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The Differences in Renal Protection between a High-dose Angiotensin II Type 1 Receptor Blocker Alone and in Combination with a Diuretic for the Treatment of Hypertension

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ABSTRACT

Background and objective : We performed a retrospective study of the differences in the renal protective effects of strict antihypertensive therapy for essential hypertension between a high dose of valsartan and a combination of the standard dose of valsartan and the diuretic trichlormethiazide by evaluating the changes in the estimated glomerular filtration rate and the urinary albumin : creatinine ratio.

Patients and methods : The subjects were 47 outpatients with hypertension who received either a high dose (160 mg/day) of valsartan (n=32) or combination therapy with the standard dose (80 mg/day) of valsartan and 1 mg/day of trichlormethiazide (n=15).

Results : Systolic and diastolic blood pressures were significantly reduced by 19 mm Hg (−13%) and 13 mm Hg (−15%) in patients treated with a high dose valsartan and by 17 mm Hg (−12%) and 6 mm Hg (−7%) in patients treated with valsartan plus trichlormethiazide. A positive correlation was found between changes in the estimated glomerular filtration rate and changes in the urinary albumin : creatinine ratio in patients treated with high dose valsartan, but not in patients treated with valsartan plus trichlormethiazide.

Conclusions : Strict antihypertensive therapy either with a high dose valsartan (160 mg/day) or with the standard dose of valsartan (80 mg/day) plus a diuretic agent was found to be highly effective for reducing poorly controlled blood pressure. However, the diuretic agent appears to have a different mechanism of renal protection in patients treated with valsartan.
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Key words : angiotensin II, blood pressure, diuretics, hypertension, kidney, renal function

INTRODUCTION

Strict antihypertensive therapy aimed at protecting organs and reducing the rate of cardiovascular events was established according to the 2009 Guidelines for the Management of Hypertension published by the Japanese Society of Hypertension[1]. The Japan Hypertension Evaluation With Angiotensin II Antagonist Losartan Therapy study, which enrolled 26,512 Japanese patients with hypertension, demonstrated that, in order to reduce the risk of cardiovascular events, blood pressure should be maintained at less than 140/90 mm Hg in patients with hypertension[2]. However, antihypertensive therapy in the routine management of hypertension is often insufficient[3], and proposed changes to

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antihypertensive therapy guidelines include new doses for existing antihypertensive agents and the use of a combination of two types of antihypertensive agents.

Diuretics can reduce blood pressure by inducing urinary sodium excretion, but this may result in activation of the circulating renin-angiotensin system (RAS). Combination therapy with an angiotensin II receptor blocker (ARB) and a diuretic potently inhibits RAS activities in both the circulation and in tissues, resulting in blood pressure reduction and cardiovascular protection[4]. In addition, at low doses, diuretic agents produce antihypertensive effects with minimal adverse effects[5] and have attracted attention owing to their antihypertensive potentiating effect. A meta-analysis of 42 clinical trials showed that these agents prevent cardiovascular events[6].

The renal protective effects of ARBs would be of particular importance for improving the prognosis of patients with hypertension complicated by type 2 diabetes mellitus[7-9]. Numerous studies have shown that ARBs, as well as having antihypertensive effects, also decrease microalbuminuria and may protect renal function[10]. However, to our knowledge, no published studies have compared the effects of ARB monotherapy with those of the combination of an ARB and a low dose of diuretic agent on the biochemical variables indicative of renal protection.

In the present study, we investigated the estimated glomerular filtration rate (eGFR) and microalbuminuria levels as evaluated using the urinary albumin : creatinine ratio (UACR) in patients receiving strict antihypertensive therapy for essential hypertension either with a high dose (160 mg/day) of valsartan alone or with a standard dose (80 mg/day) of valsartan plus 1 mg/day of the diuretic trichlormethiazide.

METHODS

Patient population and protocol

The subjects consisted of outpatients at The Jikei University Hospital whose previous antihypertensive agents had been changed to a high dose valsartan (160 mg/day) (the high-dose valsartan group ; 32 patients) or to a combination of the standard dose of valsartan (80 mg/day) plus trichlormethiazide (1 mg/day) (the valsartan plus trichlormethiazide group ; 15 patients) according to the new 2009 guidelines of the Japan Society of Hypertension[1]. All clinical data were collected before and after the agents were changed, and the follow-up period ranged from 6 to 12 months.

The study protocol (21-279 [6,157]) was approved by the Ethics Committee of The Jikei University.

Blood pressure measurement

The systolic and diastolic blood pressures were measured with a mercury sphygmomanometer and a cuff matching the patient's arm in our hospital after the patient had rested for at least 5 minutes in the sitting position.

