

Effects of irbesartan on 24-h blood pressure changes and urinary albumin levels in Japanese outpatients

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Abstract. In Japan, ambulatory blood pressure monitoring (ABPM) became covered by health insurance in April 2008. In The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH2009), the importance of 24-h blood pressure monitoring was also described in an additional section. Therefore, ABPM may be increasingly applied in hypertension treatment. However, in Japan, few studies have presented data on the effects of various anti-hypertensive agents on 24-h blood pressure changes. Irbesartan became commercially available in July 2008 as the sixth angiotensin II type 1 receptor blocker in Japan. In the present study, 24-h blood pressure control was examined using ABPM in Japanese patients with essential hypertension who were treated with irbesartan, and its efficacy was evaluated. This study was completed in 30 of the 32 subjects. This agent decreased both the nocturnal and daytime blood pressures and reduced the rate of change in the systolic blood pressure early in the morning, resulting in favorable blood pressure control. It also significantly decreased the urinary albumin level, suggesting that it exhibits renoprotective effects at doses approved in Japan.

Introduction

In clinical practice, blood pressure measurement at home is employed for non-office blood pressure monitoring, which is not possible at outpatient clinics. However, ambulatory blood pressure monitoring (ABPM), which facilitates the assessment of 24-h blood pressure changes, is necessary to measure the nocturnal blood pressure, which may be associated with organ disorders (1). In Japan, National Health Insurance coverage of ABPM began in April 2008. In The Japanese

Society of Hypertension Guidelines for the Management of Hypertension (JSH2009) (2), the importance of 24-h blood pressure monitoring was also described as an additional section. Therefore, ABPM may be increasingly applied in hypertension treatment. However, in Japan few studies have presented data on the effects of various anti-hypertensive agents on 24-h blood pressure changes.

Irbesartan (3) became commercially available in July 2008 as the sixth angiotensin II type 1 receptor blocker (ARB) in Japan. Since this agent is characterized by a half-life of 10.2-15.4 h (4) and strong binding to AT₁ receptors (5), it may exhibit continuous anti-hypertensive effects over 24 h (6). However, no data on 24-h blood pressure involving Japanese outpatients have been published. In this study, we investigated 24-h blood pressure changes in patients receiving irbesartan to evaluate its anti-hypertensive/persistent effects. In addition, we measured the urinary albumin and serum creatinine levels.

Patients and methods

Among patients newly diagnosed with hypertension in the three clinics participating in the study, those without a history of anti-hypertensive therapy within 4 weeks before the start of irbesartan administration, who were able to consult the outpatient clinic every 2 weeks and who consented to participate in this study, were registered as subjects. Physicians were prohibited from additionally administering other anti-hypertensive agents. As a rule, agents that had been prescribed (for other concomitant disorders) were not changed during the study period.

Thirty-two patients were enrolled between December 2008 and May 2009. As shown in the flow chart (Fig. 1), the criteria for registration included systolic or diastolic office blood pressure of $\geq 140/90$ mmHg and age ranging from 20 to 75 years, regardless of gender and complications. Patients with a urinary protein level of ≥ 100 mg/dl by urine test paper were excluded. The daily dose of irbesartan was 100 mg (once-a-day administration); however, if necessary, the dose could be increased to 200 mg based on the attending physician's evaluation. The blood pressure and pulse were measured along with examination for general symptoms at consultations before the start and after 2, 4 and 6 weeks of administration. A blood test and urinalysis were conducted to determine the serum creatinine

