Hypertension Research (2009) 32, 748–752

www.nature.com/hr

ORIGINAL ARTICLE

Effect of switching from amlodipine to combination therapy with telmisartan and low-dose hydrochlorothiazide

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One of the most effective pairs in combination therapy is that of an inhibitor of the renin–angiotensin system (RAS) and a low-dose thiazide diuretic. Possible candidates for this combination therapy are hypertensive patients with blood pressure (BP) that is not controlled by a calcium channel blocker (CCB). Thus, we characterized the antihypertensive effect of the combination of telmisartan and low-dose hydrochlorothiazide in patients with hypertension that was not controlled by amlodipine, which is the most common CCB. A total of 75 patients with BP levels higher than 140/90 mm Hg, treated with 5 mg per day of amlodipine for at least 3 months, were divided into groups that were switched to treatment with 40–80 mg per day of telmisartan plus 12.5 mg per day of hydrochlorothiazide (TH, n=37) or that were continuously treated with 5–7.5 mg per day of amlodipine (Am, n=38). After 12 weeks of treatment, the mean BP level was significantly lower in the TH group than in the Am group (decrease in BP: -9.9 ± 11.4 *vs.* -3.7 ± 8.9 mm Hg, $P<0.02$; normalization rate: 67.6 *vs.* 30.3%, $P<0.01$). Serum uric acid was slightly higher in the TH group, but other laboratory data were not different between groups. Therefore, it is suggested that the combination of a RAS inhibitor and a low-dose thiazide is useful if treatment with a CCB cannot control BP in patients with hypertension.
Hypertension Research (2009) **32,** 748–752; doi:10.1038/hr.2009.101; published online 10 July 2009

Keywords: angiotensin II type 1 receptor blocker; calcium channel blocker; combination therapy; thiazide diuretic

INTRODUCTION

Blood pressure (BP) control is important in preventing the progression of cardiovascular damage in hypertensive patients.[1] However, it is difficult for a single class of antihypertensive drugs to achieve effective BP reduction in a majority of hypertensive patients.[2,3] Therefore, combination therapies with two or more antihypertensive drugs are often required in the management of hypertension.[4,5] However, in Japan, many patients with uncontrolled BP only receive one class of antihypertensives,[6] although combination therapy is encouraged.

One of the best combinations is that of a renin–angiotensin system (RAS) inhibitor and a low-dose thiazide diuretic because effectiveness and safety have been proven for them.[7–9] In a retrospective study that was conducted in older women, treatment with a combination of an angiotensin-converting enzyme (ACE) inhibitor and a thiazide diuretic showed a decreased probability of mortality from cardiovascular disease.[10] Recent reports suggest that the combination of a RAS inhibitor and diuretic can be useful even in diabetic[11] and very old[12] patients. In the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial,[11] a combination of perindopril and indapamide significantly decreased BP levels and the primary end point (macroangiopathy and microangiopathy) relative to placebo without adverse metabolic effects in patients with type II diabetes mellitus. The HYVET (Hypertension in the Very Elderly Trial)[12] showed that the perindopril plus indapamide combination has advantages over placebo in hypertensive patients aged 80 years or more. Therefore, combination therapy including a RAS inhibitor and a diuretic is considered one of the most powerful antihypertensive strategies developed for preventing hypertension-induced cardiovascular injury in a wide range of hypertensive patients. In Japan, few clinical trials have examined combination treatment with a low-dose thiazide diuretic and a RAS inhibitor for the management of hypertension, chiefly because thiazide diuretics are not commonly used.[2] However, because the combination of diuretic and angiotensin II type 1 receptor blocker (ARB) drugs has recently become available, it is important to determine whether combination therapy with an ARB and a diuretic is useful in Japanese hypertensive patients who are resistant to a single class of antihypertensive other than a RAS inhibitor or a diuretic.