Measurements of serum and urine biochemical parameters

Serum and urine biochemical analyses of the following parameters were performed in a central laboratory during the study : aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), gamma-glutamyltranspeptidase (γ-GT), blood urea nitrogen (BUN), creatinine, uric acid (UA), Na, K, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), fasting blood sugar (FBS), hemoglobin A1c (HbA1c), B-type natriuretic peptide (BNP), eGFR, and UACR. We calculated the eGFR according to the Modification of Diet in Renal Disease equation[11] with coefficients modified for Japanese patients[12,13] : $\mathrm{eGFR\ (ml/min/1.73\ m^2)} = 194 \times \mathrm{age}^{-0.287} \times \mathrm{creatinine}^{-1.094}$ (multiplied by 0.739 for females).

Definition of diseases

The underlying disease was determined for each patient. Patients with hypertension, diabetes, and dyslipidemia had previously received diagnoses according to the guidelines for each disease and were undergoing standard treatments for the stabilized conditions. The other underlying diseases included ischemic heart disease, valvular disease, aortic disease, arrhythmia, and cardiomyopathy. The criteria for the diagnosis of ischemic heart disease included previous myocardial infarction, angina pectoris, coronary angiography, and percutaneous coronary intervention. The criteria for heart failure included moderate valvular disease, cardiomyopathy, and ischemic cardiomyopathy. Based on the patient's height and weight on admission, the body mass index was calculated.

Exclusion criteria for patients

The serum creatinine and K values of all patients were less than 3.0 mg/dl and 5.5 mEq/L, respectively, and none of the patients had any contraindications for treatment with either valsartan or trichlormethiazide.

Statistical analysis

The results of data measurements (continuous variables) are expressed as the means±standard deviation (SD), and statistical analyses were performed with the Wilcoxon signed-rank test (paired continuous variables), the chi-square test (categorical variables), or the Mann-Whitney *U* test (unpaired continuous variables) for 2 sets of data, as appropriate. The correlation analysis between the eGFR and UACR was performed with the Pearson product-moment correlation, and the correlations were demonstrated by regression lines. All statistical analyses were performed with the SPSS software program (version 11.5J, SPSS Japan Inc., Tokyo, Japan), and differences were considered to be statistically significant for p-values<0.05.

Results

Patient characteristics

The patient backgrounds are shown for both groups in Table 1. There were fewer females than males in both groups (high-dose valsartan group, 16% ; valsartan plus trichlormethiazide group, 20%), and in both groups, the mean age of females (high-dose valsartan group, 66 years ; valsartan plus trichlormethiazide group, 74 years) was significantly higher than that of males (high-dose valsartan group, 56 years ; valsartan plus trichlormethiazide group, 64 years). The previous medications taken before the start of the study regimens are shown in Table 1, and the mean duration of treatment with high dose valsartan was 11.3±2.2 months. All previous drugs listed in Table 1 were taken at standard doses by all patients. In addition, the mean duration of treatment with valsartan plus trichlormethiazide was 7.1±3.3 months.

Results of administration of the two different strict antihypertensive therapies

Before drug treatment, systolic blood pressures were greater than 140 mm Hg in patients in both the high-dose valsartan group and the valsartan plus trichlormethiazide group ; however, after these strict therapies had been administered for 6 to 12 months, patients in both groups achieved target blood pressure reductions, i.e., systolic pressure less than 140 mm Hg and diastolic pressure less than 90 mm Hg.

The systolic and diastolic blood pressure values significantly decreased in both groups. The reductions were 19 mm Hg (-13%, $p<0.001$) and 13 mm Hg (-15%, $p<0.001$), respectively, from 149/89 mm Hg to 130/76 mm Hg in the high-dose valsartan group. Similarly, the systolic and diastolic phase blood pressures in the valsartan plus trichlormethiazide group decreased from 143/82 mm Hg to 126/76 mm Hg, and these reductions represented statistically significant reductions of 17 mm Hg (-12%, $p=0.001$) and 6 mm Hg (-7%, $p=0.027$), respectively (Table 2). However, the heart rate significantly increased ($p=0.028$) by 10%, from 68 bpm to 75 bpm, in the valsartan plus trichlormethiazide group. Additional representative serum and urine biochemical data are shown in Table 2, including the serum K, serum Na, serum UA, HbA1c, BNP, eGFR, and UACR (no significant changes were found in AST, ALT, LDH, γ-GT, BUN, LDL-C, HDL-C, TG, or FBS ; data not shown).

