

ORIGINAL ARTICLE

Current prescription status of antihypertensive drugs with special reference to the use of diuretics in Japan

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The guidelines for the management of hypertension recommend the inclusion of diuretics, especially when three or more antihypertensive drugs are used. The present study investigated the current prescription status of antihypertensive drugs with a particular focus on the use of diuretics in a local district in Japan. Prescriptions, including antihypertensive drugs, were collected from a dispensing pharmacy of the Yahata Pharmacist Association, located in Kitakyushu City, in October 2014. Of the 10 585 prescriptions, calcium channel blockers (CCBs) were prescribed in 73.5%, followed by angiotensin II receptor blockers (ARB, 62.7%), diuretics (16.5%) and β -blockers (13.6%). The average number of drugs used was 1.80. The rates of prescription of diuretics for patients with one, two, three and four drugs were 0.6%, 13.1%, 55.2% and 82.6%, respectively. Diuretics were more frequently prescribed in elderly patients, and the prescription rate of doctors in hospitals was significantly higher than that of general practitioners (19.1% vs. 15.7%, $P < 0.01$). In addition, 40% of patients with thiazide diuretics were prescribed combination tablets of hydrochlorothiazide with ARB, whereas trichlormethiazide (34.9%) and indapamide (19.8%) were used in other patients. Based on these findings, the use of diuretics remains limited, even among patients taking multiple antihypertensive drugs.

Hypertension Research (2017) 40, 203–206; doi:10.1038/hr.2016.120; published online 1 September 2016

Keywords: combination therapy; diuretics; fixed-dose combination tablets

INTRODUCTION

The Japanese Society of Hypertension guidelines for the management of hypertension (JSH2014) emphasizes that strict control of blood pressure (BP) plays an important role in preventing cardiovascular events.¹ In many cases, a combination therapy of antihypertensive drugs is needed to achieve target BP. The JSH2014 recommends using diuretics when three classes of antihypertensive drugs are necessary. As salt intake remains high in Japan, the use of diuretics presents a reasonable measure to obtain strict BP control. However, the rate of prescription of diuretics is reported to be low, partly because of doctors' concerns about the adverse metabolic effects of diuretics.² Our previous observation that the BP control among Japanese hypertensive patients was unsatisfactory may be related to the insufficient use of diuretics.³ In a large prospective observational study in Japan, that is, the HONEST study, patients enrolled between 2009 and 2010 received olmesartan-based treatment.⁴ After a mean follow-up of 2.02 years, morning BP at home remained ≥ 135 mm Hg in $\sim 50\%$ of patients using 1.5 antihypertensive drugs on average. Diuretics were used in only 9% of these patients. In recent years, however, many fixed-dose combination (FDC) tablets including angiotensin II receptor blockers (ARB) and thiazide diuretics have become available that may

promote the inclusion of diuretics in antihypertensive combination therapy.

The aim of the present study was to investigate the current prescription status of diuretics in a local district in Japan.

METHODS

Prescriptions that included antihypertensive drugs were collected from 80 dispensing pharmacies in the Yahata Pharmacist Association, located in Kitakyushu City, in October 2014. Age group (every 10 years), gender and prescribed antihypertensive drugs were recorded. Prescriptions for diabetes, dyslipidemia and hyperuricemia and for antithrombotic drugs were also investigated. Information on the doctors (general practitioner/hospital worker and physician/surgeon) was also obtained. If a patient had visited the pharmacy on multiple occasions in the month, prescriptions from the first visit were included. Study information was provided to patients who visited each pharmacy. Because the data were anonymized, informed consent was not obtained from each patient. This study was approved by the institutional ethical committee at the Steel Memorial Yawata Hospital.

Statistical analysis

All values are presented as the number or percentage. Statistical analysis was performed using unpaired t -tests. The χ^2 tests were also used when appropriate. The P -values of < 0.05 were considered statistically significant.

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Received 24 March 2016; revised 27 June 2016; accepted 28 July 2016; published online 1 September 2016

RESULTS

A total of 10 967 prescriptions were obtained. Patients without information on their age ($N=256$) were excluded. We also excluded patients who were prescribed loop and/or mineralocorticoid receptor blockers without any other class of antihypertensive drugs ($N=126$), as these diuretics can be used for congestive heart failure or other edematous diseases. As a result, 10 585 prescriptions (96.5%) were included in the analyses. Patients' ages were widely distributed, ranging from 10 to 100 patients in each age group. The 70–79-year age group contained the largest proportion of patients (33.0%), followed by 60–69 years (24.6%) and 80–89 years (23.5%). In addition, 55.3% of the patients were female. In total, 24.9% of the doctors were hospital workers, whereas another 75.1% were general practitioners. Most doctors (95.9%) were physicians. Antidiabetic, lipid-lowering and uric acid-lowering drugs were prescribed in 18.8%, 36.3% and 10.0% of the patients, respectively. Antithrombotic drugs were prescribed in 23.5% of the patients. The prescription rates for each of the

