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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

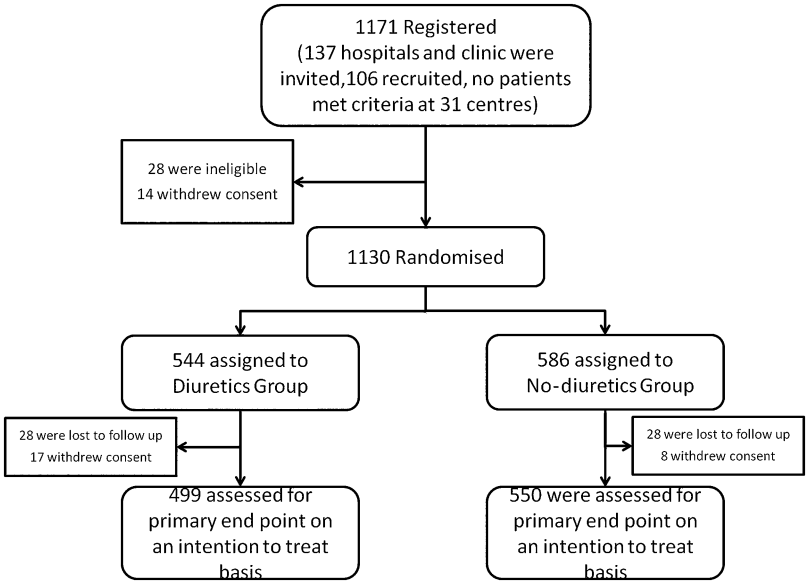

Figure 1 Enrolment, randomisation and follow-up of study participants.

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).

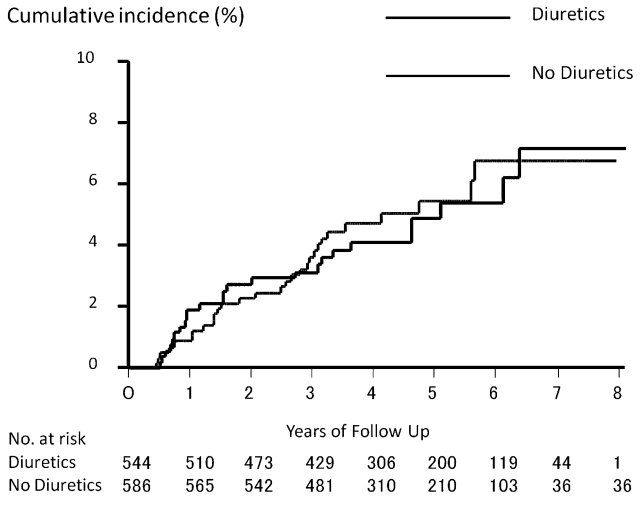

Figure 2 Kaplan–Meier curves of cumulative incidence of type 2 diabetes.

