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Relationship between office blood pressure and actual antihypertensive drug use in patients with hypertension following the promulgation of the guidelines for hypertension (JSH2019)

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To achieve appropriate blood pressure control in the treatment of hypertension in Japan, this study examined the relationship between office blood pressure and actual antihypertensive drug use in general hospitals following the promulgation of the guidelines for hypertension (JSH2019). This study focused on blood pressure levels and drug use in outpatients on antihypertensive treatment from June to July 2020. The subjects were 2,537 patients classified into four groups based on their medical history, patients with: hypertension only; hypertension and cardiovascular disease; hypertension and dyslipidaemia; and hypertension and diabetes mellitus. The results showed a significant difference in systolic blood pressure (SBP) between patients with hypertension only and those with hypertension and cardiovascular disease (138.3±17.9 mmHg vs 135.6±19.9 mmHg, $p<0.05$). Regarding actual drug use, it was found that diuretics were prescribed more frequently in patients with hypertension and cardiovascular disease than in those with hypertension alone (15.5% vs 37.9%, $p<0.05$), even though the number of drugs for hypertension did not differ significantly. In addition, the dose of diuretics was greater only in patients with cardiovascular disease. These results show the actual drug use and blood pressure for each comorbidity. Furthermore, they suggest that the results of antihypertensive treatment may differ by changing the combination and dosage of antihypertensive drugs without changing the number of antihypertensive drugs used. The study also shows the problem of using less diuretics depending on the risk the patient has, and solving the problem may lead to achieving further antihypertensive goals.

1. Introduction

Hypertension increases the risk of serious complications such as heart disease and stroke (Ikeda et al. 2009; Takashima et al. 2012). There are several different drug classes available for the treatment of hypertension, including calcium channel blockers (CCBs), angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers (BETAs), and diuretics (DIUs). However, the effectiveness of each drug differs for each individual patient and requires selection and adjustment (Taler et al. 2002). In addition, lifestyle modification, including salt reduction, and medication adherence are also issues (He et al. 2020). In recent years, treatment resistance and so-called “clinical inertia,” which is ‘to wait and see without intensifying treatment even though blood pressure levels are higher than the antihypertensive target,’ are considered clinically problematic. In Japan, according to a domestic survey, only about 40% of men and 45% of women taking antihypertensive drugs were controlled below 140/90 mmHg in 2016 (Hisamatsu et al. 2020). Globally, Japan’s blood pressure control rates are lower than in the United States and other countries (NCD Risk Factor Collaboration 2019). In Japan, hypertension treatment guidelines were revised in 2019, and antihypertensive targets are stricter than before, thereby requiring further blood pressure control. There have been few reports of blood pressure control rates and actual drug use since the publication of the JSH2019 guidelines. It would be clinically meaningful to make decisions about patient treatment based on updated reports of actual use. This study focused on office blood pressure levels and actual drug use in outpatients with hypertension

at a general hospital. Specifically, patients were divided into two groups (those with hypertension alone, and those with hypertension in combination with other diseases), and their age, medical history, prescription drugs, and blood pressure at examination were compared to examine the relationship between drug use and blood pressure. The results of this study also provide clues to the site of clinical inertia in drug use, based on drug use and associated blood pressure in clinical practice.

2. Investigations and results

Of the 4,355 patients who were prescribed antihypertensive drugs during the study period, 1,818 fulfilled the exclusion criteria or were unable to have their blood pressure collected, leaving 2,537 patients included in the study population. These patients were classified into four groups based on their medical history: those with only hypertension (pHT); those with hypertension and cardiovascular disease (withCVD); those with hypertension and dyslipidaemia (withDL); and those with hypertension and diabetes mellitus (withDM). The ICD-10 disease name on the medical record was used to evaluate the disease status of patients. However, if a patient did not have a disease name listed on the medical record, but was using drugs corresponding to a specific disease, that patient was included in the respective disease group (Fig. 1). Patients with multiple medical conditions ($n=1,646$) were excluded from the classification. Of the total number of patients, there were 362 in the pHT group, 169 in the withCVD group, 234 in the withDL group, and 126 in the withDM group.

