

Original Article

Current Status of Antihypertensive Prescription and Associated Blood Pressure Control in Japan

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The importance of tight blood pressure (BP) control has been established. We performed cross-sectional studies on the current status of BP control and the prescription and efficacy of antihypertensive drugs in hypertensive patients in Japan. The data were also evaluated in subgroups with or without diabetes mellitus (DM) and in winter and summer. Analyses were performed on the collected data of 12,437 treated hypertensive patients in winter and 5,972 in summer 2002. In winter, 50.3% of patients received calcium channel blockers (CCBs), 15.3% received angiotensin converting enzyme inhibitors (ACEIs) and 11.0% received angiotensin receptor blockers (ARBs). In the patients receiving monotherapy, 69% of patients received a CCB, 13% an ACEI and 11.0% an ARB. A total of 2,918 patients received combination therapy, and CCBs were the most frequently (89.6%) prescribed component of such therapy. Prescriptions of β -blockers (BBs) decreased and those of CCBs and diuretics (D) increased with age ($p < 0.001$). The rate of patients with adequately controlled BP less than 140/90 mmHg was 40.3% in the CCB group, 37.6% in the D group, and 36.9% in the BB group ($p < 0.001$). In patients receiving combination therapy, those with CCB+D had the best rate of BP control (40.7%). The rate of patients with adequately controlled BP was lower in winter than in summer at both a target BP of 140/90 mmHg (36.2% vs. 43.8%, $p < 0.001$) and a target BP of 130/85 mmHg in patients younger than 60 years old (15.5% vs. 18.6%, $p < 0.02$). In diabetic patients, the target BP (130/80 mmHg) was achieved in only 11.3%, which was lower ($p < 0.05$) than the rate in non-diabetic patients (13.1%). In conclusion, the present cross-sectional study showed that CCBs were the most frequently prescribed agent for the treatment of hypertension in Japan. The rate of adequate BP control was less than 50% and was even worse in patients with DM and in winter. Our results indicate that physicians should treat hypertension more intensively to achieve the target BP. (*Hypertens Res* 2006; 29: 143–151)

Key Words: antihypertensive drug, monotherapy, combination therapy, blood pressure control, diabetes mellitus

Introduction

Although tight blood pressure (BP) control is important for the prevention of cardiovascular disease in patients with essential hypertension (1–3), the rate of patients with good BP control (below the target BP) is still less than 50% in many

countries (4–6). The aim of this study was to clarify the current status of BP control, stratified by the major classes of antihypertensive drugs in hypertensive patients with or without diabetes mellitus (DM), by using cross-sectional studies in large Japanese populations. The same studies were performed in winter and in summer to clarify the seasonal change in BP control.

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Received September 30, 2005; Accepted in revised form December 28, 2005.

This study was performed as a substudy of an original work investigating the effect of deep breathing on BP (7).

Methods

Collection of Data

We asked 19,055 clinics and hospitals in Japan that were members of the Japanese Medical and Dental Practitioners for the Improvement of Medical Care (JMDPIMC) to participate in the study. The clinics and hospitals were randomly selected from locations throughout Japan and comprised about 30% of all the members of JMDPIMC. The data were collected from January 10 to 31 (7) and from July 1 to 31, 2002. The enrolled patients were divided into two groups. One group was instructed to take 6 deep breaths at about 80% maximum capacity over a period of 30 s (Deep Breathing Group: DBG) and the other was instructed to sit quietly for 30 s without deep breathing (Control Group: CG). Informed consent was obtained from all patients. Before BP measurement, patients rested in the waiting room for at least 10 min and in the office for 2 min. In the DBG, BP and pulse rate (PR) were measured before and after taking 6 deep breaths in 30 s. In the CG, BP and PR were measured before and after 30 s of rest in a seated position. Hypertension was defined as a systolic blood pressure (SBP) of 140 mmHg or more and/or a diastolic blood pressure (DBP) of 90 mmHg or more. DM was defined as a fasting plasma glucose of 126 mg/dl or more and/or a prandial glucose of 200 mg/dl or more and/or a 2 h plasma glucose of 200 mg or more after a 75 g oral glucose tolerance test. The following data were collected for each patient: the location of the hospital or clinic where the treatment was received, the sex, age, history of DM, BP, and PR, and the name of any antihypertensive drugs that had been taken.

