ORIGINAL ARTICLE

Is the reno-protective effect of valsartan dose dependent? A comparative study of 80 and 160 mg day⁻¹

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Whether the reno-protective effect of angiotensin receptor blockers is dose dependent is unknown for the Japanese population. We sought to elucidate the dose-dependent reno-protective effects of valsartan in Japanese hypertensive patients with albuminuria. This was a multi-center, open-label, parallel-group trial. A total of 181 patients were randomized to receive either 80 ($n=89$) or 160 mg day⁻¹ ($n=92$) of valsartan for 24 weeks. Then, the effects on blood pressure, urinary albumin excretion (UAE), type IV collagen and β_2 -microglobulin (β_2 MG) were determined. Systolic and diastolic blood pressures decreased substantially by almost the same extent in the low-dose and high-dose groups, showing no inter-group difference during the treatment. The UAE value decreased significantly by 35% in both groups. Urinary excretion of β_2 MG was significantly decreased in the high-dose group (17%), but not in the low-dose group (13%), although the decrease was not significantly different between the two groups ($P=0.74$). Urinary excretion of type IV collagen decreased non-significantly by 10% in the low-dose group and by 8% in the high-dose group, showing no significant inter-group difference ($P=0.78$). Low (80 mg day⁻¹) and high (160 mg day⁻¹) doses of valsartan showed a similar effect of lowering blood pressure. The high dose of valsartan resulted in a slightly greater decrease in urinary β_2 MG, but it was inconclusive whether the high dose was more reno-protective as compared with the low dose.

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INTRODUCTION

The role of angiotensin receptor blockers (ARBs) and angiotensin I-converting enzyme inhibitors (ACEIs) in the treatment of hypertension has been established in recent years.^{1–6} The blood pressure-lowering action of ARBs and ACEIs has been shown to be dose dependent. Oparil *et al.*⁷ prescribed valsartan (20, 80, 160 or 320 mg daily) to patients with essential hypertension and studied the efficacy and safety of valsartan compared with placebo in the treatment of hypertension. A dose–response effect on the reduction of blood pressure was observed with doses ≥ 80 mg, although no difference was seen in the response rate between placebo and 20 mg daily dose of valsartan. Neutel *et al.*⁸ investigated the effect of valsartan (20, 80, 160 and 320 mg daily) on blood pressure. A dose-dependent reduction of blood pressure over 24 h and a greater reduction of blood pressure were noted for doses of valsartan ≥ 80 mg compared with 20 mg. Other similar studies also showed a dose-dependent effect on the ability of different ARBs to lower blood pressure.^{9,10}

Several studies have demonstrated beneficial effects of ARBs on renal function, proteinuria and albuminuria,^{11–13} and the effects on micro-albuminuria may not correspond to blood levels of albumin.¹⁴ Suzuki *et al.*¹⁵ reported a significant decrease in urinary albumin excretion (UAE) with valsartan (40 mg day⁻¹) therapy, but there was little change in blood pressure in patients with diabetic nephropathy. A markedly high dose of an ARB, such as valsartan (640 mg daily) and candesartan (64 mg daily), resulted in a reduction in UAE without a further reduction in blood pressure.^{16,17} Recent experimental studies also reported that a very high dose of valsartan provided reno-protection independent of the effect on blood pressure in a rat model of type 2 diabetic nephropathy.¹⁸ Whether or not the reno-protective effect of valsartan is dose dependent has not been addressed in Japanese patients. In this study, we investigated the reno-protective effect of valsartan (80 or 160 mg day⁻¹) in Japanese patients with essential hypertension by means of a randomized trial.

