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Comparison between High-dose Telmisartan and Fixed dose Combination of Telmisartan and Hydrochlorothiazide in Patients with Hypertension

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SUMMARY

We compared treatment with a high-dose angiotensin II receptor blocker (ARB) and combination of ARB with a thiazide diuretic in 17 patients with hypertension. A randomized crossover study was performed giving 80 mg telmisartan or fixed-dose combination of 40 mg telmisartan and 12.5 mg hydrochlorothiazide for 16 weeks each. Although the clinic blood pressure was comparable between the high-dose ARB period (134/81 mmHg) and the combination period (134/82 mmHg), the morning home blood pressure was lower in the combination period than in the high-dose ARB period (138/82 vs. 151/88 mmHg, p = 0.026/0.013). No significant difference was observed in urinary albumin excretion, but estimated glomerular filtration rate was lower in the combination than in the high-dose ARB period (58.9 vs. 62.1 mL/min/1.73 m^2, p = 0.039). Serum uric acid was higher in the combination than in the high-dose ARB period (6.7 vs. 5.9 mg/dL p = 0.022). The indices of glucose metabolism, serum lipids, oxidative stress, inflammation and adipocytokine did not significantly differ between the two periods. There was no significant difference in the measurement of endothelium-dependent vasodilation between the two periods. It is suggested that the addition of thiazide diuretic to medium-dose ARB is more effective in lengthening the hypotensive effect than high-dose ARB, however, care should be taken for the elevation of serum uric acid and the decrease in renal function.

Key words : angiotensin II receptor blocker, diuretic, uric acid, fixed-dose combination, hypertension

INTRODUCTION

The progression of arteriosclerosis is facilitated by high blood pressure, which increases the incidence of cardiovascular diseases such as stroke and coronary heart disease. Hypertension is also a major risk factor for the development of cardiovascular organ damages such as heart failure and renal dysfunction. The population of elderly people is generally increasing and these cardiovascular disorders greatly impairs the activity and life prognosis of elderly subjects. Therefore, it is obviously important to control the blood pressure in optimal range and prevent the occurrence of cardiovascular organ damages, considering that hypertension is the most prevalent lifestyle-related disease.

Among the classes of antihypertensive drugs, angiotensin II receptor blockers (ARB) are widely used because ARB rarely cause adverse side effects and the inhibition of renin-angiotensin-aldosterone (RAA)

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system is supposedly protective against the development of cardiovascular tissue and organ injuries[1,2]. However, the hypotensive effects of renin-angiotensin system inhibitors (RASI) such as angiotensin-converting enzyme (ACE) inhibitors and ARB depend on the intrinsic activity of RAA system to a greater or lesser extent, and the usual dose of ARB alone often fails to achieve the desired blood pressure level. The next step to further lower blood pressure is to increase the dose of ARB or to add another class of antihypertensive drug. The protective effects on the cardiovascular system are expectedly enhanced by high-dose RASI and the addition of diuretics is expected to synergistically enhance the hypotensive effects of RASI[3~5].

In the present study, the therapeutic effects of high-dose ARB, 80 mg telmisartan, and fixed dose combination of 40 mg telmisartan with a diuretic, 12.5 mg hydrochlorothiazide are compared in patients with essential hypertension.

METHODS

The subjects enrolled in this study were 17 hypertensive patients being treated with medium-dose ARB (losartan 50 mg, candesartan 8 mg, valsartan 80 mg, telmisartan 40 mg, olmesartan 20 mg, irbesartan 100 mg) and the systolic blood pressure (SBP) and/or the diastolic blood pressure (DBP) did not reach the target levels ; <130/80 mmHg for two diabetic patients, four patients with chronic glomerulonephritis showing proteinuria, and<140/90 mmHg for the other 11 patients. Patients whose serum creatinine was 2.0 mg/dL or higher were not included because thiazide diuretics are contraindicated. We also excluded patients with severe hypertension exceeding 180/110 mmHg or secondary causes of hypertension other than stage 1-3 chronic kidney disease. The background characteristics of study subjects are shown in Table 1. Six patients were concomitantly given calcium channel blockers (CCB) and two diabetic patients were given antidiabetic drugs such as biguanides (n=2) and α-glucosidase inhibitors (n=1). In addition, lipid-lowering drugs (statins) and antihyperuricemic drugs (allopurinaol) were given for six and four patients, respectively. The doses of these drugs were unchanged throughout the study periods.