The recruited patients who had received antihypertensive drugs were 12,437 patients from 1,186 clinics and hospitals in winter, and 5,972 patients from 559 clinics and hospitals in summer. BP evaluation was performed on the averaged BP of two measurements.

Statistical Analysis

Statistical analyses including Student's *t*-test, one-way analysis of variance and a post-hoc multiple comparison test, and χ^2 test were carried out with SPSS Version 10 software. All values were expressed as the mean±SD. Values of *p*<0.05 were considered to be statistically significant.

Results

Characteristics of the Study Population

We analyzed 12,437 patients who had received antihypertensive drugs and who had been treated at 1,186 clinics and hospitals throughout Japan from January 10 to 31, 2002. The

Table 1. Antihypertensive Drugs Prescribed for Monotherapy

Antihypertensive drugs	Percentage (%) [cases]
CCB	69.0 [5,019]
Diuretic	3.1 [226]
ACEI	13.0 [943]
ARB	9.4 [686]
BB	5.5 [402]
Total	100.0 [7,276]

CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β -blocker.

Table 2. Antihypertensive Drugs Prescribed for Monotherapy and Combination Therapy

Antihypertensive drugs	Percentage (%) [cases]
CCB	50.3 [8,821]
Diuretic	5.4 [953]
ACEI	15.3 [2,679]
ARB	11.0 [1,936]
BB	9.0 [1,573]
AB	5.1 [894]
AMD	0.3 [56]
Other drugs	3.5 [610]
Total	100.0 [17,522]

CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β -blocker; AB, α -blocker; AMD, α -methyl dopa.

Table 3. Combination of Two Drugs

Combination of drugs	Percentage (%) [cases]
CCB+diuretic	8.4 [246]
CCB+ACEI	36.5 [1,065]
CCB+ARB	26.6 [775]
CCB+BB	18.1 [527]
ACEI+diuretic	2.4 [71]
ACEI+BB	2.5 [73]
ACEI+ARB	0.4 [13]
ARB+diuretic	1.9 [55]
BB+diuretic	1.4 [41]
ARB+BB	1.8 [52]
Total	100.0 [2,918]

CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β -blocker.

mean age of patients was 67.5±10.7 years old and 40.6% of the patients were men. In summer, from July 1 to 31, 2002, 5,973 patients with a mean age of 68.1±10.7 years old were

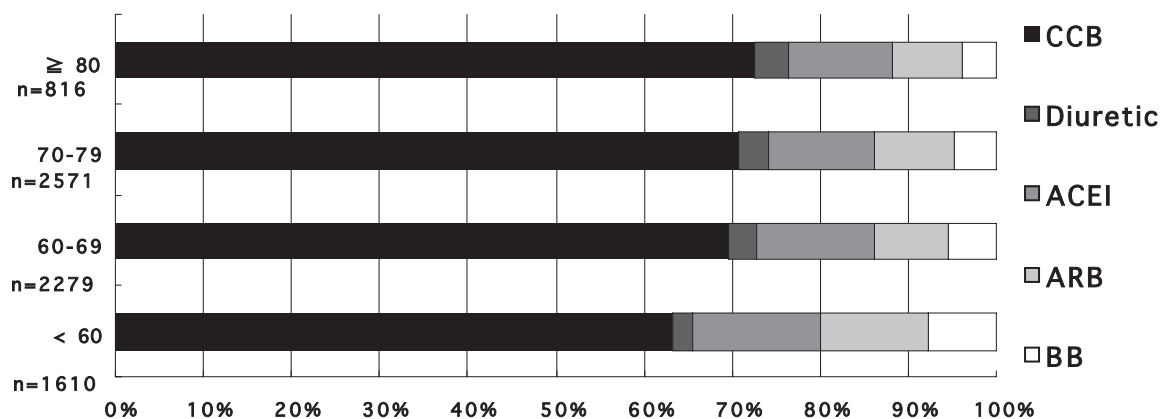


Fig. 1. Antihypertensive drugs and age for monotherapy. CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β -blocker. $p < 0.001$ (χ^2 test).

