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ORIGINAL ARTICLE

Effect of tablets with a combination of telmisartan and amlodipine on patients with hypertension: the Cotalo study

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Fixed-dose combination (FDC) therapy with telmisartan 40 mg + amlodipine 5 mg (T40/A5) is expected to achieve tight blood pressure (BP) control because of the strong efficacy and long half-life of each drug. The aims of this study were to evaluate the 24-h antihypertensive efficacy of T40/A5 FDC therapy and to explore differences that may arise owing to different administration times in Japanese patients whose hypertension was not controlled by 5 mg of amlodipine per day. In this randomized clinical trial, 44 patients who had been taking amlodipine 5 mg per day and did not achieve their optimal BP target were enrolled (mean age: 67.8 ± 10.2 years). The subjects were then randomly assigned to a T40/A5 morning or evening administration group (22 patients per group). At baseline and 8 weeks after randomization, we evaluated clinical BP and various laboratory values and performed ambulatory BP monitoring (ABPM). Clinical and mean BP evaluated with ABPM at 8 weeks (24 h, daytime, nighttime and early morning) were significantly decreased compared with BP at baseline. There were no significant differences in the diurnal BP profile change from baseline to 8 weeks between subjects in the morning and evening administration groups. There were also no significant differences in the diurnal BP profile change from baseline to 8 weeks between subjects with or without metabolic syndrome. We conclude that T40/A5 FDC therapy significantly decreased the 24-h mean and clinical BP, independent of administration time, in patients whose hypertension was not controlled by 5 mg of amlodipine.
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Keywords: ambulatory blood pressure monitoring; amlodipine; fixed-dose combination; metabolic syndrome; telmisartan

INTRODUCTION

Angiotensin II receptor blockers (ARBs) are effective and well-tolerated antihypertensive agents that inhibit aldosterone production, vasoconstriction and sodium retention by blocking the renin–angiotensin–aldosterone system.[1-3] Telmisartan is a highly selective ARB for the AT1 receptor and, as the elimination half-life of this agent is ~24 h, once-daily administration of telmisartan is reported to reduce blood pressure (BP) for an entire 24 h.[4,5] Amlodipine, a calcium channel blocker (CCB), is another highly effective and long-acting antihypertensive agent that is widely used for hypertension treatment.[6]

The current guidelines indicate that treatment with two or more antihypertensive agents is necessary to achieve optimal BP for most hypertensive patients in order to reduce cardiovascular risk.[1,2] Moreover, the Anglo-Scandinavian Cardiac Outcomes Trials Blood Pressure Lowering Arm (ASCOT-BPLA)[7] and Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH)[8] revealed the clinical benefits of combination therapy with renin–angiotensin–aldosterone system blockade and CCB.

Currently, a single-pill combination of ARB and CCB is available for once-daily administration to manage hypertension with better treatment adherence.[9,10] Telmisartan 40 mg + amlodipine 5 mg (T40/A5) fixed-dose combination (FDC) therapy is expected to achieve tight BP control because of the strong efficacy and long half-life of each agent.[11] However, to our knowledge, no studies have been conducted that employed ambulatory BP monitoring (ABPM) in Japanese hypertensive patients to show that T40/A5 FDC therapy has lasting BP-lowering efficacy. In addition, there are no data available regarding whether the administration time (morning or evening) of T40/A5 FDC influences its BP-lowering effects in Japanese patients who had uncontrolled hypertension while taking amlodipine. However, Hermida *et al.*[12] reported that telmisartan monotherapy with bedtime administration could achieve significantly better nocturnal BP regulation compared with morning administration. The aims of this study were (1) to evaluate the 24-h efficacy of

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T40/A5 FDC therapy in the control of hypertension by performing ABPM on the participants and (2) to conduct a preliminary investigation of differences owing to administration time in Japanese patients whose hypertension was not controlled by 5 mg of amlodipine per day.

