ORIGINAL ARTICLE

Effect of hydrochlorothiazide in addition to telmisartan/amlodipine combination for treating hypertensive patients uncontrolled with telmisartan/amlodipine: a randomized, double-blind study

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The efficacy and safety of telmisartan 80 mg/amlodipine 5 mg plus hydrochlorothiazide 12.5 mg (T80/A5/H12.5) was examined for its ability to treat hypertension in Japanese patients whose hypertension is uncontrolled with telmisartan 80 mg/amlodipine 5 mg (T80/A5). Patients aged ≥ 20 years who had essential hypertension despite taking two or three antihypertensive drugs entered a 6-week run-in period on T80/A5. Patients whose hypertension remained uncontrolled were randomly assigned to either the T80/A5/H12.5 group ($n = 149$) or the T80/A5 group ($n = 160$), once daily for 8 weeks. After 8 weeks, patients in the T80/A5/H12.5 group showed a significantly greater adjusted mean reduction in both seated diastolic blood pressure and seated systolic blood pressure than those in the T80/A5 group. Furthermore, more patients achieved a diastolic/systolic blood pressure of $< 90/140$ mm Hg in the T80/A5/H12.5 group compared with the T80/A5 group. The most common adverse events were nasopharyngitis, elevated blood uric acid levels and hyperuricemia, and the latter two events were more frequent in the T80/A5/H12.5 group than in the T80/A5 group. Overall, T80/A5/H12.5 administered for 8 weeks significantly reduced systolic and diastolic blood pressure and was well tolerated by patients with hypertension uncontrolled with T80/A5.

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INTRODUCTION

According to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014), it is estimated that ~ 43 million people are affected by hypertension in Japan.¹ It is concerning that the number of people with hypertension may continue to increase with aging of the population. In a survey of 4000 hypertensive subjects, the proportion with controlled blood pressure was 34.9% in 2006, and this improved to 50% in 2009; however, blood pressure control remains inadequate.² Another survey conducted in 3000 subjects in 1994, 2001 and 2010 showed that the mean number of prescribed agents per patient increased gradually from 1.64 in 1994 to 1.79 in 2001 and to 2.04 in 2010.³ For many patients, a combination of two or more treatments, or an increased dose of combination therapy, is required to achieve any antihypertensive effect.¹

Angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors, calcium channel blockers (CCBs) and diuretics are first-line drugs for the management of hypertension.¹ CCBs and ARBs lower blood pressure by vasodilating effects. Diuretics increase the excretion of excess water and sodium, thereby decreasing peripheral vascular resistance.

Among these first-line drugs, ARB/CCB combination therapy is widely used for hypertensive patients as a second-line treatment. In a phase III study, a combined antihypertension treatment containing 80 mg of the ARB telmisartan and 5 mg of the CCB amlodipine (Micamlo combination tablets BP; Nippon Boehringer Ingelheim) reduced diastolic blood pressure (DBP) to ≤ 90 mm Hg in 70.1% of patients compared with 41.5% of patients taking telmisartan monotherapy (data on file, Nippon Boehringer Ingelheim, Tokyo, Japan).

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The aim of this prospective, randomized, double-blind, active-control, parallel-group comparison study was to examine the efficacy and safety of telmisartan (80 mg), amlodipine (5 mg) and hydrochlorothiazide (12.5 mg) (T80/A5/H12.5) for the treatment of hypertensive patients whose hypertension is uncontrolled with telmisartan (80 mg) and amlodipine (5 mg) (T80/A5).

using mixed-effects model repeated measures (MMRM) on the FAS without the LOCF approach. The other secondary endpoint and other endpoints, including the proportion of patients with trough-seated DBP/SBP $\leq 90/140$ mm Hg, DBP/SBP control rates and DBP/SBP response rates after 8 weeks of the double-blind period, were analyzed by treatment group and compared between groups using logistic regression analysis with non-completers considered failure imputation. (Clinical trial registration: NCT01975246.)