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Received 16 March 2009; revised 8 May 2009; accepted 25 May 2009; published online 10 July 2009

Calcium channel blockers (CCBs) are the most frequently used medication in Japan. However, a single dose of a CCB effectively decreases BP to $<140/90$ mm Hg in only $\sim$40% of patients with hypertension,[2] and an alternative or additional antihypertensive drug is required in the remaining 60% of patients. An ARB–thiazide diuretic combination drug therapy may be a candidate as an alternative antihypertensive to CCB because of its effectiveness. Therefore, we evaluated the effectiveness of switching from therapy with a CCB to combination with an ARB and a low-dose thiazide diuretic. As some investigators have reported that the antihypertensive effect of telmisartan plus hydrochlorothiazide was superior to that of losartan plus hydrochlorothiazide, the elements of a first generation combination drug in Japan,[13,14] we compared the effects of the treatment with telmisartan plus hydrochlorothiazide and continuous administration of amlodipine, which is the most popular CCB, in patients with uncontrolled BP undergoing treatment with 5 mg per day of amlodipine for $\geqslant$3 months.

METHODS

Participants

This study was carried out at the Tokyo University Hospital and a few other hospitals in Japan from June 2007 to May 2008. This study was approved by the Institutional Review Boards of The University of Tokyo Clinical Research Center and the other hospitals, and was undertaken in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

The enrollment criteria for hypertensive patients included: (1) outpatient systolic and diastolic BPs of more than 140/90 mm Hg; (2) treatment with 5 mg per day of amlodipine for $\geqslant$3 months; and (3) age between 20 and 80 years. Exclusion criteria were: (1) secondary hypertension, including a solitary kidney or bilateral renovascular hypertension; (2) taking antihypertensives other than amlodipine, including loop diuretics; (3) cerebro-reno-cardiovascular disease that had occurred within 6 months; (4) a serum creatinine level of >2.0 mg per 100 ml; (5) a BP level of more than 180/110 mm Hg; (6) class III or IV heart failure (NYHA (New York Heart Association) classification); (7) contraindication of telmisartan (hypersensitivity to telmisartan, pregnant women and severe liver damage) or hydrochlorothiazide (hypersensitivity to thiazide, anuria, acute renal failure and apparent decrease in body sodium or potassium levels); (8) hyperkalemia (>5.5 mequiv. l^{-1}) or hypokalemia (<3.5 mequiv. l^{-1}); (9) untreated (>7.0 mg per 100 ml) or uncontrolled (>8.0 mg per 100 ml with medication) hyperuricemia; and (10) uncontrolled diabetes mellitus (glycosylated hemoglobin A1c (HbA1c) $>9.0\%$) or hypoglycemia (<50 mg per 100 ml or hypoglycemic symptoms).

Interventions

The participants were randomly allocated to two groups, namely those whose treatment was switched to 40 mg per day of telmisartan plus 12.5 mg per day of hydrochlorothiazide (TH) or those who continued treatment with amlodipine (Am). Randomization was performed according to minimization methods on the basis of stratification of age, body mass index (BMI) and baseline BP. The target BP for the study was $<140/90$ mm Hg. BP levels were measured according to the Japanese Society of Hypertension Guidelines for Management of Hypertension.[11] If the treatment failed to reduce BP to the target level, telmisartan was increased to 80 mg per day in the TH group and amlodipine was increased to 7.5 mg per day in the Am group.

Outcome measures

The primary end point was change in office BP. In addition, we measured office pulse rate and BMI. The following laboratory findings were also measured: fasting blood glucose, fasting serum insulin, HbA1c, total serum cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, liver enzymes (γ-glutamine transferase, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase (ALP)), creatinine, blood urea nitrogen, uric acid and electrolytes (sodium (Na) and potassium (K)).

Statistical analysis

Data were analyzed according to randomized treatment assignments of participants, regardless of their subsequent medication status (intention-to-treat analysis). Data were presented as means $\pm$ s.d. The mean values in the two groups were compared using unpaired *t*-tests or χ^2-tests. ANOVA (analysis of variance) with repeated measurements was applied to test the effect of treatment on BP. Statistical significance was set at $P<0.05$.