The significant changes in the high-dose valsartan group included a 48.0% decrease in BNP ($p=0.002$) and a 7.4% reduction of the eGFR ($p=0.030$). The only significantly changed variable in the valsartan plus trichlormethiazide group was the serum UA level, which increased by 8.8% ($p=0.003$; Table 2).

The diastolic blood pressure before therapy ($p=0.050$) and the serum Na levels both before ($p=0.003$) and after ($p=0.031$) therapy were significantly lower in the valsartan plus trichlormethiazide group.

The relationship between the eGFR and UACR changes on strict antihypertensive therapy

The changes in the eGFR and UACR from those before to those after strict antihypertensive therapies in both the high-dose valsartan group and the valsartan plus trichlormethiazide group are shown in Fig. 1. The eGFR values were significantly decreased after strict antihypertensive therapy in the high-dose valsartan group, but showed no significant change in the valsartan plus trichlormethiazide group (Table 2). However, the UACR values in both groups decreased, although not significantly, after strict an-

Table 1. Patient background data in the high-dose valsartan group and the valsartan plus trichlormethiazide group

Number (%) or mean ± SD	Overall	High-dose valsartan group	Valsartan plus trichlormethiazide group	*p*
Number of patients	47	32	15	-
Females	8 (17)	5 (16)	3 (20)	0.697
Age (years)	60 ± 11	57 ± 11	66 ± 10	0.012*
Body mass index (kg/m^2)	26.0 ± 3.3	26.0 ± 3.1	25.9 ± 3.7	0.665*
Complications	(% of Overall)	(% of each group)	(% of each group)	
Ischemic heart disease	19 (40)	11 (34)	8 (53)	0.217
Heart failure	3 (6)	1 (3)	2 (13)	0.182
Diabetes mellitus	10 (21)	6 (19)	4 (27)	0.654
Dyslipidemia	17 (36)	12 (38)	5 (33)	0.848
Prior medications	(% of Overall)	(% of each group)	(% of each group)	
ACE inhibitor	4 (9)	4 (12)	0 (0)	0.291
ARB	43 (91)	28 (88)	15 (100)	0.291
Candesartan	1 (2)	1 (3)	0 (0)	1.000
Losartan	2 (4)	2 (6)	0 (0)	1.000
Olmesartan	3 (6)	3 (9)	0 (0)	0.541
Telmisartan	0 (0)	0 (0)	0 (0)	N/A
Valsartan	37 (79)	22 (69)	15 (100)	0.019
Other medications	(% of Overall)	(% of each group)	(% of each group)	
Antiplatelet	19 (40)	13 (41)	6 (40)	0.968
Ca antagonist	36 (77)	27 (84)	9 (60)	0.066
Beta-blocker	23 (49)	15 (47)	8 (53)	0.680
Statin	16 (34)	8 (25)	8 (33)	0.056
Oral hypoglycemic agent	7 (15)	4 (13)	3 (20)	0.501
Insulin	3 (6)	1 (3)	2 (13)	0.182

N/A, not applicable.
Statistical analyses were performed with the chi-square test or the Mann-Whitney *U* test (*), and differences were considered to be statistically significant for *p*-values <0.05.

Table 2. Patient background data and laboratory findings before and after strict antihypertensive therapy in the high-dose valsartan and valsartan plus trichlormethiazide groups

		High-dose valsartan group				Valsartan plus trichlormethiazide group			*Comparison between groups
Number or mean ± SD	*n*	Before	After	*p*	*n*	Before	After	*p*	*p* (Before/After)
SBP (mm Hg)	32	149 ± 10	130 ± 7	<0.001	15	143 ± 10	126 ± 6	0.001	0.059/0.063
DBP (mm Hg)	32	89 ± 11	76 ± 8	<0.001	15	82 ± 11	76 ± 7	0.027	0.050/0.845
Heart rate (bpm)	23	68 ± 13	71 ± 10	0.258	15	68 ± 8	75 ± 6	0.028	0.857/0.321
Serum K (mEq/L)	29	4.2 ± 0.3	4.2 ± 0.3	0.403	15	4.2 ± 0.3	4.2 ± 0.3	0.871	0.542/0.921
Serum Na (mEq/L)	28	143 ± 2	143 ± 2	0.401	15	142 ± 1	142 ± 1	0.927	0.003/0.031
UA (mg/dL)	28	6.3 ± 1.3	6.3 ± 1.3	0.799	15	5.7 ± 1.3	6.2 ± 1.2	0.003	0.108/0.767
HbA1c (%)	24	5.7 ± 0.9	5.7 ± 1.0	0.208	15	6.1 ± 1.0	6.1 ± 1.0	0.357	0.112/0.129
BNP (pg/ml)	16	50 ± 59	26 ± 22	0.002	12	35 ± 25	30 ± 34	0.272	0.642/0.756
eGFR (ml/min/1.73 m^2)	28	68 ± 14	63 ± 14	0.030	15	68 ± 15	65 ± 16	0.116	0.819/0.858
UACR (mg/g/creatinine)	6	45 ± 56	22 ± 21	0.069	13	62 ± 101	15 ± 20	0.142	0.586/0.325