RESULTS

Patients

We enrolled 442 male and female Japanese patients in this study. Of these, 309 patients had uncontrolled blood pressure despite treatment with T80/A5 during the run-in period (Figure 2). The study population consisted predominantly of males (83.2%) and people aged <65 years (85.4%), with the mean (s.d.) age of all patients being 54.7 (9.4) years (Table 1). The majority of patients had hypertension severity grade I or II (72.8% and 24.6%, respectively) according to JSH 2014.¹ The mean (s.d.) body mass index of the study population was 26.92 (4.34) kg m⁻² and the mean (s.d.) waist circumference was 92.90 (10.76) cm. In total, 73.8% of the treated patients had abdominal obesity. Overall, of the 309 patients in the treated set, 93.5% had at least one concomitant diagnosis; the most frequent was metabolic and nutrition disorders (72.2%), followed by hepatobiliary disorders (27.8%).

In accordance with the inclusion criteria, patients were previously treated with two (82.2%) or three (17.8%) antihypertensive drugs. In 74.4% of patients, this consisted of an ARB and a CCB, and for 10.7% it consisted of an ARB, a CCB and a diuretic. The mean (s.d.) seated DBP at reference baseline was 96.5 (5.6) mm Hg and 95.7 (5.1 mm Hg) in the T80/A5/H12.5 and the T80/A5 groups,

respectively. The mean seated SBP at reference baseline was 142.3 (12.9) and 142.3 (12.1) mm Hg in the T80/A5/H12.5 and the T80/A5 groups, respectively. In general, the demographic and reference baseline characteristics of both groups were similar (Table 1).

The disposition of the study patients is shown in Figure 2. Of the 442 enrolled patients, 393 entered the run-in period and 49 were excluded, largely because of violations of the inclusion/exclusion criteria. Following the run-in period, 309 patients were randomly assigned to T80/A5/H12.5 ($N=149$) and T80/A5 ($N=160$) groups and 84 were excluded, mainly because of not meeting the blood pressure inclusion/exclusion criteria. Of the 309 patients who entered the treatment period, 303 (98.1%) patients completed the 8-week treatment period, and the proportion of patients who completed the study was similar between groups (145 [97.3%] and 158 [98.8%] for the T80/A5/H12.5 and T80/A5 groups, respectively). The most frequent cause for discontinuation was adverse events that occurred in 2 (1.3%) and 1 (0.6%) patients in the T80/A5/H12.5 and T80/A5 groups, respectively (Figure 2).

DBP change

After 8 weeks of treatment, the adjusted mean (s.e.) reduction in trough-seated DBP was 8.4 (0.6) mm Hg in the T80/A5/H12.5 group compared with 4.5 (0.5) mm Hg in the T80/A5 group in the FAS (ANCOVA with LOCF). The T80/A5/H12.5 group showed a statistically significantly greater adjusted mean reduction in seated DBP compared with the T80/A5 treatment group, with a difference of -3.9 mm Hg (95% CI: -5.3 to -2.4 ; $P<0.0001$). Figure 3a shows the results of a sensitivity analysis performed using a MMRM on the FAS that provided results that were consistent with those of the primary analysis. An ANCOVA on the PPS also provided results consistent with those of the primary analysis. In addition, the adjusted mean (s.e.) change from reference baseline in trough-seated DBP at week 4 based on the MMRM analysis was -6.6 (0.5) mm Hg in the T80/A5/H12.5 group and -3.2 (0.5) mm Hg in the T80/A5 group. Compared with T80/A5, T80/A5/H12.5 had a greater reduction in trough-seated DBP, with a treatment difference of -3.5 mm Hg (95% CI: -4.8 to -2.1 ; $P<0.0001$). These data indicate that treatment with the combination T80/A5/H12.5 achieved a superior reduction in seated DBP compared with treatment with T80/A5.

SBP change

Following 8 weeks of treatment, the adjusted mean (s.e.) reduction in trough-seated SBP was 12.3 (0.8) mm Hg in the T80/A5/H12.5 group compared with 6.9 (0.8) mm Hg in the T80/A5 group in the FAS (ANCOVA with LOCF). The T80/A5/H12.5 group showed a statistically significantly greater adjusted mean reduction in SBP compared with the T80/A5 group, with a difference of -5.3 mm Hg (95% CI: -7.6 to -3.1 ; $P<0.0001$). The sensitivity analysis, including a MMRM analysis on the FAS (Figure 3b), provided results that were consistent with those of the primary analysis. Furthermore, the adjusted mean (s.e.) change from reference baseline in trough-seated SBP at week 4 based on the MMRM analysis was -9.7 (0.8) mm Hg in the T80/A5/H12.5 group and -5.2 (0.8) mm Hg in the T80/A5 group. Compared with the T80/A5 group, the T80/A5/H12.5 group had a greater reduction in trough-seated SBP, with a treatment difference of -4.5 mm Hg (95% CI: -6.6 to -2.3 ; $P<0.0001$; MMRM analysis; Figure 3b). These data indicate that treatment with the combination T80/A5/H12.5 achieved a superior reduction in SBP compared with treatment with T80/A5.