Table 1 Baseline characteristics of the study subjects

Age, years	65.4±10.1
Gender, male/female	6/11
Body mass index, kg/m^2	26.4±4.8
Systolic blood pressure, mmHg	146.1±7.6
Diastolic blood pressure, mmHg	88.1±8.2
Heart rate, bpm	69.6±10.0
Duration of hypertension, years	19.4±8.3
Smoking, +/past/−	4/4/9
Habitual alcohol intake, +/−	7/10
Complications	
Chronic glomerulonephritis	4
Diabetes mellitus	2
Dyslipidemia	7
Hyperuricemia	4
Cardiovascular disease	1

Data are the mean±SD.

The patients were given 80 mg (high dose) telmisartan or a fixed-dose combination product of 40 mg (medium dose) telmisartan and 12.5 mg hydrochlorothiazide once daily after breakfast for 16 weeks each, according to a randomized crossover design. The sequence of treatment periods with high-dose ARB and combination therapy was randomized. Office blood pressure was measured with a sphygmomanometer in the sitting position after resting for at least 20 min at each visit every 4 weeks. Home blood pressure was measured consecutively for 7 days before each visit using an arm-cuff oscillometric automatic manometer within 1 hour of awakening (before drug administration) as morning blood pressure and before going to bed as evening blood pressure, and the mean values were obtained. The type of manometer was not specified if an arm-cuff was equipped. Home blood pressure values were recorded to a notebook by the patient and the data were collected at each visit.

After overnight fasting blood samples were collected at rest in the sitting position for more than 20 minutes on the final day of each treatment period. In addition to the routine blood chemistry and blood cell counts, plasma high-sensitivity C-reactive protein (HSCRP), a marker of inflammation, was measured by a highly sensitive sandwich ELISA. The plasma levels of malondialdehyde-modified low-density lipoprotein (MDA-LDL), a marker of oxidative stress, and total adiponectin were also measured by respective ELISA system. The estimated glomerular filtra-

Table 2 Office blood pressure, heart rate and body weight at the ends of high-dose ARB and fixed-dose combination therapy periods.

Variable	High-dose ARB	Combination	P value
SBP, mmHg	134.2±10.9	133.9±13.5	0.927
DBP, mmHg	81.0±8.8	82.2±9.3	0.529
Heart rate, bpm	71.3±10.6	70.6±10.7	0.662
Body weight, kg	64.7±12.4	64.1±12.3	0.033

Data are the mean±SD. ARB : angiotensin II receptor blocker, SBP : systolic blood pressure, DBP : diastolic blood pressure.

tion rate (eGFR) was calculated from the serum creatinine level and age by the following equation[6] : eGFR $=194\times Age^{-0.287}\times sCr^{-1.094}$ ($\times 0.739$ for females). Casual urine samples were collected on the final day of each treatment period. Urinary albumin was measured by an immunoturbidimetric method and corrected using the urinary creatinine level.

Reactive hyperemia index (RHI), an index of endothelial function, and augmentation index (AI), an index of arterial stiffness, were measured using the EndoPAT 2000 device (Itamar Medical, Israel)[7,8]. Measurements were performed by the manufacturer's instruction. Briefly, after longer than 15 minutes of supine rest in a quiet and temperature-controlled (21-24℃) room, beat-to-beat plethysmographic arterial pulse wave amplitude of the middle finger of both hands were simultaneously recorded using inflatable latex air cuffs. The measurement protocol consists of 3 consecutive recordings of 5 minutes each. After a 5 minutes of baseline recording, the blood pressure cuff on one arm was inflated to 60 mmHg above the baseline systolic blood pressure for 5 minutes. Then, the arm cuff was deflated and another 5-minute recording was performed. RHI and AI were calculated using a computerized automated algorithm. RHI is the difference between the post-occlusion and pre-occlusion amplitude on the arm with occlusion divided by the same measurement on the control arm.

The study protocol was in accordance with the recommendations of the World Medical Association for biomedical research involving human subjects and was approved by the institutional review board. Informed consent was obtained from all subjects after explaining the study objective and design.

Clinical data were expressed as means±standard deviations (SD). Values between the 2 periods were compared by paired t-test, however, Wilcoxon signed-rank test was applied for the data with skewed distribution. A P value of less than 0.05 was considered to be statistically significant.

