Original Article

Clinical Efficacy of a New Angiotensin II Type 1 Receptor Blocker, Pratosartan, in Hypertensive Patients

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To evaluate the clinical efficacy and safety of a new angiotensin II type 1 receptor blocker, pratosartan, in patients with mild-to-moderate essential hypertension, a multicenter, open-label study was conducted. A 2- to 4-week run-in period was followed by a 12-week core study with pratosartan monotherapy, or a combination of pratosartan with a calcium channel blocker (CCB) or diuretic. Patients took a daily dose of 40, 80, or 160 mg pratosartan, with titration at 4-week intervals. Patients who tolerated pratosartan at the end of a 12-week core study then participated in a 9-month follow-up period (*i.e.*, long-term study). Responder rates by pratosartan were 82.1% in the monotherapy, 81.3% in the combination with CCB, and 60.0% in the combination with diuretic group at 12 weeks. Pratosartan was efficacious throughout the long-term study, without serious adverse effects. Pratosartan significantly decreased serum total cholesterol in patients with hypercholesterolemia and uric acid in patients with hyperuricemia. In conclusion, pratosartan is an effective and well tolerated antihypertensive drug, and may have beneficial effects on hypertensive patients with some metabolic disorders. (*Hypertens Res* 2008; 31: 281–287)

***Key Words*: pratosartan, angiotensin II receptor blocker, hypertension, uric acid, cholesterol**

Introduction

It has been established that angiotensin II type 1 receptor blockers (ARBs) are useful antihypertensive drugs. Pratosartan (PRT) (*1*) is a new ARB that bears an oxo (C=O) moiety in its head part chemical structure, rather than a carboxylic acid moiety such as candesartan, olmesartan, valsartan and other ARBs possess, to accommodate a postulated second positive charged portion of angiotensin II receptors (*2*). PRT is an active form but not a prodrug. In rabbit and rat aorta vascular smooth muscle *in vitro*, PRT shifted the dose response curve of angiotensin II to the right and suppressed maximal contraction insurmountably (*3*). In rat models of spontaneous hypertension and renal hypertension, once daily administration of PRT resulted in a maintenance of blood pressure (BP) reduction (*4*). And in a study using ambulatory BP measurements to measure the antihypertensive effects of PRT in Caucasians, the drug was shown to achieve good blood pressure control (*5*).

Despite the successful use of losartan and other ARBs in hypertension therapy, several issues remain to be resolved. One of these is the elevation of serum uric acid that occurs with ARBs other than losartan (*6–10*). The various ARBs have different effects on uric acid levels, depending on their chemical structures, and this is of particular importance in Japanese patients, who are more susceptible to uric acid elevation (*11*). In this context, it is noteworthy that the active

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Table 1. Baseline Characteristics of All Patients

	Monotherapy	Combination therapy	
	PRT (n=106)	CCB+PRT (n=32)	DIU+PRT (n=30)
Male (%)/female (%)	64/36	69/31	60/40
Age (years)	58.0±10.2	56.0±8.8	61.3±7.8
Height (cm)	161.5±9.0	162.2±7.9	160.1±8.4
Weight (kg)	65.4±11.5	65.3±11.9	65.8±9.1
Current smoker (%)	37.7	25.0	46.7
Current drinker (%)	64.2	71.9	50.0
SBP (mmHg)	166.0±10.0	162.6±7.8	164.7±10.2
DBP (mmHg)	99.9±6.1	99.9±4.6	102.2±8.0
Pulse rate (beats/min)	70.5±8.2	78.3±15.7	75.1±8.0
Serum total cholesterol (mg/dL)	211.2±42.6	209.7±34.1	209.7±34.9
Serum uric acid (mg/dL)	5.8±1.4	5.4±1.5	6.0±1.6
Fasting plasma glucose (mg/dL)	105.2±26.4	111.1±33.5	104.6±24.6

Data are presented as mean±SD. PRT, pratosartan; CCB, calcium channel blocker; DIU, diuretic; SBP, systolic blood pressure; DBP, diastolic blood pressure. Comparisons among three groups were performed by χ^2 test for frequencies or analysis of variance for mean value. There was no significant difference in baseline characteristics among three groups except pulse rate (p=0.0006).

metabolite of losartan, Exp3174, whose alcoholic moiety is metabolized to a carboxylic moiety, is reported to have lost the uricosuric activity of losartan (*12*). In the present study, therefore, we monitored and carefully analyzed the uric acid levels in patients receiving PRT therapy.