Figure 2 Patient disposition. AE, adverse event; T80/A5, telmisartan 80 mg +amlodipine 5 mg; T80/A5/H12.5, telmisartan 80 mg/amlodipine 5 mg +hydrochlorothiazide 12.5 mg.

Table 1 Demographic and reference baseline characteristics of the treated set

	T80/A5/H12.5	T80/A5	Total
N	149	160	309
Gender, N (%)			
Male	127 (85.2)	130 (81.3)	257 (83.2)
Female	22 (14.8)	30 (18.8)	52 (16.8)
Age, years			
Mean (s.d.)	54.4 (9.1)	55.0 (9.7)	54.7 (9.4)
Median (range)	54.0 (27–80)	54.5 (30–83)	54.0 (27–83)
Age, N (%)			
<65 Years	130 (87.2)	134 (83.8)	264 (85.4)
≥65 Years	19 (12.8)	26 (16.3)	45 (14.6)
Reference baseline BMI, kg m ⁻²			
Mean (s.d.)	27.10 (4.16)	26.76 (4.51)	26.92 (4.34)
Median (range)	26.96 (17.5–44.6)	26.12 (16.8–43.8)	26.66 (16.8–44.6)
BMI, N (%)			
<25.0 kg m ⁻²	46 (30.9)	67 (41.9)	113 (36.6)
≥25.0 To <30.0 kg m ⁻²	70 (47.0)	60 (37.5)	130 (42.1)
≥30.0 kg m ⁻²	33 (22.1)	33 (20.6)	66 (21.4)
Abdominal obesity ^a , N (%)			
No	34 (22.8)	47 (29.4)	81 (26.2)
Yes	115 (77.2)	113 (70.6)	228 (73.8)
Reference baseline blood pressure (mm Hg)			
DBP mean (s.d.)	96.5 (5.6)	95.7 (5.1)	96.1 (5.3)
SBP mean (s.d.)	142.3 (12.9)	142.3 (12.1)	142.3 (12.4)
Duration of hypertension, N (%)			
≤1 Year	11 (7.4)	5 (3.1)	16 (5.2)
>1–5 Years	36 (24.2)	44 (27.5)	80 (25.9)
>5–10 Years	46 (30.9)	43 (26.9)	89 (28.8)
>10 Years	56 (37.6)	68 (42.5)	124 (40.1)
Hypertension severity ^b at reference baseline, N (%)			
Grade I	107 (71.8)	118 (73.8)	225 (72.8)
Grade II	36 (24.2)	40 (25.0)	76 (24.6)
Grade III	5 (3.4)	2 (1.3)	7 (2.3)
Missing	1 (0.7)	0 (0.0)	1 (0.3)
eGFR (ml min ⁻¹ 1.73 m ⁻²), N (%)			
≥90 (Normal)	24 (16.1)	32 (20.0)	56 (18.1)
≥60 To <90 (mild)	109 (73.2)	104 (65.0)	213 (68.9)
≥30 To <60 (moderate)	16 (10.7)	24 (15.0)	40 (12.9)
<30 (Severe)	0 (0.0)	0 (0.0)	0 (0.0)
Concomitant diagnoses, N (%)	137 (91.9)	152 (95.0)	289 (93.5)
Number of previous antihypertensives used, N (%)			
Two	125 (83.9)	129 (80.6)	254 (82.2)
Three	24 (16.1)	31 (19.4)	55 (17.8)

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; T80/A5, telmisartan 80 mg/amlodipine 5 mg; T80/A5/H12.5, telmisartan 80 mg/amlodipine 5 mg+hydrochlorothiazide 12.5 mg.