METHODS

Study subjects and study design

Figure 1 shows the study design. In this randomized clinical trial, we initially recruited patients who had been taking 5 mg of amlodipine/day for >4 weeks. Written informed consent was obtained from all of the participants. Patients taking other CCBs or ARBs were excluded, and there was no change to the other antihypertensive agents throughout the observation period. After a screening period of >2 weeks, subjects with a clinical systolic BP (SBP) of $\geqslant 140$ mm Hg, a clinical diastolic BP (DBP) of $\geqslant 90$ mm Hg, or both were enrolled in this study. We then switched the patients from 5 mg of amlodipine per day to T40/A5 FDC therapy. The subjects were randomly assigned to either a morning ($n=22$) or an evening ($n=22$) administration group. At baseline and 8 weeks after randomization, we evaluated the clinical BP, ABPM and various laboratory values.

We assessed changes from baseline in the 24 h, daytime, nighttime and early morning BP after 8 weeks of treatment and changes from baseline in the clinical BP and laboratory values after 8 weeks of treatment. We also performed comparisons of the above assessments between the morning and evening administration groups. The Clinical Investigations Ethics Committee of Osaka University Hospital approved the study protocol. The study was performed in adherence with the principles of the Declaration of Helsinki and according to Good Clinical Practice standards.

BP measurements

Conventional BP was measured by trained observers with an electronic sphygmomanometer. Following guidelines for the management of hypertension, clinical BP was measured at least two times in a sitting position after 5 min of rest, and we adopted the average of two readings as the clinical BP if the difference in measured values was <5 mm Hg. When the difference in measured values was $\geqslant 5$ mm Hg, additional measurements were conducted to obtain stable BP readings and we adopted the average of the two stable readings as the clinical BP.

Ambulatory BP monitoring

Ambulatory BP was evaluated with portable monitors (FB-270 device; Fukuda Denshi Co. Ltd., Tokyo, Japan) at 30-min intervals from 0600 to 2300 hours and at 60-min intervals from 2300 to 0600 hours. From the ABPM value, we calculated the 24-h mean BP, daytime (0900 to 2100 hours) mean BP, nighttime (0100 to 0600 hours) mean BP, and early morning (2 h after rising) mean BP.[13]

Clinical evaluations

The estimated glomerular filtration ratio (eGFR) was calculated with the following equation: $\mathrm{eGFR}\ (\mathrm{ml\,min^{-1}\,1.73\,m^{-2}}) = 194 \times \mathrm{creatinine}^{-1.094} \times \mathrm{age}^{-0.287}$ ($\times 0.739$ if female).[14] Patients with diabetes mellitus were diagnosed according to the diagnostic criteria of the American Diabetes Association: fasting plasma glucose (FPG) $\geqslant 126\ \mathrm{mg\,dl^{-1}}$, HbA1c $\geqslant 6.5\%$, 2-h value in oral glucose tolerance test $\geqslant 200\ \mathrm{mg\,dl^{-1}}$, random plasma glucose concentration $\geqslant 200\ \mathrm{mg\,dl^{-1}}$ in the presence of symptoms, or taking drugs for diabetes. Patients with considered to have hyperlipidemia if total cholesterol was $\geqslant 220\ \mathrm{mg\,dl^{-1}}$, low-density lipoprotein cholesterol was $\geqslant 140\ \mathrm{mg\,dl^{-1}}$, triglycerides were $\geqslant 150\ \mathrm{mg\,dl^{-1}}$, or they were taking drugs for hyperlipidemia. We evaluated insulin resistance by means of the HOMA-R (homeostasis model assessment ratio), which was calculated with the following equation: HOMA-R = FPG $\times$ fasting plasma insulin/405.

Metabolic syndrome was defined as the presence of two or more of the following abnormalities in addition to abnormally high waist circumference ($\geqslant 85$ cm for men and $\geqslant 90$ cm for women): (1) triglycerides $\geqslant 150\ \mathrm{mg\,dl^{-1}}$ and/or high-density lipoprotein cholesterol $<40\ \mathrm{mg\,dl^{-1}}$ or under treatment for dyslipidemia, (2) SBP $\geqslant 130$ mm Hg and/or DBP $\geqslant 85$ mm Hg or under treatment for hypertension, and (3) FPG $\geqslant 110\ \mathrm{mg\,dl^{-1}}$ or under treatment for diabetes mellitus.[15] Potential metabolic syndrome was also defined as one of above abnormalities in addition to BMI $\geqslant 25$.