Another issue to be resolved in ARB therapy is its adjunctive effects on metabolic disorders. At least one of the ARBs, telmisartan, has been reported to improve glucose and lipid metabolism (*13*, *14*). In the case of cholesterol, however, the effects of ARBs on serum cholesterol level have rarely been evaluated in a clinical setting, despite the fact that the total cholesterol level is known to be an important risk factor for cardiovascular events. In the present study, therefore, we also investigated the effect of PRT on glucose and lipid metabolism, in addition to evaluating the general efficacy and safety of PRT in patients with mild-to-moderate hypertension.

Methods

We conducted a multicenter, open-label study in Japan, in accordance with the Japanese Clinical Evaluation Guidelines for antihypertensive drugs (1989), the Declaration of Helsinki, and Good Clinical Practice guidelines. The study protocol was approved by the institutional review board at each study site. All patients provided written informed consent prior to participation.

Study Population

All participants were outpatients with mild-to-moderate essential hypertension. Those who had not received any antihypertensive drugs for the duration of the 2–4 week run-in period were enrolled in the PRT monotherapy group. Patients whose hypertension had been insufficiently controlled with dihydropyridine calcium channel blockers (CCBs) or diuretics (DIUs) alone were enrolled in the combined treatment study, in which PRT was added to a fixed dose of CCB or DIU. Average dosages of CCBs were as follows: 5 mg of amlodipine (n=21), 15 mg of barnidipine (n=1), 10 mg of cilnidipine (n=1), 15 mg of manidipine (n=4), 40 mg of nifedipine (n=4), and 4 mg of nilvadipine (n=1). Average dosages of DIUs were as follows: 17.5 mg of hydrochlorothiazide (n=15), 1 mg of indapamide (n=4), and 1.9 mg of trichloromethiazide (n=11).

All participants met the following inclusion criteria: age ≥20 years; systolic BP (SBP)/diastolic BP (DBP) ≥150/95 mmHg or ≥160/90 mmHg, with DBP <119 mmHg; and absence of any associated clinical conditions, as defined by the 1999 World Health Organization–International Society of Hypertension (WHO-ISH) guidelines.

Patients were not eligible for the study if they had severe hypertension (*i.e.*, DBP >120 mmHg); suspected or proven secondary hypertension; cerebrovascular attack or myocardial infarction within the previous 3 months; severe cardiac, hepatic (*i.e.*, not less than 100 IU/L aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) or renal (*i.e.*, not less than 1.6 mg/dL serum creatinine) diseases; uncontrolled diabetes mellitus (*i.e.*, fasting blood glucose >200 mg/dL, or postprandial blood glucose >300 mg/dL); hyperkalemia (*i.e.*, not less than 5.5 mEq/L blood potassium); malignant tumor requiring treatment; pregnancy; or a history of severe adverse drug reactions. Patients judged ineligible at the discretion of an investigator were also excluded.

Study Design

The study was designed to assess the efficacy and safety of PRT as a monotherapy or in combination with CCB and DIU

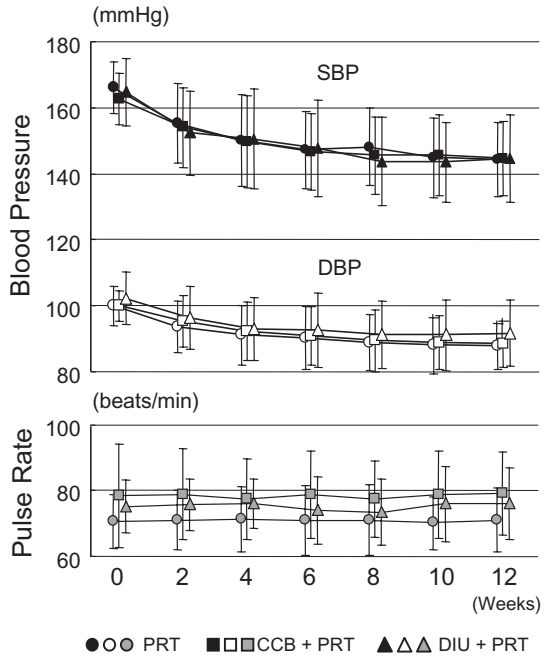

Fig. 1. *Blood pressure and pulse rate of patients in the core study. The number of patients in the PRT, CCB+PRT, and DIU+PRT groups was 106, 32, and 30, respectively. Data represent the means±SD. Systolic and diastolic blood pressure (SBP and DBP) were significantly decreased 2 weeks after PRT treatment in all groups (paired t-test, $p<0.001$). Pulse rate did not change in any group.*