^aAbdominal obesity: Yes = reference baseline waist circumference >85 cm (male) and >90 cm (female).

^bHypertension severity: grade I = seated SBP 140 to <160 mm Hg or seated DBP 90 to <100 mm Hg; Grade II = seated SBP 160 to <180 mm Hg or seated DBP 100 to <110 mm Hg; Grade III = seated SBP ≥180 mm Hg or seated DBP ≥110 mm Hg.

Other outcomes

Following 8 weeks of treatment, the proportion of patients who achieved a trough-seated DBP/SBP of <90/140 mm Hg was 51.7% in the T80/A5/H12.5 group and 36.9% in the T80/A5 group (Table 2).

Based on logistic regression analysis, patients in the T80/A5/H12.5 group were estimated to be 2.1 times more likely to achieve a DBP/SBP of <90/140 mm Hg than were patients in the T80/A5 group (95% CI: 1.2 to 3.4). In addition, more patients achieved

Figure 3 Change in trough-seated DBP and SBP from reference baseline using a mixed-effects model for repeated measures on the full analysis set with no imputation. (a) Adjusted mean change in DBP compared with reference baseline at 4 and 8 weeks for both treatment groups in the FAS. (b) Adjusted mean change in SBP compared with reference baseline at 4 and 8 weeks of treatment for both treatment groups in the FAS. DBP, diastolic blood pressure; SBP, systolic blood pressure; T80/A5, telmisartan 80 mg+amlodipine 5 mg; T80/A5/H12.5, telmisartan 80 mg+amlodipine 5 mg+hydrochlorothiazide 12.5 mg.

trough-seated DBP control (DBP <90 mm Hg) in the T80/A5/H12.5 group than in the T80/A5 group (Table 2). The probability of achieving DBP control at week 8 was estimated to be 1.9 times higher in the T80/A5/H12.5 group than in the T80/A5 group (95% CI: 1.2 to 3.2) on the basis of a logistic regression analysis.

Of the patients within the FAS who had SBP ≥140 mm Hg at reference baseline, a greater portion achieved trough-seated SBP control (SBP <140 mm Hg) by week 8 in the T80/A5/H12.5 group compared with patients in the T80/A5 group (Table 2). The probability of achieving SBP control at week 8 was estimated to be 2.5 times higher

Table 2 DBP and SBP control rates and response rates in the full analysis set

Endpoint	Week	T80/A5/H12.5			T80/A5			OR ^a	95% CI
		N	n	(%)	N	n	(%)		
DBP control	4	147	70	47.6	160	47	29.4	2.4	(1.5–4.1)
	8		83	56.5		68	42.5	1.9	(1.2–3.2)
SBP control	4	76	37	48.7	89	27	30.3	2.3	(1.2–4.8)
	8		48	63.2		40	44.9	2.5	(1.2–5.3)
DBP <90 mm Hg or decrease by 10 mm Hg	4	147	80	54.4	160	49	30.6	3.0	(1.8–5.0)
	8		98	66.7		72	45.0	2.8	(1.7–4.8)
SBP <140 mm Hg or decrease by 20 mm Hg	4	76	41	53.9	89	30	33.7	2.4	(1.2–4.8)
	8		54	71.1		40	44.9	4.1	(1.9–9.1)
DBP/SBP <90/140 mm Hg	4	147	66	44.9	160	39	24.4	2.9	(1.7–5.1)
	8		76	51.7		59	36.9	2.1	(1.2–3.4)

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure; T80/A5, telmisartan 80 mg/amlodipine 5 mg; T80/A5/H12.5, telmisartan 80 mg/amlodipine 5 mg/hydrochlorothiazide 12.5 mg. Only patients in the full analysis set with a trough-seated DBP of ≥ 90 mm Hg or a SBP of ≥ 140 mm Hg at reference baseline were included in the analysis.
^aFor T80/A5/H12.5 vs. T80/A5.

in the T80/A5/H12.5 group than in the T80/A5 group (95% CI: 1.2 to 5.3) on the basis of a logistic regression analysis. Furthermore, the proportion of patients who had an adequate response in trough-seated DBP (DBP <90 mm Hg or a reduction in DBP of ≥ 10 mm Hg) at week 8 was larger in the T80/A5/H12.5 group than in the T80/A5 group. Of the patients within the FAS who had SBP ≥ 140 mm Hg at reference baseline, more had an adequate response in trough-seated SBP (SBP <140 mm Hg or a reduction in SBP of ≥ 20 mm Hg) at week 8 in the T80/A5/H12.5 group than in the T80/A5 group.