Table 4. Antihypertensive Drugs Prescribed as Monotherapy in Men and Women

Antihypertensive drugs	Men (%) [cases]	Women (%) [cases]	χ^2 test
CCB	68.6 [1,884]	69.2 [3,135]	$p < 0.001$
Diuretic	2.1 [58]	3.7 [168]	
ACEI	14.5 [399]	12.0 [544]	
ARB	9.2 [254]	9.5 [432]	
BB	5.5 [151]	5.5 [251]	
Total	100.0 [2,746]	100.0 [4,530]	

CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β -blocker.

Table 5. Rates of Monotherapy and Combination Therapy in Winter and Summer

	Winter (number [%])	Summer (number [%])	χ^2 -test
Monotherapy	7,811 (63.7)	3,715 (63.0)	NS
Combination therapy	4,458 (36.3)	2,184 (37.0)	
Total	12,269 (100.0)	5,899 (100.0)	

NS, not significant.

also analyzed. The percentage of men in the summer group was 39.3%, which was not significantly different from the percentage in winter. The mean age of patients in summer was older than that in winter ($p < 0.001$, t -test).

Prescription of Antihypertensive Drugs

Among the 12,437 treated hypertensive patients, 62.3% received monotherapy, and 28.7% received two, 5.7% three, 0.8% four and 0.1% five kinds of drugs. Combination therapy

Table 6. Antihypertensive Drugs Prescribed as Monotherapy in Winter and Summer

Antihypertensive drugs	Winter (number [%])	Summer (number [%])	χ^2 -test
CCB	5,019 (69.0)	2,334 (67.1)	$p < 0.05$
ACEI	226 (3.1)	115 (3.3)	
Diuretic	943 (13.0)	426 (12.2)	
ARB	686 (9.4)	389 (11.2)	
BB	402 (5.5)	212 (6.1)	
Total	7,276 (100.0)	3,476 (100.0)	

CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β -blocker.

was prescribed in 35.3% of patients, and lifestyle modification alone was used in 2.4% of patients.

As monotherapy, calcium channel blockers (CCBs) were most frequently prescribed, followed by angiotensin converting enzyme inhibitors (ACEIs) (Table 1). When all cases of monotherapy and combination therapy were considered together, CCBs were again the most commonly prescribed agents, followed by ACEIs (Table 2).

The number of patients who received a combination of two kinds of drugs was 2,918, with CCBs included in the majority of the prescriptions (89.6%). The most frequent combination of drugs was CCB+ACEI, followed by CCB+angiotensin receptor blocker (ARB) (Table 3).

There were age-dependent differences in the prescription of antihypertensives in the monotherapy group. Namely, age-dependent increases in the prescription of CCBs and diuretics (D), and age-dependent decreases in the prescription of β -blockers (BB) were found (Fig. 1).

There were also significant sex-dependent differences in the prescription of agents in the monotherapy group ($p < 0.001$). ACEIs were prescribed more in men than in

Table 7. Seven Groups of Prefectures in Japan

Group	Prefectures
Hokkaido	Hokkaido
Tohoku	Aomori, Iwate, Miyagi, Akita, Yamagata, Fukushima
Kanto	Ibaraki, Tochigi, Gunma, Saitama, Chiba, Tokyo, Kanagawa
Chubu	Niigata, Toyama, Ishikawa, Fukui, Yamanashi, Nagano, Gifu, Shizuoka, Aichi, Mie
Kinki	Shiga, Kyoto, Osaka, Nara, Hyogo, Wakayama
Chugoku and Shikoku	Tottori, Shimane, Okayama, Hiroshima, Yamaguchi, Tokushima, Kagawa, Ehime, Kochi
Kyushu and Okinawa	Fukuoka, Saga, Nagasaki, Kumamoto, Miyazaki, Oita, Kagoshima, Okinawa