SBP, systolic blood pressure ; DBP, diastolic blood pressure.
Statistical analyses were performed with the Wilcoxon signed-rank test between data obtained before and after strict antihypertensive therapy from both groups. Statistical comparisons between the high-dose valsartan group and the valsartan plus trichlormethiazide group "before therapy" and "after therapy" were performed using the Mann-Whitney *U* test (*). Differences with a *p*-value <0.05 were considered to be statistically significant.

tihypertensive therapy. The changes in the eGFR and UACR values did not differ significantly between the high-dose valsartan group and the valsartan plus trichlormethiazide group (data not shown). In the high-dose valsartan group (Fig. 1), the eGFR correlated with the UACR ($n=6$, $r=0.842$, $p=0.035$), but there was no correlation between the eGFR and UACR in the valsartan plus trichlormethiazide group ($n=13$, $r=0.014$, $p=0.963$).

Adverse events associated with strict antihypertensive therapy

During the study period, there were no adverse events associated with strict antihypertensive therapy in either the high-dose valsartan group or the valsartan plus trichlormethiazide group.

Discussion

Two recent clinical studies of valsartan for the treatment of Japanese patients with cardiovascular diseases suggest that valsartan has multiorgan protective effects[14,15]. In the present study, we compared treatment with a high dose valsartan or a combination of the standard dose of valsartan and trichlormethiazide, with regard to the renal function as indicated by changes in the eGFR and UACR. The degree of renal protection provided by these different therapies while managing hypertension was evaluated.

Changes in laboratory data other than the eGFR and UACR after strict antihypertensive therapy

After these different strict therapies had been administered for 6 to 12 months, patients in both groups achieved target blood pressure reductions. The changes in the laboratory data after antihypertensive therapies included a significant reduction in the BNP in the high-dose valsartan group and an increase in the serum UA in the valsartan plus trichlormethiazide group (Table 2). The reductions in the plasma BNP levels were likely dose-dependent effects of valsartan, and the increases in the serum UA levels in the valsartan plus trichlormethiazide group, the levels of which were still within the normal limits, might have been caused by combined therapy with the diuretic, because the serum UA levels did not change significantly in the high-dose valsartan group (Table 2).

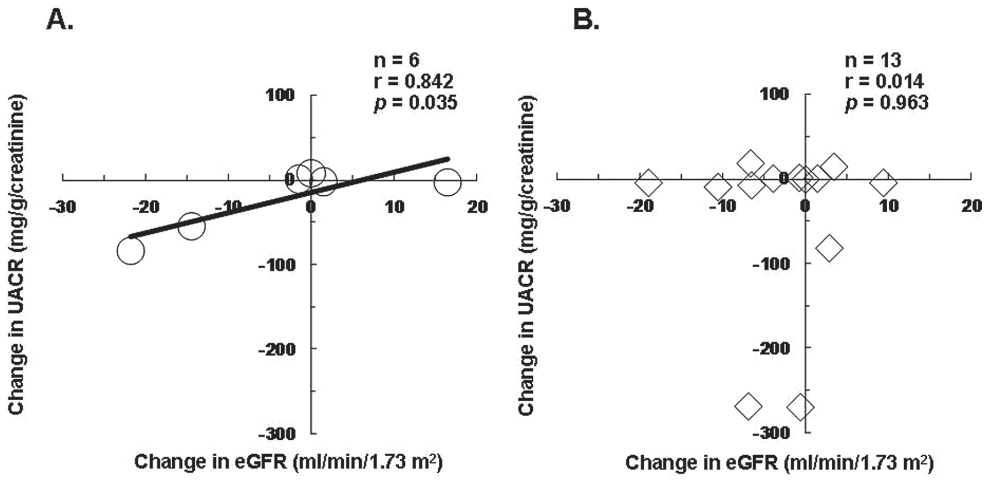

Fig. 1. The relationships between the changes in the eGFR and UACR in the high-dose valsartan group and the valsartan plus trichlormethiazide group
Scatterplots show the changes in the eGFR on the horizontal axis and the changes in the UACR on the vertical axis in the high-dose valsartan group (A, open circles) and the valsartan plus trichlormethiazide group (B, open diamonds). The regression line for this correlation in the high-dose valsartan group (A) is also shown as a scatterplot ($n=6$, $r=0.842$, $p=0.035$). There was no correlation between the changes in the eGFR and the UACR in the valsartan plus trichlormethiazide group ($n=13$, $r=0.014$, $p=0.963$) (B).