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METHODS

Patients

Patients were recruited from 34 clinics and hospitals in Kyushu Island, Japan, between January 2006 and December 2007. The study subjects were male and female outpatients with systolic blood pressures of 140–159 mm Hg and/or diastolic blood pressure of ≥ 90 mm Hg, regardless of medication status. The subjects were aged 20 years or older and had a UAE of 10–1000 mg per g Cr. Patients with any of the following conditions were excluded: (1) secondary hypertension; (2) serum creatinine > 2 mg 100 ml⁻¹; (3) severe liver dysfunction; (4) recent acute myocardial infarction or stroke (< 6 months); (5) use of ACEIs or ARBs in the past 6 months; (6) allergy to valsartan; and (7) study physician's assessment of inappropriateness for participation.

Study design

This was a multi-center, open-label, parallel-group trial. Eligible patients were enrolled at the central registration center and were randomized to receive either of two doses of valsartan (80 or 160 mg day⁻¹), which are currently approved in Japan. A computer-generated list of 220 random assignments was prepared by a statistician at the registration center using the random permutation block method with equal assignments to the two treatment groups. The first 200 assignments were created in two blocks of 100 random assignments each, and the last 20 assignments were generated in two blocks of 10 random assignments each for supplemental registration. Allocation to each treatment was made according to the sequence of the randomization list, which was kept confidential throughout the study period.

After obtaining informed consent, study physicians reported eligible patients to the registration center by fax and were informed of the assigned dose during the pre-study period. All study physicians followed the allocation correctly. The treatment period was preceded by a trial period, without blood pressure-lowering agents, of 2–4 weeks; an interval chosen to correspond to the typical time between clinic visits.

Concomitant use of ARBs other than valsartan and ACEIs was prohibited during the study. Use of a small dose of diuretics and calcium antagonists was permitted when the target blood pressure level, as defined by the Japanese Society of Hypertension, was not achieved after 8–12 weeks of treatment with valsartan. Diet and exercise were not specifically mandated. Agents prescribed before enrollment were permitted on the condition that the doses were not changed during the study. Adherence to the study drug was assessed by asking patients to report their use of the assigned dose at weeks 12 and 24 with four options regarding drug use during the interval between clinic visits (daily, 5–6 days per week, 3–4 days per week and 1–2 days per week). Daily use or 5–6 days-per-week use was defined as good adherence. The study protocol was reviewed and approved by the ethics committee of each institution.

Blood pressure measurements

Systolic and diastolic blood pressures were measured by an automatic apparatus (Omron HEM-1000), which was provided for each participating clinic or hospital by the central administration office. Measurements were repeated thrice with patients sitting on a chair for at least 5 min in a relaxed position. The second and third readings were averaged and adopted as the measurements for use.

Laboratory measurements

Blood and urine samples were collected after an overnight fast at baseline and after 12 and 24 weeks of treatment. A 10-ml sample of venous blood was drawn for the determination of serum creatinine and blood urea nitrogen (BUN) levels. A 10-ml sample of urine was collected for the determination of UAE, type IV collagen and β_2 -microglobulin (β_2 MG) levels. All determinations were performed at an external laboratory (SRL, Hachiohji, Japan) where the biochemical measurements under study were routinely under quality-control procedures. All results of the measurements were forwarded to the study physicians within 3 working days.

Effectiveness outcomes

The primary effectiveness outcome measures were changes in UAE, type IV collagen, β_2 MG, blood pressure, serum creatinine and BUN levels.

Tolerability outcomes

Tolerability was assessed at each visit and included adverse events either spontaneously reported or elicited by questioning, physical examination findings, and clinical laboratory test results. Study physicians rated the causal relationship of adverse events to study medication as unrelated, suspected or probable. These ratings were finalized by the Safety Monitoring Committee in a blinded manner. Serious adverse events were defined as any untoward medical conditions that resulted in death, hospitalization, life-threatening condition or birth defect.

Abnormal laboratory test results were defined as values > 1.5 times the upper limit of the reference range.