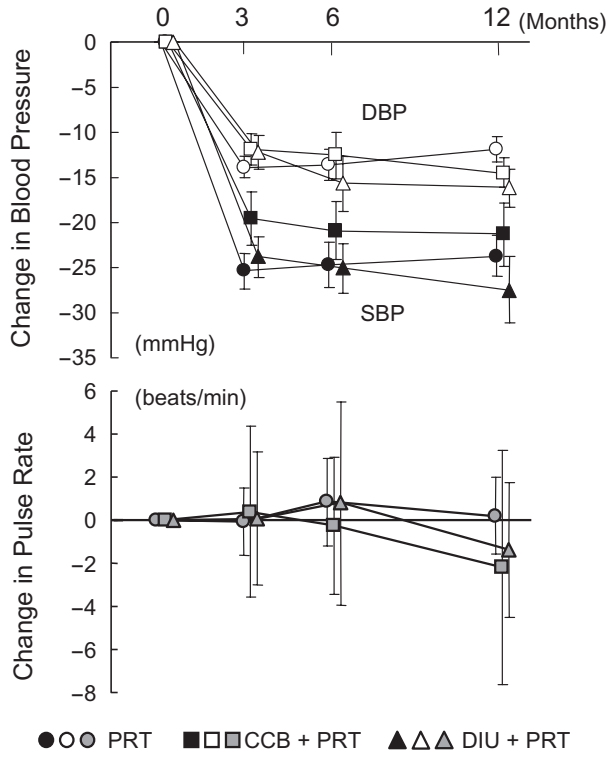

Fig. 2. *Changes in blood pressure and pulse rate of patients in the long-term study. The number of patients enrolled in the PRT, CCB+PRT, and DIU+PRT groups was 73, 29, and 23, respectively. Baseline blood pressure and pulse rate during the run-in period were 165.8±10.3/98.9±5.6 mmHg and 70.8±8.2/min in the PRT group, 162.0±7.3/100.0±4.7 mmHg and 78.6±16.1/min in the CCB+PRT group, and 164.8±10.6/102.0±8.3 mmHg and 74.7±7.1/min in the DIU+PRT group. Bars represent 95% confidence intervals. SBP, systolic blood pressure; DBP, diastolic blood pressure.*

regimens in patients whose hypertension was not controlled by CCB or DIU monotherapy. The study consisted of 3 stages: A 2- to 4-week run-in period, a 12-week treatment period (*i.e.*, core study), and an additional, optional 9-month follow-up (*i.e.*, long-term study). In the placebo run-in period, patients who had been taking any antihypertensive medications except for single CCBs or DIUs took one tablet of placebo (indistinguishable from PRT) once a day after breakfast for 2–4 weeks. If BP inclusion criteria were met at the end of the run-in period (*i.e.*, SBP/DBP ≥150/95 mmHg or ≥160/90 mmHg, DBP <119 mmHg), patients entered the 12-week core study.

During the 12-week core study, patients in the PRT monotherapy group and in each of the combination groups (CCB+PRT, DIU+PRT) took a daily dose of 40, 80, or 160 mg PRT, with titration at 4-week intervals. The dosage of CCB or DIU remained unchanged during the core study. Patient visits occurred at 2-week intervals during the core study.

Patients identified as responders and/or tolerators at the end of the 12-week core study entered into the subsequent, optional long-term study. All subjects provided additional written informed consent prior to participating in the long-term study. During the 9-month study extension, the PRT dose was adjusted to between 40 and 160 mg/day, according to the patient's response. Patient visits were set at 4-week intervals.

Study Assessments

Sitting BP and pulse rate (PR) were measured at each visit throughout the study by automated instrumentation. Each patient rested for a minimum of 5 min in a sitting position before BP was measured at least two times at an appropriate interval. Baseline BP was defined as the mean value of the BP measurement from the final two visits during the run-in period. All additional BP measurements were obtained 2–4 h after drug administration.

