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Trend of office and home blood pressure control in treated hypertensive patients: changes in antihypertensive medication and salt intake*

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Abstract

Blood pressure (BP) control in hypertensives has improved in recent years; however, it remains insufficient. We investigated the trend of BP control status in hypertensive patients with antihypertensive medication and salt intake. Two hundred and eight treated hypertensive patients were prospectively followed between 2007 and 2012. During this period, average clinic BP significantly decreased from 137 ± 12/80 ± 9 to 133 ± 11/76 ± 8 mmHg, and the achievement rate of BP control defined as <140/90 mmHg increased from 58% to 71% ($p < 0.01$). Morning home BP also significantly decreased from 132 ± 8/80 ± 8 to 130 ± 8/76 ± 7 mmHg, and the percentage of patients with sustained hypertension (CBP ≥140/90 mmHg and HBP ≥135/85 mmHg) decreased from 27% to 16% ($p < 0.05$). The number of antihypertensive drugs increased significantly from 2.1 ± 1.2 to 2.3 ± 1.1 ($p < 0.01$), while no differences were observed in urinary salt excretion (9.0 ± 2.4 g/day in 2007, 9.0 ± 2.6 g/day in 2012). Office and home BP decreased and the rate of BP control increased in treated hypertensive patients in the past 5 years. Intensive pharmacological therapy, but not a reduction in salt intake appears to have contributed to improved BP control.

Keywords

Hypertension, blood pressure control, antihypertensive drugs, urinary salt excretion, home blood pressure

History

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Introduction

Blood pressure (BP) levels have been closely associated with the incidence of cardiovascular disease (1,2), and reductions in BP in hypertensive patients have been shown to improve cardiovascular outcomes in clinical trials (3,4). Many guidelines for the management of hypertension, such as the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment on High Blood Pressure (JNC 7), guidelines of the European Society of Hypertension (ESH) and European Society of Cardiology (ESC) (ESH/ESC 2013), and the Japanese Society of Hypertension guidelines (JSH 2009), recommend intensive antihypertensive treatment to attain strict BP control and combination therapy including diuretics is warranted to achieve target BP levels (5–7). However, the BP control status of hypertensive patients remains insufficient (8,9). The poor control of hypertension has frequently been reported in patients with high risk of cardiovascular diseases, such as those with diabetes mellitus (DM), chronic kidney disease (CKD) and metabolic syndrome (10–13).

Home BP (HBP) monitoring has become a standard tool and is recommended in the treatment of hypertension. HBP was reported to be more closely associated with hypertensive target organ damage and cardiovascular morbidity and mortality than clinic BP (CBP) (14–18). The diagnostic threshold of hypertension was defined as 140/90 mmHg for CBP and 135/85 mmHg for HBP (7). The JSH 2009 guidelines also proposed the target HBP to be <135/85 mmHg for elderly patients, <125/80 mmHg for young/middle-aged patients and <125/75 mmHg for patients with DM, CKD or myocardial infarction (MI) (7). No such proposal was made in the previous JSH 2004 guidelines (19).

Excessive salt intake plays an important role in the pathophysiology of hypertension, and causes kidney and cardiovascular damage through BP-dependent and -independent mechanisms (20–23). The importance of salt restriction is well recognized, and all guidelines recommend salt restriction for the management of hypertension (5,7). Salt intake has decreased in the Japanese population; however, it is still higher than that of most other countries. We previously reported that salt restriction to achieve the target level recommended by the JSH guidelines (<6 g/day) appeared to be difficult for Japanese patients (24).

In the present study, we investigated the trend of CBP and HBP, antihypertensive medication, and salt intake in treated hypertensive patients between 2007 and 2012, which represented periods before and after the JSH 2009 guidelines.

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Patients and methods

Two hundred and eight hypertensive patients (110 women and 98 men, mean age 66 ± 11 years in 2007), who measured Na concentration and creatinine concentration in a spot urine sample in 2007 and 2012 and were continuously followed at the hypertension clinic during 2007–2012, were investigated retrospectively. Casual BP as well as clinical characteristics and the antihypertensive regimens used for each patient when the urinary salt excretion was measured were investigated during this period. We assessed the CBP control status based on the average CBP on every occasion in 2007 and 2012. Casual BP was measured with a sphygmomanometer by doctors while the patients were quietly seated. Goal BP was defined as a systolic BP (SBP) of <140 mmHg and diastolic BP (DBP) of <90 mmHg in elderly patients (≥65 years), SBP of <130 mmHg and DBP of <85 mmHg in young or middle-aged patients, and SBP of <130 mmHg and DBP of <80 mmHg in patients with DM, CKD or MI according to JSH 2009 (7). This study was conducted following the guidelines of the National Cerebral and Cardiovascular Center.

Of the 208 patients, 153 hypertensive patients (81 women and 72 men) measured and recorded HBP during this period. HBP was assessed based on morning records, and the value of the first measurement was adopted. HBP values on the preceding 3 days of every clinical visit were averaged and used for analysis. The cut-off values of CBP and HBP used to determine the BP category were defined as <140/90 and <135/85 mmHg, respectively.

Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Diabetes was defined as fasting serum glucose ≥126 mg/dl, serum glucose ≥200 mg/dl at any time, HbA1c ≥6.5%, or the current use of hypoglycemic agents. Chronic kidney disease was considered to be present if the patient had either a decreased estimated glomerular filtration ratio (eGFR) (<60 ml/min) or persistent proteinuria or urinary albuminuria (≥30 mg/gCr). Estimated GFR was calculated using the formula: $194 \times \text{serum creatinine levels}^{-1.094} \times \text{age}^{-0.287}$ for men; $194 \times \text{serum creatinine levels}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ for women (25). Myocardial infarction was diagnosed based on the patient's medical history as well as the findings of electrocardiography, echocardiography or coronary angiography. Twenty-four-hour sodium (Na) excretion (mEq/day) was calculated using the formula: {21.98 × (Na concentration in a spot urine sample/creatinine (Cr) concentration in a spot urine sample) × estimated 24-h urinary Cr excretion}$^{0.392}$ (26).

Values are presented as the mean ± SD. Differences in variables were compared by either a paired t test or unpaired t test. A chi-squared test was also utilized when appropriate. p Values <0.05 were considered significant.

Results

The characteristics of 208 subjects are shown in Table 1. Average CBP in 2012 was significantly lower than that in 2007 (133 ± 11/76 ± 8 versus 137 ± 12/80 ± 9 mmHg). The rate of patients with good BP control increased from 58% to 71% when good BP control was defined as SBP of <140 mmHg and DBP of <90 mmHg (Figure 1).

Table 1. Clinical characteristics of subjects in 2007 and 2012 (n = 208).

	2007	2012
Age	66 ± 11	71 ± 11
Body mass index (kg/m^2)	24 ± 3	24 ± 3
Number of antihypertensive drugs	2.1 ± 1.2	2.3 ± 1.1**
Average clinic SBP (mmHg)	137 ± 12	133 ± 11**
Average clinic DBP (mmHg)	80 ± 9	76 ± 8**
Morning home SBP (mmHg, n = 153)	132 ± 8	130 ± 7*
Morning home DBP (mmHg, n = 153)	80 ± 8	76 ± 7**
Evening home SBP (mmHg, n = 153)	128 ± 10	128 ± 10
Evening home DBP (mmHg, n = 153)	76 ± 8	74 ± 8**
Urinary salt excretion (g/day)	9.0 ± 2.4	9.0 ± 2.6
Urinary albuminuria (mg/gCr)	63 ± 323	48 ± 109
Serum LDL cholesterol (mg/dl)	112 ± 26	107 ± 23**
Serum triglycerides (mg/dl)	125 ± 104	116 ± 61
Serum HDL cholesterol (mg/dl)	58 ± 17	56 ± 15
Blood glucose (mg/dl)	107 ± 18	109 ± 17*
Estimated GFR (ml/min/1.73 m^2)	70 ± 19	63 ± 18**
Serum uric acid (mg/dl)	5.7 ± 1.4	5.8 ± 1.4

Values are means ± SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; GFR, glomerular filtration rate.
**p < 0.01.
*p < 0.05 versus 2007.

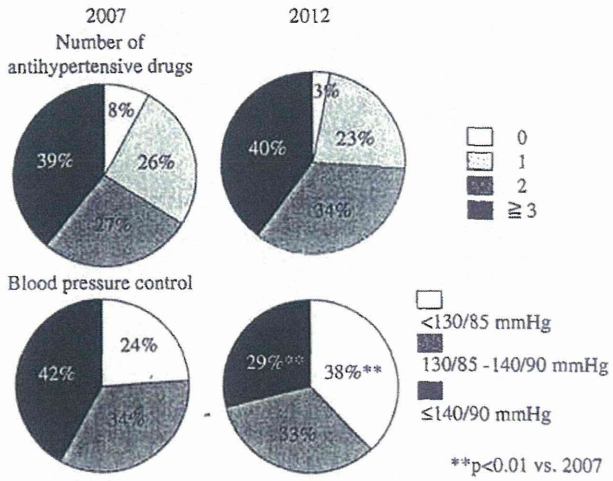

Figure 1. Number of antihypertensive drugs and blood pressure control status in 2007 and 2012.

This improvement in BP control was associated with an increase in the number of antihypertensive drugs during this period (from 2.1 ± 1.2 to 2.3 ± 1.1, Table 1 and Figure 1).

Figure 2 shows trend of the antihypertensive drug classes used during this period. The use of angiotensin II receptor antagonists (ARBs) was significantly higher in 2012 than in 2007. The achievement rate of target BP in subgroups in 2012 is shown in Figure 3. Approximately 70% of elderly patients achieved goal BP (<140/90 mmHg). However, the achievement rate of target BP in young/middle-aged patients (<130/85 mmHg) and in patients with DM/CKD/MI (<130/80 mmHg) was <40%. The average number of antihypertensive drugs in 2012 was 2.3 ± 1.1 for elderly patients, 2.3 ± 1.1 for young/middle patients and 2.4 ± 1.1 for patients with DM/CKD/MI.