Statistical analysis

Descriptive data are presented as the mean $\pm$ s.d. value unless otherwise specified. Means and proportions were compared between the two groups using an unpaired *t*-test and Fisher's exact test, respectively. Serum creatinine, UAE, type IV collagen and β_2 MG levels were skewed to higher values, and medians and inter-quartile ranges (25th and 75th percentiles) were presented for the baseline comparison by the Wilcoxon rank sum test. The values for serum creatinine, UAE, type IV collagen and β_2 MG levels were transformed to natural logarithms, and their geometric means were obtained. Exponentiation of the mean of the difference in the log-transformed values before and after the treatment corresponded to the percent change after treatment. Inter-group comparison of percent changes was done by an unpaired *t*-test. Analysis of covariance was used to adjust for the baseline values of urinary parameters. Spearman correlation coefficients were used to assess the relationship between percent changes in blood pressure and in renal parameters. All statistical computations were performed using Stata Release 8.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Baseline characteristics

A total of 194 patients were enrolled and randomized to one of the two doses: 95 patients were in the 80-mg group and 99 patients in the 160-mg group (Figure 1). However, five patients did not start medication because they did not meet study criteria ($n=3$), withdrew informed consent ($n=1$) or had no baseline visit ($n=1$). Of the 189 patients who started the medication (92 in the low-dose group and 97 in the high-dose group), eight were excluded due to lack of follow-up visits ($n=2$), discontinuation of treatment due to adverse effects before 12 weeks ($n=2$) and failure to submit blood and urine sampling at baseline ($n=4$). Thus, 181 patients remained in the efficacy analysis.

The baseline characteristics of the patients in the efficacy analysis are shown in Table 1. There were no significant differences in the ratio of men to women, smoking habits, alcohol consumption or comorbid conditions (diabetes mellitus (DM), renal disease and coronary artery disease) between the 80 and 160-mg day⁻¹ groups.

Calcium channel blockers were used by 47 patients (53%) in the low-dose group and 35 patients (38%) in the high-dose group, and the difference was nearly significant ($P=0.053$). Four patients in the low-dose group and one in the high-dose group used β -blockers ($P=0.21$), and only one in the high-dose group used α -blockers ($P=1.00$).

Furthermore, there was no significant difference between the two groups in terms of blood pressure, serum creatinine levels, or urinary β_2 MG excretion. Both urinary type IV collagen and UAE were statistically significantly greater in the 160-mg group than in the 80-mg group at the baseline measurements.

Blood pressure

Both systolic and diastolic blood pressure decreased to the same extent in the two groups (Table 2). In the 80-mg group, means of systolic/diastolic blood pressure levels were 156/87 mm Hg at baseline, 136/76 mm Hg at week 12 and 137/76 mm Hg at week 24.

Figure 1 The design of the study and patient recruitment, including dose escalation in the 160-mg group.

Table 1 Characteristics of the study subjects used in efficacy analysis

Characteristic	Dose (mg day ⁻¹)		P-value ^a
	80 (n=89)	160 (n=92)	
Males, n (%)	40 (44.9)	40 (43.5)	0.88
Age (years)	65.6 (11.6)	64.3 (12.9)	0.47
Height (cm)	157.9 (7.9)	156.5 (9.5)	0.29
Body weight (kg)	60.4 (9.0)	60.6 (12.4)	0.88
Smoking, n (%)	22 (24.7)	18 (19.6)	0.48
Alcohol use, n (%)	36 (40.4)	34 (37.0)	0.65
Comorbid condition, n (%)			
Diabetes mellitus	22 (24.7)	31 (33.7)	0.20
Renal disease	5 (5.6)	4 (4.4) ^b	0.75
Coronary heart disease	5 (5.6)	4 (4.3)	0.74
Heart failure	2 (2.2)	2 (2.2)	1.00
Stroke	2 (2.2)	3 (3.3)	1.00
Dyslipidemia	39 (43.8)	41 (44.6)	1.00
Use of other drugs, n (%)	71 (79.8)	67 (72.8)	0.30
Systolic blood pressure (mm Hg)	155.6 (10.1)	155.1 (10.3)	0.74
Diastolic blood pressure (mm Hg)	86.6 (10.6)	87.6 (9.7)	0.51
Pulse (beats per min)	73.3 (8.5)	75.4 (10.5) ^b	0.14
Serum BUN (mg per 100 ml)	15.2 (4.1)	14.3 (3.4)	0.10
Serum creatinine (mg per 100 ml) ^c	0.72 (0.61–0.84)	0.68 (0.59–0.80)	0.44
Urinary type IV collagen (µg per g Cr) ^c	4.2 (2.7–7.7) ^d	5.5 (3.7–7.9)	0.01
Urinary albumin (mg per g Cr) ^c	21.2 (11.2–54.0)	34.5 (16.6–73.2)	0.05
Urinary β ₂ microglobulin (µg per g Cr) ^c	160 (85–270)	167 (106–332)	0.25