Laboratory examinations (hematology and biochemistry evaluations and urinalysis), a 12-lead ECG, and a physical examination were conducted during the run-in period and at the 12-week, 6-month, and 12-month visits. At each visit, patients reported any adverse events (AEs), and all such AEs

Table 2. Changes in Total Cholesterol (Core Study)

T-Cholesterol (mg/dL)	Group	*N**	Baseline	12 weeks	Change from baseline	*p* (paired *t*-test)
All	PRT	107	211.2±42.6	199.6±40.2	−11.7±29.7	<0.0001
	CCB+PRT	36	209.7±34.1	197.0±39.2	−12.7±23.0	0.002
	DIU+PRT	36	209.7±34.9	199.8±30.9	−9.9±26.2	0.029
≥220	PRT	44	252.0±26.0	227.1±38.5	−24.9±37.3	<0.0001
	CCB+PRT	12	247.3±21.2	227.4±39.1	−19.8±29.8	0.041
	DIU+PRT	11	251.0±19.5	220.5±24.4	−30.5±23.3	0.002
<220	PRT	63	182.7±25.0	180.3±28.6	−2.4±18.2	n.s.
	CCB+PRT	24	190.9±21.2	181.8±29.8	−9.1±18.4	0.024
	DIU+PRT	25	191.6±22.3	190.6±29.3	−0.9±22.4	n.s.

Data are presented as mean±SD. PRT, pratosartan; CCB, calcium channel blocker; DIU, diuretic; T-Cholesterol, serum total cholesterol; n.s., not significant. *N**: number of patients for safety analysis including patients who were administered PRT but did not complete the study.

were recorded, evaluated, and monitored by an investigator.

Study Endpoints

The primary efficacy variable of the study was the responder rate at the completion of the 12-week core study. All responders met one or both of the following criteria as defined by the Japanese Clinical Evaluation Guidelines for antihypertensive drugs (1989): 1) reduction in SBP/DBP ≥20/10 mmHg compared to baseline, and/or 2) SBP/DBP <150/90 mmHg after treatment. The secondary efficacy variable was mean BP change from baseline.

For safety assessment, the incidence of AEs and adverse drug reactions (ADRs; events for which a causal relationship to PRT could not be ruled out) and changes in hematology, biochemistry, and urinalysis parameter were analyzed.

Statistical Analysis

The efficacy evaluation of the study was carried out using a per-protocol analysis. Patients who took at least one dose of PRT during the core study were included in the safety analysis. All statistical analyses were conducted separately for the PRT monotherapy group, the CCB+PRT group, and the DIU+PRT group. In the treatment groups, changes between baseline and the end of treatment were analyzed using two-tailed, paired *t*-tests. The type I error rate was set at $\alpha=0.05$. ADRs were summarized by treatment group and system organ class. Data are presented as the means±SD, except when stated otherwise.

Results

Patient Demographics and Baseline Characteristics

A total of 168 patients ($n=106$ in the PRT monotherapy group, $n=32$ in the CCB+PRT group, and $n=30$ in the DIU+PRT group) were evaluated for efficacy analysis in the 12-week core study. Patient baseline characteristics are summarized in Table 1.

Responder Rate and Changes in BP and PR

Accumulated responder rates at 40, 80 and 160 mg of PRT were 29.2%, 61.3%, and 82.1% (95% confidence interval [CI]: 73.4% to 88.9%) for the PRT monotherapy group, 12.5%, 53.1%, and 81.3% (95% CI: 63.6% to 92.8%) for the CCB+PRT group, and 23.3%, 46.7%, and 60.0% (95% CI: 40.6% to 77.4%) for the DIU+PRT group, respectively. SBP and DBP decreased significantly 2 weeks after treatment in all groups and then continued to decrease gradually until the end of the core study (Fig. 1). The percentage of patients for whom an SBP of less than 140 mmHg was achieved was 40.6% in the PRT monotherapy group, 28.1% in the CCB+PRT group, and 46.7% in the DIU+PRT group. The percentage of patients for whom a DBP of less than 90 mmHg was achieved was 70.8% in the PRT monotherapy group, 59.4% in the CCB+PRT group, and 53.3% in the DIU+PRT group. The percentages of patients for whom an SBP/DBP of less than 140/90 mmHg was achieved was 34.9% in the PRT monotherapy group, 25.0% in the CCB+PRT group, and 36.7% in the DIU+PRT group. BP reduction was sustained for 12 months as shown by the long-term study results (Fig. 2). There were no significant differences in PR among the three treatment groups (Fig. 2).

