

Original Article

Current Usage of Diuretics among Hypertensive Patients in Japan: The Japan Home *versus* Office Blood Pressure Measurement Evaluation (J-HOME) Study

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In the Japan Home *versus* Office Blood Pressure Measurement Evaluation (J-HOME) study, we examined the current situation with respect to the prescription of diuretics, including the prevalence of diuretic treatment and the dosages used for patients with essential hypertension in primary care settings. Of the 3,400 hypertensive patients included in the study, 315 (9.3%) patients (mean age: 66.9±10.4 years; males: 43.5%) were prescribed diuretics. Compared with patients who were not using diuretics, those who were using diuretics were more obese and had more complications. The most commonly prescribed diuretic among the 331 prescriptions in the 315 diuretic users was trichlormethiazide (44%), followed by indapamide (15%) and spironolactone (14%). Among patients being treated with diuretics, monotherapy was used in only 5% of patients; in the majority of patients combination therapy including diuretics (95%) was used. Relatively low dosages of diuretics were generally used. There was a difference between the actual dosages prescribed and those recommended by the Japanese Society of Hypertension (JSH) guidelines or the product information approved in Japan. Compared with previous estimates of the prevalence of diuretic use in hypertensives in Japan (4.0–5.4%), the rate in the J-HOME study (9.3%) was higher. This may be attributable at least in part to the results of the many published, large-scale intervention trials confirming the clinical significance of diuretics. Although a relatively high dosage is recommended in the diuretic product information and in the JSH guidelines, dosages of diuretics should be reconsidered in Japan. (*Hypertens Res* 2006; 29: 857–863)

Key Words: diuretics, prescribed doses, hypertension

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Introduction

A recent study in the United States used data from the pharmacy system of the Health Maintenance Organization (HMO) to demonstrate that prescription of thiazide diuretics significantly increased after the results of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (1) were published (2). In Japan, it has been reported that the percentage of treated hypertensives being prescribed diuretics was only 4.0–5.4% for the period from 1999 to 2002 (3–5), but was 13.0–14.0% between 2003 and 2004 (6, 7). However, the dosages of diuretics used were not mentioned in these reports. Several studies have shown that even a low dosage of diuretics has a satisfactory effect on hypertension (8–10). Therefore, it is important to evaluate the dosages of diuretics, as well as the prevalence of the use of diuretics. The objective of the present study was to investigate the current usage of diuretics, including the prevalence and the dosages of diuretics used, in Japan from the Japan Home *versus* Office Blood Pressure Measurement Evaluation (J-HOME) study.

Methods

Patients

Details of the methods used in this study have been described previously (11, 12). Briefly, in March 2003, 7,354 physicians randomly selected from all over Japan were invited to take part in this project. Of the 1,477 who agreed to participate, 751 collected data for the study. By the end of August 2003, 3,586 patients who gave their informed consent to participate in the study were enrolled. We asked each doctor to enroll 5 patients. Most doctors (79.3%) enrolled 5 patients or fewer (mean 4.7, median 5, mode 5, range 1–25). About half of the doctors enrolled 5 patients. The proportion of doctors who enrolled 1 or 2 patients was 11.1%, 3 or 4 patients was 21.3%, 5 patients was 46.9%, 6 or 7 patients was 19.7%, and 8 or more patients was 0.9%. Of those, 66 were excluded because their blood pressure (BP) levels were within normal ranges without being treated with antihypertensive medication. An additional 120 patients were excluded because insufficient data on BP values or patient characteristics were provided. Thus, the study population consisted of 3,400 hypertensive patients. Of the 3,400 patients, 315 (9.3%) were prescribed diuretics. The study protocol was approved by the Institutional Review Board of Tohoku University School of Medicine.

Home BP Measurements

Patients were asked to measure their BP once every morning within 1 h of waking, in the sitting position after 2 min or more of rest, before drug ingestion and breakfast, and to

record the results over 2 weeks, as specified by the Japanese guidelines for home BP measurement (13). The patients used electronic arm-cuff devices that operate using the cuff-oscillometric method. The mean of all measurements recorded over a 2-weeks period was calculated for each patient and used for analysis.

Office BP Measurements

Office BP was measured twice consecutively in the sitting position after a rest of at least 2 min at each office visit with the patient's treating physician. The physicians or nurses used either the auscultatory method with a mercury or an aneroid sphygmomanometer, or the cuff-oscillometric method with an electronic arm-cuff device. The office BP value that was used for analysis for each patient was the average of four measurements taken at two office visits during the time period that home measurements were being carried out.