RESULTS

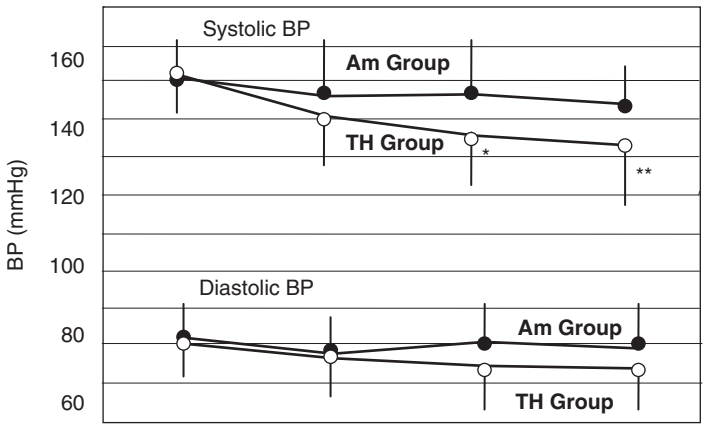
Study population

A total of 75 participants were enrolled in this study. They were allocated to either the TH group (n=37) or the Am group (n=38). Table 1 shows baseline characteristics of the participants in the two groups. Systolic (TH and Am groups: 151.5 ± 8.8 *vs.* 150.6 ± 9.0 mm Hg, respectively) and diastolic (82.3 ± 9.0 *vs.* 83.6 ± 8.3 mm Hg, respectively) BP levels were not different between the two groups (Figure 1). The mean BP was also similar between the TH and Am groups (105.4 ± 6.7 *vs.* 105.9 ± 6.2 mm Hg, respectively). There were no significant differences between the two groups, except for slight increases in pulse rate and ALP in the TH group. Baseline serum uric acid was marginally (P=0.069) higher in the TH group (Table 1 and Figure 2). The frequency of coexisting illness did not differ between the TH and Am groups (Table 2). Diabetes and/or dyslipidemia was present in 28 (75.7%) patients in the TH group and in 26 (68.4%) patients in the Am group. The frequencies of statin use (14 (37.8%) *vs.* 12 (31.6%, respectively)) and antidiabetic agent use (13 (35.1%) *vs.* 16 (42.1%, respectively)) were also not different. The average final dose of telmisartan was 44.5 ± 8.8 mg per day and that of amlodipine was 5.9 ± 0.7 mg per day. During treatment, one patient from the TH group (violation of the protocol) and three patients from the Am group (discontinuation: n=2, violation of the protocol: n=1) were excluded from the study.

Table 1 The baseline characteristics of the participants in the telmisartan plus hydrochlorothiazide (TH) and amlodipine (Am) groups

Parameter	*TH group*	*Am group*	P-*value*
Age (years)	67.4 ± 9.3	65.6 ± 10.4	NS
Male/female	15/22	18/20	NS
BMI (kg m^{-2})	24.1 ± 3.8	24.2 ± 4.5	NS
Pulse rate (b.p.m.)	79.3 ± 12.0	73.8 ± 9.4	<0.05
FBG (mg per 100 ml)	131.8 ± 33.2	120.9 ± 34.6	NS
FBI (μU per ml^{-1})	10.2 ± 8.5	13.3 ± 18.2	NS
HBA1c (%)	6.0 ± 1.0	6.1 ± 0.7	NS
T-chol (mg per 100 ml)	196 ± 30	193 ± 32	NS
TG (mg per 100 ml)	119 ± 62	114 ± 86	NS
HDL-chol (mg per 100 ml)	66 ± 23	62 ± 17	NS
LDL-chol (mg per 100 ml)	110 ± 25	109 ± 29	NS
γ-GTP (IU l^{-1})	44.1 ± 50.3	35.1 ± 28.1	NS
AST (IU l^{-1})	26.2 ± 9.2	24.4 ± 10.8	NS
ALT (IU l^{-1})	28.2 ± 19.6	24.2 ± 13.9	NS
ALP (IU l^{-1})	252 ± 83	212 ± 69	<0.05
Creatinine (mg per 100 ml)	0.76 ± 0.20	0.76 ± 0.16	NS
BUN (mg per 100 ml)	15.3 ± 4.2	15.4 ± 3.6	NS
Uric acid (mg per 100 ml)	5.36 ± 1.33	4.83 ± 1.13	NS
Na (mequiv. l^{-1})	140.3 ± 2.1	140.5 ± 2.3	NS
K (mequiv. l^{-1})	4.3 ± 0.4	4.3 ± 0.5	NS

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; FBG, fasting blood glucose; FBI, fasting blood insulin; γ-GTP, γ-glutamine transferase; HbA1c, glycosylated hemoglobin A1c; HDL-chol, high-density lipoprotein cholesterol; K, potassium; LDL-chol, low-density lipoprotein cholesterol; Na, sodium; NS, non-significant; T-chol, total cholesterol; TG, triglyceride.
Data are expressed as mean ± s.d.