Abbreviation: BUN, blood urea nitrogen.

Means (standard deviations) unless otherwise specified.

^aBased on *t*-test for the comparison of means and Fisher's exact test for the comparison of proportions, unless otherwise specified.

^bn=91 due to missing information.

^cMedian (interquartile range) with Wilcoxon rank sum test for the between-group comparison.

^dn=88 because of no measurement.

Table 2 Means (s.e.) of blood pressure at baseline, 12 weeks and 24 weeks of treatment

Variable	Week	80		160		P-value
		N	Mean (s.e.)	N	Mean (s.e.)	
SBP	0	89	155.6 (1.1)	92	155.1 (1.1)	0.74
	12	86	136.5 (1.2)	89	136.9 (1.3)	0.82
	24	83	137.4 (1.2)	91	137.1 (1.2)	0.89
DBP	0	89	86.6 (1.1)	92	87.6 (1.0)	0.51
	12	86	76.0 (1.0)	89	76.6 (1.1)	0.69
	24	83	76.3 (1.1)	91	76.5 (1.0)	0.89

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

of type IV collagen, albumin and β₂MG. Serum levels of BUN and creatinine did not change during the treatment, and there was no significant difference between the two dosing groups.

None of the urinary parameters showed a statistically significant difference between the two groups during treatment (Table 3). When the initial values were adjusted for the baseline difference, the magnitude by which UAE decreased during the treatment period was almost the same in the low- and high-dose groups (Table 4). Both groups showed a statistically significant 35% decrease in UAE after 24 weeks of treatment. Urinary β₂MG decreased significantly by 22% at 12 weeks and 17% at 24 weeks in the high-dose group, whereas the decrease in the low-dose group (13% at both 12 and 24 weeks) was not statistically significant. Urinary excretion of type IV collagen showed moderately statistically non-significant decreases at 12 and 24 weeks in both groups, although the decreases were greater at 24 weeks than at 12 weeks.

Correlation between changes of blood pressure and urinary markers

Changes of blood pressure were not related to changes in type IV collagen, albumin or β₂MG at either 12 or 24 weeks of treatment. For instance, the Spearman correlation coefficients of the percent change of the systolic blood pressure with type IV collagen, albumin and β₂MG at week 24 were 0.09, 0.00 and 0.04, respectively.

The corresponding values in the high-dose group (160 mg day⁻¹) were 155/88, 137/77 and 137/76 mm Hg, respectively.

Laboratory measurements

Table 3 summarizes mean values, at baseline and 12 and 24 weeks after treatment, of serum BUN and creatinine levels and urinary excretion