Table 2 shows the characteristics of patients with good BP control (CBP < 140/90 mmHg) and those with uncontrolled BP (CBP ≥ 140/90 mmHg) in 2012. No significant

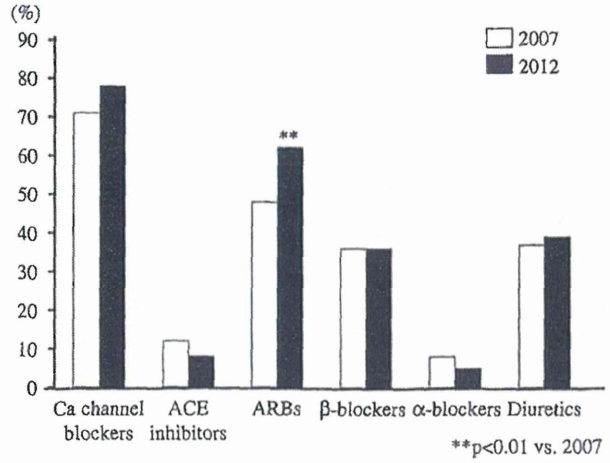

Figure 2. Use of antihypertensive drugs in 2007 and 2012. ACE, angiotensin converting enzyme; ARBs, angiotensin II receptor antagonists.

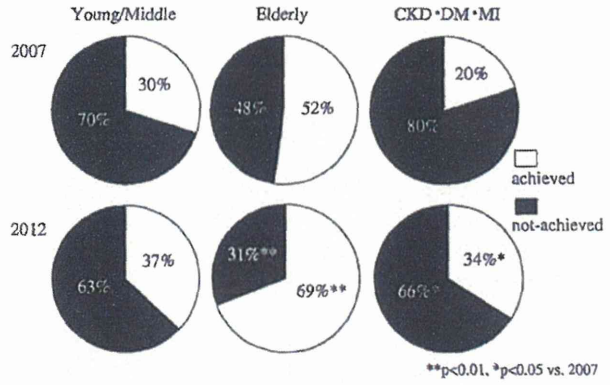

Figure 3. Blood pressure control status in young/middle-aged patients, elderly patients, and patients with DM/CKD/MI in 2012. DM, diabetes mellitus; CKD, chronic kidney disease; MI, myocardial infarction.

differences were observed in the number of antihypertensive drugs or urinary salt excretion between the two groups. However, average clinic SBP of the uncontrolled patients was significantly higher than that of patients with good BP control in 2007. In addition, uncontrolled patients were more likely to be women and had a lower prevalence of habitual alcohol intake than that of patients with good BP control.

In all patients with HBP measurement, CBP and morning HBP in 2007 were $137 \pm 12/80 \pm 9$ and $132 \pm 8/80 \pm 8$ mmHg, which significantly decreased to $132 \pm 12/75 \pm 8$ and $130 \pm 7/76 \pm 7$ mmHg in 2012, respectively ($p < 0.01$, Table 1). Figure 4 shows the distribution of patients according to the BP category based on CBP and HBP in 2007 and 2012. The prevalences of masked hypertension and white coat hypertension in 2007 were 22% and 15%, respectively. The percentage of patients with sustained hypertension significantly decreased from 27% in 2007 to 16% in 2012, while that of patients with white coat hypertension significantly increased during this period. CBP of patients with sustained hypertension decreased significantly from $153 \pm 8/82 \pm 10$ mmHg in 2007 to $144 \pm 13/77 \pm 9$ mmHg in 2012. Similarly, CBP of patients with normotension decreased

Table 2. Clinical characteristics of patients with good BP control (clinic BP < 140/90 mmHg) and uncontrolled BP in 2012.

	Controlled patients	Uncontrolled patients
Number of patients	149	59
Age in 2012 (years)	70 ± 11	71 ± 13
Men (%)	58	21**
Body mass index in 2012 (kg/m^2)	24 ± 3	23 ± 4
Average clinic SBP in 2007 (mmHg)	133 ± 11	146 ± 10**
Average clinic SBP in 2012 (mmHg)	127 ± 8	146 ± 8**
Average clinic DBP in 2007 (mmHg)	80 ± 8	81 ± 10
Average clinic DBP in 2012 (mmHg)	75 ± 7	79 ± 9**
Number of antihypertensive drugs in 2007	2.1 ± 1.1	2.1 ± 1.2
Number of antihypertensive drugs in 2012	2.3 ± 1.1	2.3 ± 1.1
Urinary salt excretion in 2007 (g/day)	9.0 ± 2.4	8.9 ± 2.4
Urinary salt excretion in 2012 (g/day)	9.1 ± 2.5	8.8 ± 2.7
Prevalence of habitual alcohol intake (%)	35.4	19.7*
Diabetes mellitus (%)	16.3	6.6
Chronic kidney disease (%)	55.8	50.8

Values are means ± SD.
*$p < 0.05$.
**$p < 0.01$ versus controlled patients.

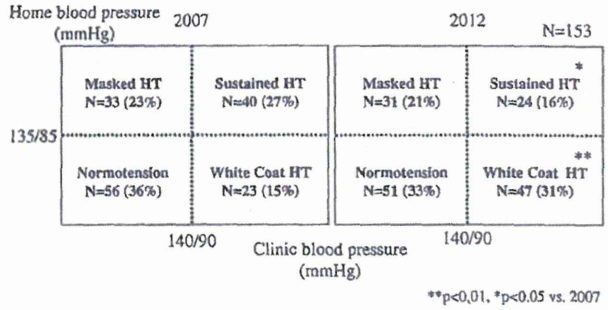

Figure 4. Distribution of patients according to the blood pressure category based on clinic and home blood pressure in 2007 and 2012. HT, hypertension.

from $125 \pm 7/76 \pm 6$ mmHg in 2007 to $122 \pm 7/72 \pm 7$ mmHg in 2012.