BP (mmHg)	Group	Before	4 weeks	8 weeks	12 weeks
Systolic	Am	150.6±9.0	145.8±13.5	146.4±15.8	143.9±10.1
	TH	151.5±8.8	140.5±15.5	135.6±14.7	133.0±15.5
	p	0.35	0.20	0.002	<0.001
Diastolic	Am	83.6±8.3	80.1±8.6	82.7±10.4	81.3±11.8
	TH	82.3±9.0	79.1±12.0	77.4±10.1	76.9±11.1
	p	0.76	0.91	0.080	0.20

Figure 1 Systolic and diastolic blood pressures (BPs) in TH (open circle) and Am (solid circle) groups. *$P<0.01$ and **$P<0.001$, *vs.* Am group. Data are expressed as mean ± s.d. For abbreviations, see Table 1.

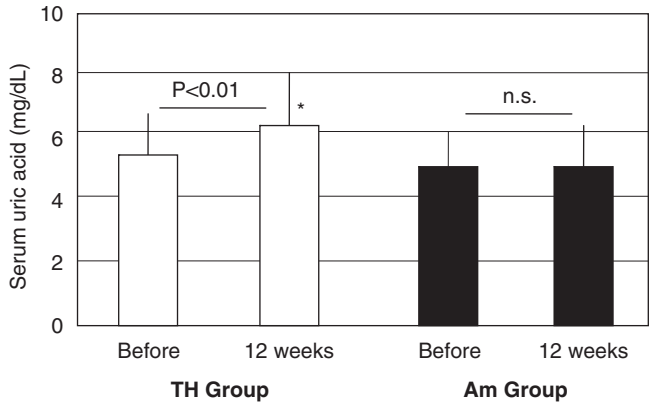


Figure 2 Serum uric acid in TH (open bar) and Am groups (solid bar) before and after 12 weeks of the treatment. *$P<0.01$ *vs.* Am group. Data are expressed as mean ± s.d. For abbreviations, see Table 1.

Table 2 The number of the coexisting illness in TH and Am groups

Coexisting illness	*TH group*	*Am group*	P-*value*
Cardiovascular disease	1	2	NS
Renal disease	1	4	NS
Diabetes	25	16	NS
Hyperlipidemia	12	19	NS
Hyperuricemia	6	4	NS

Abbreviation: Am, amlodipine; NS, non-significant; TH, telmisartan plus hydrochlorothiazide.

Changes in BP

Systolic BP was significantly decreased after the 8- (135.6 ± 14.7 *vs.* 146.4 ± 15.8 mm Hg, $P<0.01$, respectively) and 12-week (133.0 ± 15.5 *vs.* 143.9 ± 10.1 mm Hg, $P<0.001$, respectively) treatments in the TH group relative to the Am group (Figure 1). Moreover, diastolic BP was slightly, but not significantly, decreased in the TH group (at 8 weeks: 77.4 ± 10.1 *vs.* 82.7 ± 10.4 mm Hg, $P=0.08$, respectively; 12 weeks: 76.9 ± 11.1 *vs.* 81.3 ± 11.8 mm Hg, $P=0.20$, respectively). In addition, the mean BP was also decreased after the 8- (96.8 ± 9.9 *vs.* 103.9 ± 98 mm Hg, $P<0.01$, respectively) and 12-week (95.6 ± 10.7 *vs.* 102.2 ± 9.7 mm Hg, $P<0.05$, respectively) treatments in the TH group. As shown in Figure 3, systolic and mean BPs were decreased