Table 8. Antihypertensives Prescribed as Monotherapy in the 7 Groups

	Hokkaido	Tohoku	Kanto	Chubu	Kinki	Chugoku and Shikoku	Kyushu and Okinawa	χ^2 -test
CCB	102 (72.3)	403 (65.7)	1,118 (71.0)	1,113 (68.7)	1,033 (68.6)	496 (66.8)	754 (69.9)	
Diuretics	8 (5.7)	26 (4.2)	37 (2.4)	37 (2.3)	58 (3.9)	34 (4.6)	26 (2.4)	
ACEI	17 (12.1)	79 (12.9)	175 (11.1)	251 (15.5)	180 (12.0)	105 (14.2)	136 (12.6)	
ARB	5 (3.5)	49 (8.0)	150 (9.5)	133 (8.2)	159 (10.6)	81 (10.9)	109 (10.1)	
BB	9 (6.4)	56 (9.1)	94 (6.0)	87 (5.4)	76 (5.0)	26 (3.5)	54 (5.0)	$p < 0.001$
Total	141 (100)	613 (100)	1,574 (100)	1,621 (100)	1,506 (100)	742 (100)	1,079 (100)	

CCB, calcium channel blocker; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β -blocker.

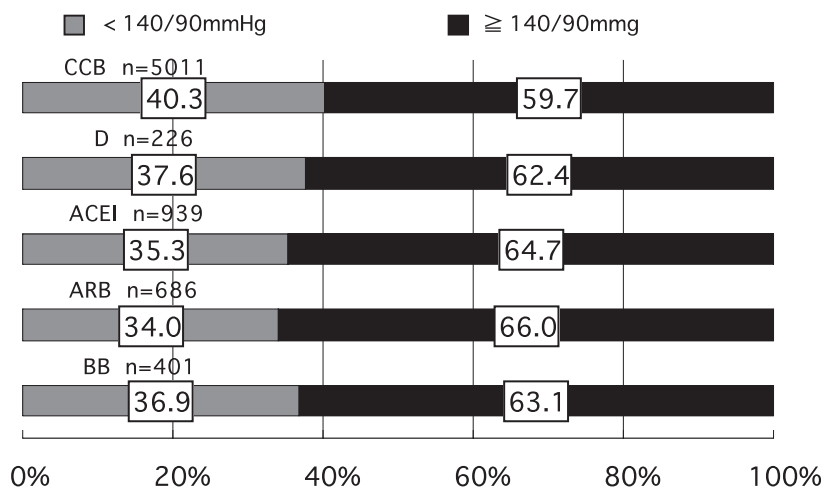


Fig. 2. Percentage of patients who attained target blood pressure with main antihypertensive drugs with monotherapy. $p < 0.001$ (χ^2 test). CCB, calcium channel blocker; D, diuretic; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β -blocker.

women, and diuretics more in women than in men (Table 4).

We compared the ratio of monotherapy to combination therapy between winter and summer, and found no significant difference between them (Table 5). However, the specific

antihypertensive drugs prescribed showed significant difference between winter and summer (Table 6); the prescription of CCBs was decreased and that of ARBs was increased in summer.