Discussion

In the present study, the average office and home BP of treated hypertensive patients significantly decreased and patients with good BP control increased during the past 5 years. Intensive antihypertensive therapy and low target BP as advocated by the guidelines may have contributed to the increase in the control rate of CBP as well as HBP in the present study. The JSH 2009 guidelines proposed the target HBP as <135/85 mmHg for elderly patients, <125/80 mmHg for young/middle-aged patients and <125/75 mmHg for patients with DM, CKD or myocardial infarction (MI) (7). No such proposal was made in the previous JSH 2004 guidelines (19). Regarding CBP, both guidelines proposed the target BP to be <140/90 mmHg for elderly patients, <130/85 mmHg for young/middle-aged patients and <130/80 mmHg for patients with DM or CKD. The JSH 2009, but not the JSH 2004 guidelines proposed the target CBP to be <130/80 mmHg for patients with prior MI.

The decrease in BP and increase in the control rate in this study appeared to have been due to intensive pharmacological

therapy because the number of antihypertensive drugs increased significantly in 2012. The use of ARBs increased significantly, while that of calcium channel blockers and diuretics increased slightly during the 5 years. Although the dose of antihypertensive agents and time of administration may be involved in the change in BP control status observed, we did not analyze these in this study.

However, the achievement rate of target BP in patients with DM/CKD/MI and in young/middle-aged patients was still low in 2012. We previously reported that BP control in patients with DM/CKD/MI was poor (10,11). The poor achievement rate in these patients appears to be attributed to their low BP target because the use of antihypertensive drugs and the level of BP were not significantly different from those of patients without such complications. Nonetheless, more aggressive antihypertensive therapies may be needed in patients with DM/CKD/MI and in young/middle-aged patients.

A comparison of patients with controlled CBP (<140/90 mmHg) and uncontrolled CBP (≥140/90 mmHg) revealed that the uncontrolled patients in 2012 also had higher BP in 2007 than the controlled patients. The number of antihypertensive drugs, urinary salt excretion and body weight were not significantly different between the two groups. Therefore, pharmacological therapies should be intensified for uncontrolled patients unless HBP is well controlled. Since the hypotensive effect of salt restriction and reductions in body weight have been established (23,27), comprehensive lifestyle modifications may also help to improve BP control. In addition, uncontrolled patients were more likely to be women and had a lower prevalence of habitual alcohol intake than that of patients with good BP control in the present study. It may in part reflect the physicians' awareness of the importance of strict BP control in man, because man seems to have higher risk factor than woman. Furthermore, we defined alcohol intake everyday as habitual alcohol intake, however, we have not assessed "amount" and "history" of alcohol intake.

We evaluated salt intake from spot urine samples using a calculation formula incorporating the estimated 24-h urinary Cr excretion based on age, height and body weight (26). This method is recommended in the Report of the Working Group for Dietary Salt Reduction of the JSH (28). As awareness of salt restriction has not been associated with actual salt restriction in hypertensive patients (29), an assessment of actual salt intake in individual patients is important for the management of hypertension. In the present study, urinary salt excretion in 2012 was similar to that in 2007; therefore, the reduction in BP during the 5 years was not attributed to changes in salt intake. However, although the average estimated salt intake was 9.0 g/day, which was lower than that consumed by the general Japanese population, it was still higher than the recommended amount (<6 g/day) for the management of hypertension (7). More attention and effort are needed to further reduce salt intake.

The control of HBP appears to be very important for the management of hypertension because it is more closely associated with hypertensive target organ damage and cardiovascular morbidity and mortality than CBP (14–18). Sustained hypertension and masked hypertension in treated hypertensive patients were also shown to have more advanced organ damage and a poorer prognosis than those with controlled hypertension or white coat hypertension (15,30). In the present study, the level of HBP and proportion of sustained hypertension decreased significantly in 2012. These changes may be attributed to the proposal of a target HBP level by the JSH 2009 guidelines in which the target HBP is lower than the target CBP by 5/5 mmHg (7). Although the target level of HBP was not based on the results of clinical trials, a recent clinical trial demonstrated that lower achieved HBP was associated with better cardiovascular outcomes (31).

The limitation of our study is that we assessed 24-h sodium excretion by using one-spot urine samples in the present study. This method is recommended in the Report of the Working Group for Dietary Salt Reduction of the JSH, because the reliability of spot urine samples is improved using a calculation formula incorporating the estimated 24-h urinary Cr excretion based on age, height and body weight. However, one measurement does not necessarily reflect everyday eating habits, because there is a circadian rhythm in urinary sodium excretion and the influence of a meal is not avoided. Another limitation is that doctors may change the prescription during the years, however, CBP values of all visits of each year were averaged. The average value of many measured value induced smaller BP variability and it seems to be easy to compare BP of each year, because BP has a seasonal variation.

In conclusion, office and home BP decreased and BP control rate increased during the past 5 years in treated hypertensive patients. Intensive pharmacological treatment, but not changes in salt intake contributed to improved BP control. Lifestyle modifications including salt restriction or reductions in body weight as well as intensive antihypertensive treatment are needed in order to achieve more strict BP control.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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BMJ Open

A randomised controlled trial for the evaluation of risk for type 2 diabetes in hypertensive patients receiving thiazide diuretics: Diuretics In the Management of Essential hypertension (DIME) study

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ABSTRACT

Objectives: Thiazide diuretics are one of the first choice antihypertensives but not optimally utilised because of concerns regarding their adverse effects on glucose metabolism. The Diuretics In the Management of Essential hypertension (DIME) study was designed, for the first time, to assess the risk for type 2 diabetes mellitus in patients with essential hypertension during antihypertensive treatment with low-dose thiazide diuretics compared to those not treated with diuretics.