Data Collection and Statistical Analysis

Information on the characteristics of patients, on antihypertensive medications, on home BP and on office BP was provided by the attending physicians. Variables were compared by using Student's *t*-test, ANOVA and χ^2 test as appropriate. Data are shown as the mean \pm SD. Among the 315 patients who received diuretics, 16 patients were prescribed two kinds of diuretics. Therefore, the total number of diuretic prescriptions was 331. The percentage of diuretics used represented the proportion among these 331 prescriptions. A *p* value less than 0.05 was accepted as indicative of statistical significance. All statistical analyses were conducted using the SAS package (version 9.1; SAS Institute, Cary, USA).

Results

Of the 3,400 hypertensive patients, 315 (9.3%) patients (mean age: 66.9 \pm 10.4 years; males: 43.5%) were being treated with diuretics. The characteristics of patients treated and not treated with diuretics are shown in Table 1. With respect to the sub-classes of diuretics used, thiazide diuretics was the most commonly used (45.0%), followed by thiazide-like diuretics (22.4%), loop diuretics (13.6%), and potassium-sparing diuretics (9.4%). In patients not being treated with diuretics, the mean home diastolic BP was significantly higher (81.8 *vs.* 80.4 mmHg, *p* < 0.02) and the mean body mass index was significantly lower (23.7 *vs.* 24.3 kg/m², *p* < 0.003) than in patients being treated with diuretics. Patients being treated with diuretics had significantly higher prevalence of renal disease (8.6% *vs.* 4.8%, *p* = 0.004), hypercholesterolemia (46.0% *vs.* 39.6%, *p* = 0.03), and high uric acid (18.7% *vs.* 10.8%, *p* < 0.001) than patients not being treated with diuretics. Diuretics were used in 8.6% of patients with stroke. With regard to patients treated with diuretics, elderly patients with many complications often received loop

Table 1. Comparison of Patients' Characteristics According to Diuretics Ingestion

	With diuretics (n=315 [9.3%])					p*-value	Without diuretics (n=3,085 [90.7%])	
	Total	Thiazide (n=149 [45.0%]†)	Thiazide-like (n=74 [22.4%]†)	Loop (n=45 [13.6%]†)	Potassium-sparing (n=31 [9.4%]†)		Total	p**-value
Age (years)	66.9±10.4	66.9±9.7	65.2±10.4	70.2±10.0	64.2±12.1	0.03	66.1±10.5	0.2
Men (%)	43.5	43.0	39.2	40.0	48.4	0.8	44.9	0.6
Home BP								
Systolic (mmHg)	138.7±13.7	139.4±13.6	137.4±13.4	142.3±15.5	135.4±13.0	0.1	139.7±13.8	0.2
Diastolic (mmHg)	80.4±9.9	81.2±9.0	82.6±10.0	76.5±11.0	80.0±9.8	0.008	81.8±9.5	0.02
Office BP								
Systolic (mmHg)	141.9±14.9	142.3±14.9	139.2±12.8	148.4±17.9	141.7±12.7	0.01	142.9±14.4	0.3
Diastolic (mmHg)	80.0±10.3	80.9±10.4	79.9±10.6	77.9±9.7	81.2±10.6	0.4	80.8±9.3	0.2
Current smoker (%)	11.1	10.7	14.9	8.9	9.7	0.7	14.5	0.1
Current drinker (%)	32.7	36.2	32.4	24.4	29.0	0.5	35.0	0.4
BMI (kg/m ²)	24.3	24.4	24.8	23.5	24.3	0.2	23.7	0.003
History of stroke (%)	8.6	6.0	12.2	13.3	6.5	0.3	9.1	0.7
History of IHD (%)	8.6	6.0	2.7	17.8	12.9	0.01	8.1	0.8
Renal disease (%)	8.6	2.0	2.7	33.3	3.2	<0.0001	4.8	0.004
Diabetes mellitus (%)	16.8	12.8	6.8	28.9	29.0	0.001	13.4	0.09
Hypercholesterolemia (%)	46.0	39.6	52.7	53.3	58.1	0.09	39.6	0.03
High uric acid (%)	18.7	16.1	18.9	17.8	12.9	0.9	10.8	<0.0001

BP, blood pressure; BMI, body mass index; IHD, ischemic heart disease. **p*-value calculated by ANOVA for continuous variables and χ^2 test for categorical variables among the four types of diuretics. ***p*-value between with and without diuretics. †Percentages are calculated as the proportion among 331 cases. Continuous variables are shown as mean±SD.