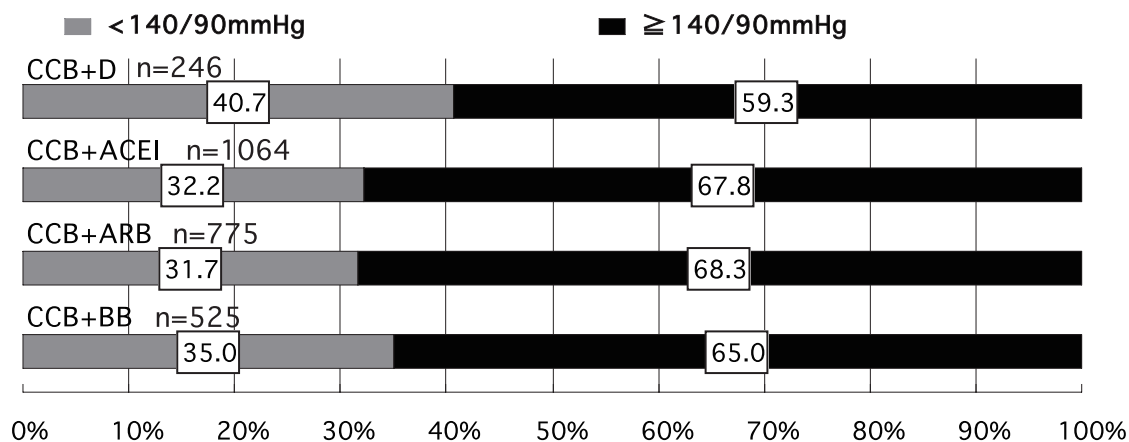


Fig. 3. Percentage of patients who attained target blood pressure with calcium channel blocker–based combination therapy. $p < 0.001$ (χ^2 test). CCB, calcium channel blocker; D, diuretic; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β -blocker.

Table 9. BP and PR of Treated Hypertensives in the 7 Groups

	Hokkaido	Tohoku	Kanto	Chubu	Kinki	Chugoku and Shikoku	Kyushu and Okinawa	Test
SBP (mmHg)	145.6±18.4	142.0±16.1	143.9±15.9	144.9±16.4	145.0±16.8	143.9±16.7	145.1±17.1	
n	276	1,145	2,657	2,831	2,483	1,292	1,733	$p < 0.001$
DBP (mmHg)	80.7±11.3	81.2±10.5	82.2±10.7	81.0±11.0	81.6±11.3	79.2±11.2	80.8±11.0	
n	276	1,145	2,657	2,831	2,483	1,292	1,733	$p < 0.001$
PR (bpm)	73.1±10.7	71.8±10.4	73.7±10.9	71.9±10.5	72.8±11.0	72.6±10.5	73.5±10.5	
n	272	1,143	2,639	2,783	2,476	1,290	1,712	$p < 0.001$

Test: one-way analysis of variance and a post-hoc multiple comparison test. BP, blood pressure; PR, pulse rate; SBP, systolic BP; DBP, diastolic BP.

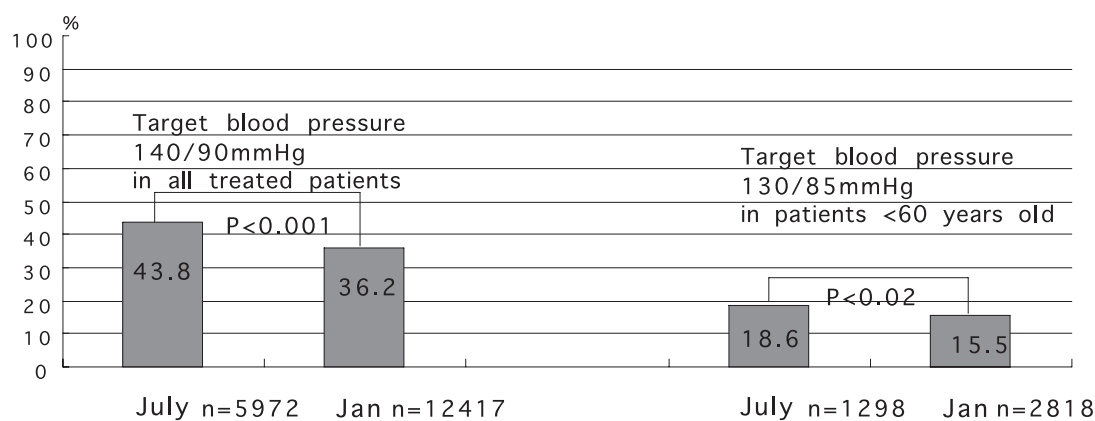


Fig. 4. Attained target blood pressure rate in all treated hypertensives and in patients who were less than 60 years old (χ^2 test).