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,

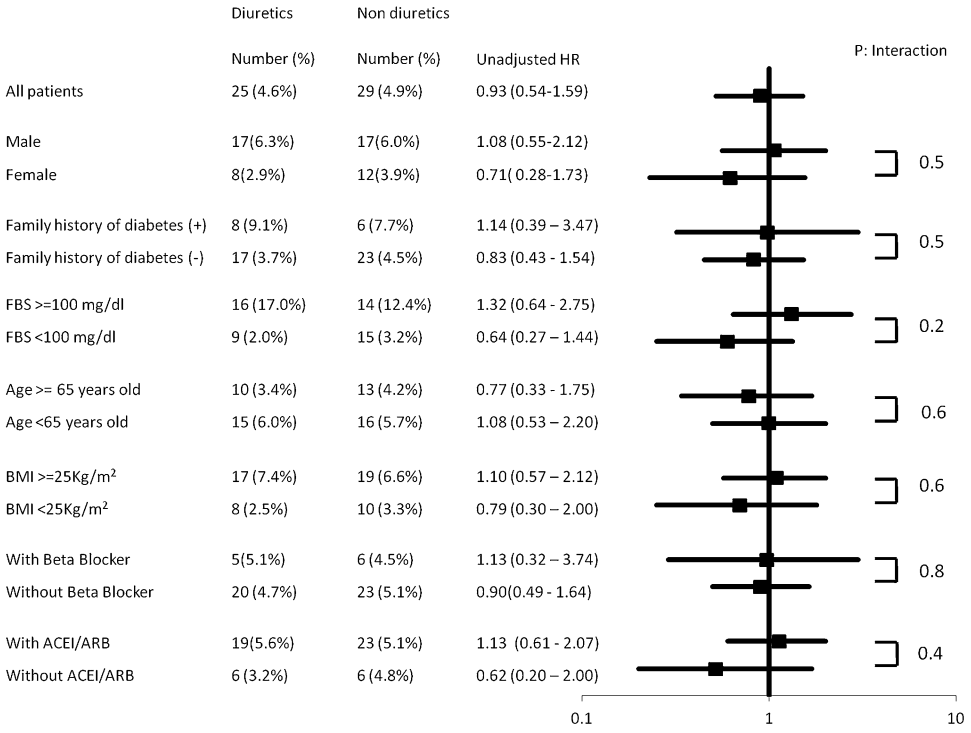

Figure 3 Effects of diuretics use on risk of new onset of diabetes according to the baseline characteristics. FBS, fasting blood sugar; BMI, body mass index; ACEI/ARB, ACE inhibitor or angiotensin receptor blocker.

potassium and uric acid but not blood pressure. Results from our study suggest that treatment with diuretics at the dose of 12.5 mg of hydrochlorothiazide equivalent may not increase the risk for new onset of diabetes; that is, the diabetogenic effect of thiazide diuretics may also be dose dependent. One might claim that there is no evidence to support that diuretics at the doses used in this study reduce cardiovascular events. However, improved cardiovascular outcome can be expected as long as target blood pressure is achieved by a combination of drugs including thiazide diuretics even at low doses (12.5 mg of hydrochlorothiazide or equivalent).

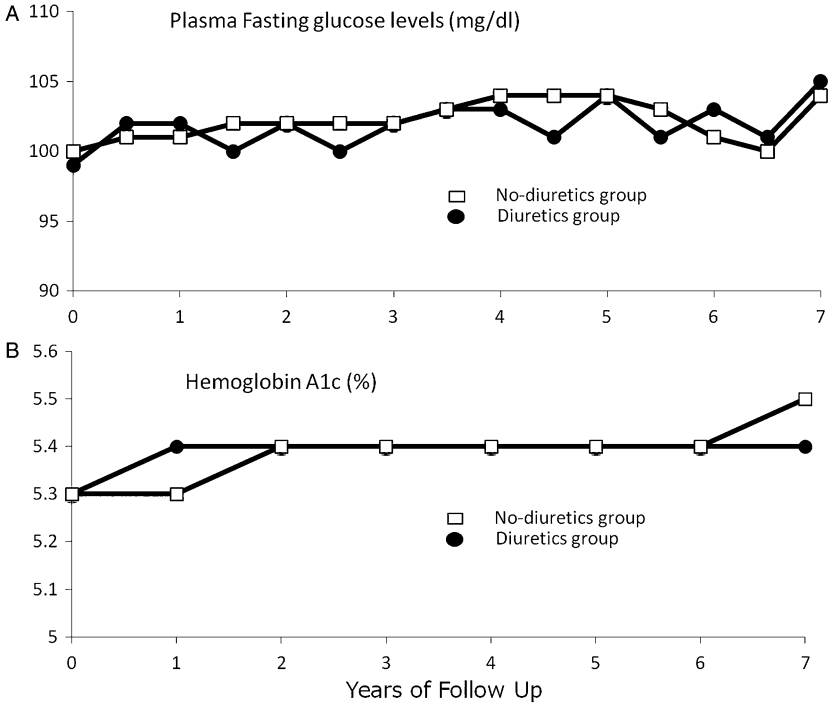

Figure 4 Plasma fasting glucose (A) and glycated hemoglobin (B) over time by groups.

Table 3 Blood pressure, glucose, uric acid, electrolytes, renal function and lipid profile at the end of follow-up

	Diuretics group (n=544)	No-diuretics group (n=586)	p Value
Systolic BP (mm Hg)	135 (16)	135 (15)	0.900
Diastolic BP (mm Hg)	78 (11)	77 (11)	0.800
Pulse rate (bpm)	73 (11)	73 (11)	0.998
Fasting glucose (mg/dL)	102 (14)	103 (16)	0.423
HbA1c (%)	5.4 (0.4)	5.4 (0.4)	0.194
Uric acid (mg/dL)	5.8 (1.4)	5.6 (1.3)	0.044
K (mmol/L)	4.1 (0.4)	4.2 (0.4)	0.005
Na (mmol/L)	140.7 (2.4)	141.0 (2.2)	0.038
eGFR (mL/min/1.73 m^2)	68.8 (16.7)	69.6 (16.4)	0.448
Total cholesterol (mg/dL)	197 (32)	197 (33)	0.828
HDL cholesterol (mg/dL)	59 (16)	59 (16)	0.492
Triglyceride (mg/dL)	138 (104)	131 (71)	0.201

Data are mean (SD). p Values indicate statistical difference between groups.
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.