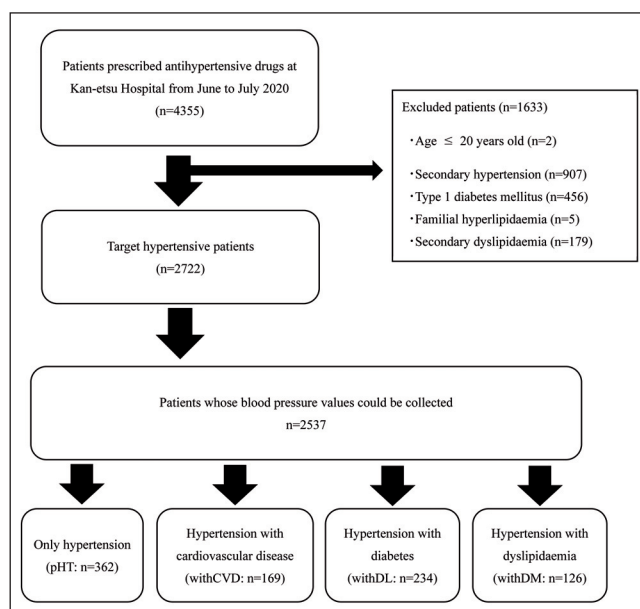


Fig. 1: Flow chart of the study selection process and classification by complications. Of the 4,355 patients eligible for antihypertensive treatment who visited the outpatient clinic between June and July 2020, a total of 2,537 were enrolled, and 1,818 were excluded due to age <20 years or secondary hypertension. Of the eligible patients, 362 were in the pHT, 169 in the withCVD, 234 in the withDL, and 126 in the withDM groups. pHT, patient with only hypertension; withCVD, patient with hypertension and cardiovascular disease; withDL, patient with hypertension and dyslipidaemia; and withDM, patient with hypertension and diabetes mellitus

Sex, age, blood pressure, heart rate, and achievement of JSH2019 guideline targets are shown for each group in Table 1. There was a significant difference in SBP between the pHT and withCVD groups ($p=0.027$), but sex, diastolic blood pressure (DBP), heart rate, SBP achievement, DBP achievement, and total achievement did not differ significantly in the groups compared to the pHT group.

Table: Sex, age, blood pressure, heart rate, and achievement of JSH2019 guideline targets in the study cohort

	pHT (n=362)	withCVD (n=169)	withDL (n=234)	withDM (n=126)
Males (%)	236 (65.2%)	109 (64.5%)	136 (58.1%)	89 (70.6%)
Age, median[IQR] (years)	72[64-79]	74[67-80]	73[68-78]	73[65-78]
SBP, median[IQR] (mmHg)	137[127-150]	134[123-144] *	137[128-148]	137[129-147]
DBP, median[IQR] (mmHg)	77[67-84]	75[67-83]	75[66-83]	76[67-84]
Heart rate, median[IQR] (beats/min)	77[68-86]	75[67-85]	76[68-84]	79[71-89]
SBP achievement (%)	136 (37.6%)	68 (40.2%)	81 (34.6%)	42 (33.3%)
DBP achievement (%)	237 (65.5%)	112 (66.3%)	171 (73.1%)	79 (62.7%)
Total achievement (%)	120 (33.1%)	64 (37.9%)	71 (30.3%)	37 (29.4%)

Continuous variables are expressed as median [interquartile Range]. * $p<0.05$ vs pHT: post hoc Steel test. Categorical variables are expressed as frequencies (percentages). Patients whose blood pressure values were below the target blood pressure in JSH2019 were defined as having achieved the treatment goal. SBP, systolic blood pressure; and DBP, diastolic blood pressure.

2.2. Drug use characteristics of each group

The prescription rates for different classes of antihypertensive drugs are shown by group in Fig. 2A. There was no significant difference in the prescription rates of any class between the pHT and withDL (or withDM) groups. However, in the withCVD group, the prescribing rates for CCB were lower than those for the pHT group ($p<0.001$), and the prescribing rates for DIU ($p<0.001$) and BETA ($p<0.001$) were higher. The number of drugs being taken

by patients is shown in Fig. 2B. Whereas there was no significant difference in the number of antihypertensive drugs prescribed among the groups, there was a significant difference in the total number of drugs being taken by patients. The usage rates of the five recommended combination patterns by JSH2019 are shown in Fig. 2C. Compared to the pHT group, the withCVD group had lower usage rates of CCB·ARB ($p=0.006$) and higher usage rates of CCB·DIU ($p=0.033$) or ARB·DIU ($p=0.040$). In addition, compared to the pHT group, the withDM group had significantly higher usage rates of ARB·DIU ($p=0.004$).