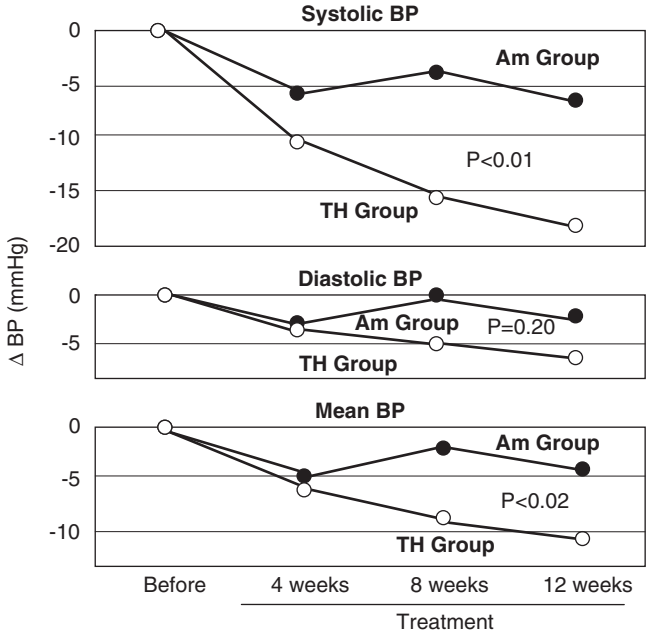


Figure 3 Changes in systolic, mean, and diastolic BP in TH (open circle) and Am groups (solid circle). Data are expressed as mean ± s.d. For abbreviations, see Table 1 and Figure 1.

during the treatment in both groups, but the extent of decrease was significantly greater in the TH group ($P<0.01$). The decrease in diastolic BP was not significant and its extent was marginally greater than that in the TH group ($P=0.20$). After 12 weeks of treatment, the decreases in systolic (-18.5 ± 16.9 *vs.* -6.4 ± 10.9 mm Hg, $P<0.01$, respectively) and mean (-9.9 ± 11.4 *vs.* -3.7 ± 8.9 mm Hg, $P<0.02$, respectively) BP levels were significantly greater in the TH group, and the change in diastolic BP was slightly, but not significantly, higher in the TH group (-5.6 ± 10.7 *vs.* -2.3 ± 9.5 mm Hg, $P=0.12$, respectively). The small changes in diastolic BP may be due to the fact that the average pretreatment levels of diastolic BP were already normal (Figure 1). As expected, participants with a BP $<140/90$ mm Hg accounted for 23 (67.6%) and 10 (30.3%) patients in the TH and Am groups ($P<0.01$), respectively. Moreover, in patients with diabetes, the number of patients with a BP level of $<130/80$ mm Hg accounted for 4 of 16 (25.0%) patients in the TH group, but none in the Am group. Therefore, the switch to combination therapy with telmisartan plus low-dose hydrochlorothiazide was useful in controlling BP in hypertensive patients with uncontrolled BP under amlodipine monotherapy.

Pulse rate and BMI

Pulse rate (78.9 ± 10.2 *vs.* 73.5 ± 11.5 per min, respectively) and BMI (data not shown) did not differ with treatment in either of the two groups.

Laboratory data

Glucose levels and lipid metabolism were not different between the TH and Am groups (Table 3). Although serum K was not different, serum uric acid was higher ($P<0.01$) in the TH group. Serum uric acid was significantly increased in the TH group, but not in the Am group (Figure 1). A total of 10 patients in the TH group and 4 patients in the Am group ($P=0.13$) showed abnormally high uric acid levels.

Table 3 Laboratory data after 12 weeks of treatment in the TH and Am groups

Parameter	*TH group*	*Am group*	P-*value*
FBG (mg per 100 ml)	128.6 ± 31.9	118.5 ± 23.6	NS
FBI (μU/ml)	11.2 ± 11.5	9.7 ± 6.8	NS
HBA1c (%)	6.3 ± 1.0	6.1 ± 0.9	NS
T-chol (mg per 100 ml)	206 ± 41	192 ± 28	NS
TG (mg per 100 ml)	132 ± 61	105 ± 51	NS
HDL-chol (mg per 100 ml)	60 ± 20	62 ± 15	NS
LDL-chol (mg per 100 ml)	119 ± 34	111 ± 27	NS
γ-GTP (IU l^{-1})	41.7 ± 46.0	34.4 ± 29.0	NS
AST (IU l^{-1})	24.5 ± 6.8	28.9 ± 30.7	NS
ALT (IU l^{-1})	25.7 ± 13.8	23.3 ± 13.9	NS
ALP (IU l^{-1})	224 ± 75	213 ± 50	NS
Creatinine (mg per 100 ml)	0.81 ± 0.19	0.78 ± 0.18	NS
BUN (mg per 100 ml)	16.6 ± 4.5	14.6 ± 3.4	NS
Uric acid (mg per 100 ml)	6.31 ± 1.65	4.83 ± 1.31	<0.01
Na (mequiv. l^{-1})	139.8 ± 3.0	139.9 ± 2.6	NS
K (mequiv. l^{-1})	4.3 ± 0.4	4.2 ± 0.4	NS