Statistical analysis

Data were analyzed with SAS 9.3 (SAS, Cary, NC, USA) and are presented as the mean ± s.d. Differences in patient characteristics and laboratory test results between the groups were analyzed with Fisher's exact test and two-sample *t*-test. Differences in the clinical BP, clinical heart rate and ABPM values between the groups were analyzed with analysis of covariance. A value of $P<0.05$ was regarded as significant.

RESULTS

Table 1 lists the baseline clinical characteristics of the participants in the present study. The mean age of the 44 subjects was 67.8 ± 10.2 years. Although the subjects in the morning administration group had significantly higher triglyceride levels (193.5 ± 145.1 *vs.* 109.2 ± 59.0 mg dl^{-1}, $P=0.022$) and significantly lower high-density lipoprotein cholesterol (50.5 ± 13.4 *vs.* 72.9 ± 21.5 mg dl^{-1}, $P<0.001$) than subjects in the evening administration group, there were no significant differences in the other characteristics between the two groups.

First, we analyzed the BP profile of the study subjects. Figure 2 shows a comparison of the 24-h BP profile for ABPM at baseline and at 8 weeks. The mean SBP at 8 weeks was significantly decreased compared with the mean SBP at baseline (121.8 ± 13.2 *vs.* 130.5 ± 11.4, 125.6 ± 13.2 *vs.* 134.4 ± 11.2, 116.1 ± 16.2 *vs.* 123.5 ± 13.6, and 127.4 ± 14.5 *vs.* 135.2 ± 12.0 mm Hg for 24 h, daytime, nighttime and early morning, respectively) (Table 2). The mean DBP at 8 weeks was also significantly decreased compared with the mean DBP at baseline (74.8 ± 9.3 *vs.* 80.3 ± 10.7, 77.1 ± 9.0 *vs.* 83.0 ± 10.1, 69.5 ± 11.0 *vs.* 75.1 ± 11.9, and 78.7 ± 9.8 *vs.* 84.8 ± 12.5 mm Hg for 24 h, daytime, nighttime and early morning, respectively) (Table 2). However, there

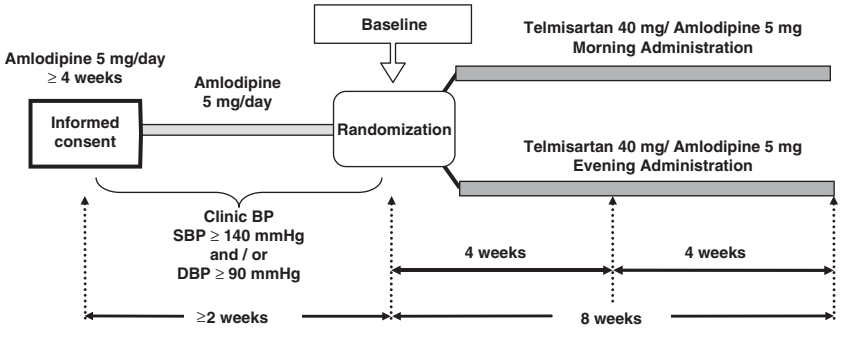

Figure 1 Study design.