It is of note that almost 80% of patients in the Diuretic Use group of our study used inhibitors of RAS, while β-blockers were the main combination drug with diuretics in most studies included in the meta-analysis such as ALLHAT study.[5] The combination of diuretics and inhibitors of RAS is common in current clinical practice and appears to be associated with a lesser risk of diabetes compared to the combination with a β-blocker, as shown by the LIFE (Losartan Intervention For End point reduction in hypertension) study.[23] Therefore, it can be assumed that current therapeutic strategy with diuretics at low doses mostly combined with RAS inhibitors does not carry a high risk for diabetes. However, we could not show clear interactions of concurrent drugs (β-blockers and RAS inhibitors) and the risk for diabetes in subgroup analysis, largely because the study was underpowered. Recently, subanalysis of the NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research) study demonstrated that use of diuretics was associated with excess risk for type 2 diabetes.[24] There is, however, limitation in the interpretation of this result because use of diuretics was not randomised and the doses of diuretics were not as low as our study.

Table 4 Incidence of secondary end points

	Diuretics group (n=544)	No-diuretics group (n=586)
Gout	6 (1.2)	7 (1.3)
Treatment resistant hypokalaemia	2 (0.4)	1 (0.2)
Stroke	11 (2.2)	5 (1.1)
Myocardial infarction	2 (0.4)	5 (1.0)
Heart failure	2 (0.4)	6 (1.1)
Peripheral arterial disease	2 (0.4)	3 (0.5)
Renal dysfunction	1 (0.2)	1 (0.2)
Sudden death	0 (0.0)	1 (0.2)

Data are number (%).

Our study is, as far as we know, the first randomised, controlled trial to assess, as the primary end point, risk in essential hypertensive patients for new onset of diabetes associated with treatment by thiazide diuretics. Most studies showing a higher risk for diabetes from diuretics use were primarily designed to assess cardiovascular events as the primary end point, and new onset of diabetes was assessed by post hoc analysis or, at best, as a prespecified secondary end point.

The mechanisms responsible for the increased incidence of diabetes with use of thiazide diuretics at a high dose have not been fully elucidated. A recent quantitative review showed that thiazide-induced hypokalemia is associated with increased blood glucose.[25] In the current study, no clinically significant difference in averaged plasma potassium levels were seen during the observation period, which may be attributable to the low dose of diuretics and frequent use of RAS inhibitors, and may partly explain why no difference in the incidence of diabetes between the groups was found.

Serum uric acid levels during the study were significantly higher in the Diuretic group than were those in the No-diuretics group. This may suggest that elevation of uric acid cannot be avoided even by use of low dose with RAS inhibitors. However, the clinical significance of such a small elevation of uric acid is unclear, because treatment with diuretics did not increase the incidence of gout, which is consistent with results from another epidemiological study, in which no significant increase in risk for gout was seen with use of lower doses of diuretics (12.5 mg/day in hydrochlorothiazide equivalents).[26]

Limitation of our study

As we could not achieve the target sample size, our study is statistically underpowered for the assessment of