RESULTS

All the 17 patients showed good adherence to the therapy and fulfilled the whole study periods. Table 2 shows the office blood pressure and heart rate at the ends of high-dose ARB and fixed-dose combination therapy periods. Body weight was significantly lower in the high-dose ARB period than in the combination period. There were no significant differences in the office SBP, DBP or heart rate between the two treatment periods. However, as shown in Table 3, home SBP and DBP in the morning and evening were significantly lower in the combination therapy period than in the high-dose ARB period, while the heart rate did not significantly differ between the two periods.

Table 4 shows the data of routine blood cell counts and blood chemistry at the end of each treatment period. The blood hemoglobin concentration and hematocrit were slightly but significantly lower in the combination period than in the high-dose ARB period. Among the blood chemistry data, the serum levels of creatinine and uric acid were significantly higher in the combination period than in the high-dose ARB period. As for the serum electrolytes, serum sodium was significantly lower in the combination period than in the high-dose ARB period, although the serum potassium levels were not significantly different between the two periods. Blood glucose, serum insulin and serum lipids were shown in Table 5. These parameters of glucose and lipid metabolisms were not significantly different between the two treatment peri-

Table 3 Averaged home blood pressure and heart rate in the last weeks of high-dose ARB and fixed-dose combination therapy periods.

Variable	High-dose ARB	Combination	P value
Morning			
SBP, mmHg	151.2 ± 19.9	138.7 ± 14.5	0.026
DBP, mmHg	88.5 ± 11.2	82.6 ± 6.4	0.013
Heart rate, bpm	70.6 ± 11.7	70.2 ± 11.0	0.789
Evening			
SBP, mmHg	141.9 ± 19.2	131.8 ± 14.6	0.043
DBP, mmHg	82.8 ± 14.0	76.9 ± 76.0	0.017
Heart rate, bpm	71.4 ± 8.5	71.7 ± 10.5	0.863

Data are the mean ± SD. ARB : angiotensin II receptor blocker, SBP : systolic blood pressure, DBP : diastolic blood pressure.

Table 4 Laboratory data at the ends of high-dose ARB and fixed-dose combination therapy periods.

Variable	High-dose ARB	Combination	P value
White blood cell, $x10^3/mm^3$	6.46 ± 2.15	6.12 ± 1.66	0.174
Red blood cells, $x10^6/mm^3$	4.50 ± 0.34	4.54 ± 0.44	0.028
Blood hemoglobin, g/dL	13.9 ± 1.0	14.0 ± 1.4	0.035
Hematocrit, %	41.5 ± 2.6	41.9 ± 4.1	0.015
Platelet, $x10^3/mm^3$	21.5 ± 6.7	51.4 ± 5.6	0.709
Serum			
Aspartate transaminase, U/L	15.8 ± 7.7	18.1 ± 12.7	0.146
Alanine transaminase, U/L	18.2 ± 16.4	17.6 ± 16.5	0.758
Total protein, g/dL	7.1 ± 0.3	7.2 ± 0.3	0.096
Albumin, g/dL	4.0 ± 0.3	4.0 ± 0.3	0.670
Na, mEq/L	141.1 ± 2.2	140.2 ± 1.7	0.025
K, mEq/L	4.3 ± 0.3	4.2 ± 0.3	0.720
Urea nitrogen, mg/dL	16.5 ± 4.1	17.6 ± 6.2	0.245
Creatinine, mg/dL	0.86 ± 0.24	0.91 ± 0.27	0.040
Uric acid, mg/dL	5.9 ± 0.8	6.7 ± 1.4	0.022

Data are the mean ± SD. ARB : angiotensin II receptor blocker.

Table 5 Indices of glucose metabolism and serum lipids at the ends of high-dose ARB and fixed-dose combination therapy periods.

Variable	High-dose ARB	Combination	P value
Blood gluocose, mg/dL	106 ± 17	107 ± 21	0.753
Hemoglobin A1c, %	5.7 ± 0.8	5.9 ± 0.9	0.147
Serum			
Insulin, mU/L	14.4 ± 11.1	12.9 ± 12.4	0.410
HDL-cholesterol, mg/dL	56 ± 12	56 ± 14	0.948
LDL-cholesterol, mg/dL	125 ± 36	129 ± 39	0.591
Triglycerides, mg/dL	139 ± 73	136 ± 90	0.876

Data are the mean ± SD. ARB : angiotensin II receptor blocker, HDL : high-density lipoprotein, LDL : low-density lipoprotein.

