and pulse waves (HEM-9000AI, Omron Healthcare Co., Ltd., Kyoto, Japan) facilitates the simple, noninvasive calculation of the AI, an indicator of the central artery reflex wave, in the radial artery. The subjects were allowed to rest in the seated position at least 15 minutes before the examination. The brachial blood pressure was determined by means of oscillometry with the patient in the seated position. The HEM-9000AI algorithm automatically detected the second peak based on the radial pressure waveform to determine late SBP (SBP2). The CBP can be estimated from the SBP2 of the radial pulse waveform<sup>9,11</sup>. The noninvasive estimations of CBP closely correlate with invasive measurements<sup>12</sup>. The AI was calculated with the formula:  $(\text{SBP2} - \text{DBP}) / (\text{the first peak SBP} - \text{DBP}) \times 100 (\%)$ .

The radial AI can be used as a substitute for the

Table 1 Changes in various variables from baseline after 12 weeks of treatment with a standard dose of the DRI

Variables	Baseline	After 12 weeks
SBP (mmHg)	163.1 ± 19.8	147.0 ± 19.4**
DBP (mmHg)	87.7 ± 16.5	83.8 ± 12.9*
CBP (mmHg)	168.8 ± 15.2	153.0 ± 11.6**
AI (%)	93.0 ± 14.3	88.3 ± 14.3*
Sokolow-Lyon index (mm)	2.98 ± 1.10	2.74 ± 1.02*
eGFR (mL/min/1.73 m <sup>2</sup> )	65.7 ± 17.6	66.2 ± 16.2
ACR (mg/g/creatinine)	66.0 ± 122.6	44.2 ± 67.1
hs-CRP (mg/L)	0.12 ± 0.16	0.13 ± 0.17

DRI, direct renin inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure; CBP, central blood pressure; AI, augmentation index; eGFR, estimated glomerular filtration rate; ACR, albumin-to-urinary creatinine ratio; and hs-CRP, high-sensitivity C-reactive protein. The values are the means ± SD. \*p<0.05, \*\*p<0.001 compared with before treatment.

aortic AI<sup>11</sup>. In this study, we calculated the mean of 2 measurements with the HEM-9000AI of the brachial blood pressure, the CBP, and the AI. To eliminate bias, measurements of the CBP and AI were made by a third party blinded to the subject's treatment group.

#### The Sokolow-Lyon index

The SV1 + RV5 is a representative variable proposed by Sokolow and Lyon for the evaluation of LVH in ECGs. The commonly used Sokolow-Lyon ECG voltage criterion, when the amplitude of SV1 + (max RV5 or RV6) is greater than or equal to 3.5 mV, is easy to use for assessing LVH<sup>13</sup>. The high specificity and low cost make this simple ECG method employing the Sokolow-Lyon criterion the most frequently used, and in recent guidelines, it remains a routine test to determine cardiac damage, together with the Cornell index<sup>14</sup>. All ECGs were recorded at 1-mV cm<sup>-1</sup> calibration.

#### Relevant clinicopathological factors

The patients' height and weight were measured at the time of the ECG measurement, and the body-mass index (BMI: kg/m<sup>2</sup>) was calculated as an index of obesity. The value for HbA1c (%) was estimated as an NGSP equivalent value (%) calculated with the formula HbA1c (%) = HbA1c (Japan Diabetes Society [JDS]; %) + 0.4%, considering the relational expression of HbA1c (JDS; %) measured with the previous Japanese standard substance and measurement methods for HbA1c (NGSP). Diabetes

mellitus was defined as HbA1c (JDS) ≥6.1% or the current use of a hypoglycemic agent. Dyslipidemia was defined as low-density lipoprotein cholesterol level ≥3.62 mmol/L or the current use of a lipid-lowering agent. Chronic kidney disease was defined as a glomerular filtration rate <60 mL/min/1.73 m<sup>2</sup>. The glomerular filtration rate was estimated with the simplified prediction equation derived from the Modification of Diet in Renal Disease study<sup>15</sup>.