Table 3 Means (95% confidence intervals) of renal function markers

Parameter	Week	80 mg day ⁻¹		160 mg day ⁻¹		P-value ^a
		n	Mean (95% CI)	n	Mean (95% CI)	
Serum BUN (mg per 100 ml)	0	89	15.2 (14.3–16.1)	92	14.3 (13.6–15.0)	0.10
	12	86	15.8 (14.8–16.8)	89	15.4 (14.6–16.2)	0.55
	24	83	15.8 (14.6–16.7)	91	15.5 (14.7–16.3)	0.73
Serum creatinine (mg per 100 ml) ^b	0	89	0.72 (0.68–0.76)	92	0.70 (0.67–0.74)	0.51
	12	86	0.74 (0.69–0.78)	89	0.72 (0.69–0.76)	0.67
	24	83	0.73 (0.68–0.77)	91	0.72 (0.68–0.76)	0.82
Urinary type IV collagen (μg per g Cr) ^b	0	88 ^c	4.4 (3.7–5.2)	92	5.6 (4.8–6.4)	0.03
	12	85	4.4 (3.8–5.1)	89	5.0 (4.4–5.7)	0.17
	24	82	4.2 (3.6–4.9)	91	4.8 (4.2–5.6)	0.16
Urinary albumin (mg per g Cr) ^b	0	89	27.2 (20.2–36.7)	92	35.0 (26.6–45.9)	0.22
	12	86	22.0 (16.7–29.1)	89	24.3 (19.2–30.9)	0.59
	24	83	17.5 (13.1–23.4)	91	21.8 (16.8–28.3)	0.27
Urinary β ₂ microglobulin (μg per g Cr) ^b	0	89	171.2 (134.6–217.8)	92	199.1 (157.5–251.7)	0.37
	12	86	155.4 (122.3–197.5)	89	154.1 (121.6–195.3)	0.96
	24	83	150.6 (118.3–191.7)	91	161.9 (132.0–198.5)	0.65

Abbreviations: BUN, blood urea nitrogen; CI, confidence interval.

Means (95% confidence intervals) of renal function markers at baseline, 12 weeks and 24 weeks of treatment by daily dose of valsartan.

^aBased on *t*-test for the between-group comparison.^bGeometric means (95% confidence interval).^cOne subjects was excluded because of missing value at baseline.**Table 4 Adjusted mean percent changes from the baseline in urinary markers of renal function at 12 and 24 weeks of treatment by daily dose^a**

Parameter	Week	80 mg day ⁻¹		160 mg day ⁻¹		P-value
		n	Mean (95% CI)	n	Mean (95% CI)	
Urinary type IV collagen (μg per g Cr)	12	85	–5.6 (–16.1; 6.2)	89	–5.1 (–15.4; 6.5)	0.95
	24	82	–10.4 (–21.5; 2.2)	91	–8.1 (–18.9; 4.2)	0.78
Urinary albumin (μg per g Cr)	12	86	–23.6 (–35.7; –9.3)	89	–28.2 (–39.3; –14.9)	0.62
	24	83	–34.9 (–47.2; –19.8)	91	–35.3 (–47.0; –21.0)	0.97
Urinary β ₂ microglobulin (μg per g Cr)	12	86	–12.9 (–27.0; 4.0)	89	–21.9 (–34.4; –7.1)	0.39
	24	83	–13.4 (–26.5; 2.0)	91	–16.7 (–28.7; –2.6)	0.74

Abbreviation: CI, confidence interval.

^aBased on analysis of covariance with control for the baseline value.

Adherence to drug use

Adherence to drug use was good in 171 of 176 patients (97.2%) at 12 weeks and 165 of 174 patients (94.8%) at 24 weeks, and no significant difference was noted between the 80 and 160-mg day⁻¹ groups. Of the 92 patients in the high-dose group, 61 patients started at a dose of 160 mg day⁻¹ from the beginning of the treatment, and 27 patients started at a dose of 80 mg day⁻¹ and increased the dose to 160 mg day⁻¹ after a median of 14 days (ranging from 7 to 111 days) of the treatment period. No dose increase was reported in the remaining four patients.

Adverse events

Four cases of serious adverse events were noted in the 80-mg day⁻¹ group, including adult T cell type leukemia, unstable angina pectoris, cardiogenic stroke and bone fracture. No such serious adverse events were observed in the 160-mg day⁻¹ group.