Subgroup analysis

Within the treatment groups, patients were divided into subgroups based on patient characteristics, including age (<65, ≥ 65 years), sex, body mass index (<25, 25–<30 and ≥ 30 kg m⁻²), hypertension severity, hypertension duration (≤ 1 , >1–5, >5–10 and >10 years) and the number of previous antihypertension drugs used (two or three). The reductions in both DBP and SBP in each subgroup tended to be greater in patients treated with T80/A5/H12.5 than in patients treated with T80/A5 (Supplementary Tables 1 and 2).

Safety

Adverse events and laboratory findings. The number of patients who experienced adverse events during the double-blind 8-week period was higher in the T80/A5/H12.5 group (41.6%) than in the T80/A5 group (28.1%) (Table 3). The most common adverse events were increased blood uric acid levels, nasopharyngitis and hyperuricemia. Higher incidences in the T80/A5/H12.5 group compared with the T80/A5 group were seen for increased blood uric acid levels and hyperuricemia.

The frequencies of drug-related adverse events are shown in Table 3. The incidences of drug-related adverse events were higher in the T80/A5/H12.5 group (23.5%) compared with the T80/A5 group (3.8%). This difference in the number of drug-related adverse events

Table 3 Summary of AEs and frequency of drug-related AEs experienced by $\geq 1\%$ of the patients in any one of the treatment groups in the treated set

Variable	T80/A5/H12.5		T80/A5	
	N	%	N	%
Number of patients	149	100	160	100
Patients with an AE	62	41.6	45	28.1
Patients with investigator-defined drug-related AEs	35	23.5	6	3.8
Patients with other significant AEs	2	1.3	1	0.6
Patients with AEs leading to discontinuation	2	1.3	1	0.6
<i>System organ class and preferred term</i>				
Metabolic and nutrition disorders	10	6.7	1	0.6
Hyperuricemia	8	5.4	1	0.6
Dyslipidemia	2	1.3	0	0.0
Investigations (laboratory data abnormalities)	21	14.1	4	2.5
Blood uric acid increased	20	13.4	3	1.9
Blood creatinine increased	2	1.3	0	0.0
Blood urea increased	2	1.3	0	0.0

Abbreviations: AE, adverse event; T80/A5, telmisartan 80 mg+amlodipine 5 mg; T80/A5/H12.5, telmisartan 80 mg+amlodipine 5 mg+hydrochlorothiazide 12.5 mg.

was largely because of the higher incidence of increased uric acid levels in the T80/A5/H12.5 group compared with the T80/A5 group (13.4% vs. 1.9%).

Indeed, regarding laboratory parameters (Supplementary Table 3), noteworthy differences between groups were observed for the mean change from reference baseline in uric acid (1.0 mg dl⁻¹ in the T80/A5/H12.5 group vs. 0.2 mg dl⁻¹ in the T80/A5 group). In patients who had no abnormalities at reference baseline, possible clinically relevant abnormalities included the development of high triglycerides and high total cholesterol that were detected in 11.2% and 4.3% of patients in the T80/A5/H12.5 group, respectively, and 7.3% and 5.9% of the patients in the T80/A5 group, respectively.

The adverse events experienced by patients were mild or moderate in severity and no severe adverse events or deaths were reported in either treatment group. Two patients in the T80/A5/H12.5 group discontinued the study because of adverse events: atrial fibrillation and tachycardia (one patient) and hypotension (one patient). In the T80/A5 group, one patient discontinued because of ventricular extrasystoles. For all three patients, the adverse events were mild in intensity.

Adherence. The overall compliance during the double-blind period was >80% in both treatment groups; 2 (1.3%) of the 149 patients in the T80/A5/H12.5 group and none of the 160 patients in the T80/A5 group had a compliance rate of <80%.

Vital signs and other safety parameters. Following the 8-week treatment period, no clinically relevant changes in DBP, SBP or pulse rate following a position change were detected in either group compared with reference baseline. Furthermore, the seated pulse rate and pulse rate after a position change remained relatively unchanged at week 8 (Supplementary Table 4). Overall, both T80/A5/H12.5 and T80/A5 were well tolerated.