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; Am, amlodipine; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FBG, fasting blood glucose; FBI, fasting blood insulin; γ-GTP, γ-glutamine transferase; HbA1c, glycosylated hemoglobin A1c; HDL-chol, high-density lipoprotein cholesterol; K, potassium; LDL-chol, low-density lipoprotein cholesterol; Na, sodium; NS, non-significant; T-chol, total cholesterol; TG, triglyceride; TH, telmisartan plus hydrochlorothiazide.
Data are expressed as mean ± s.d.

Adverse events

Four adverse events (light-headedness on standing, vertigo, headache and dermal pruritus) were observed in the TH group, and six (heaviness of the head, vertigo, anxiety attack, bone fracture, gout attack and fundal hemorrhage) were observed in the Am group. None of the patients discontinued participation because of the above-mentioned adverse events.

DISCUSSION

In this study, we showed that combination therapy with telmisartan plus low-dose hydrochlorothiazide has a superior antihypertensive effect relative to amlodipine monotherapy. Therefore, these results support the claim that patients with uncontrolled hypertension undergoing treatment with amlodipine monotherapy may benefit from alternative antihypertensive strategies to achieve target BP control, including initiation of combination therapy with telmisartan plus low-dose hydrochlorothiazide. Our data are in agreement with the results of the ATHOS (A Comparison of Telmisartan plus Hydrochlorothiazide with Amlodipine plus Hydrochlorothiazide in Older Patients with Predominantly Systolic Hypertension) study,[15] in which the combination of telmisartan plus hydrochlorothiazide decreased ambulatory BP to a greater extent than did amlodipine plus hydrochlorothiazide. In this study, even in combination with a thiazide diuretic, amlodipine showed a smaller depressive effect on BP than did telmisartan plus hydrochlorothiazide.

The antihypertensive effects of RAS inhibitors are greatly enhanced with salt depletion. In fact, the addition of low-dose hydrochlorothiazide doubled the antihypertensive effect of losartan.[16] Similarly, hydrochlorothiazide greatly enhances the BP depressor effects of telmisartan.[17,18] Moreover, in mild-to-moderate hypertensive patients who did not respond to telmisartan monotherapy, the addition of low-dose hydrochlorothiazide effectively decreased BP in the first 4 weeks of use.[18] More importantly, the antiproteinuric effects of ACE inhibitors are blunted with salt excess, but the addition of hydrochlorothiazide suppresses the salt-induced increase in urinary protein.[19] Moreover, in the GUARD (Gauging Albuminuria Reduction with Lotrel in Diabetic Patients With Hypertension) trial,[20] benazepril plus hydrochlorothiazide showed superior antialbuminuric effects relative to benazepril plus amlodipine. Thus, the combination of a RAS inhibitor and a thiazide diuretic may be beneficial, especially in hypertensive patients with kidney disease. In addition, the combination of a RAS inhibitor and a thiazide diuretic has been shown to be useful even in patients with type II diabetes mellitus[11] and in very old patients with hypertension.[12]

Despite its effectiveness, increases in the number of antihypertensive drugs may suppress compliance. Combination drugs can resolve this problem; a recent report[21] indicated that the percentages of patients taking combination drugs with lisinopril plus hydrochlorothiazide and with enalapril plus hydrochlorothiazide were significantly greater (18.8 and 21.7%, $P<0.05$, respectively) than the percentages of patients taking lisinopril plus concurrent diuretic therapy and enalapril plus concurrent diuretic therapy.