Table 1 Patient characteristics

	Total (n = *44*)		*Morning admin* (n = *22*)		*Evening admin* (n = *22*)		
Variable	n	*Mean* ± *s.d.*	n	*Mean* ± *s.d.*	n	*Mean* ± *s.d.*	P-*value*
Male (%)	23	52.3	12	54.5	11	50.0	1.000[a]
Age (years)	44	67.8 ± 10.2	22	67.7 ± 11.8	22	68.0 ± 8.5	0.942[b]
Body weight (kg)	44	64.7 ± 14.0	22	65.2 ± 13.6	22	64.1 ± 14.8	0.808[b]
BMI (kg m^{-2})	44	25.2 ± 4.8	22	25.1 ± 4.1	22	25.4 ± 5.5	0.865[b]
Abdominal circumference (cm)	42	89.7 ± 11.3	20	90.0 ± 12.0	22	89.4 ± 10.9	0.851[b]
Complications (%)	33	75.0	20	90.9	13	59.1	0.034[a]
Type 2 diabetes mellitus (%)	10	22.7	6	27.3	4	18.2	0.721[a]
Dyslipidemia (%)	20	45.5	11	50.0	9	40.9	0.763[a]
Others (%)	12	27.3	7	31.8	5	22.7	0.736[a]
Non metabolic syndrome (%)	13	29.5	6	27.3	7	31.8	0.310[a]
Metabolic syndrome (%)	17	38.6	11	50.0	6	27.3	
Potential metabolic syndrome (%)	14	31.8	5	22.7	9	40.9	
Concomitant medications							
Antidiabetic agents (%)	8	18.2	4	18.2	4	18.2	
Antidyslipidemic agents (%)	14	31.8	6	27.3	8	36.4	
Antihypertensive agents (%)	2	4.5	1	4.5	1	4.5	
Clinic systolic blood pressure (mm Hg)	44	150.7 ± 10.3	22	150.4 ± 9.4	22	151.0 ± 11.4	0.852[b]
Clinic diastolic blood pressure (mm Hg)	44	83.5 ± 10.1	22	82.5 ± 8.8	22	84.4 ± 11.3	0.526[b]
Clinic heart rate (b.p.m.)	44	79.3 ± 11.5	22	77.8 ± 9.7	22	80.9 ± 13.0	0.385[b]
Fasting plasma glucose (mg dl^{-1})	37	110.0 ± 25.4	18	111.1 ± 30.0	19	109.0 ± 20.9	0.810[b]
Fasting plasma insulin (μU ml^{-1})	19	18.2 ± 19.3	10	17.3 ± 15.2	9	19.1 ± 23.9	0.839[b]
HOMA-R	19	5.7 ± 7.3	10	5.8 ± 6.7	9	5.7 ± 8.3	0.990[b]
HbA1c (NGSP) (%)	41	6.0 ± 0.8	19	5.9 ± 0.6	22	6.0 ± 0.9	0.540[b]
Triglyceride (mg dl^{-1})	39	150.3 ± 116.4	19	193.5 ± 145.1	20	109.2 ± 59.0	0.022[b]
HDL cholesterol (mg dl^{-1})	39	62.0 ± 21.1	19	50.5 ± 13.4	20	72.9 ± 21.5	0.000[b]
LDL cholesterol (mg dl^{-1})	39	109.2 ± 28.9	19	113.0 ± 34.1	20	105.6 ± 23.2	0.433[b]
eGFR (ml min^{-1} 1.73 m^{-2})	41	71.7 ± 20.9	20	66.9 ± 21.5	21	76.3 ± 19.8	0.151[b]
Urinary albumin/creatinine ratio (mg g^{-1} Cr)	39	148.3 ± 383.2	19	178.7 ± 417.9	20	119.5 ± 355.6	0.636[b]
Serum adrenaline (pg ml^{-1})	38	41.3 ± 34.1	19	33.8 ± 22.4	19	48.8 ± 42.0	0.176[b]
Serum noradrenaline (pg ml^{-1})	38	616.1 ± 360.6	19	615.6 ± 337.7	19	616.5 ± 391.5	0.994[b]
Serum dopamine (pg ml^{-1})	31	41.8 ± 95.7	16	24.3 ± 18.0	15	60.5 ± 136.2	0.301[b]
Urinary 8-OHdG (ng mg^{-1} Cr)	31	11.6 ± 8.4	15	12.9 ± 10.7	16	10.4 ± 5.7	0.409[b]

Abbreviations: BMI, body mass index; Cr, creatinine; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HOMA-R, homeo- stasis model insulin resistance; LDL, low-density lipoprotein; NGSP, national glycohemoglobin standardization program; 8-OHdG, 8-hydroxy-20-deoxyguanosine.
[a]Fisher's exact test.
[b]2-sample *t*-test.