We also analyzed differences in the antihypertensives prescribed as monotherapy among 7 groups of prefectures in Japan (Table 7). There were significant differences in the agents prescribed for monotherapy among the 7 groups (Table 8).

Target Blood Pressure Achievement in All Patients

With monotherapy, the averaged BP was less than the target BP (149/90 mmHg) in 40.3% of patients on CCBs, 37.6% of

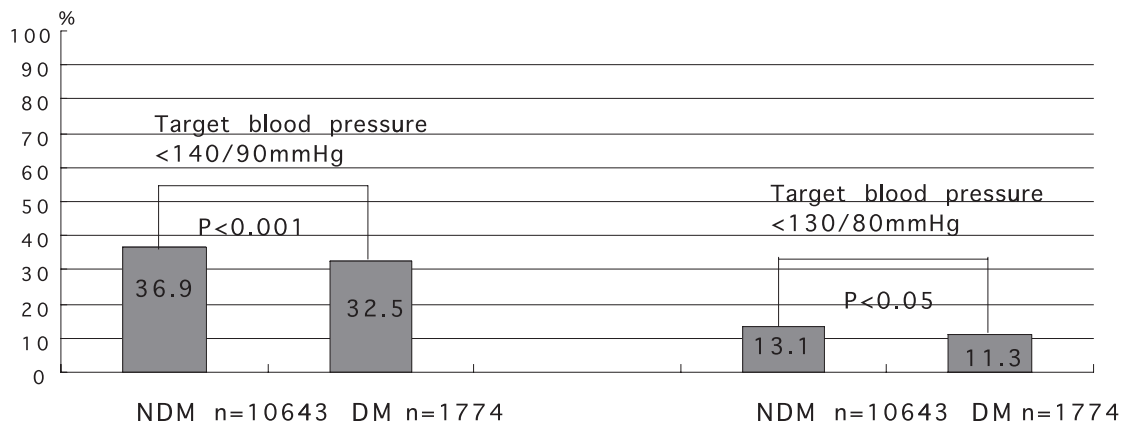


Fig. 5. Attained rate of target blood pressure in non-diabetic and diabetic hypertensives (χ^2 test). NDM, non-diabetic hypertensive group; DM, diabetic hypertensive group.

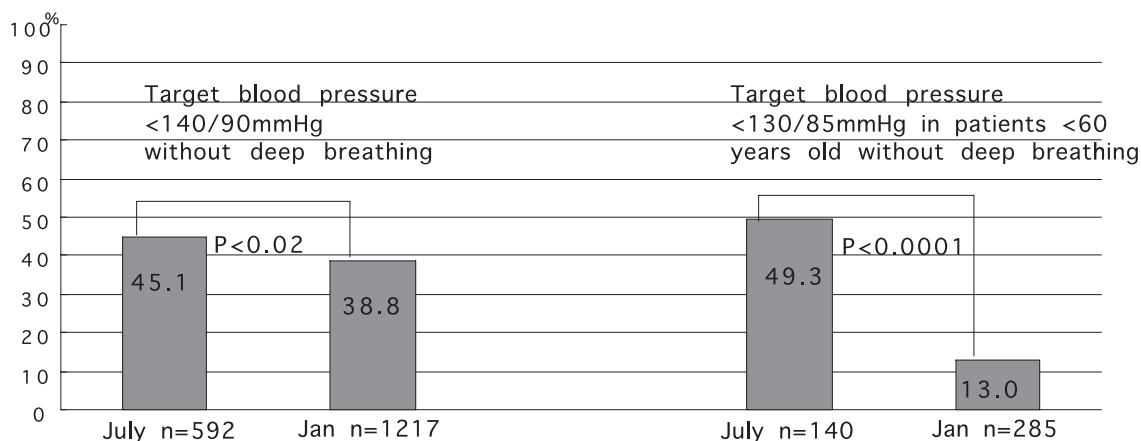


Fig. 6. Attained target blood pressure rate in all treated hypertensives and in treated hypertensives less than 60 years old in the control group (χ^2 test).