antihypertensive drugs are shown in Figure 1. Calcium channel blockers (CCBs) were the most frequently prescribed, followed by ARB, diuretics and β -blockers. Concerning diuretics, thiazide diuretics were used in 9.4% of the patients, followed by loop diuretics in 5.3% and mineralocorticoid receptor blockers in 4.1%. The combinations of thiazide+loop, thiazide+mineralocorticoid receptor blockers and loop +mineralocorticoid receptor blockers were prescribed in a small number of patients (0.4%, 0.4%, and 1.5%, respectively). The use of angiotensin-converting enzyme (ACE) inhibitors (6.1%) and α -blockers (2.4%) was limited. FDC tablets containing ARB/CCB were used in 12.1% of the patients, whereas ARB/diuretics tablets were used in 3.8% of the patients. The average number of prescribed antihypertensive drugs was 1.80. Hospital workers prescribed diuretics more frequently than general practitioners (19.1% vs. 15.7%, $P<0.01$). The total number of antihypertensive drugs prescribed was also higher in hospital workers (1.85 vs. 1.79, $P<0.01$). Table 1 shows the prescribed drugs according to the number of antihypertensive drugs. In patients with monotherapy, CCBs were most frequently prescribed, followed by ARB. Diuretics were used as monotherapy in only 0.6%. In diabetic patients who received monotherapy, ARB or ACE inhibitors were chosen as the first-line drug in 53.1% of the patients, whereas CCB were chosen in 43.0% of the patients. The combination of CCB and ARB was the most frequent prescription pattern in patients taking two antihypertensive drugs, and the prescription of diuretics remained low (13.1%). In patients taking three antihypertensive drugs, diuretics were used in approximately half of the subjects (55.2%). Figure 2 shows the prescription rate of FDC drugs. ARB/CCB tablets were used in 20.6% of the patients taking two antihypertensive drugs. Furthermore, ARB/CCB and ARB/diuretic tablets were used in 20.5% and 12.9%, respectively, of those taking three antihypertensive drugs. As shown in Table 2, elderly patients (≥ 60 years old) and patients taking uric acid-lowering drugs or antithrombotic drugs were more prevalent among patients taking diuretics compared with those without diuretics. In patients taking three or more antihypertensive drugs, diuretics were more frequently prescribed in elderly and female patients. The coadministration of

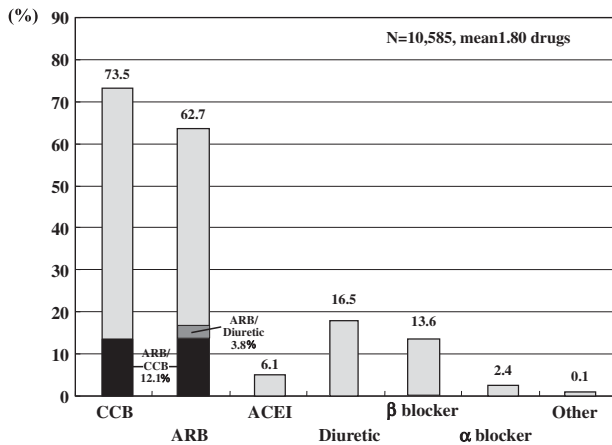


Figure 1 Prescription rate of each class of antihypertensive drug in all subjects. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

Table 1 Prescribed drugs according to the number of antihypertensive drugs

No. of drugs	CCB (%)	ARB (%)	ACEI (%)	Diuretic (%)	β -Blocker (%)	α -Blocker (%)
1($N=4553$)	56.3	37.4	2.3	0.6	3.1	0.3
2($N=4158$)	85.6	80.3	6.9	13.1	11.2	1.7
3($N=1393$)	87.7	84.1	11.6	55.2	38.2	5.9
4($N=407$)	88.7	87	19.2	82.6	61.4	14.5

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker. All values are given as percentage.

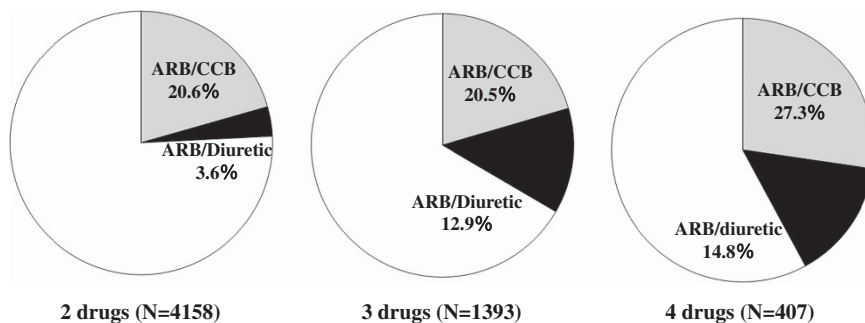


Figure 2 Prescription rate of fixed-dose combination (FDC) drugs. ARB, angiotensin II receptor blocker; CCB, calcium channel blocker.