DISCUSSION

Hypertension is a disease with a high incidence in Japan. The currently used monotherapies, including ARBs, CCBs and diuretics, are effective only in a limited proportion of patients. For those who remain resistant to therapy, a combination of antihypertensive agents is required.¹ The aim of this study was to investigate the efficacy and safety of a combination of T80/A5/H12.5 for the treatment of hypertension in patients with an inadequate response to telmisartan 80 mg and amlodipine 5 mg. The results indicate that the T80/A5/H12.5 group achieved significantly greater reductions in seated DBP and SBP relative to those achieved in the T80/A5 group. In addition, significantly more patients achieved DBP and SBP control in the T80/A5/H12.5 group compared with patients treated with T80/A5.

The adverse events reported in this study were mild or moderate in severity, and those events were already observed in those receiving monotherapy or two-agent combination therapy. The incidence of drug-related adverse events was higher in the T80/A5/H12.5 group than in the T80/A5 group. The frequent drug-related adverse events in the T80/A5/H12.5 group were elevated uric acid levels and hyperuricemia. The cause of the increase in uric acid can likely be explained by the addition of hydrochlorothiazide, because elevated uric acid is a common side effect of diuretics.⁴ These adverse events were manageable and did not pose a health risk.

In this study, each patient received two tablets: T80/A5 fixed-dose combination and H12.5 or T80/A5 fixed-dose combination and placebo. It is possible that a single tablet T80/A5/H12.5 combination treatment would improve patient adherence. Previous studies reported that the fixed combination of valsartan/amlodipine/hydrochlorothiazide or olmesartan/amlodipine/hydrochlorothiazide improved adherence and persistence compared with administration of each drug as individual tablets.^{5–7} This suggests that the fixed combination of T80/A5/H12.5 may increase the adherence relative to a combination of three individual treatments.

A similarly designed study of a combination of losartan 50 mg, hydrochlorothiazide 12.5 mg and amlodipine 5 mg compared with coadministration of losartan 50 mg plus amlodipine 5 mg in Japanese patients with essential hypertension did not demonstrate a significant difference in DBP reduction with hydrochlorothiazide 12.5 mg at week 8 (additional effect of -1.1 mm Hg; 95% CI: -2.7 to 0.6 ; $P=0.205$).⁸ However, there was a significant additional effect of hydrochlorothiazide 12.5 mg on SBP reduction at week 8 (-3.2 mm Hg; -5.7 to -0.8 ; $P=0.011$).⁸ The difference between the results of the losartan study and ours is possibly because of the profile of ARBs, that is, usual dosage range, terminal half-life and volume of distribution.⁹ The high-dose ARB with a large volume of distribution is suitable to completely inhibit the renin–angiotensin system activated by CCBs and diuretics.¹⁰ Among ARBs, telmisartan is a long-acting antihypertensive drug that may provide sustained reductions in blood pressure throughout a 24-h dosing period.^{9,11}

The results of this study should be considered in light of its limitations. The main limitation of this study was that the mean age of the patients was 54.7 years and only 14.6% of patients were ≥ 65 years old. Therefore, the efficacy and safety profiles of T80/A5/H12.5 in older patients could not be determined. The study was also only conducted in institutions within Japan, and hence the results are not generalizable to populations of other ethnicities. Another limitation was the short duration of the study, as 8 weeks may not have been sufficient to observe the full benefit provided by the combination therapy, or the benefits may have been reduced over a longer period. Finally, we did not include patients with severe impaired kidney

function (estimated glomerular filtration rate <30 ml min⁻¹ 1.73 m⁻²) who may also require combination therapies to manage hypertension.

CONCLUSIONS

The results from this phase III study indicate that the combination of telmisartan, amlodipine and hydrochlorothiazide is more effective than that of only telmisartan and amlodipine at reducing blood pressure in hypertensive patients. The addition of hydrochlorothiazide to a ARB/CCB combination therapy provides clinicians with a suitable treatment option for patients unresponsive to ARB/CCB combinations. This triple combination therapy is effective and well tolerated.

CONFLICT OF INTEREST

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