Table 2. Comparison of Patients' Antihypertensive Medication According to Diuretics Ingestion

	With diuretics (n=315 [9.3%])					p*-value	Without diuretics (n=3,085 [90.7%])	
	Total	Thiazide (n=149 [45.0%]†)	Thiazide-like (n=74 [22.4%]†)	Loop (n=45 [13.6%]†)	Potassium-sparing (n=31 [9.4%]†)		Total	p**-value
Number of drugs								
Mean±SD	2.7±1.0	2.6±1.0	2.5±0.9	3.0±1.1	2.6±0.9	0.7	1.6±0.8	<0.0001
1 drug (%)	5.1	6.0	5.4	2.2	6.5		53.2	
2 drugs (%)	40.3	40.9	48.7	31.1	48.4	0.4	34.9	<0.0001
3 or more drugs (%)	54.6	53.0	46.0	66.7	45.2		12.0	
Classes of drug combined with diuretics (%)							Classes of drug used (%)	
CCBs	60.6	59.1	51.4	75.6	74.2	0.02	70.5	0.0003
ARBs	47.6	51.7	43.2	53.3	32.3	0.2	43.2	0.1
ACE-inhibitors	19.4	20.1	17.6	17.8	16.1	0.9	16.5	0.2
α -Blockers	16.5	14.1	18.9	26.7	9.7	0.2	13.0	0.08
β -Blockers	12.4	11.4	12.2	17.8	16.1	0.7	11.6	0.7

CCBs, calcium channel blockers; ARBs, angiotensin receptor blockers; ACE, angiotensin-converting enzyme. **p*-value calculated by ANOVA for continuous variables and χ^2 test for categorical variables among the four types of diuretics. ***p*-value between with and without diuretics. †Percentages are calculated as the proportion among 331 cases. Continuous variables are shown as mean±SD.

diuretics. Of the patients treated with diuretics, approximately 5% were given diuretics as monotherapy, but in most cases diuretics were used as an element of combination therapy

together with other antihypertensive drugs (Table 2). Of the combination therapies, combination with calcium channel blockers (CCBs) was the most common (60.6%), followed by

Table 3. Comparison of Doses of Diuretics

Class and drug (number of cases prescribed in J-HOME)	Recommended usual dose range		Actual dose prescribed in the J-HOME study*
	JNC-7	Product information in Japan	
Thiazide diuretics			
Trichlormethiazide (<i>n</i> =145)	—	2–8	1.9±0.8 (1–7)
Hydrochlorothiazide (<i>n</i> =7)	12.5–50	25–200	18.8±6.8 (12.5–25)
Thiazide-like diuretics			
Indapamide (<i>n</i> =50)	1.25–2.5	2	1.3±0.5 (0.5–2)
Chlorthalidone (<i>n</i> =4)	12.5–25	50–100	50
Tripamide (<i>n</i> =6)	—	15–30	15
Meticrane (<i>n</i> =1)	—	150–300	150
Mefruside (<i>n</i> =17)	—	25–50	21.3±12.3 (12.5–50)
Loop diuretics			
Azosemide (<i>n</i> =11)	—	60	48.0±29.0 (30–120)
Furosemide (<i>n</i> =44)	20–80	40–80	28.4±15.1 (10–80)
Potassium-sparing diuretics			
Triamterene (<i>n</i> =1)	50–100	90–200	50
Spironolactone (<i>n</i> =45)	25–50	50–100	29.6±12.4 (12.5–75)

JNC-7, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; J-HOME, Japan Home *versus* Office Blood Pressure Measurement Evaluation. *Data is shown as mean±SD (range) mg/day.

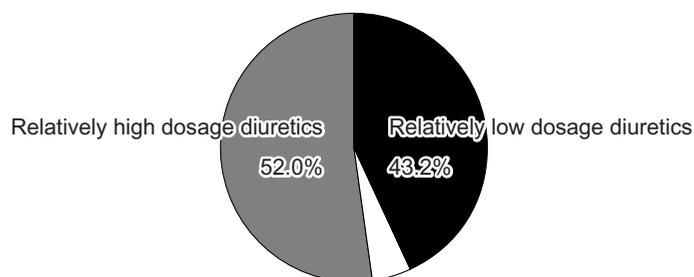


Fig. 1. Proportion of various dosages among 331 prescriptions of diuretics. A relatively low dosage was defined as a half or less of the minimal dose recommended by the Japanese Society of Hypertension (JSH) treatment guideline 2000 and 2004 or the product information. A relatively high dosage was defined as the minimal recommended dose or more by the JSH guidelines or the product information. Percentages of each doses were calculated as the proportion among 331 cases.

combination with angiotensin receptor blockers (ARBs) (47.6%), with angiotensin-converting enzyme (ACE) inhibitors (19.4%), and with renin-angiotensin system (RAS) inhibitors (64.4%). The number of patients treated by 3 or more antihypertensive drugs and the rate of combination with CCBs were significantly greater in patients who received loop diuretics than in patients who received the other types of diuretic.