#### Statistical analysis

The SPSS Version 14.0 software package was employed for statistical analysis. The results are expressed as the means ± standard deviation. Differences in variables before and after treatment were analyzed with paired *t*-tests. The variables were compared between groups by means of Student's *t*-test. Differences with P<0.05 were considered significant.

## Results

A total of 34 subjects were initially enrolled. The changes in the various biochemical variables after 12 weeks of treatment are shown in **Table 1**. The brachial blood pressure (SBP and DBP) and the CBP were significantly reduced after 12 weeks of treatment with 150 mg/day of the DRI (p<0.001). Four patients were excluded because they had achieved a good SBP and CBP after the 12 weeks of treatment with 150 mg/day of the DRI.

## Direct Renin Inhibitor Decreases the CBP

Table 2 Changes in various variables from 12 weeks to 24 weeks of treatment in the high-dose DRI group and the combination group

Variables	High-dose DRI group		Combination group	
	12 weeks	After 24 weeks	12 weeks	After 24 weeks
SBP (mmHg)	152.5 ± 19.7	137.4 ± 18.6**	141.5 ± 18.0	133.5 ± 15.3*
DBP (mmHg)	83.9 ± 13.2	81.2 ± 14.1*	83.7 ± 13.0	80.7 ± 10.9
CBP (mmHg)	158.9 ± 15.0	144.9 ± 16.9**	147.1 ± 6.3	140.0 ± 7.9*
AI (%)	87.4 ± 14.0	82.1 ± 12.9*	89.3 ± 15.0	87.0 ± 13.3
Sokolow-Lyon index (mm)	2.85 ± 1.07	2.77 ± 1.02*	2.63 ± 0.98	2.59 ± 0.94
eGFR (mL/min/1.73 m <sup>2</sup> )	70.6 ± 16.6	69.6 ± 12.1	60.8 ± 17.7	62.1 ± 17.9
ACR (mg/g/cr)	32.2 ± 47.8	17.1 ± 15.3	56.2 ± 82.1	46.5 ± 69.4
hs-CRP (mg/L)	0.11 ± 0.11	0.07 ± 0.07*	0.14 ± 0.19	0.11 ± 0.10

DRI, direct renin inhibitor; SBP, systolic blood pressures; DBP, diastolic blood pressures; CBP, central blood pressures; AI, augmentation index; eGFR, Estimated glomerular filtration rate; ACR, urinary albumin-to-creatinine ratio; hs-CRP, high-sensitivity C-reactive protein. The values are means ± SD. \*p<0.05, \*\*p<0.001 as compared with before treatment.