Design: Multicentre, unblinded, pragmatic, randomised, controlled trial with blinded assessment of end points and intention-to-treat analysis that was started in 2004 and finished in 2012.

Setting: Hypertension clinics at 106 sites in Japan, including general practitioners' offices and teaching hospitals.

Participants: Non-diabetic patients with essential hypertension.

Interventions: Antihypertensive treatment with low-dose thiazide diuretics at 12.5 mg/day of hydrochlorothiazide or equivalent (Diuretics group) or that without thiazide diuretics (No-diuretics group).

Main outcome: The primary outcome was new onset of type 2 diabetes diagnosed according to WHO criteria and the criteria of Japanese Society of Diabetes.

Results: 1130 patients were allocated to Diuretics (n=544) or No-diuretics group (n=586). Complete end point information was collected for 1049 participants after a median follow-up of 4.4 years. Diabetes developed in 25 (4.6%) participants in the Diuretics group, as compared with 29 (4.9%) in the No-diuretics group (HR 0.93; 95% CI 0.55 to 1.58; p=0.800).

Conclusions: Antihypertensive treatment with thiazide diuretics at low doses may not be associated with an increased risk for new onset of type 2 diabetes. This result might suggest safety of use of low doses of thiazide diuretics.

Trial registration number: ClinicalTrials.gov NCT00131846.

Strengths and limitations of this study

- This is one of very few randomised controlled trials that assessed effects of low dose thiazide diuretics on risk for type 2 diabetes.
- The main strengths of our trial are that our results might suggest safety of antihypertensive treatment with low dose thiazide diuretics.
- The limitation of our study is insufficient statistical power for equivalency of the primary endpoint.

INTRODUCTION

Antihypertensive treatment with thiazide diuretics effectively reduces cardiovascular risk in hypertensive patients[1–4] and there has been evidence to suggest no inferiority when compared to 'newer' antihypertensive drugs.[5] However, concern remains regarding adverse effects of diuretics on glucose metabolism and the prognostic implications of such effects on cardiovascular events.[6 7]

The diabetogenic effect of diuretics seems to be taken for granted. In fact, in addition to results from a large cohort study,[8] a recent network meta-analysis conclusively showed a higher risk for new onset of type 2 diabetes in patients receiving thiazide diuretics than in those receiving calcium antagonists, ACE inhibitors, angiotensin receptor blockers (ARB) or placebo.[9] It is of note, however, that relatively high doses of thiazide diuretics (25 mg of hydrochlorothiazide equivalent or more) were used mainly with β-blockers in most studies included in this meta-analysis. Antihypertensive treatment with diuretics in this way is no longer relevant to current antihypertensive therapeutic practice. Thiazide

diuretics are currently used at relatively low doses, more likely in combination with inhibitors of the renin-angiotensin system (RAS) and calcium antagonists, according to the clinical background of the patient, rather than as a single agent with dose titration. Therefore, there is a need for assessment of the metabolic effects of treatment with low-dose diuretics rather than of those of diuretics per se. In addition, from the methodological point of view, as no study thus far has assessed the diabetogenic effect of diuretics as the primary end point, this study is being done to fill that gap.

Although there is no universal agreement that thiazide diuretics are the first-choice antihypertensive drug, evidence from clinical trials in 'salt sensitive' patients, such as ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial),[5] and pathophysiological considerations regarding salt intake and blood pressure control, suggest that appropriate use of thiazide diuretics is undoubtedly necessary for a large subpopulation of hypertensive patients.

This study of Japanese patients with essential hypertension was performed to assess the hypothesis that antihypertensive treatment with low-dose thiazide diuretics may not be associated with a higher risk for new onset of type 2 diabetes and other metabolic abnormalities compared to treatment of such patients without diuretics.

METHODS

Trial design

This was an independent, investigator-initiated, multicentre, pragmatic, randomised, open, blinded-end point, parallel group study conducted in Japan (NCT00131846).

Study setting

This study was conducted in Japan at hypertension clinics of 106 sites including general practitioners' offices (n=61) and teaching hospitals (n=45). All members of committees for this Diuretics In the Management of Essential hypertension (DIME) study and the DIME investigators who participated in the study settings, data collection and management are listed in the online supplementary appendix.

Participant

Patients were eligible if they were aged 30–79 years at randomisation, and had either untreated hypertension with systolic blood pressure of 150 mm Hg or more, diastolic blood pressure of 90 mm Hg or more, or both; or treated hypertension with systolic blood pressure of 140 mm Hg or more, diastolic blood pressure 90 mm Hg or more, or both. Patients were excluded if they had type 2 diabetes, gout, systolic blood pressure of 200 mm Hg or more, diastolic blood pressure of 120 mm Hg or more, hypokalaemia (<3.5 mmol/L), erectile dysfunction, renal dysfunction (serum creatinine levels of 2.0 mg/dL or more), history of stroke or myocardial infarction within 3 months, history of revascularisation of coronary arteries within 6 months, heart failure or left ventricular dysfunction (ejection fraction <40%), history of serious adverse reaction to thiazide diuretics, or history of malignant tumour within 5 years. Patients who were pregnant, breastfeeding, already on thiazide treatment or on any antihypertensive treatment if the duration of treatment and drugs used were not identified, and those deemed not eligible for this study for any other reason, were also excluded.