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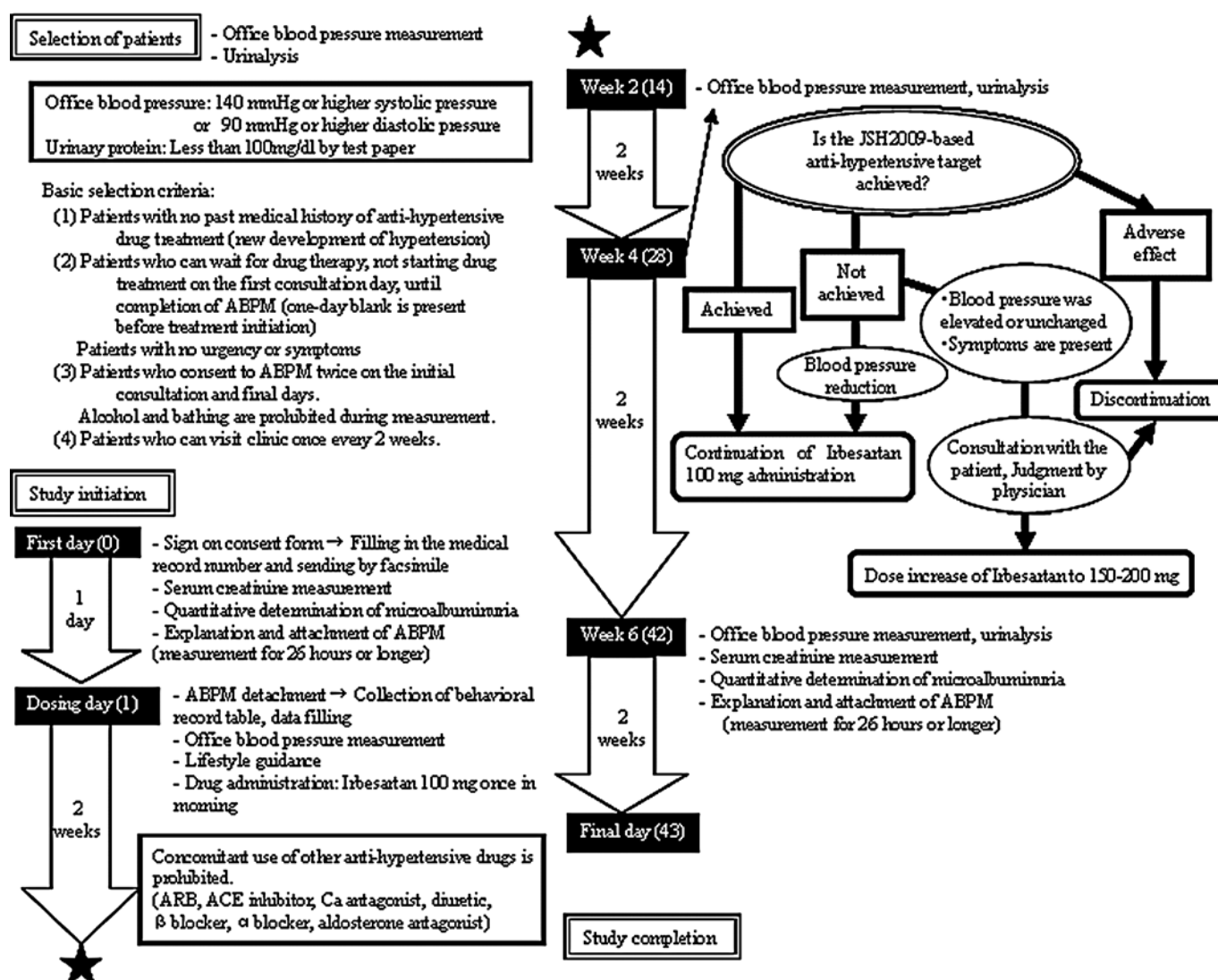


Figure 1. Treatment and study schedule.

and urinary albumin levels before and 6 weeks after the start of administration. At these points, an ABPM device was worn for ≥ 26 h from the time of consultation until the following day. The blood pressure was measured at 1-h intervals. For each patient, the mean of the values obtained between 9:00 pm and 5:00 am was regarded as the nocturnal blood pressure. The mean of the values obtained between 8:00 am and 6:00 pm was regarded as the daytime blood pressure. As an index of blood pressure changes early in the morning, differences in the mean blood pressure between two intervals: 3:00-5:00 am and 7:00-9:00 am were calculated. The estimated glomerular filtration rate (eGFR) was calculated using the formula [eGFR (ml/min/1.73 m²) (7) = 194 \times Cr^{-1.094} \times age^{-0.287} (female: \times 0.739)] as established by the Japanese Society of Nephrology. Patients showing an eGFR of <60 ml/min/1.73 m² or a urinary albumin level of ≥ 30 mg/g-Cr before the start of irbesartan administration were regarded as having nephropathy. The study objective and method were fully explained to the subjects, and written informed consent was obtained.

Statistical analysis. Various parameters were expressed as the mean \pm standard deviation, excluding those with notes. To

compare the mean 24-h blood pressure and pre-/post-treatment values, the Student's t-test was employed. When comparing data on repetitive blood pressure/pulse measurements to the pre-treatment values, Bonferroni's correction was performed, considering test multiplicity. $P < 0.0167$ ($\approx 0.05 \div 3$) was regarded as significant. Concerning other items, $P < 0.05$ was regarded as significant. With respect to the urinary albumin level, significance was tested after routine logarithmic transformation, as a log-normal distribution was assumed.