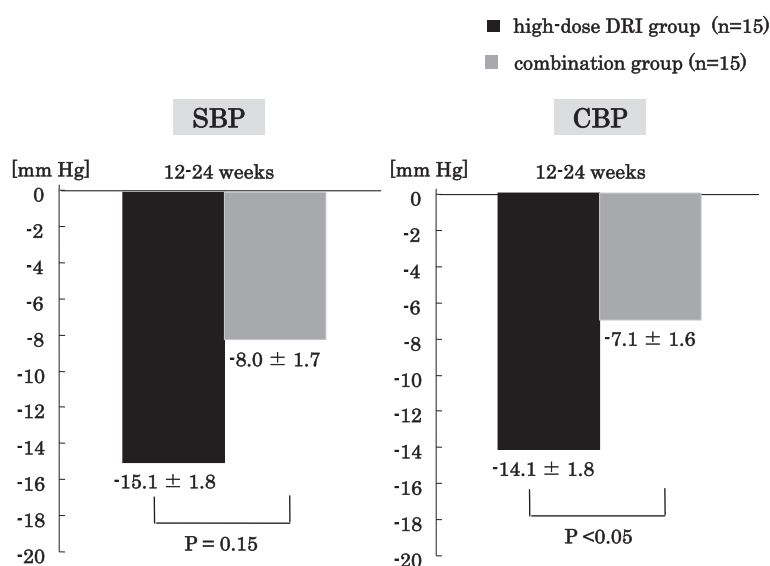


Fig. 2 Mean changes in SBP and CBP from 12 to 24 weeks after assignment

The mean changes in CBP from 12 to 24 weeks after assignment were  $-14.1 \pm 1.8$  mm Hg in the high-dose DRI group and  $-7.1 \pm 1.6$  mm Hg in the combination group. The high-dose DRI group showed a greater decrease in CBP, but not in SBP, than did the combination group ( $p < 0.05$ ). SBP, systolic blood pressure; CBP, central blood pressure; DRI, direct renin inhibitor.

The patients' backgrounds at 12 weeks did not differ significantly between the groups in any variable (age, sex, smoking, BMI, dyslipidemia, diabetes mellitus, chronic kidney disease, SBP, DBP, CBP, AI, or use of antihypertensive drugs).

The SBP and CBP were significantly decreased from 12 to 24 weeks after assignment in both groups ( $p < 0.01$ , **Table 2**). The mean change in the CBP from

12 to 24 weeks after assignment was significantly greater in the high-dose DRI group ( $-14.1 \pm 1.8$  mm Hg) than in the combination group ( $-7.1 \pm 1.6$  mm Hg  $p < 0.05$ , **Fig. 2**), but the mean change in SBP did not differ significantly between the groups. The radial AI was significantly decreased after 12 weeks of treatment with a standard dose of the DRI (week 0:  $93.0\% \pm 14.3\%$ ; week 12:  $88.3\% \pm 14.3\%$ ;  $p < 0.05$ ).

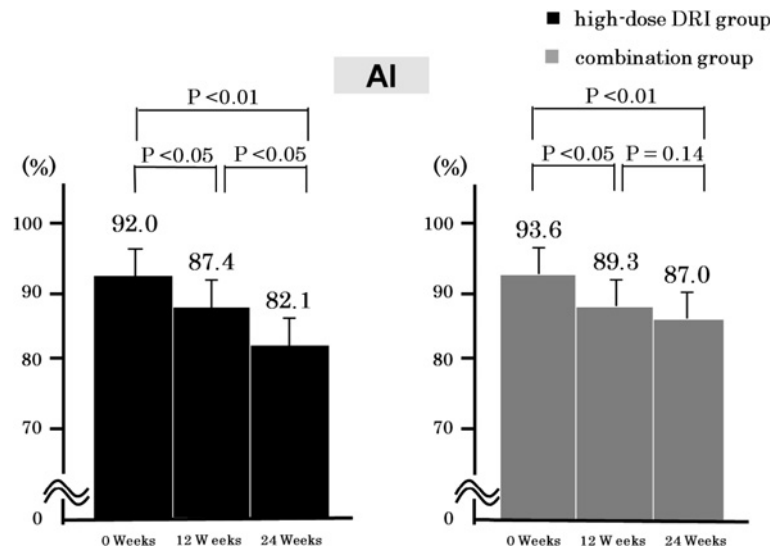


Fig. 3 Changes in the AI before and after treatment with DRI  
The radial AI was significantly reduced after 12 weeks of treatment with 150 mg/day of the DRI (week 0: 93.0% ± 14.3%; week 12: 88.3% ± 14.3%; p < 0.05). Furthermore, the AI was decreased from 12 to 24 weeks in both the high-dose DRI group (week 12: 87.4% ± 14.0%; week 24: 82.1% ± 12.9%; p < 0.05) and the combination group (week 12: 89.3% ± 15.0%; week 24: 87.0% ± 13.3%; p = 0.14). AI, augmentation index; DRI, direct renin inhibitor.