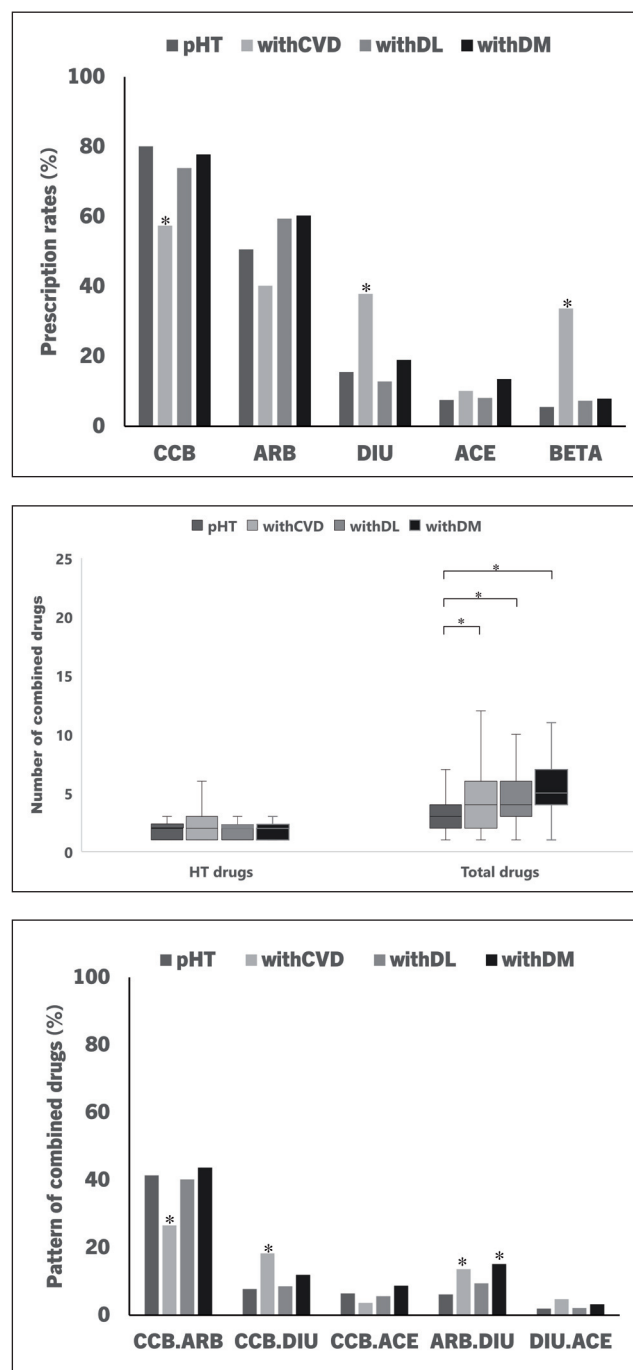


Fig. 2: Drug use characteristics of each group. Prescription rates for antihypertensive drug classes. (A) Number of combined drugs. (B) HT drugs is the number of concomitantly used antihypertensive drugs. Total drugs are the number of all drugs the patient was taking concomitantly. (C) Pattern of combined drugs. (C) Combination patterns mainly recommended by JSH2019. pHT, patient with only hypertension; withCVD, patient with hypertension and cardiovascular disease; withDL, patient with hypertension and dyslipidaemia; and withDM, patient with hypertension and diabetes mellitus; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; BETA, β -blocker; and DIU, diuretic * $p<0.05$ vs pHT: post hoc Steel test or Fisher's exact test.

The dosages of medication administered to each patient in the pHT group were compared with those in the other groups. For this comparison, the intensity of drug usage for each patient was calculated by determining the dosage administered as a percentage of the maximum approved dosage set by the Ministry of Health, Labour and Welfare, with 100% representing the maximum approved dosage. The medication usage intensity for each group in each class is shown in Fig. 3. Compared to the pHT group, only the dosage of DIU in the withCVD group was significantly higher ($p < 0.001$).

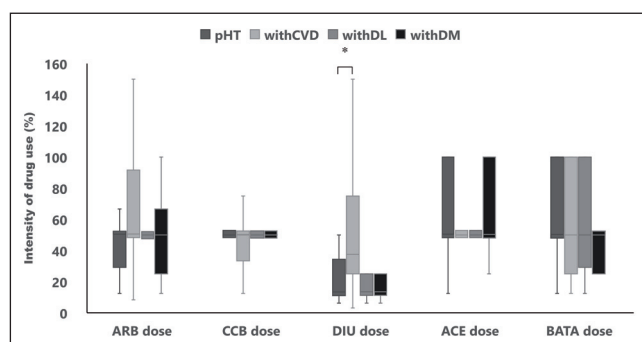


Fig. 3: Intensity of drug use. Drug use intensity was defined as 100% of the maximum Pharmaceuticals and Medical Devices Agency-approved dose for each individual drug. Then, drug use intensity was calculated and averaged for each drug used by individual patients. pHT, patient with only hypertension; withCVD, patient with hypertension and cardiovascular disease; withDL, patient with hypertension and dyslipidaemia; and withDM, patient with hypertension and diabetes mellitus; CCB, calcium channel blocker; ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; BETA, β -blocker; and DIU, diuretic. * $p < 0.05$ vs pHT: post hoc Steel test.