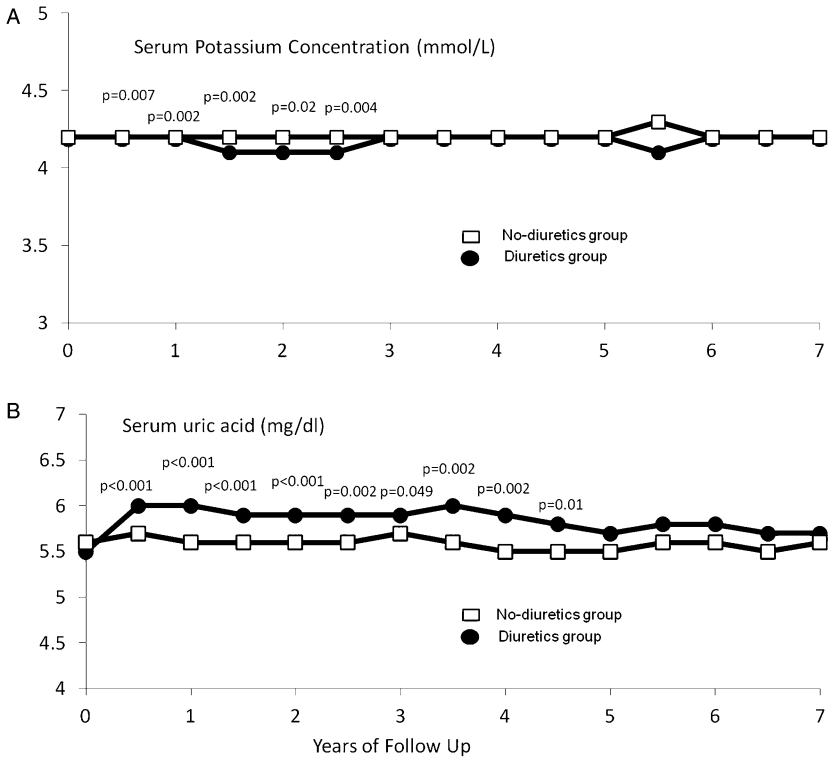

Figure 5 Serum potassium (A, *p=0.007, **p=0.002, †p=0.020, ††p=0.004) and uric acid (B, *p<0.0001, **p=0.0004, †p=0.0008, ††p=0.002, ¶p=0.049, §p=0.010) concentrations over time by treatment groups.

equivalency. Therefore we are able to state that we found no evidence of a difference in outcome, but not that the treatments were equivalent in terms of incidence of diabetes. We conducted a pragmatic trial for the assessment of effectiveness of treatment with low-dose diuretics but not the efficacy of the diuretics per se by using an unblinded study design without any prespecified therapeutic algorithm, which may have impaired internal validity to some extent partly because of clustering of antihypertensives or other drugs such as drugs for hyperuricaemia.

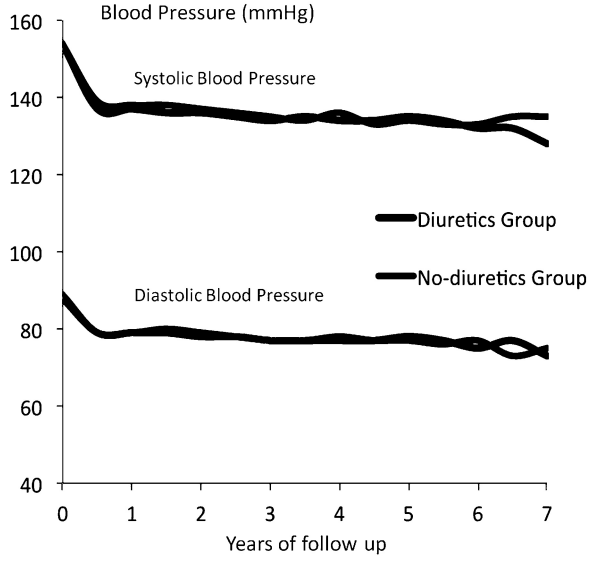

Figure 6 Blood pressure over time by treatment groups.

The ascertainment bias was much less likely even though it was an open study without placebo because we regularly assessed the incidence of diabetes for all patients. However, given that time course of development of type 2 diabetes is uncertain, validity of diagnosis of diabetes in trials such as ours is limited.

Conclusion

Results from the present randomised controlled trial suggest that current practice of antihypertensive treatment with thiazide diuretics at low doses may not be associated with increased risk for new onset of type 2 diabetes or other clinically significant metabolic abnormalities. These results might suggest safety of use of low doses of thiazide diuretics.

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Contributors TM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. SU, TM, S-iA, S-iT, YK, KS, TO and TS participated in development of the study protocol. SU, TM and S-iA supervised data collection and management. TM conducted the statistical analyses. SU led the writing of the report, which was co-led by TM and assisted by all other authors. While TM

had full access to all of the study data under the supervision of SU and other authors, SU and other authors could not assess the individual data. All authors assisted in interpretation of the data, and have seen and approved the final version of the report. SU is the guarantor.

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Patient consent Obtained.

Ethics approval The study was conducted in accord with the Declaration of Helsinki and the ethics guidelines for clinical research from the Ministry of Health, Labour and Welfare, Japan. The protocol and all subsequent amendments to the protocol were reviewed and accepted by the ethics committees of the University of the Ryukyus, as the central ethics committee, and by each site where this study was conducted.

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