Assignment to study treatment

Eligible patients were randomly assigned to receive thiazide diuretics at a low dose that was defined as 12.5 mg/day of hydrochlorothiazide, 1 mg/day of indapamide or 1 mg/day of trichloromethiazide along with any other antihypertensive drugs as required to achieve target blood pressure (<140/<90 mm Hg) (Diuretics group) or receive any antihypertensive drugs other than thiazide diuretics to achieve target blood pressure (<140/<90 mm Hg) (No-diuretics group) by minimisation method[10 11] with assignment factors being impaired fasting glycaemia (fasting blood glucose ≥110 mg/dL or <110 mg/dL), family history of type 2 diabetes mellitus and body mass index (≥25 or <25 kg/m^2) and region of trial sites.

Concealment of assignment

We developed a web-based minimisation system that was controlled by the data centre and effectively concealed the assignment sequence from investigators assessing and recruiting patients.

Follow-up schedule

Patients regularly visited their outpatient clinic monthly or bimonthly. Sitting blood pressure, heart rate and plasma concentrations of fasting glucose, creatinine, uric acid, potassium and sodium were measured and recorded every 6 months. Glycated haemoglobin (HbA1c) and lipid profiles were measured yearly.

End points and outcome measure

The primary end point of DIME study was new onset of type 2 diabetes mellitus. The secondary end points were all-cause mortality, ischaemic and haemorrhagic strokes excluding transient ischaemic attacks and secondary causes, myocardial infarction, hospitalisation due to heart failure, gout, treatment-resistant hypokalaemia and peripheral artery disease including arteriosclerosis obliterans (ASO), aortic aneurysm, blood pressure, lipid profiles, HbA1c, fasting blood glucose and direct cost.

Investigators submitted all information relevant to any of the potential end points to the data centre for review by the end point committee, who were blinded to the treatment assignment. We collected data continuously even after patients suffered a non-fatal secondary end point in order to assess whether onset of diabetes

occurs. Diagnostic criteria for each end point were defined a priori and were used by the end point committee. Briefly, diagnosis of the primary end point was made according to WHO criteria 1998[12] and the criteria of the Japanese Diabetes Society[13] based on the results from regular assessment of blood glucose. Gout was diagnosed according to the American College of Rheumatology 1977 criteria C.[14] Treatment-resistant hypokalaemia was defined as continuous hypokalaemia (<3.5 mmol/L) even after the addition of potassium-sparing drugs or potassium supplementation in patients without any evidence of secondary hypertension. Diagnosis of stroke, myocardial infarction or heart failure was made by WHO MONICA Project diagnostic criteria,[15] AHA Scientific Statement 2003[16] or diagnostic criteria of the Framingham study,[17] respectively. Renal dysfunction was defined as doubling of serum creatinine concentrations, of 4 mg/dL or more, or progression to end-stage renal disease (renal transplantation or haemodialysis). Dissection of aortic aneurysm was diagnosed by medical history, symptoms and imaging. Deterioration of ASO was defined according to the Fontaine classification.[18]

Statistical analyses

Sample size

The trial was designed as an equivalence trial, which was powered for equivalence of Diuretics to No-diuretics group on the primary end point. With the assumption of 5.5% of occurrence of type 2 diabetes among Diuretics and No-diuretics groups for 4 years based on the previous reports,[19 20] 955 patients per group would yield 90% power to detect equivalence with an equivalence margin of 3% at a level of two-sided type 1 error of 0.05 in one group. We also calculated that 713 patients per group would yield 80% power. Thus, a total of 2400 and 1800 patients as the total sample size were to be enrolled, accommodating a possible 20% dropout during the follow-up period, in order to provide 90% and 80% power, respectively.

Evaluation of effects of antihypertensive treatment with low-dose thiazide diuretics

Continuous variables were expressed as mean±SD or median with IQR. Continuous variables were compared using the Student t test or Wilcoxon rank-sum test based on their distributions. Clinical outcomes were analysed according to the intention-to-treat principle. Each end point was assessed by the Kaplan-Meier method and compared by the log-rank test. Time-to-events analysis of the primary end point should be justified because of regular assessment of glucose with short intervals. Effect of treatment was compared by the Cox proportional hazard model, and was expressed by HR with 95% CI. Comparison was also made with the adjustment by assignment factors. As a sensitivity analysis, we compared incidence of diabetes diagnosed by WHO criteria only between the groups. Treatment effect was evaluated in several prespecified subgroups, including stratified variables, concomitant antihypertensives and dose of diuretics as a subgroup analysis. In addition, we also performed on-treatment analysis to assure results from intention-to treat analysis. No-diuretics group was defined as patients receiving no diuretics throughout the study period and diuretics group was defined as patients receiving diuretics at the end of the observation period irrespective of allocated treatment. The study statistician conducted all statistical analyses with the use of JMP V.8.0 and SAS V.9.3 (SAS Institute Inc, Cary, North Carolina, USA). All reported p values were two-sided with the significance level set at α=0.05.