Table 2 Characteristics of the patients with and without diuretics

	Total patients	Diuretics (-)	Diuretics (+)	Patients ≥ 3 anti-HT drugs	Diuretics (-)	Diuretics (+)
Number	10 585	8842	1743	1874	703	1171
Age (≥ 60 years), %	86.3	85.9	88.3**	87.9	85.5	89.3*
Female, %	55.3	55.0	56.5	49.5	42.9	53.5**
Hospital doctors, %	24.9	24.1	28.7**	28.5	24.6	30.8**
No. of antihypertensive drugs	1.80	1.58	2.93**	3.30	3.12	3.41**
Antidiabetic drugs, %	18.8	18.6	19.6	22.2	23.2	21.6
Lipid-lowering drugs, %	36.3	35.9	38.0	41.2	43.7	39.7
Uric acid-lowering drugs, %	10.0	8.7	16.6**	18.2	16.8	19.0
Antithrombotic drugs, %	23.5	21.3	34.7**	37.1	34.1	38.9*

Abbreviation: anti-HT, antihypertensive.
All values are given as number or as percentage.
* $P < 0.05$, ** $P < 0.01$ vs. diuretics (-).

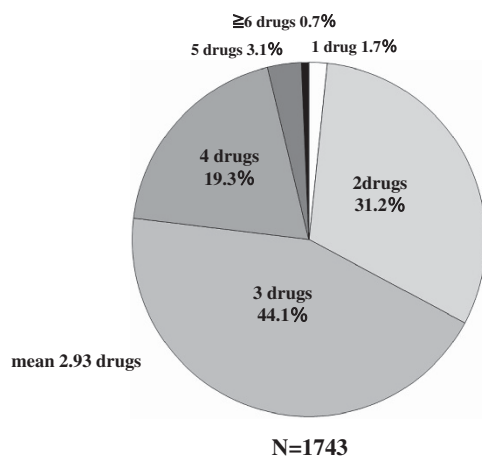


Figure 3 Number of antihypertensive drugs in patients taking diuretics.

antithrombotic drugs was also higher (38.9%) in patients receiving diuretics. However, the prescription of diuretics tended to be less frequent among patients taking antidiabetic drugs or lipid-lowering drugs, but these differences were not statistically significant. The distribution of the number of antihypertensive drugs in patients taking diuretics is shown in Figure 3. The average number of antihypertensive drugs was 2.93, and approximately two-thirds of the patients were taking three or more drugs. Finally, the classification of thiazide diuretics was analyzed (Figure 4). Of the 990 patients who were prescribed thiazide diuretics, hydrochlorothiazide (HCTZ) was used in 40.0%, and trichlormethiazide and indapamide were used in 34.9% and 19.8%, respectively. HCTZ was provided as FDC tablets with ARB, and doses of 12.5 and 6.25 mg were used in 83.2% and 16.8%, respectively.

DISCUSSION

The present study disclosed the current prescription status of diuretics in a local district in Japan. The preferential use of diuretics, especially in patients who required three or more antihypertensive drugs, is recommended in the JSH2014.¹ However, the prescription rate of diuretics in patients taking three drugs remained at 55.2%, indicating that doctors may hesitate to use diuretics even in patients requiring multiple antihypertensive medications. One possible reason for this finding may be concern regarding the adverse metabolic effects of diuretics. Indeed, antidiabetic and uric acid-lowering drugs were coadministered in a significant number of patients in this study.

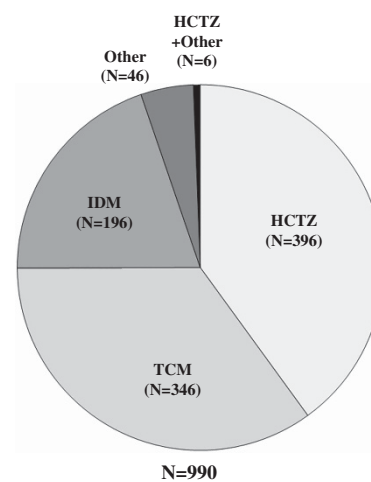


Figure 4 Prescription rate of thiazide diuretics. HCTZ, hydrochlorothiazide; IDM, indapamide; TCM, trichlormethiazide.