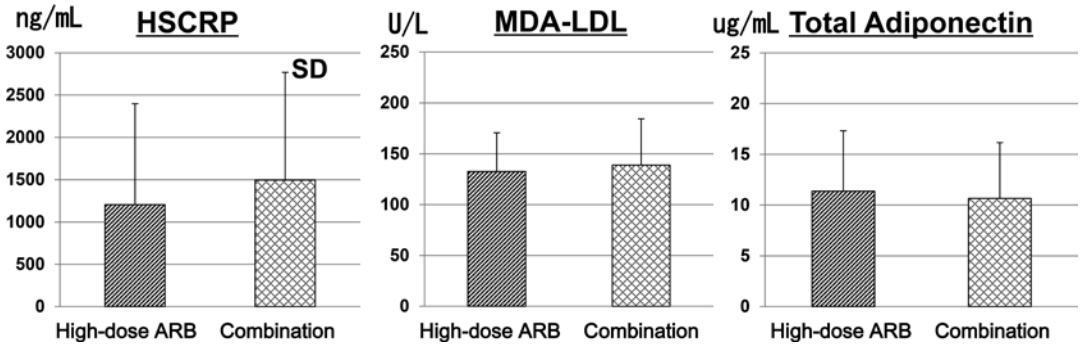

Figure 1 Plasma levels of high-sensitivity C-reactive protein (HSCRP, left panel), malondialdehyde-modified low-density lipoprotein (MDA-LDL, middle panel), and total adiponectin (right panel) at the ends of high-dose ARB and fixed-dose combination therapy periods. Data are mean ± SD. ARB : angiotensin II receptor blocker.

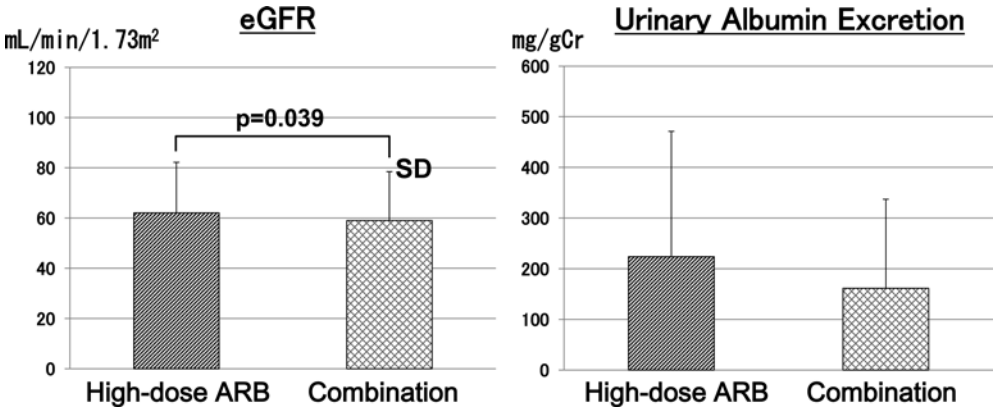

Figure 2 Estimated glomerular filtration rate (eGFR, left panel) and urinary albumin excretion (right panel) at the ends of high-dose ARB and fixed-dose combination therapy periods. Data are mean ± SD. ARB : angiotensin II receptor blocker.

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The left panel of Figure 1 shows plasma HSCRP and the middle panel shows plasma MDA-HDL. These markers of inflammation and oxidative stress did not significantly differ between the high-dose ARB and the combination periods. Regarding adiponectin, a beneficial cytokine produced by adipocytes, the plasma levels were not significantly different between the two periods as shown in the right panel of Figure 1.

The eGFR and the urinary albumin excretion of the study subjects at the end of each treatment period were depicted in Figure 2. While the eGFR slightly reduced during the combination period, the urinary albumin excretion did not significantly differ in the high-dose ARB and the combination periods.

Figure 3 presents RHI, an index of endothelium-dependent vasodilation, and AI, an index of arterial stiffness, measured at the end of each treatment period. Either the values of RHI or AI were not significantly different between the two periods.

DISCUSSION

The blood pressure level of 140/90 mmHg or higher is generally recognized as hypertension and the latest versions of guidelines for the management of hypertension recommend the target blood pressure lower than this[9~11]. However, there is not an apparent threshold level from which higher blood pressure is associated with the increase in cardiovascular diseases. Meta-analysis of prospective observational studies have indicated that there is a linear relationship between blood pressure and the risk of cardiovascular diseases such as stroke and myocardial infarction[12].