With respect to the diuretics used, trichlormethiazide was used most commonly (43.8%), followed by indapamide (15.1%), spironolactone (13.6%) and furosemide (13.3%) (Table 3). The range of dosages of diuretics used in the present study was very wide. The mean dosage of trichlormethiazide was 1.9±0.8 (range 1–7) mg/day, that of indapamide was 1.3±0.5 (0.5–2) mg/day, and that of spironolactone was 29.6±12.4 (12.5–75) mg/day (Table 3). We defined a “rela-

tively low dosage” as a dosage that was a half or less of the minimal dose recommended by the Japanese Society of Hypertension (JSH) 2000 and 2004 treatment guidelines (14, 15) or the product information (e.g., ≤1 mg of trichlormethiazide, ≤1 mg of indapamide, ≤25 mg of spironolactone). Using this definition, a relatively low dosage of diuretics was used in 143 of 331 instances (43.2% of prescriptions) (Fig. 1). Details of the dosages of trichlormethiazide, indapamide and spironolactone are shown in Fig. 2. We defined a “relatively high dosage” as the minimal recommended dose or more according to JSH guidelines or the product information (e.g., ≥2 mg of trichlormethiazide, ≥2 mg of indapamide, ≥50 mg of spironolactone). Using this definition, a relatively high dosage was used in 172 of 331 instances (52.0% of prescriptions) (Fig. 1). Among patients treated with diuretics, those receiving monotherapy were more likely to be prescribed a

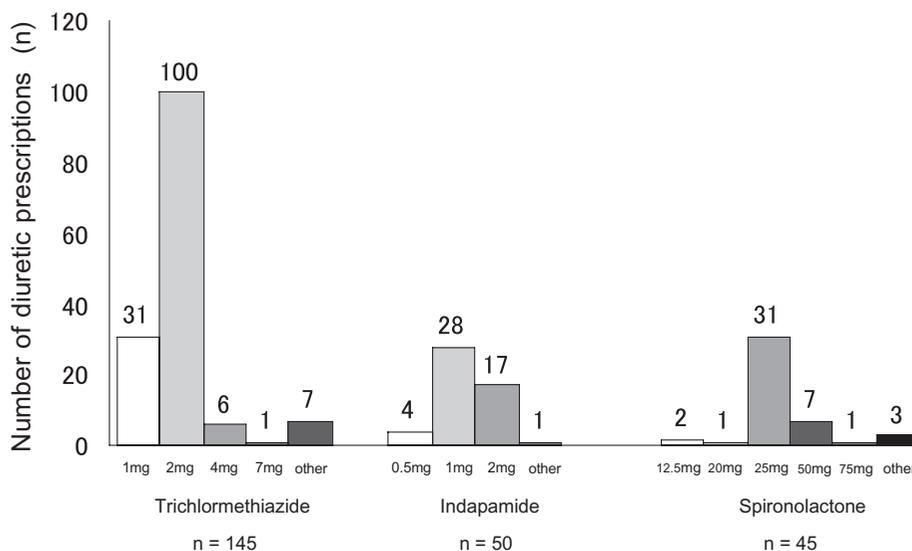


Fig. 2. Number of diuretic prescriptions by dosage and type of diuretics.

Table 4. Comparison of the Prevalence of Complications According to Doses of Diuretics

	Dose of diuretics		p-value
	Relatively high dose (n=165 [55.2%]*)	Relatively low dose (n=118 [39.5%]*)	
History of stroke (n (%))	17 (10.3)	9 (7.6)	0.4
History of IHD (n (%))	13 (7.9)	9 (7.6)	0.9
Renal disease (n (%))	13 (7.9)	7 (5.9)	0.5
Diabetes mellitus (n (%))	25 (15.2)	18 (15.3)	0.98
Hypercholesterolemia (n (%))	76 (46.1)	58 (49.2)	0.6
High uric acid (n (%))	31 (18.8)	18 (15.3)	0.4

IHD, ischemic heart disease. *The percentage represented the proportion among patients treated with diuretics.

relatively high dosage of diuretics than those receiving combination therapy (data not shown). There were no significant differences in the prevalence of any complication between patients receiving a relatively high dosage and those administered a relatively low dosage (Table 4). However, the prevalence of patients with high uric acid tended to be higher in the former (18.8% vs. 15.3%, $p=0.4$).