An alternative explanation is that the doctors were not accustomed to using diuretics because the prescription of diuretics remained low after the development of CCB and ARB. The development of FDC tablets with ARB may have facilitated the use of diuretics. Indeed, the rate of diuretic prescriptions has been reported to show a steady increase since December 2006, and this is when losartan/HCTZ FDC tablets became available.² In their report, the prescription rate of diuretics was $\sim 10\%$ in 2011. Our findings of a diuretics prescription rate of 16.5% may indicate that the availability of FDC tablets promoted the use of diuretics. However, this study also showed that ARB/CCB FDC tablets were prescribed three times more frequently than ARB/diuretic tablets and that the use of ARB/diuretic tablets was limited to 40% of the total diuretic prescriptions. The increase from 12.5 mg HCTZ to 50 mg losartan led to an effective reduction in BP and proteinuria in patients with essential hypertension or chronic kidney disease,^{5,6} and the efficacy of FDC tablets containing high-dose ARB/HCTZ was also reported.⁷ Considering the value of drug adherence, the use of ARB/diuretic tablets seems helpful when diuretics are included in a combination therapy.

The intake of salt in Japan has gradually been decreasing, but the average salt intake among men (10.9 g per day) and women (9.2 g per day) is reported to still be high.⁸ Although the JSH2014 recommends reducing salt intake to ≤ 6 g per day, salt intake remains high among hypertensive patients; we have shown that long-term

compliance to salt reduction is quite difficult and that the effect of repeated salt reduction guidance is limited.^{9,10} Patients who fail to reduce salt intake tend to require more antihypertensive drugs to control their BP.¹¹ It is reasonable that the addition of diuretics in patients who cannot control their BP with the use of antihypertensive drugs such as ARB leads to significant reductions in BP, especially in those with high salt intake.¹² Thus, the use of diuretics is warranted in patients whose target BP has not been achieved with a regimen including ARB or ACE inhibitors. Our observation that the prescription rate of antithrombotic drugs was higher in patients taking diuretics may indicate that doctors intended to achieve strict BP control by using diuretics in patients receiving antithrombotic therapy.

The most frequently prescribed thiazide diuretic was HCTZ (40.0%), followed by trichlormethiazide (34.9%) and indapamide (19.8%). Some differences in BP-lowering effects and adverse metabolic effects are suggested to occur in thiazide diuretics. A meta-analysis of prospective studies that indirectly compared HCTZ and chlorthalidone concluded that chlorthalidone resulted in fewer cardiovascular events than treatment with HCTZ.¹³ Another meta-analysis that compared thiazide-type diuretics (chlorothiazide, HCTZ and trichlormethiazide) and thiazide-like diuretics (chlorthalidone and indapamide) also revealed that thiazide-like diuretics showed greater reductions in cardiovascular risk, although the incidence of adverse events was comparable.¹⁴ Furthermore, head-to-head comparisons of HCTZ with indapamide showed that the latter had more potent antihypertensive effects, whereas there were no detectable differences in adverse metabolic effects between the drugs.¹⁵ These observations may indicate the superiority of thiazide-like diuretics over thiazide-type diuretics. However, it may be difficult to identify the differences between the drugs because diuretics are mostly used at low doses in combination with ARB in Japan.

The limitations of the present study should be noted. First, we did not investigate the BP levels of the patients and were thus unable to address the status of BP control, particularly in association with antihypertensive drugs. Second, we did not obtain patients' diagnoses and were thus unable to exclude the possibility that antihypertensive drugs were used to treat congestive heart failure, angina pectoris, arrhythmia or other conditions. We excluded patients who were prescribed loop and/or mineralocorticoid receptor blockers and not any other class of antihypertensive drugs. However, ACE inhibitors and β -blockers tended to be prescribed more often in patients who took loop and/or mineralocorticoid receptor blockers. This observation may indicate that these drugs were used to treat congestive heart failure or ischemic heart disease rather than hypertension. Because CCBs were coadministered in >60% of these patients, it was difficult to identify the purpose of the administration of diuretics in this study. Finally, the current investigation was conducted in a dispensing pharmacy located in the Yahata area of Kitakyushu city. Therefore, the present findings may not be extrapolated to the general population of Japan.

In conclusion, the prescription rate of diuretics was 16.5% among 10 585 Japanese hypertensive patients. The use of diuretics remains limited, even among patients taking multiple antihypertensive drugs.

CONFLICT OF INTEREST

TT received funding for clinical research from the MSD KK and honoraria from the MSD KK and Dainippon Sumitomo Pharma. The other authors declare no conflict of interest.

ACKNOWLEDGEMENTS

We sincerely thank the members of the Yahata Pharmacist Association.

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