Glucose levels and lipid metabolism were similar between the two groups, although the study population included a number of patients with metabolic disorder. Although treatment with thiazide diuretics raises concerns regarding deteriorating glucose and lipid metabolisms, low-dose diuretics such as 12.5 mg per day of hydrochlorothiazide do not significantly alter serum lipid and blood glucose levels.[22] The metabolically harmful effects of thiazide diuretics are believed to be mostly due to hypokalemia. A meta-analysis of patients treated with a thiazide diuretic showed that serum potassium was inversely

correlated with blood glucose.[23] A dose of 12.5 mg per day of hydrochlorothiazide is sufficient enough to increase renal sodium excretion, but not potassium excretion.[24] Thus, disturbances in glucose and lipid metabolism are not apparent in patients treated with a low-dose diuretic due to the small decreases in serum potassium. In addition, the potassium-retaining effects of ARB resulting from decreases in aldosterone levels antagonize thiazide-induced hypokalemia.[25] In this study, serum potassium levels did not differ between the TH and Am groups.

Hyperuricemia was observed more frequently in the TH group than in the Am group. However, in the TH group, higher levels of serum uric acid may have been overestimated because of a higher baseline value (P=0.069). In the TH group, patients with treatment-induced hyperuricemia had relatively high baseline values of serum uric acid ($\geqslant$6.1 mg per 100 ml). The effects on uric acid excretion vary among the different ARBs.[26] In urate transporter 1 (URAT1)-expressing *Xenopus* oocytes, losartan and telmisartan showed *cis*-inhibitory effects on the uptake of uric acid, although telmisartan, which is not excreted into the renal tubule, cannot affect URAT1. On the other hand, candesartan showed a trans-stimulatory effect, whereas telmisartan did not. Thus, telmisartan does not modify the effects of thiazide diuretics to induce hyperuricemia. Therefore, it is suggested that low-dose hydrochlorothiazide, with or without combined telmisartan, should be carefully administered in patients with high normal serum uric acid, although serum uric acid is easily controlled by antihyperuricemic drugs.

In conclusion, combination therapy with telmisartan and low-dose hydrochlorothiazide is an antihypertensive treatment alternative in hypertensive patients with uncontrolled BP on CCB monotherapy because of its powerful depressor effect and less harmful effects on glucose and lipid metabolism. As appropriate BP reduction has an important role in the effects of antihypertensive drugs in preventing cardiovascular disease, the combination of a RAS inhibitor and a low-dose thiazide diuretic may be one of the most beneficial strategies for managing hypertension.

ACKNOWLEDGEMENTS

We express our sincere thanks to Dr Takeshi Kojima (Horinouchi Hospital, Saitama), Dr Masao Kawamitsu (Kawamitsu Surgery Hospital, Tokyo) and Dr Hidetaka Takahashi (Takahashi Clinic, Yamanashi) for the enrollment of patients in this study.