Discussion

This is the first detailed nationwide study of diuretics use among essential hypertensive patients in Japan. The percentage of patients using diuretics (9.3%) in the J-HOME study was higher than that (4.0–5.4%) found in previous studies (3–5), but was similar to that found (12.6%) in another recent study (6). This trend could be attributable to the impact of recently published, large-scale intervention trials, such as the ALLHAT study, which emphasized the clinical significance of diuretics (1, 16, 17). These studies had a considerable effect on the development of the Seventh Report of the Joint

National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) (18). Diuretics have been found to be effective and well-tolerated as an initial therapy (16, 17). However, as shown in the present study, monotherapy with diuretics is rare, and combination therapy with diuretics and other classes of antihypertensive drugs is common in Japan. The JSH guidelines do not necessarily recommend an initial therapy based on diuretics (15). In the J-HOME study, combination therapy with diuretics and CCBs was observed in 60.6% of patients being treated with diuretics, in particular, CCBs was used in patients treated with loop diuretics, whereas combination therapy with diuretics and RAS inhibitors was observed in 64.4% of patients being treated with diuretics. Loop diuretics were mainly prescribed in combination with two or more antihypertensive drugs, especially in patients with renal disease or diabetes mellitus who needed to achieve lower target BP levels. Thus the fact that the most prevalent combination was loop diuretics and CCBs may be simply attributable to the fact that CCBs were the most frequently used agent in the present study. The

previous studies showed a high prescription rate of CCBs for both monotherapy and combination therapy (5).

We found that a considerable proportion of physicians who participated in the present study prescribed relatively low dosages of diuretics. Although use of diuretic therapy is limited in Japan because of adverse effects such as hypokalemia, hypercholesterolemia, hyperglycemia and hyperuricemia, many studies have demonstrated that using low doses of diuretics can minimize the adverse effects (19). In addition, diuretics have a long-acting BP-lowering effect, even in a low-dose monotherapy (20), and potentiate the antihypertensive effects of other drugs (21). In the present study, the prevalence of high uric acid was higher in patients taking a high dose of diuretic than in those taking a low dose of diuretic. It has been demonstrated that diuretic-induced elevations in serum uric acid are dose-dependent (22). However, since this study was a cross-sectional study, it was difficult to examine the causal relationship between the dosage of diuretics and the presence of high uric acid.

Recently, several guidelines have recommended that home BP measurements be used for the management of hypertension (15, 18). In the present study, all patients measured their own BP at home, suggesting that physicians participating in the present study had an up-to-date understanding of the recommended best practice. Such physicians might also have been influenced by recent guidelines published in the United States and Europe, which may partly explain the high prevalence of diuretics use and the low dosages of diuretics used in the present study. A previous study showed that achieved levels of BP differed among physicians and that physician's attitudes regarding antihypertensive therapy were an important factor in the adequate BP control (23). In contrast, a considerable proportion of patients were still being treated with a relatively high dosage of diuretics. In the present study, we defined the minimal dosage of diuretics recommended by the JSH treatment guidelines or the product information in Japan as a relatively high dosage, because this dosage is nearly the maximal dosage recommended by the JNC-7 (Table 3). The dosages of diuretics used in Japan have been based on historical dose-finding studies, which were carried out in an era when no effective antihypertensive drugs were available. Thus, it is time to reconsider the dosages of diuretics recommended in the JSH guidelines and the product information.

Although the percentage of patients using diuretics in the present study was higher than that found in previous reports from Japan (3–5), the prescription rate of diuretics (8.6%) among patients with a history of stroke still seems to be low. In the Perindopril Protection against Recurrent Stroke study (PROGRESS), it was shown that combination therapy with an ACE-inhibitor (perindopril) and a diuretic (indapamide) appeared to reduce the risk of stroke (8). The use of low dosages of diuretics in patients with stroke has been recommended by several recent guidelines in Japan (15, 24).

We conclude that recent guidelines published in the United States and Europe have influenced the usage of antihyperten-

sive drugs in Japan; there has been a gradual increase in the prevalence of the low-dosage use of diuretics. The recommended dosages of diuretics given in the JSH treatment guidelines and in the product information for the diuretics should be revised to lower dosages.

Appendix

This study was conducted by the J-HOME Study Group.

Members of the J-HOME Study Group

Principal Investigator: Yutaka Imai.

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All names of participating practitioners have been previously described (11).

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