RESULTS

The recruitment of patients was started on 5 April 2004 and terminated on 7 February 2012 despite insufficient statistical power at that point because the steering committee thought that further extension would not promote the enrolment of patients. The follow-up was then terminated at the end of August 2012. We did not conduct interim analyses because of insufficient enrolment of patients. 1130 patients were randomised (figure 1). Randomised patients were similar between groups with regard to demographic and clinical characteristics (table 1). Complete end point information was collected at the end of the study for 1049 (92.9%) participants after a median follow-up of 4.4 years (figure 1). Twenty-five (2.2%) patients withdrew consent and 56 (4.9%) were lost to follow-up. At the end of follow-up, 75% of participants randomly assigned to Diuretic group were still taking thiazide diuretics and 6% of participants assigned to No-diuretics group were taking thiazide diuretics. Approximately 80% of patients received RAS inhibitors and approximately 20% of them received β-blockers in Diuretics and No-diuretics groups at the end of follow-up period (table 2).

The primary end point and glucose-related outcome

The primary end point of new onset of type 2 diabetes did not differ significantly between the groups (figure 2). During the study, diabetes developed in 25 (4.6%) participants in the Diuretics group, as compared with 29 (4.9%) in the No-diuretics group (HR 0.93; 95% CI 0.54 to 1.59; log-rank test: p=0.800). Actual statistical power became 60%. Comparison by the Cox proportional hazard model with the adjustment by assignment variables showed similar results (HR 0.91; 95% CI 0.53 to 1.58; p=0.741). The incidence of diabetes was 19 in No-diuretics and 19 in Diuretics groups when diagnosed according to WHO criteria only. There was no significant difference between the groups (HR 1.07, 95% CI 0.56 to 2.03, p=0.8438). Although statistically underpowered, subgroup analysis did not identify any factors interacting with effects of use of diuretics on development of diabetes (figure 3). On treatment analysis there was no significant difference in incidence of type 2 diabetes

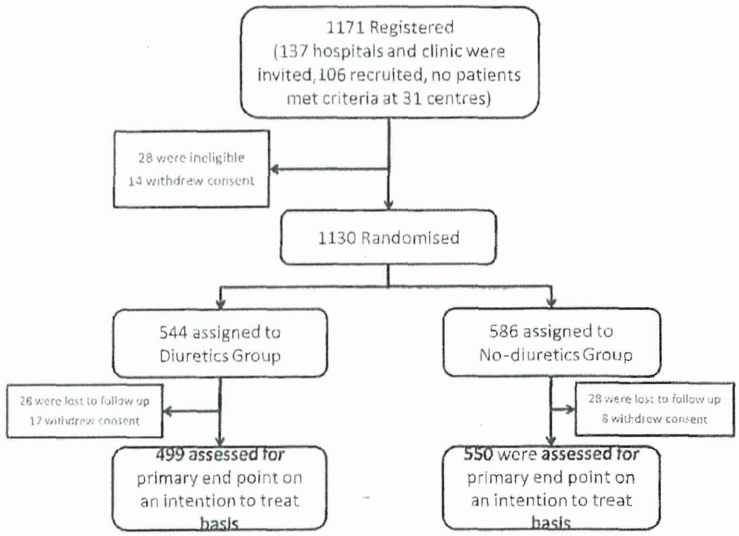

Figure 1 Enrolment, randomisation and follow-up of study participants.

between No-diuretics and Diuretics groups (HR 1.21; 95% CI 0.70 to 2.06; p=0.489).

Averaged fasting plasma glucose concentrations and HbA1c levels overtime and at the end of follow-up period are shown in figure 4 and table 3, respectively. Levels of fasting glucose or HbA1c in the Diuretics group throughout the study were not significantly higher than those in the No-diuretics group.

Secondary end points

There were no apparent differences between the groups in measured secondary end point including gout, treatment resistant hypokalaemia, death and cardiovascular events (table 4). Averaged serum potassium concentrations overtime and at the end of follow-up period were shown in figure 5A and table 3, respectively. At 0.5, 1, 1.5, 2 and 2.5 years and at the end of follow-up period,

Table 1 Baseline characteristics of participants

	Diuretics group (n=544)	No-diuretics group (n=586)
Men (%)	269 (49.4)	281 (48.0)
Age (years)	63 (10)	63 (10)
Body weight (kg)	62 (12)	63 (12)
Body mass index (kg/m^2)	24.6 (3.5)	25.3 (4.1)
On drug treatment (%)	461 (84.7)	507 (86.5)
Positive family history of type 2 diabetes (%)	88 (16.1)	78 (13.2)
History of stroke (%)	11 (1.9)	20 (3.4)
History of myocardial infarction (%)	10 (1.8)	11 (1.9)
History of peripheral arterial disease (%)	2 (0.4)	5 (0.9)
Left ventricular hypertrophy (%)	73 (13.4)	61 (10.4)
Alcohol intake (+) (%)	256 (47.1)	267 (45.6)
Current smoker (%)	84 (15.4)	86 (14.7)
Systolic BP (mm Hg)	154 (11)	154 (10)
Diastolic BP (mm Hg)	88 (10)	88 (10)
Pulse rate (bpm)	74 (11)	75 (11)
Fasting plasma glucose (mg/dL)	99 (11)	100 (10)
HbA1c (%)	5.3 (0.4)	5.3 (0.4)
Uric acid (mg/dL)	5.5 (1.3)	5.6 (1.2)
K (mmol/L)	4.2 (0.4)	4.2 (0.4)
Na (mmol/L)	141 (2)	141 (3)
eGFR (mL/min/1.73 m^2)	73.7 (15.5)	74.0 (16.0)
Total cholesterol (mg/dL)	207 (32)	204 (33)
HDL cholesterol (mg/dL)	60 (18)	59 (17)
Triglyceride (mg/dL)	137 (94)	136 (84)

Data are mean (SD) or number (%).
SI conversion factors: To convert total and HDL cholesterol and triglyceride to mmol/L, multiply values by 0.0259 and 0.0113, respectively. To convert glucose and uric acid to mmol/L and μmol/L, multiply values by 0.0555 and 59.48, respectively.
BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein.