patients on diuretics, 35.3% of patients on ACEIs, and 34.0% of patients on ARBs (Fig. 2). In the combination therapy group, 89.6% of patients were receiving CCB-based therapy (Table 3). The percentage of patients achieving the target BP varied significantly ($p<0.001$) according to the combination therapy used, with CCB+D resulting in the highest rate of target BP achievement (40.7%), followed by 35.0% for CCB+BB, 32.2% for CCB+ACEI and 31.7% for CCB+ARB (Fig. 3).

We analyzed SBP, DBP and PR of treated hypertensive patients among the 7 groups of prefectures in Japan. The largest difference in SBP was 3.6 mmHg among the 7 groups ($p<0.001$) (Table 9).

Comparison of BP Control between Winter and Summer and between Patients with and without DM

The percentage of patients attaining a target BP of less than 140/90 mmHg was 36.2% in winter and 43.8% in summer ($p<0.001$). The same rates were seen in patients younger than 60 years old. The percentage of patients achieving BP control of less than 130/85 mmHg was 15.5% in winter and 18.6% in summer ($p<0.02$) (Fig. 4).

In hypertensive patients with DM, 32.5% attained a target BP of less than 140/90 mmHg, which was lower than the rate in those without DM (36.9%). Similar findings were observed with a target BP of less than 130/80 mmHg (11.3% vs. 13.1%, Fig. 5).

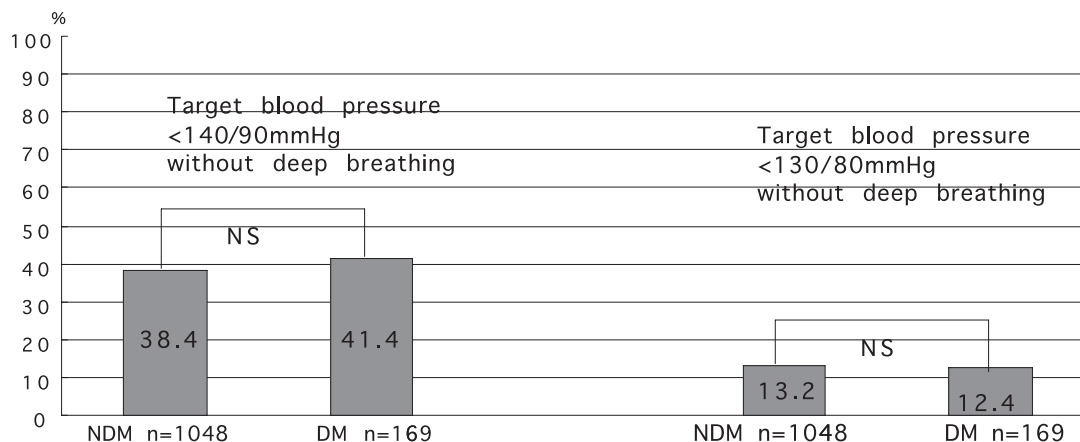


Fig. 7. Attained rate of target blood pressure in non-diabetic and diabetic hypertensives in the control group (χ^2 test). NDM, non-diabetic hypertensive group; DM, diabetic hypertensive group.

Target BP Control in the DBG and CG

The BP control rates in winter and summer were similar between the DBG and CG (Fig. 6). However, in the CG, no significant difference was found between patients with and without DM, possibly due to the small number of patients in the CG (Fig. 7).