Antihypertensive effects of valsartan

Recent studies have also shown that microalbuminuria can be prevented by treatment with an ARB or an angiotensin-converting enzyme (ACE) inhibitor[16-19], thereby leading to renal protection. Additionally, Hollenberg et al.[20] have demonstrated that the reduction of microalbuminuria by valsartan is dose-dependent[21]. These results suggest that a strong inhibition of RAS is important for the reduction of microalbuminuria. However, these studies did not consider the renal function by evaluations of the eGFR or serum creatinine values. In the present study, we compared high dose valsartan therapy and combination therapy with standard doses of valsartan and a diuretic in terms of renal protection by investigating the correlation between the eGFR and UACR values.

Mechanisms by which ARBs reduce microalbuminuria

In the present study, the decreases in the systolic and diastolic blood pressures were similar in the high-dose valsartan group and the valsartan plus trichlormethiazide group. These decreases might have been caused by a reduction in the glomerular filtration rate as a result of reduction in the glomerular pressure. In the present study, the rate of decline in the eGFR in the high-dose valsartan group (−7.4%, significant decrease at $p=0.030$) was greater than that in the valsartan plus trichlormethiazide group (−4.4%, not a significant decrease) (Table 2), despite the decreases in blood pressure being similar in both groups. Therefore, the decrease in glomerular pressure was also greater in the high-dose valsartan group, although the eGFR did not decrease to less than 60 ml/min/1.73 m^2, which is a diagnostic criterion for chronic kidney disease[22]. The decrease in glomerular pressure, which might be a direct dose-dependent effect of valsartan, favors renal protection, suggesting that the greater decrease in eGFR might be the result of the higher dose of valsartan. The microalbuminuria was then decreased as a consequence of this effect. Moreover, a high dose valsartan might more effectively reduce microalbuminuria than combination therapy with standard doses of valsartan and a diuretic, owing to the strong inhibition of the RAS. This effect on microalbuminuria, in addition to the reduced blood pressure[16], may be expected with an ARB (or an ACE inhibitor) because of the preservation of the glomerular microcirculation[23], reduced glomerular capillary wall hyperpermeability[24], and the prevention of glomerulosclerosis, via inhibition of tissue fibrosis, inflammatory activity, and the preservation of endothelial function by these agents[25,26].

In contrast, the decreases in UACR were similar in both of our study groups (but neither decrease was significant) (Table 2). These discrepancies in the reductions of the eGFR and UACR could not be adequately explained by

our data. In the future, a larger number of patients in each group will be needed to explain these changes in laboratory data after the administration of the different antihypertensive therapies.

Comparisons between high-dose ARB and diuretics in terms of renal protection

We found a significant correlation between the eGFR and UACR, and found that the decrease in UACR was dependent on the decreased eGFR in the high-dose valsartan group, but not in the valsartan plus trichlormethiazide group (Fig. 1). These results suggest the existence of differences between valsartan and diuretics regarding the mechanisms by which the UACR levels are observed to decrease, i.e., the effects of both are primarily dependent on decreases in the glomerular pressure, while valsartan may also strongly affect glomerular functions, but the effects of diuretics on the decreased UACR levels may differ among patients.

In addition, because this was a retrospective study with limited therapeutic agents and examination data, the total number of patients was small. As the number of patients assigned to each group was limited, it was not possible to adjust for any potentially confounding background variables, such as the rate of cardiovascular disease, which is high in patients with hypertension treated at outpatient clinics. As a result, other risk factors may therefore have influenced our results.

In summary, treatment with either a high dose valsartan (160 mg/day) or a diuretic agent in combination with the standard dose of valsartan (80 mg/day) achieved a satisfactory antihypertensive effect. Strict antihypertensive therapy with either regimen was highly effective for treating poorly controlled hypertension. The rates of changes in the eGFR and UARC differed between patients treated with a high dose valsartan and those treated with both a diuretic agent and valsartan, suggesting that the diuretic agent has a different mechanism of action in the kidneys of patients treated with valsartan. In particular, antihypertensive therapy with a high dose valsartan is recommended as a means of preserving the cardiovascular function (remodeling) and also providing renal protection in the long term.

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Disclosures

None of the authors has any conflicts of interests to disclose.

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