Changes in Serum Cholesterol, Glucose, and Uric Acid Levels

PRT administration was associated with significant decreases in serum total cholesterol, particularly in patients with hypercholesterolemia (Table 2). These decreases were seen in all three treatment groups, and were sustained for 12 months in

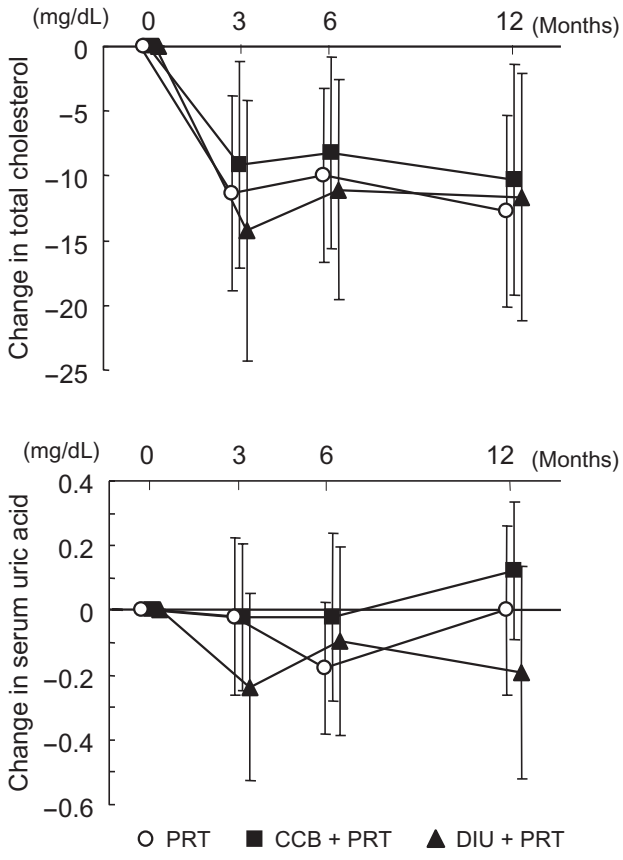

Fig. 3. *Changes in serum total cholesterol and serum uric acid of patients in the long-term study. The upper panel shows the changes in total cholesterol. The number of patients enrolled in the PRT, CCB+PRT, and DIU+PRT groups was 75, 29, and 27, respectively. Baseline levels of serum total cholesterol during the run-in period were 213.8±42.8 mg/dL in the PRT group, 211.0±29.5 mg/dL in the CCB+PRT group, and 215.3±35.4 mg/dL in the DIU+PRT group. The lower panel shows the changes in serum uric acid. The number of patients enrolled in the PRT, CCB+PRT, and DIU+PRT groups was 74, 29, and 27, respectively. Baseline levels of serum uric acid during the run-in period were 5.59±1.44 mg/dL in the PRT group, 5.23±1.48 mg/dL in the CCB+PRT group, and 6.15±1.66 mg/dL in the DIU+PRT group. Bars represent 95% confidence intervals.*

all treatment groups (Fig. 3). There were no significant changes in body weight, fasting plasma glucose, or total serum protein, which are indicators of nutritional status (data not shown).

Serum uric acid levels did not change in any of the groups. However, serum uric acid in the PRT monotherapy and DIU+PRT groups was significantly decreased in hyperuricemic patients (baseline uric acid ≥7.0 mg/dL for males, ≥6.0 mg/dL for females) in the 12-week core study (Table 3). Further reduction or reversal increases in serum uric acid were not observed during the long-term study (Fig. 3).

Safety and Tolerance

Twenty-four symptomatic ADRs (*i.e.*, events for which a causal relationship with treatment could not be ruled out) were reported. Four patients (2.2% of the total) reported the symptomatic ADR of headache. One patient with headache was the only patient to withdraw from PRT due to treatment-related AEs.

Fifty-six ADRs in laboratory parameters were reported. The most frequently reported laboratory ADRs were increased blood alkaline phosphatase, increased blood uric acid and positive urine protein, each reported in 2.2% (4/183). There were no dose-related increases in ADRs. No ADR posed a clinical threat. PRT was well tolerated as a monotherapy and in combination with CCBs and DIUs.