Discussion

In order to survey BP control in patients with hypertension, the present cross-sectional study was performed. The results showed an inadequate rate of BP control for all antihypertensive drugs used, especially in patients with DM. The study also showed that the BP control rate was worse in winter than in summer. These results suggest the need to treat hypertensive patients more intensively to achieve the target BP, especially those with DM and in winter. The study also showed a high prescription rate of CCBs for both monotherapy and combination therapy for hypertension, and an age-dependent increase in the prescription of CCBs in Japanese. This is consistent with previous reports that more than half of Japanese clinicians use CCBs as an initial drug treatment for mild-to-moderate hypertension (5), and that prescription of CCBs in elderly Japanese and the rate of monotherapy with CCBs increases with advancing age (4). Our results also showed an age-dependent increase in the prescription of diuretics and an age-dependent decrease in BB prescription.

Prescriptions for hypertension were significantly different between men and women, with fewer ACEIs being prescribed in women. The actual reason for the lower prescription rate of ACEIs in women is not clear. One possible reason is the higher rate of cough due to ACEIs in women than in men. There were also significant differences in the antihypertensives prescribed between winter and summer, mainly due to the increased prescription of ARBs in summer.

The antihypertensives prescribed differed among the 7 groups of prefectures in Japan, but CCBs were the most widely prescribed agents in all groups. The prescription rate of ARBs differed among the groups. The reason for the differences in prescription is not clear. Among patients treated by monotherapy with a CCB, D, ACEI, or BB, those receiving a CCB showed the highest rate of achieving the target BP. Among patients receiving combination therapy, those who received CCB+D showed the highest rate of achieving the target BP. Recent large-scale clinical studies have also reported that CCBs achieved a higher rate of BP control than ACEIs (8) or ARBs (9). These results are consistent with a report that showed a higher BP control rate with an increase in use of CCBs (10), as well as with a previous report that showed CCBs comprise the most popular drug class for treatment of hypertension in Japan (5).

There were significant differences in both SBP and DBP in treated hypertensive patients among the 7 prefecture groups and the largest difference in SBP was only 3.6 mmHg. The reasons for these differences are not clear.

The attained target BP rate was lower in winter than in summer among all treated hypertensives, even in patients less than 60 years old. Comparing hypertensive patients with and without DM, the attained target BP rate was lower in those with DM than without DM, and only 11.3% of patients with DM attained a BP less than 130/80 mmHg. To eliminate the effect of deep breathing on BP, we evaluated BP level in the CG. The results were similar as those in all hypertensives and in all hypertensives less than 60 years old. However, the significant differences between those with DM and without DM disappeared.

Though there are some differences in the prescription of antihypertensive drugs and the status of BP control (11–17) among countries, the rate of BP control is still low in most of the world's nations, the same as the present result. Since the risk of increasing BP on the incidence of cardiovascular dis-

ease starts at 115/75 mmHg and roughly doubles for every 10-year increase in age, 20 mmHg increase in SBP, 10 mmHg increase in DBP or concomitant DM or any cardiovascular disease (18), inadequate BP control is one of the main issues in the field of hypertension management. This phenomenon is sometimes referred to as the rule of halves (19). Several factors affect this inadequate BP control, including patients' behavior (20), physicians' motivation (14, 21–24) and patients' education and living district (24–27). Since adequate control of hypertension with monotherapy is effective in a minority of hypertensives, combination therapy is needed in the majority of hypertensive patients (28, 29). Furthermore, a recent report has shown the importance of controlling home BP (30). Thus physicians should treat BP more intensively to achieve the target BP not only in the office but also at home.

In conclusion, the present cross-sectional study showed that CCBs were the most frequently prescribed agent for the treatment of hypertension in Japanese primary care practice, and that combination treatment was not prevalent. The rate of adequate BP control was less than 50% and was even worse in patients with DM and in winter. Our results indicate that physicians should treat hypertension more intensively to achieve the target BP.

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