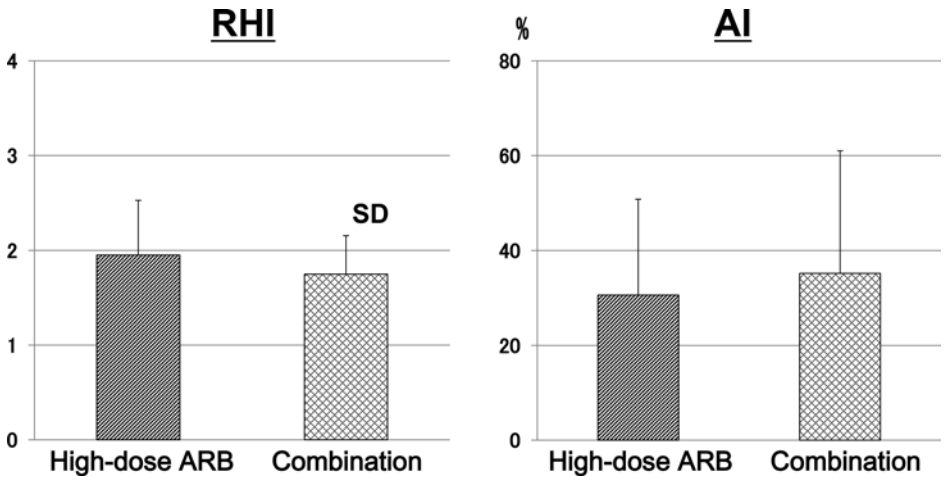

Figure 3 Comparisons of relative hyperemia index (RHI) and augmentation index (AI) at the ends of high-dose ARB and fixed-dose combination therapy periods. Data are mean ± SD. ARB : angiotensin II receptor blocker.

This relationship also exists even in the normal blood pressure range below 140/90 mmHg down to 115/75 mmHg. Moreover, in the recent Systolic Blood Pressure Intervention Trial (SPRINT), the intensive treatment hypertensive patients with target SBP less than 120 mmHg showed lower rates of cardiovascular events and death than in the standard treatment group targeted less than 140 mm Hg[13]. Therefore, stricter target blood pressure level such as 130/85 mmHg may be preferable in order to achieve better prevention of cardiovascular diseases in hypertensive patients. In the real world clinical practice, generally half hypertensive patients under antihypertensive treatment do not achieve even the target blood pressure level of 140/90 mmHg and intensification of antihypertensive drug therapy such as increasing the dose and combination of multiple agents is needed.

In the present study, therapeutic effects of high-dose ARB and combination therapy with medium-dosed ARB and thiazide diuretic were compared, and office blood pressure was comparably lowered in either treatment period, however, the morning and evening home blood pressure was better lowered by the combination therapy than by the high-dose ARB therapy. Out of office blood pressure values obtained by ambulatory blood pressure monitoring (ABPM) or home blood pressure measurement have been shown to yield better prediction than office blood pressure for the incidence of target organ damages and cardiovascular diseases. Although telmisartan has relatively long plasma half-life as compared with other ARB clinically used, the duration of hypotensive effect by high-dose telmisartan may not be sufficient to cover 24 hours.

Even if the office blood pressure is controlled in normal range, diurnal blood pressure changes such as morning surge and the lack of nocturnal dipping are known to raise the risk of cardiovascular organ injuries. Inappropriate renal excretion of Na is thought to contribute to the non-dipping pattern of blood pressure change, and it has been reported that the addition of diuretics reduce the necessity to maintain high blood pressure level to excrete Na during nighttime and change the non-dipper pattern into dipper[14]. Thus, the hypotensive effect is expectedly lengthened by the combination of RASI and thiazide diuretics.

Among the various components of the RAA system, angiotensin II enhances the production of free radicals, promotes cell growth, and increases the synthesis of inflammatory and profibrotic cytokines[15,16]. In addition, it has been revealed that aldosterone also promotes free radical production and endothelial dysfunction, as well as having mitogenic and profibrotic actions[17,18]. These nonhemodynamic effects of angiotensin II and aldosterone are deleterious to the cardiovascular system and cause inflammation, fibrosis, and scarring of various tissues that lead to cardiovascular organ injuries and increase the incidence of cardiovascular diseases. Therefore, high-dose RASI are expected to exhibit protective effects against cardiovascular