3. Discussion

This retrospective, observational study evaluated the relationship between medication use and blood pressure in June and July 2020, following the publication of JSH2019. The findings indicate that patients with comorbid coronary artery disease had better blood pressure reduction and used the same number of drugs, but there were differences in drug selection between patients with comorbid coronary artery disease and those with hypertension alone. However, no difference in treatment goal attainment was identified because of the different treatment goals for comorbidities. This result is considered comparable to the hypertension control rate reported in a Japanese survey (about 40%) (Hisamatsu et al. 2020). In addition, the fact that the goal was not achieved in more than half of the patients suggested that there was some clinical inertia. The results suggest that prescribers may be resisting clinical inertia in treating patients with higher-risk coronary artery disease complications compared to patients with hypertension alone. A Dutch study reported that the presence of renal and heart failure was inversely related to the presence of clinical inertia, suggesting that adequate monitoring is more likely to occur in the high-risk group (Ali et al. 2021). Furthermore, better blood pressure control in the coronary artery disease group compared to the other groups was similar to that previously reported (Kudo et al. 2015). Moreover, in the group of non-coronary artery disease patients with different drug use trends, the drug use rates were considered similar to those in previous Japanese reports (Ibaraki et al. 2017). The present results also showed that CCBs have the highest prescribing rate among all drug categories in this study. Diuretics resulted in lower prescription rates than CCBs and ARBs, despite being listed equally as first-line drugs in JSH2019. This indicates that diuretics are prescribed less frequently than ARBs and CCBs, even though they are also first-line drugs in JSH2019. This was unchanged from the trend prior to the publication of JSH2019 (Umamura et al. 2019). Interestingly, studies analysing antihypertensive medications in Japan suggest that the low use of diuretics is a factor in the low rate of blood pressure control in the Japanese population (Oishi et al. 2018).

Clinical inertia is defined as clinicians' failure to appropriately increase treatment despite the fact that treatment goals are not being met (Phillips et al. 2001). Indeed, ARBs and CCBs are easier to add to treatment than diuretics because they have fewer lifestyle side effects. On the other hand, diuretics have been reported to have low adherence and require long-term follow-up due to dehydration and, especially for thiazide diuretics, effects on glucose tolerance (Nishimura et al. 2019). The present results may be due to the prescribing behavior of physicians to achieve blood pressure goals beyond the difficulty of using diuretics in the coronary artery disease group. In other words, a form of resistance to clinical inertia may be associated with increased diuretic use. Conversely, it appears that this tendency toward "diuretic avoidance" relative to the target is particularly high in Japan. In support of the present results, diuretic use ranks first or second in Canada, the United States, and Germany, which have high rates of control of blood pressure in treated patients (McInnis et al. 2008; Ernst et al. 2020; Sarganas et al. 2016).

The total number of concomitant medications was higher in the comorbid group than in the hypertension alone group due to the increased number of medications used to treat comorbidities. However, pharmacotherapy with antihypertensive medications has been reported to become more difficult as the number of concomitant medications increases (Ishida et al. 2019). Prescribers may have had difficulty increasing the number of medications for patients with comorbid conditions with a high total number of concomitant medications. Despite this, the number of antihypertensive medications did not differ significantly among the groups. Furthermore, none of the groups in the present results had higher blood pressure values compared to the hypertension alone group. From another perspective, the difference in blood pressure values with the same number of antihypertensive drugs, as observed in the group with coronary artery disease, suggests that blood pressure values may be reduced with appropriate drug selection, suggesting that drug selection is important with respect to blood pressure control, as outlined in JSH2019. Rather than increasing the dose of one antihypertensive drug, JSH2019 recommends monotherapy followed by smaller doses of two drugs. The present results suggest that prescribers are using an average of two drugs and have reached this stage. On the other hand, as the next step in case of further deterioration of control, the guidelines recommend either the "A way: increasing the two concomitant drugs to normal dosage" or the "B way: changing the concomitant drugs". The present results suggest that the prescribing rate was too low to consider that frequent changes in medication according to the B way had occurred. As in previous studies, it is possible that prescribers commonly prescribe the first CCB and the second ARB, and that subsequent changes are not considered.