Patient backgrounds. This study was completed in 30 of the 32 subjects. Two patients did not consult the outpatient clinic as scheduled, dropping out of the study. There was no discontinuation related to adverse reactions. The backgrounds of the 30 patients are shown in Table I. They consisted of 11 males and 19 females with a mean age of 61.3 years. The mean systolic and diastolic blood pressures determined at the outpatient clinic were 169.9 \pm 18.5 and 92.4 \pm 11.8 mmHg, respectively.

The mean urinary albumin and serum creatinine levels were 60.8 \pm 155.5 mg/g-Cr and 0.671 \pm 0.173 mg/dl, respectively. The eGFR was 81.2 \pm 18.8 ml/min/1.73 m². Of the 30 patients,

Table I. Patient characteristics at baseline.

Demographics	
Male/female	11/19
Age (years)	61.3±13.3
Office blood pressure	
SBP (mmHg)	169.9±18.5
DBP (mmHg)	92.4±11.8
Renal parameters	
Serum creatinine (mg/dl)	0.671±0.173
eGFR (ml/min/1.73 m ²)	81.2±18.8
Urinary albumin (μg/g·Cr)	60.8±155.5

SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate.

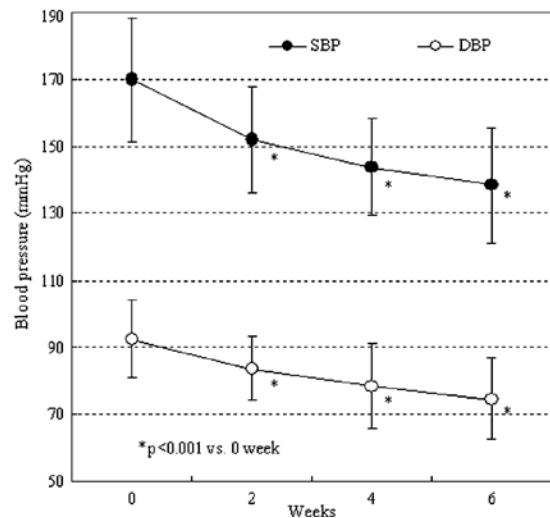


Figure 2. Office blood pressure.

Table II. Patient distribution: baseline urinary albumin (U-Alb) and estimated glomerular filtration rate (eGFR).

eGFR	≥90	60-90	≤60	Total
U-Alb				
≤30	5	13	2	20
30-300	2	6	1	9
≥300	-	1	-	1
Total (n)	7	20	3	30

10 showed abnormal urinary albumin levels (microalbuminuria 9; manifest albuminuria 1). In 3 patients, the eGFR was <60 ml/min/1.73 m². The distribution of the urinary albumin

level/eGFR-stratified patients is shown in Table II. A total of 12 patients had nephropathy, showing an eGFR of <60 ml/min/1.73 m² or a urinary albumin level of ≥30 mg/g·Cr.

Results

Both the systolic and diastolic office blood pressures were significantly decreased after 2 weeks of irbesartan administration ($P < 0.001$). After 6 weeks of administration, the values were 138.8 and 74.4 mmHg, respectively (Fig. 2). As shown in Fig. 3, 24-h blood pressure control was achieved by administration of irbesartan. The mean 24-h systolic and diastolic blood pressures significantly decreased from 162.7±17.7 and 85.5±5.8 to 131.9±9.0 and 75.5±7.5 mmHg, respectively. Both the nocturnal and daytime blood pressures significantly