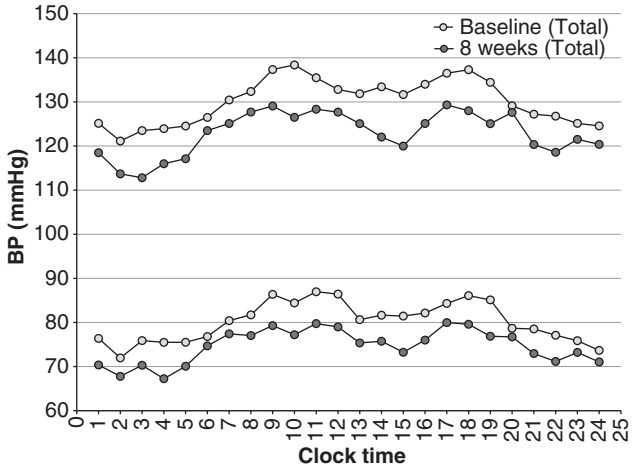

Figure 2 Twenty-four-hour profile of mean hourly blood pressure: baseline (gray) and 8 weeks (black).

were no significant differences in the mean BP change (24 h, daytime, nighttime and early morning) from baseline to 8 weeks between the subjects in the morning and evening administration groups (Table 2). Similarly, the clinical BP at 8 weeks was significantly diminished compared with the clinical BP at baseline (SBP: 135.7 ± 15.0 *vs.* 150.2 ± 10.4, DBP: 75.0 ± 10.0 *vs.* 83.0 ± 10.2 mm Hg). However, there was no significant difference in the change in clinical BP from baseline to 8 weeks between subjects in the morning and evening administration groups (Table 3). In addition, the time at which T40/A5 FDC therapy was administered (morning or evening) did not appear to make a difference in the clinical heart rate (Table 3) or mean heart rate as evaluated by ABPM (data not shown). To further investigate, we analyzed the effect of T40/A5 FDC on dipper and non-dipper type hypertension in the subjects. The mean nighttime BP at 8 weeks in subjects with dipper type hypertension did not significantly decrease compared with the mean BP at baseline and showed no excessive BP lowering; however, the daytime BP at 8 weeks in subjects with dipper type hypertension, and both the daytime and nighttime BP at 8 weeks in subjects with non-dipper type hypertension, was significantly

Table 2 ABPM Value

Variable	Group	n	Baseline Mean ± s.d.	8 weeks Mean ± s.d.	Change from baseline to 8 weeks Mean ± s.d.	95% confidence interval Lower	95% confidence interval Upper	P-value[a]
24 h (mm Hg)								
SBP	Total	33	130.5 ± 11.4	121.8 ± 13.2	−8.7 ± 9.6	−12.1	−5.3	
	Morning admin	17	130.7 ± 10.0	122.6 ± 13.6	−8.1 ± 10.6	−13.5	−2.7	0.700
	Evening admin	16	130.2 ± 13.2	120.9 ± 13.1	−9.3 ± 8.7	−13.9	−4.7	
DBP	Total	33	80.3 ± 10.7	74.8 ± 9.3	−5.5 ± 6.3	−7.8	−3.3	
	Morning admin	17	79.1 ± 8.5	74.4 ± 8.1	−4.7 ± 7.6	−8.6	−0.8	0.635
	Evening admin	16	81.6 ± 12.7	75.2 ± 10.7	−6.4 ± 4.8	−9.0	−3.8	
Daytime (mm Hg)								
SBP	Total	38	134.4 ± 11.2	125.6 ± 13.2	−8.8 ± 10.6	−12.3	−5.3	
	Morning admin	20	135.0 ± 11.4	127.5 ± 13.2	−7.5 ± 11.6	−12.9	−2.1	0.380
	Evening admin	18	133.7 ± 11.3	123.5 ± 13.4	−10.2 ± 9.7	−15.0	−5.4	
DBP	Total	38	83.0 ± 10.1	77.1 ± 9.0	−5.9 ± 7.4	−8.4	−3.5	
	Morning admin	20	81.5 ± 7.7	76.6 ± 7.1	−4.9 ± 8.3	−8.8	−1.0	0.628
	Evening admin	18	84.8 ± 12.1	77.6 ± 11.0	−7.1 ± 6.4	−10.3	−4.0	
Nighttime (mm Hg)								
SBP	Total	35	123.5 ± 13.6	116.1 ± 16.2	−7.4 ± 11.2	−11.3	−3.5	
	Morning admin	18	124.9 ± 11.5	118.4 ± 17.6	−6.5 ± 13.2	−13.1	0.0	0.575
	Evening admin	17	122.0 ± 15.8	113.7 ± 14.8	−8.3 ± 9.0	−13.0	−3.7	
DBP	Total	35	75.1 ± 11.9	69.5 ± 11.0	−5.6 ± 8.4	−8.5	−2.7	
	Morning admin	18	73.6 ± 10.5	69.7 ± 10.4	−3.9 ± 8.5	−8.1	0.3	0.328
	Evening admin	17	76.6 ± 13.3	69.2 ± 11.9	−7.4 ± 8.1	−11.5	−3.2	
Early morning (mm Hg)								
SBP	Total	39	135.2 ± 12.0	127.4 ± 14.5	−7.8 ± 10.3	−11.1	−4.4	
	Morning admin	20	135.5 ± 10.9	128.6 ± 15.6	−6.9 ± 10.8	−11.9	−1.8	0.565
	Evening admin	19	134.9 ± 13.3	126.2 ± 13.5	−8.7 ± 10.0	−13.5	−3.9	
DBP	Total	39	84.8 ± 12.5	78.7 ± 9.8	−6.1 ± 12.0	−10.0	−2.2	
	Morning admin	20	82.9 ± 13.0	78.4 ± 9.8	−4.5 ± 14.1	−11.2	2.1	0.821
	Evening admin	19	86.8 ± 11.9	79.1 ± 10.2	−7.7 ± 9.3	−12.2	−3.2	