system in addition to their hypotensive effects. Especially, telmisartan is known to dose-dependently activate peroxisome proliferator-activated receptor-gamma (PPAR-γ), a transcription factor of nuclear hormone receptor, which has actions such as improving insulin resistance, reducing inflammatory cytokines and increasing adiponectin[19~21]. Adiponectin produced by adipocytes also has beneficial actions such as inhibiting inflammatory vascular injuries and improving glucose and lipid metabolism[22,23]. On the contrary, reduction of body fluid volume by diuretics stimulates circulating RAA system factors, such as angiotensin II and aldosterone, which could possibly have an adverse influence on the development of cardiovascular organ damage in hypertensive patients, although the RAA system in cardiovascular tissues may not always show a parallel response to circulating hormone levels. However, in the present study, high-dose telmisartan did not significantly influence the glucose metabolism, serum lipids plasma adiponectin and circulating markers of oxidative stress and inflammation as compared with medium-dose. Therefore, the dose-dependent beneficial effects of telmisartan may not be apparent in clinical situations.

It is assumed that atherosclerotic lesions in the arterial system are initiated by functional disorder of the vascular endothelium. This causes the reduced capacity to generate nitric oxide (NO) in response to various stimuli resulting in impaired endothelium-dependent vasorelaxation. On the other hand, AI examined in this study reflects functional and structural stiffening of arterial system and increases with the development of arteriosclerosis. The development of endothelial dysfunction and arterial stiffening is contributed by aging, smoking and lifestyle-related diseases such as diabetes, hypertension and dyslipidemia. In addition to these classical risk factors of atherosclerosis, novel factors such as inflammation and oxidative stress are thought to participate in the etiology and pathogenesis of vascular injuries[24~27]. It is recognized that the existence of endothelial dysfunction and arterial stiffening is predictive of the incidence of cardiovascular events[28~31]. Therefore, it is desirable to consider vascular protection in the treatment of hypertensive patients in order to effectively prevent cardiovascular diseases. In this context, RASI such as ACE inhibitors and ARB are expected to exhibit protective effects against the development vascular injuries by suppressing the actions of angiotensin II and aldosterone[1,2]. However, the results of present study suggest that clinical significance of such vascular effects by telmisartan are not prominent although this drug activates PPAR-γ dose-dependently.

Two drugs or more are often required in order to achieve the target blood pressure. The combination of RASI and diuretics is thought to be effective in intensifying the hypotensive effects of each other and avoiding the occurrence of adverse effects. The RAA system enhanced by the natriuretic action of diuretics is suppressed by RASI and salt-sensitivity induced by RASI is reduced by diuretics. As for the adverse effects, diuretics and RASI exert opposite influences on the metabolism of K, glucose and lipids thereby canceling the demerits of each other. Conformably in our study, serum K, lipids and glucose metabolism markers were not adversely affected in the combination period as compared with the high-dose ARB period in this study. On the other hand, thiazide diuretics increase serum uric acid, while RASI generally do not affect the serum uric acid level. Among ARB, losartan and irbesartan have been shown to facilitate uric acid excretion by inhibiting URAT-1, an transporter of uric acid reabsorption in the renal tubules and reduce serum uric acid[32,33]. In the present study, serum uric acid was significantly higher in the combination period than in the high-dose ARB period. Although telmisartan has been also shown to inhibit URAT-1, the lipophilic property may hamper its penetration to the apical side of renal tubules and inhibition of URAT-1 in vivo.

The protective effects of RASI on cardiovascular system are supposed to grow with increasing dose[3,4]. Also in the kidney, RASI have shown to reduce proteinuria and albuminuria in a dose-dependent manner[34,35]. In the earlier studies examined the renoprotective effects of antihypertensive therapy combined RASI with diuretics or CCB, the diuretic combination is superior in reducing albuminuria but inferior in preserving eGFR as compared to the CCB combination[36,37]. In the present study compared high-dose ARB and combination of medium-dose ARB with a

thiazide diuretic, serum creatinine was higher resulting in lower eGFR in the combination period than in the high-dose ARB period, while the urinary albumin excretion did not significantly differ between the two periods. Thus, when thiazide diuretics are used in antihypertensive treatment, it should be kept in mind for the reduction of renal function as well as for hyperuricemia.

In summary, we compared the therapeutic effects of antihypertensive therapies with high-dose ARB and the fixed-dose combination of medium-dose ARB with a thiazide diuretic in hypertensive patients showing poor blood pressure control by medium-dose ARB. It is suggested that the combination therapy is superior to the high-dose ARB in controlling blood pressure over 24 hours, however, care should be taken for the increase in serum uric acid the reduction of renal function.

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