Discussion

The results of the present study demonstrated that PRT, as monotherapy or in combination with a CCB or DIU, reduced BP in Japanese patients with mild-to-moderate hypertension. In patients whose hypertension was not controlled by CCB or DIU monotherapy, the addition of PRT effectively reduced BP. The antihypertensive efficacy of PRT was steady, and patients tolerated the treatment for 1 year without serious AEs. The responder rate at 12 weeks was 78% for the entire study population. This rate is similar to that reported in previous Japanese studies of ARBs (*e.g.*, losartan (*15*, *16*), candesartan (*17–19*), valsartan (*20–22*), telmisartan (*23*, *24*) and olmesartan (*25*, *26*)). The BP reduction in our present study (about 20/10 mmHg) was not inferior to that in the previous study using PRT in Caucasians (13.7/8.0 mmHg) (*5*). These results indicate that PRT is qualified as a new member of ARBs which are recommended to treat hypertension in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (*27*), the European Society of Hypertension–European Society of Cardiology (ESH-ESC) (*28*), and the 2004 Japanese Society of Hypertension (JSH 2004) (*29*) guidelines.

Recent reports indicate that the pharmacokinetic and pharmacodynamic properties of ARBs are not identical. For example, telmisartan has been reported to be beneficial for glucose and lipid metabolism (*13*, *14*), and losartan to be beneficial for uric acid reduction (*6–10*). The present study demonstrated that PRT may be of benefit in cholesterol and uric acid metabolism, although we can not exclude the possibility that the reduction of uric acid and cholesterol may be affected by diet, because we did not control diet during the study period.

A stratified analysis of the laboratory data demonstrated that total cholesterol levels decreased significantly compared to baseline, even though medications for concomitant dis-

Table 3. Changes in Serum Uric Acid (Core Study)

UA (mg/dL)	Group	*N**	Baseline	12 weeks	Change from baseline	*p* (paired *t*-test)
All	PRT	109	5.79±1.44	5.64±1.43	−0.15±1.01	n.s.
	CCB+PRT	36	5.44±1.50	5.36±1.56	−0.08±0.65	n.s.
	DIU+PRT	36	5.98±1.61	5.83±1.42	−0.15±0.84	n.s.
M: ≥7.0, F: ≥6.0	PRT	21	7.71±1.24	6.97±1.29	−0.74±1.23	0.012
	CCB+PRT	8	7.39±0.84	7.34±1.07	−0.05±0.91	n.s.
	DIU+PRT	13	7.55±0.91	6.84±0.89	−0.71±0.73	0.004
M: <7.0, F: <6.0	PRT	88	5.33±1.05	5.32±1.27	−0.01±0.91	n.s.
	CCB+PRT	28	4.89±1.13	4.80±1.16	−0.09±0.58	n.s.
	DIU+PRT	23	5.10±1.17	5.27±1.36	0.17±0.74	n.s.

Data are presented as mean±SD. PRT, pratosartan; CCB, calcium channel blockers; DIU, diuretic; UA, serum uric acid; M, male; F, female; n.s., not significant. *N**: number of patients for safety analysis including patients who were administered PRT but did not complete the study.

eases, such as hypercholesteremia, were not altered during the study. Since body weight, fasting plasma glucose, and total protein did not decrease during the study, the decrease in total cholesterol was not related to a nutritional disorder. Of course, the effects of PRT on lipid profiles should be confirmed by prospective clinical studies, including evaluations of the different classes of lipoprotein cholesterols, *i.e.*, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. These topics are currently being investigated.

The present study further revealed that PRT did not elevate uric acid levels, even when administered in combination with DIUs. This observation is compatible with an *in vitro* study demonstrating that PRT significantly enhanced uric acid uptake in urate transporter 1 (URAT-1)–expressing oocytes (*30*). In general, long-term treatment with DIUs increases serum uric acid levels, probably by preventing the re-absorption of uric acid at the renal tubules by specific transporters (*31–33*). This limitation of DIUs has recently attracted attention because uric acid is a suspected risk factor for cardiovascular events (*34*). In the Systolic Hypertension in the Elderly Program (SHEP) study (*35*), a post-hoc analysis showed that reduction in cardiovascular disease associated with DIU treatment was restricted to patients whose uric acid levels increased by <1 mg/dL after 1 year. It will be interesting to clarify whether different ARBs have an effect on serum uric acid levels, particularly in combination with DIUs. Very few reports have addressed this issue, and only losartan has been reported to compensate for uric acid elevation induced by DIUs in a clinical setting (*36*). Therefore, PRT may have a beneficial effect on uric acid through a metabotropic action.

In conclusion, PRT decreased BP in Japanese patients with mild-to-moderate essential hypertension without serious adverse events. Further, the drug's potent reduction of serum uric acid and total cholesterol may be advantageous for hypertensive patients with multiple risk factors.

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