Abbreviations: ABPM, ambulatory BP monitoring; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]Analysis of covariance (ANCOVA).

Table 3 Clinic blood pressure and clinic heart rate

Variable	Group	n	Baseline Mean ± s.d.	8 weeks Mean ± s.d.	Change from baseline to 8 weeks Mean ± s.d.	95% confidence interval Lower	95% confidence interval Upper	P-value[a]
Clinic blood pressure (mm Hg)								
SBP	Total	40	150.2 ± 10.4	135.7 ± 15.0	−14.4 ± 12.7	−18.5	−10.4	
	Morning admin	21	149.9 ± 9.3	134.6 ± 13.5	−15.3 ± 11.2	−20.4	−10.2	0.630
	Evening admin	19	150.5 ± 11.8	137.1 ± 16.9	−13.5 ± 14.5	−20.4	−6.5	
DBP	Total	40	83.0 ± 10.2	75.0 ± 10.0	−8.0 ± 8.1	−10.6	−5.4	
	Morning admin	21	82.6 ± 9.0	74.6 ± 8.2	−8.0 ± 8.6	−11.9	−4.1	0.902
	Evening admin	19	83.5 ± 11.6	75.5 ± 11.9	−8.0 ± 7.8	−11.8	−4.3	
Clinic heart rate (b.p.m.)								
	Total	40	78.5 ± 11.1	77.3 ± 13.5	−1.2 ± 9.2	−4.2	1.8	
	Morning admin	21	77.2 ± 9.6	75.3 ± 10.2	−1.9 ± 7.4	−5.3	1.5	0.546
	Evening admin	19	79.9 ± 12.8	79.5 ± 16.4	−0.4 ± 11.1	−5.8	4.9	

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]Analysis of covariance (ANCOVA).

decreased compared with the mean SBP at baseline. In our subjects, 18.2% changed from non-dipper to dipper type hypertension, 12.1% changed from dipper to non-dipper type hypertension, 30.3% remained in dipper type hypertension and 39.4% remained in non-dipper type hypertension. There were no significant differences between the subjects in the morning and evening administration groups ($P = 0.345$).