Another possibility, although not thought to contribute significantly to mean blood pressure, may be clinically related to inertia, in which the maximum ACE dosage in Japan is set at 1/4 to 1/2 of that used overseas, yet usage is not higher than for other classes. Because this study was conducted using office blood pressure data, there was a possibility of confounding due to differences from home blood pressure. In addition, the study was conducted mainly from the therapist's perspective, with the clinical inertia of non-achievement of antihypertensive goals, but it was not possible to consider medication adherence rates or adherence on the patients' side. Although there is seasonal variation in blood pressure, this study was conducted only during the summer season, and it is unclear whether the same results would be obtained during the winter season. Because of the retrospective, observational design, it was not possible to provide specific measures or treatments.

Even with these limitations, due to the similarities with the results of previous studies, this study highlighted issues such as antihypertensive medication use and low diuretic use in Japan since the publication of JSH2019. To overcome clinical inertia as an obstacle to treatment, the appropriate use of diuretics should be promoted beyond the "diuretic avoidance" that Japanese clinicians may have.

4. Experimental

4.1. Study design and patients

This single-centre, retrospective study included patients undergoing outpatient care who had been prescribed antihypertensive medication at KAN-ETSU Hospital, located in Tsurugashima City, Saitama Prefecture, Japan. The study included patients aged 20 years or older who visited the outpatient department of KAN-ETSU Hospital between June 1 and July 31, 2022, and were prescribed antihypertensive medication, regardless of sex. Patients with secondary hypertension (renal, endocrine, cardiovascular, neurological, pregnancy-induced, exogenous, malignant), type 1 diabetes mellitus, familial hyperlipidaemia, secondary dyslipidaemia (renal, endocrine, neurological, glycogen storage diseases, pregnancy/menopause-related, lipodystrophy), dialysis, those who refused to provide information for the study, and those deemed medically inappropriate for the study by the attending physician based on evidence were excluded from this study.

4.2. Data collection, definitions, and outcomes

The following basic information was collected: age, sex, presence/absence of comorbidities other than lipid or glucose intolerance, family history of diabetes mellitus, dyslipidaemia, cardiovascular disease, or cerebrovascular disease, and antihypertensive agents, lipid-lowering agents, and antidiabetic agents that were continuously administered during the survey period. However, medications taken on a temporary basis were excluded. If the patient received multiple prescriptions during the survey period, the latest prescription was used for the analysis. Antihypertensive agents were grouped according to their pharmacological effects. The usage intensity for each medication was calculated by determining the percentage of the maximum approved dosage set by the Ministry of Health, Labour and Welfare, with 100% representing the maximum approved dosage for each therapeutic effect. The purpose of this study was to investigate the relationship between medication use and blood pressure, as well as the occurrence of clinical inertia. The main outcome of this study was the relationship between comorbidities and blood pressure values, with secondary outcomes including the prevalence of antihypertensive medication use.

4.3. Statistical analysis

Categorical variables are summarised as percentages or frequencies, and continuous variables are summarised as median values and interquartile ranges. The statistical analysis of continuous variables was performed using the Kruskal-Wallis test, followed by the Steel post hoc test. For categorical variables, Fisher's exact test was used. A level of $p < 0.05$ was considered significant. All statistical analyses were conducted using EZR (Kanda et al. 2012), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

4.4. Ethics

The study was conducted in compliance with the Declaration of Helsinki and the "Ethical Guidelines for Medical and Health Research Involving Human Subjects". All study protocols were approved by the Ethics Review Committee of Nihon University College of Pharmacy (approval number: 19-016) and the Clinical Study Review Committee of KAN-ETSU Hospital (approval number: 2019-006).

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Conflicts of interest: none declared.

Author contributions: Tomohiro Ogawa, Motoki Arakawa and Shinji Hidaka contributed to the design of the study. Tomohiro Ogawa, Motoki Arakawa, Toshihisa Suzuki, Nobuhiro Yasuno, Masahiko Tanaka and Shinji Hidaka participated in the data collection and analysis. Tomohiro Ogawa, Motoki Arakawa and Shinji Hidaka contributed to the drafting of the manuscript. All authors participated in the critical revision of the manuscript and approved the final version of the manuscript for submission.

Data availability: Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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