1 Staessen JA, Wang J-G, Thijs L. Cardiovascular protection and blood pressure reduction: a meta-analysis. *Lancet* 2001; **358**: 1305–1315.
2 Mori H, Ukai H, Yamamori H, Saito S, Hirao K, Yamauchi M, Umemura S. Current status of antihypertensive prescription and associated blood pressure control in Japan. *Hypertens Res* 2006; **29**: 143–151.
3 Elliott WJ. Is fixed combination therapy appropriate for initial hypertension treatment? *Curr Hypertens Rep* 2002; **4**: 278–285.
4 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, Jones DW, Materson BJ, Oparil S, Wright Jr JT, Roccella EJ, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**: 1206–1252.
5 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B, Management of Arterial Hypertension of the European Society of Hypertension; European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**: 1105–1187.
6 Ohkubo T, Obara T, Funahashi J, Kikuya M, Asayama K, Metoki H, Oikawa T, Takahashi H, Hashimoto J, Totsune K, Imai Y, J-HOME Study Group. Control of blood pressure as measured at home and office, and comparison with physicians' assessment of control among treated hypertensive patients in Japan: First Report of the Japan Home versus Office Blood Pressure Measurement Evaluation (J-HOME) study. *Hypertens Res* 2004; **27**: 755–763.
7 Saruta T, Ogihara T, Matsuoka H, Suzuki H, Toki M, Hirayama Y, Nonaka K, Takahashi K. Antihypertensive efficacy and safety of fixed-dose combination therapy with losartan plus hydrochlorothiazide in Japanese patients with essential hypertension. *Hypertens Res* 2007; **30**: 729–739.
8 Maillard M, Burnier M. Telmisartan/hydrochlorothiazide: a new fixed dose combination. *Expert Rev Cardiovasc Ther* 2005; **3**: 375–386.
9 Neldam S. Telmisartan/hydrochlorothiazide in the treatment of hypertension. *Aging Health* 2006; **2**: 395–408.
10 Wassertheil-Smoller S, Psaty B, Greenland P, Oberman A, Kotchen T, Mouton C, Black H, Aragaki A, Trevisan M. Association between cardiovascular outcomes and antihypertensive drug treatment in older women. *JAMA* 2004; **292**: 2849–2859.
11 ADVANCE collaborative group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007; **370**: 829–840.
12 Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ, for the HYVET study group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008; **358**: 1887–1898.
13 Neutel JM, Littlejohn TW, Chrysant SG, Singh A, on behalf of the Telmisartan Study Group. Telmisartan/hydrochlorothiazide in comparison with losartan/hydrochlorothiazide in managing patients with mild-to-moderate hypertension. *Hypertens Res* 2005; **28**: 555–563.
14 Lacourcière Y, Gil-Extremera B, Mueller O, Byrne M, Williams L. Efficacy and tolerability of fixed-dose combinations of telmisartan plus HCTZ compared with losartan plus HCTZ in patients with essential hypertension. *Int J Clin Pract* 2003; **57**: 273–279.
15 Neldam S, Edwards C, ATHOS Study Group. Telmisartan plus HCTZ vs amlodipine plus HCTZ in older patients with systolic hypertension: results from a large ambulatory blood pressure monitoring study. *Am J Geriatr Cardiol* 2006; **15**: 151–160.
16 MacKay JH, Arcuri KE, Goldberg AI, Snapinn SM, Sweet CS. Losartan and low-dose hydrochlorothiazide in patients with essential hypertension. A double-blind, placebo-controlled trial of concomitant administration compared with individual components. *Arch Intern Med* 1996; **156**: 278–285.
17 McGill JB, Reilly PA. Telmisartan plus hydrochlorothiazide versus telmisartan or hydrochlorothiazide monotherapy in patients with mild to moderate hypertension: a multicenter, randomized, double-blind, placebo-controlled, parallel-group trial. *Clin Ther* 2001; **23**: 833–850.
18 Lacourcière Y, Tytus R, O'Keefe D, Lenis J, Orchard R, Martin K. Efficacy and tolerability of a fixed-dose combination of telmisartan plus hydrochlorothiazide in patients uncontrolled with telmisartan monotherapy. *J Hum Hypertens* 2001; **15**: 763–770.
19 Buter H, Hemmelder MH, Navis G, de Jong PE, de Zeeuw D. The blunting of the antiproteinuric efficacy of ACE inhibition by high sodium intake can be restored by hydrochlorothiazide. *Nephrol Dial Transplant* 1998; **13**: 1682–1685.
20 Bakris GL, Toto RD, McCullough PA, Rocha R, Purkayastha D, Davis P, GUARD (Gauging Albuminuria Reduction With Lotrel in Diabetic Patients With Hypertension) Study Investigators. Effects of different ACE inhibitor combinations on albuminuria: results of the GUARD study. *Kidney Int* 2008; **73**: 1303–1309.
21 Dezii CM. A retrospective study of persistence with single-pill combination therapy vs concurrent two-pill therapy in patients with hypertension. *Manag Care* 2000; **9**(9 Suppl): 2–6.
22 Neutel JM. Metabolic manifestations of low-dose diuretics. *Am J Med* 1996; **101** (3A): 71S–85S.
23 Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL. Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension* 2006; **48**: 219–224.
24 Beermann B, Groschinsky-Grind M. Pharmacokinetics of hydrochlorothiazide in man. *Eur J Clin Pharmacol* 1977; **12**: 297–303.
25 Parhofer KG, Münzel F, Krekler M. Effect of the angiotensin receptor blocker irbesartan on metabolic parameters in clinical practice: the DO-IT prospective observational study. *Cardiovasc Diabetol* 2007; **6**: 36.
26 Iwanaga T, Sato M, Maeda T, Ogihara T, Tamai I. Concentration-dependent mode of interaction of angiotensin II receptor blockers with uric acid transporter. *J Pharmacol Exp Ther* 2007; **320**: 211–217.