Adverse events occurred in 22 (24.7%) and 15 patients (16.3%) in the 80- and 160-mg day⁻¹ groups, respectively, including mild elevation of aspartate aminotransferase, alanine aminotransferase, lactic dehydrogenase and creatinine (≤3 times of baseline readings). Discontinuation of valsartan was only necessary in the abovementioned

four patients with serious adverse events, and termination of valsartan was not necessary in the remaining patients.

DISCUSSION

Two major findings in this study were that both low-dose valsartan treatment regimens (80 mg day⁻¹) and high-dose treatment regimens (160 mg day⁻¹) resulted in a blood pressure decrease to a similar level. There was no dose-dependent difference or substantial reduction of UAE of the same magnitude with either low- or high-dose valsartan therapy. Notably, a significant decrease in urinary excretion of β₂MG was observed only in the high-dose group, but not in the low-dose group. The degree of decrease in β₂MG from baseline was not significantly different between the two groups.

It is rather surprising that the reduction in blood pressure did not differ secondary to the different doses of valsartan, because it has generally been known that ARBs decrease blood pressure in a dose-dependent manner.^{7–10} The blood pressure at baseline did not differ in the low-dose vs. high-dose groups. Therefore, a more frequent use of calcium channel blockers at baseline in the low-dose group may be a possible explanation for a reduction of blood pressure in the low-dose group similar to that in the high-dose group. In addition, although 61

patients in the high-dose group did take a high dose at the beginning of the treatment period, 27 patients followed a high-dose regimen after 2 weeks of the low-dose treatment period, and four patients stayed at 80 mg though the treatment period. Thus, this finding suggests that valsartan does not necessarily exert a dose-dependent effect on lowering blood pressure, at least in the range of 80–160 mg day⁻¹, in the present cohort of patients. The changes in urinary parameters were not measurably correlated with a reduction in blood pressure. Therefore, the above findings about urinary parameters may suggest that a reno-protective effect of valsartan is independent of the drug's effect on lowering blood pressure.

The reason for why we did not observe a dose-dependent difference in UAE is not clear. It has been previously reported that a single dose of valsartan can have a reno-protective effect in Japanese populations. In the SMART study,¹⁹ a dose of valsartan (80 mg day⁻¹), as compared with 5 mg day⁻¹ of amlodipine, decreased micro-albuminuria significantly in 153 patients with type 2 DM. The HARB²⁰ study compared the effect of valsartan (160 mg daily) and 12 mg of candesartan daily in 55 hypertensive patients by changing over the drugs. The HARB study disclosed a significant reduction in urinary protein excretion (UPE) by both valsartan and candesartan; however, there was no significant reduction in UAE for the 44 patients studied. Sato *et al.*²¹ also reported that both ACEIs and ARB (candesartan) decreased UAE; however, urinary excretion of type IV collagen was decreased by candesartan, but not by ACEIs.

Thus, no direct dose-effect comparison has been studied, such as this study's comparison of 80 vs. 160 mg valsartan daily. This comparative study was the first that compared two different doses of valsartan on renal function. Urinary β 2MG and UAE have been known to be surrogate markers of renal function measured by glomerular filtration rate (GFR) and proximal tubular re-absorption. According to a recent review, UAE depends on the balance of glomerular filtration, retrieval and degradative pathways in the proximal tubule, but not on charge effect.²² The molecular weights of albumin and β 2MG are roughly 60 000 and 11 800, whereas that of type IV collagen is much larger—estimated at more than 540 000. Therefore, the mechanisms of urinary excretion of albumin and β 2MG, which are rather small molecules compared with type IV collagen, may be different from that of type IV collagen.

It was recently suggested that urinary β 2MG is an important prognostic marker in patients with membranous nephropathy.^{23,24} Although the mechanism of proximal tubule injury between idiopathic membranous nephropathy and hypertension may not be the same, β 2MG may also be used as a surrogate marker of renal function in those with hypertension. If so, although the present findings were not conclusive, they may be evidence of the dose-dependent reno-protective effect of ARBs.