Furthermore, the AI decreased from week 12 to week 24 in both the high-dose DRI group (87.4% ± 14.0% to 82.1% ± 12.9%, p < 0.05) and the combination group (89.3% ± 15.0% to 87.0% ± 13.3%, p = 0.14). The rate of decrease was greater in the high-dose DRI group than in the combination group (**Fig. 3**). In addition, the Sokolow-Lyon index results were similar to the AI (**Fig. 4**).

The hs-CRP level was not significantly decreased after 12 weeks of treatment with the standard dose of the DRI (**Table 1**). However, the high-dose DRI group showed a significant decrease from 12 to 24 weeks (p < 0.05), whereas the combination group did not (**Table 2**).

The ACR was not significantly improved during the study in either group (**Table 1, 2**). However, patients with microalbuminuria (ACR ≥ 30 mg/g/creatinine) showed a significant decrease in ACR after 12 weeks of treatment with the standard dose of the DRI (p < 0.05, data not shown).

## Discussion

The SBP, DBP, CBP, and AI were significantly decreased after 12 weeks of treatment with 150 mg/

day of the DRI. The mean change in the CBP between 12 and 24 weeks after assignment showed that the antihypertensive effects were greater in the high-dose DRI group than in the combination group (p < 0.05). Therefore, the DRI decreased the CBP, and increasing the DRI dose was more effective than continuing the same dose and adding a diuretic.

The target blood pressure is rarely achieved with a single drug, and combination treatment with 2 or more drugs is often necessary in patients with hypertension. Both DRI dose elevation and combination therapy with a standard-dose DRI and a low-dose diuretic have been shown to have more marked antihypertensive effects than continued treatment with standard-dose DRI<sup>16</sup>. The present study showed that the CBP was more markedly decreased in patients treated with a high dose of the DRI than in patients receiving the standard-dose DRI/diuretic combination therapy. Many studies have found that hypertension increases oxidative stress and leads to inactivation of nitric oxide (NO)<sup>17,18</sup>. Furthermore, inactivation of NO increases the blood pressure by enhancing the vasoconstrictive reaction<sup>18,19</sup>. On the other hand, direct renin inhibition protects against

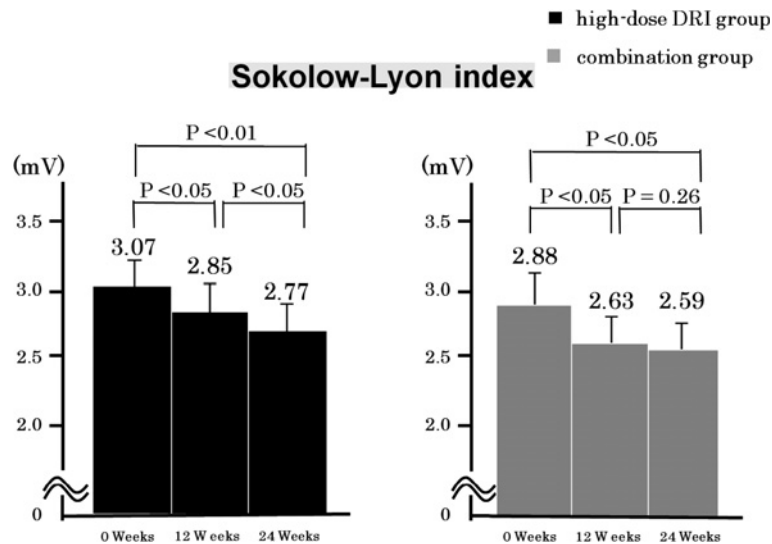


Fig. 4 Changes in the Sokolow-Lyon index before and after treatment with DRI

The Sokolow-Lyon index (SV1 + RV6 in ECGs) decreased significantly after 12 weeks of treatment with 150 mg/day of the DRI (week 0:  $2.98 \pm 1.10$  mm; week 12:  $2.74 \pm 1.02$  mm;  $p < 0.05$ ). Furthermore, the Sokolow-Lyon index decreased from 12 to 24 weeks in both the high-dose DRI group (week 12:  $2.85 \pm 1.07$  mm; week 24:  $2.77 \pm 1.02$  mm;  $p < 0.05$ ) and the combination group (week 12:  $2.63 \pm 0.98$  mm; week 24:  $2.59 \pm 0.94$  mm;  $p = 0.14$ ). DRI, direct renin inhibitor.