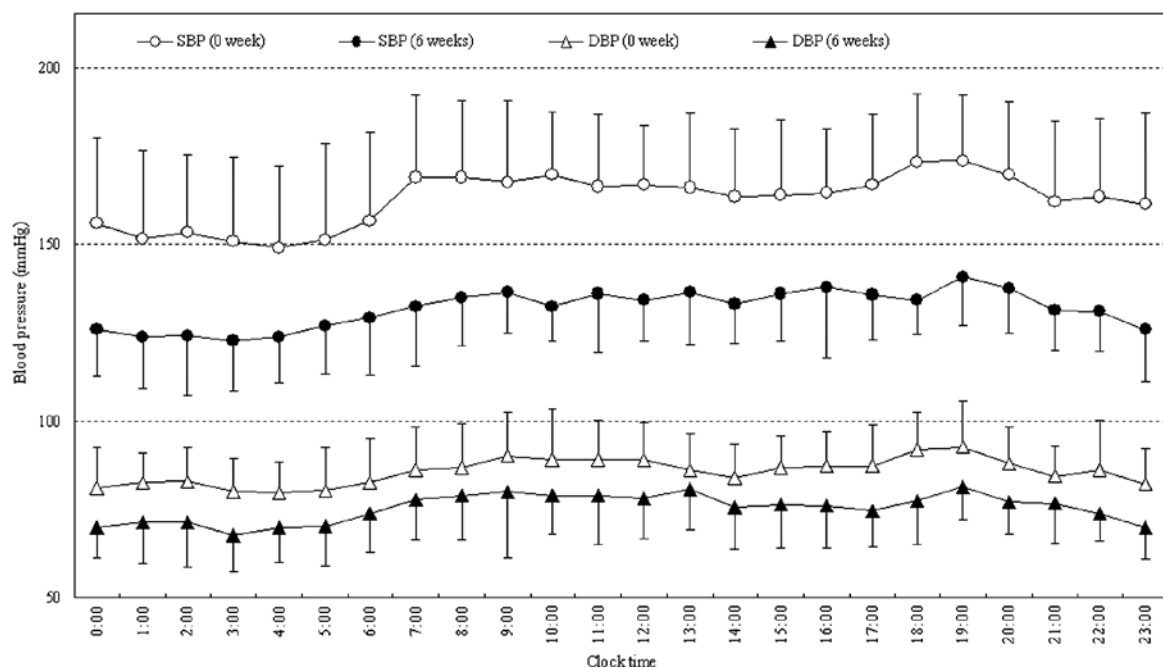


Figure 3. Effect of irbesartan on 24-h ambulatory blood pressure.

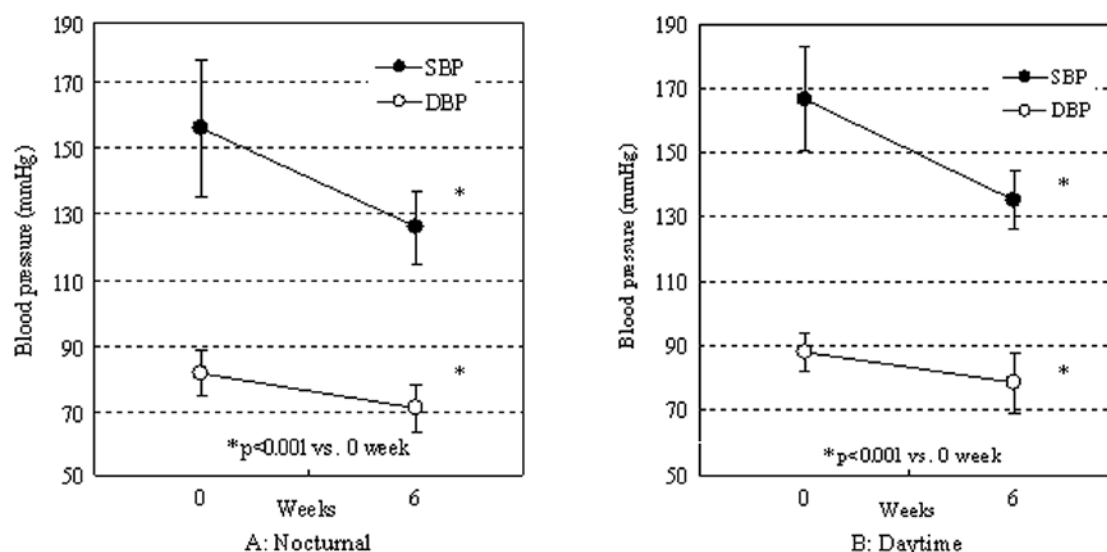


Figure 4. Effect of irbesartan on nocturnal/daytime blood pressure.

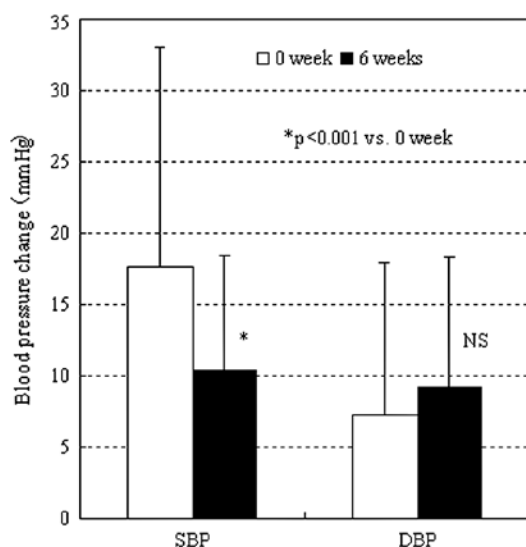


Figure 5. Effect of irbesartan on morning surge.

decreased (Fig. 4A and B). The rate of decrease was similar between the nocturnal and daytime blood pressures (systolic: 29.8 ± 20.1 vs. 31.5 ± 19.4 mmHg; diastolic: 10.8 ± 6.7 vs. 9.7 ± 6.8 mmHg, respectively).