Regarding urinary excretion of type IV collagen, we did not find any significant decrease in either the 80- or the 160-mg day⁻¹ valsartan group. Ogawa *et al.*²⁵ reported that ARBs (candesartan and valsartan) reduced oxidative stress and inflammation in 66 diabetic patients, resulting in a decrease in UAE and type IV collagen excretion. They also noted a significant correlation between the reduction in urinary 8-epiprostaglandin F2 α and 8-hydroxydeoxyguanosine levels, as well as a reduction in urinary excretion of albumin and type IV collagen. Sato *et al.*²¹ also reported a decrease in urinary excretion of type IV collagen secondary to candesartan therapy. The reason for the discrepancy between our results and those of Ogawa *et al.*²⁵ and Sato *et al.*²¹ regarding type IV collagen is not clear. We did not measure urinary excretion of oxidative stress markers, nor was our entire patient population diabetic. Importantly, Takizawa *et al.*²⁶ reported

urinary excretion of type IV collagen in the absence of UAE, and the progression of nephropathy increased the excretion of type IV collagen. Banu *et al.*²⁷ also reported urinary excretion of type IV collagen in those with normo-albuminuria. Taken together, it is still debatable whether UAE, β 2MG or type IV collagen is the most sensitive marker of renal injury, as measured by urine secretion, in patients with hypertension. This question requires further study in patients with hypertension.

Clinical implications

In this study, although UAE is almost equally decreased by both 80 and 160 mg valsartan daily, β 2MG excretion was decreased significantly only in the high-dose group under the conditions of equal blood pressure level. Therefore, a high dose of valsartan may leave the door open for further study on reno-protection in the Japanese population. The high-dose group did not show increased adverse effects, including serum potassium level.

These adverse effects of ARBs, including hyperkalemia, should be carefully monitored in patients treated with high-dose valsartan and possibly other ARBs. Finally, the importance of addressing and treating potential risks for the development of chronic kidney disease, such as DM and hypertension must also be considered.

Limitations

Although the patients were randomly allocated to one of the two regimens, urinary type IV collagen and albumin excretion at baseline were greater in the high-dose group. As other parameters, such as blood pressure and serum creatinine at baseline, did not show any difference between the two groups, it is unlikely that random allocation was deliberately distorted with respect to the severity of albuminuria. Nevertheless, unequal baseline values between the two groups cause difficulty in interpretation of this findings, as discussed above. The UAE level was expressed in units of mg per g $\bullet$ Cr in this study instead of total albumin excretion per day, so the patients enrolled in the study may well have both micro- and macro-albuminuria, which were analyzed together.²⁸

Conclusion

This study showed that both 80 and 160 mg of valsartan daily lowered blood pressure and UAE to similar levels with no significant difference. Furthermore, high-dose valsartan (160 mg daily) reduced urinary excretion of β 2MG. Direct comparison of low-dose and high-dose therapy did not show a significant difference. The significant predominant reduction of β 2MG only in the high-dose group, however, may suggest dose-dependent reno-protection independent of attained blood pressure levels.

Further study with more patients is warranted.

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APPENDIX

The study's Executive Committee consisted of J Sasaki (Principal Investigator and Member of Protocol Committee), International University of Health and Welfare Graduate School of Public Health Medicine, Fukuoka, Japan; T Saikawa (member of Protocol Committee), Oita University, Oita, Japan; T Kuribayashi, Koga General Hospital, Miyazaki; S Biro (member of Protocol Committee), Tsukasa Hospital, Kagoshima, Japan; K Yamamoto (member of the Safety Monitoring Committee), Takagi Hospital, Fukuoka, Japan; S Ikeda, Second Department of Internal Medicine, Nagasaki University, Nagasaki, Japan. The Safety Monitoring Committee consisted of N Okabe, Ayasugi Building Clinic, Fukuoka, Japan. The head of the Registration Center and Data Center was S Kono (member of Protocol Committee), Kyushu University Faculty of Medical Sciences, Fukuoka, Japan.