cardiovascular complications, glucose intolerance, and pancreatic injury in a mouse model of type 2 diabetes, through the attenuation of oxidative stress and inflammation<sup>20,21</sup>. Therefore, patients treated with the increased dose of the DRI showed decreases in oxidative stress, inflammation, and activation of NO, which induce vasodilation, leading to decreased CBP. This might also explain the improvement of the hs-CRP in the high-dose DRI group and of the ACR in patients with microalbuminuria after treatment with 150 mg of the DRI. In fact, DRIs, ARBs, and angiotensin-converting enzyme (ACE) inhibitors have both antihypertensive effects and antiproteinuria effects<sup>22-25</sup>.

The radial AI is significantly higher in patients with a history of cardiovascular events than in healthy controls<sup>26,27</sup>. The radial AI is also thought to be a useful screening index for LVH<sup>5,6</sup>. The Sokolow-Lyon index, which is used to evaluate LVH in ECGs, is also used to evaluate the effects of drug therapy. DRIs inhibit myocardial remodeling, which leads to a decrease in the left ventricular mass by reducing oxidative stress<sup>21</sup>. DRIs are as effective as ARBs in

attenuating this measure of myocardial end-organ damage in patients with hypertension and LVH<sup>28</sup>. The present study found that the rates of decrease in the AI and Sokolow-Lyon index from 12 to 24 weeks were greater in the high-dose DRI group than in the combination group ( $p < 0.05$ ). The improvement in the AI observed in our study might reflect the left ventricular weight, as this is a pleiotropic effect of DRIs.

Previous studies have shown that in some patients tissue levels of angiotensin II and aldosterone initially decrease but then increase again during the long-term use of ACE inhibitors or ARBs (the breakthrough phenomenon)<sup>29</sup>. One previous study has shown that organ damage due to this phenomenon progresses even after the target blood pressure has been achieved. On the other hand, DRIs block renin, which is upstream of the renin-angiotensin system. Therefore, unlike ACE inhibitors or ARBs, DRIs infrequently induce the aldosterone breakthrough phenomenon. Indeed, DRIs have been shown to reduce the plasma aldosterone concentration. Of the various inhibitors of the renin-

angiotensin system, DRIs are among the most potent inhibitors of intracellular angiotensin II levels in human podocytes<sup>7,30</sup>. Furthermore, DRIs generally have a longer half-life and circulate for more than 24 hours after once-daily administration: their absorption and excretion have little effect on their efficacy. DRIs that have pleiotropic effects may become indispensable for their future use as antihypertensive drugs.

Our results suggest that DRIs improve the CBP of prognostic factor for cardiovascular events and may have a protective effect on the heart.

### Limitations

A limitation of this study is that it was performed at a single hospital. The subjects had a CBP of 140 mm Hg or greater after being treated with a standard dose of the DRI (150 mg) for 12 weeks. Whether this result can be generalized to other patients is unknown. In addition, patients received other medications that may have affected the CBP and AI (e.g., calcium channel blockers and ACE inhibitors), but their use at baseline was similar in both groups, and patients were requested not to change medications during the study. Patients with hypertension who showed a CBP of 140 mm Hg or greater after 12 weeks of treatment with the standard dose of DRI were divided into 2 groups, because monitoring the brachial blood pressure alone can underestimate the improvement of the CBP<sup>1</sup>.

### Conclusions

The results of this study suggest that DRI administration contributes to a decrease in the CBP and that this effect is more greater with high-dose DRI therapy. These observations need to be confirmed in large cardiovascular outcome studies with long-term follow-up.

**Acknowledgements:** We have no potential conflicts of interest to report.

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