Table 2 Concurrent drug treatment at the baseline and the end of follow-up

	At the baseline after randomisation		At the end of follow-up	
	Diuretics group (n=544)	No-diuretics group (n=586)	Diuretics group (n=504)	No-diuretics group (n=565)
Thiazide diuretics	518 (98.9)	0 (0)	379 (75.2)	32 (5.7)
ACE inhibitors	53 (10.1)	86 (14.9)	42 (8.3)	70 (12.4)
ARB	292 (55.7)	388 (67.0)	349 (69.3)	377 (66.7)
Ca antagonist	284 (54.2)	437 (75.5)	313 (62.1)	436 (77.2)
β-blocker	99 (18.9)	132 (22.8)	107 (21)	132 (23)
α-blocker	12 (2.3)	34 (5.9)	18 (3.6)	30 (5.3)
Anti-aldosterone	6 (1.2)	13 (2.3)	23 (4.6)	31 (5.5)
Others	1 (0.2)	1 (0.2)	2 (0.4)	4 (0.7)
Statins	140 (26.7)	141 (24.4)	188 (37.3)	211 (37.4)
Antiplatelet	80 (15.3)	73 (12.6)	87 (17.3)	82 (14.5)
K supplement	0 (0)	0 (0)	1 (0.2)	2 (0.4)
Drugs for hyperuricaemia	34 (6.5)	36 (6.2)	58 (11.5)	51 (9.0)

Data are number (%).
ARB, angiotensin receptor blocker.

serum potassium levels were very slightly but significantly lower by 0.1 mmol/L in the Diuretics group than those in the No-diuretics group. Serum sodium levels at the end of follow-up period were also slightly but significantly lower by <1 mmol/L in the Diuretics group than those in No-diuretics group (table 3). Averaged serum uric acid concentrations overtime and at the end of follow-up period were shown in figure 5B and table 3, respectively. From 0.5 to 4.5 years during the study period and at the end of follow-up period, serum uric acid levels were significantly higher in the Diuretics group than those in the No-diuretics group. There were no significant differences in estimated glomerular filtration rate and lipid profile between the groups (table 3).

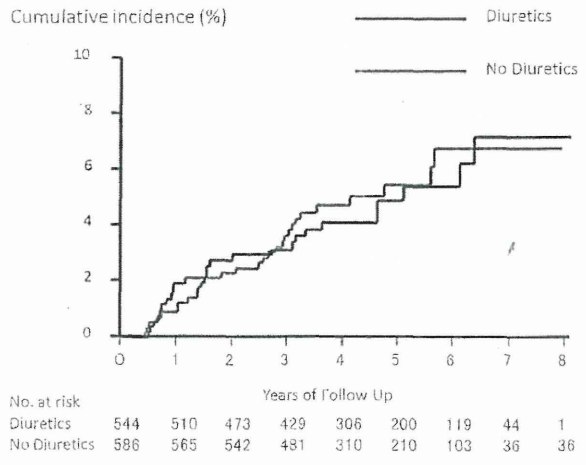

Figure 2 Kaplan–Meier curves of cumulative incidence of type 2 diabetes.

Blood pressure

There was no significant difference in blood pressure between the groups during the study or at the end of follow-up period (figure 6 and table 3).

DISCUSSION

We demonstrate that the incidence of type 2 diabetes was not higher in our Japanese patients with essential hypertension receiving antihypertensive treatment with low-dose thiazide diuretics compared to those treated without diuretics although statistically underpowered for equivalency. Consistency between intention-to-treat analysis and on-treatment analysis might assure our conclusion. A lack of adverse effects of low-dose diuretics on glucose metabolism, represented by fasting glucose levels and HbA1c (which were consistent with the incidence of diabetes), was also demonstrated.

Unlike our results, a recent meta-analysis of 22 clinical trials showed that diuretics use was associated with a greater risk of new onset of diabetes compared to other antihypertensive drugs and placebo in hypertensive patients.[6] We assume that differences in the dose of diuretics used, concurrent antihypertensive drugs used with diuretics and the study design may explain different results regarding incidence of diabetes. Doses of thiazide diuretics in most studies included in the meta-analysis by Elliot and Meyer were higher (25 mg of hydrochlorothiazide or more) than those used in the current study. Similarly, although Bakris *et al*[21] showed that the fixed combination of losartan and hydrochlorothiazide impaired glucose tolerance in hypertensive patients with metabolic syndrome, the dose of this combination was titrated to 100 mg of losartan and 25 mg of hydrochlorothiazide in approximately 80% of patients. As Carlsen *et al*[22] showed previously, there is a clear relationship between dose of thiazide diuretics and effect on glucose,