The rates of increase in the systolic blood pressure early in the morning before and 6 weeks after the start of administration were 17.6 ± 15.5 and 10.5 ± 10.8 mmHg, respectively, showing a significant difference (Fig. 5) ($P < 0.05$). There was no significant difference in the rate of change in the diastolic blood pressure.

We compared changes in blood pressure-associated parameters between the 12 patients with nephropathy and the other 18 patients. There were no marked differences. For influence on kidney-associated parameters, in 10 patients with abnormal urinary albumin levels before irbesartan administration, the mean urinary albumin level was significantly decreased from 152.9 ± 252.3 (before administration) to 45.9 ± 38.6 mg/g·Cr after 6 weeks of administration ($P < 0.05$).

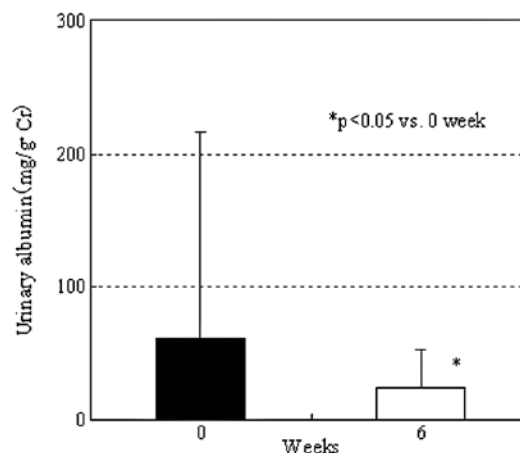


Figure 6. Effect of irbesartan on urinary albumin excretion.

In 5 patients, the urinary albumin levels were normalized. In 20 patients, in whom the pre-treatment urinary albumin levels were within the normal range, there was no significant change (from 14.8 ± 6.8 to 13.8 ± 11.5 mg/g·Cr) (Fig. 6). However, in 1 patient the urinary albumin level increased from 27.2 to 55.9 mg/g·Cr, showing deterioration from the normal range to the microalbuminuria level. In this patient, subsequent examination confirmed a decrease, despite continuous therapy with irbesartan, suggesting a transient change. After 6 weeks of administration, there was a slight increase in the eGFR (83.8 ± 23.1 ml/min/1.73 m²) in comparison to that before irbesartan administration (81.2 ± 18.8 ml/min/1.73 m²), although the difference was not significant. There were no serious side effects requiring discontinuation of the test agent.

Discussion

In humans, the daily heart rate is approximately 100,000 beats. The blood pressure changes on every beat depending on the sympathetic nervous system and humoral factors. Recent studies have indicated that the non-office blood pres-

sure markedly influences the prognosis, such as the onset of cardiovascular events (8,9). Therefore, it may be important to evaluate not only office, but also daytime/nocturnal blood pressures during activities/sleep (10,11).

The half-life of irbesartan at a clinical dose is long (10.2-15.4 h) (4). In addition, this agent exhibits stable, continuous, anti-hypertensive and renoprotective effects over 24 h (6,12,13). However, in Japan few studies have reported its efficacy. As evidence regarding irbesartan involves doses employed in other countries (150-300 mg/day) (3), the anti-hypertensive and renoprotective effects of this agent at doses approved in Japan, 50-200 mg/day, should be compared to those of other ARBs.

In this study, we examined 24-h blood pressure control using ABPM in Japanese patients with essential hypertension who were treated with irbesartan and evaluated its efficacy. This agent decreased both the nocturnal and daytime blood pressures and reduced the rate of change in the systolic blood pressure early in the morning, resulting in favorable blood pressure control. It also significantly decreased the urinary albumin level, suggesting that it exhibits renoprotective effects at doses approved in Japan.

According to Kario *et al* (14), blood pressure changes early in the morning, morning surge, may be an important factor influencing the prognosis of cardiovascular events. The approved doses differing between Japan and other countries remain controversial, considering the clinical efficacy. However, in this study, irbesartan at a standard dose (100 mg/day, once a day) employed in Japan reduced the daytime/nocturnal blood pressures and morning surge, suggesting its potent effects as a long-acting anti-hypertensive agent.

A meta-analysis involving 36 international studies showed that the effects on 24-h blood pressure changes depended on the type of ARB (15). ARB selection in anti-hypertensive treatment may be important for blood pressure control. All ARBs approved in Japan, consisting of six components, are administered once a day. Although there are marked differences in the half-life and pharmacokinetics, few studies have compared 24-h blood pressure control among the ARBs. Further investigations are required.

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