Table 4 contains comparisons of the laboratory test values measured at baseline and after 8 weeks of treatment. There were no significant changes in FPG, HOMA-R, HbA1c, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, eGFR, urinary albumin/creatinine ratio, serum noradrenaline, serum dopamine and urinary 8-OHdG in all subjects, subjects in the morning administration group or subjects in the evening

Table 4 Laboratory test

			Baseline		*8 weeks*	
Variable	*Group*	n	*Mean ± s.d.*	n	*Mean ± s.d.*	P-*value*[a]
Fasting plasma glucose (mg dl^{-1})						
	Total	28	109.0 ± 26.2	28	101.3 ± 20.5	0.070
	Morning admin	15	109.4 ± 30.9	15	102.3 ± 21.7	0.329
	Evening admin	13	108.6 ± 20.7	13	100.1 ± 19.9	0.051
Fasting plasma insulin (μU ml^{-1})						
	Total	10	18.3 ± 14.3	10	15.2 ± 16.1	0.587
	Morning admin	7	22.5 ± 15.4	7	19.1 ± 18.1	0.693
	Evening admin	3	8.7 ± 2.1	3	6.1 ± 2.2	0.025
HOMA-R						
	Total	10	6.1 ± 6.5	10	4.7 ± 5.9	0.584
	Morning admin	7	7.6 ± 7.3	7	5.9 ± 6.8	0.663
	Evening admin	3	2.6 ± 1.5	3	1.8 ± 1.2	0.079
HbA1c (NGSP) (%)						
	Total	34	6.0 ± 0.8	34	6.0 ± 0.7	0.495
	Morning admin	15	5.9 ± 0.6	15	5.9 ± 0.9	0.944
	Evening admin	19	6.1 ± 0.9	19	6.0 ± 0.6	0.391
Triglyceride (mg dl^{-1})						
	Total	34	150.2 ± 121.3	34	139.0 ± 91.2	0.339
	Morning admin	17	196.1 ± 150.5	17	171.6 ± 111.3	0.252
	Evening admin	17	104.3 ± 57.1	17	106.3 ± 49.9	0.849
HDL cholesterol (mg dl^{-1})						
	Total	34	61.9 ± 22.6	34	61.8 ± 22.3	0.939
	Morning admin	17	49.7 ± 14.0	17	49.2 ± 11.5	0.799
	Evening admin	17	74.1 ± 23.3	17	74.4 ± 23.6	0.868
LDL cholesterol (mg dl^{-1})						
	Total	34	110.2 ± 27.9	34	110.2 ± 24.3	0.985
	Morning admin	17	115.5 ± 34.2	17	109.6 ± 25.0	0.158
	Evening admin	17	105.0 ± 19.3	17	110.8 ± 24.3	0.227
eGFR (ml min^{-1} 1.73 m^{-2})						
	Total	37	70.4 ± 19.9	37	71.1 ± 20.0	0.560
	Morning admin	19	67.3 ± 22.0	19	67.3 ± 20.5	0.997
	Evening admin	18	73.7 ± 17.5	18	75.1 ± 19.2	0.381
Urinary albumin/creatinine ratio (mg g^{-1} Cr)						
	Total	31	82.2 ± 244.6	31	49.5 ± 125.1	0.154
	Morning admin	17	120.5 ± 326.7	17	67.2 ± 166.5	0.201
	Evening admin	14	35.8 ± 49.6	14	27.9 ± 32.9	0.394
Serum adrenaline (pg ml^{-1})						
	Total	33	39.3 ± 31.0	33	34.7 ± 25.5	0.090
	Morning admin	17	34.8 ± 22.5	17	27.6 ± 20.4	0.032
	Evening admin	16	44.1 ± 38.2	16	42.2 ± 28.8	0.674
Serum noradrenaline (pg ml^{-1})						
	Total	33	637.7 ± 369.8	33	646.7 ± 442.6	0.873
	Morning admin	17	646.2 ± 344.6	17	520.6 ± 265.8	0.066
	Evening admin	16	628.6 ± 406.1	16	780.6 ± 552.6	0.081
Serum dopamine (pg ml^{-1})						
	Total	28	44.2 ± 100.5	28	43.3 ± 113.1	0.860
	Morning admin	15	25.3 ± 18.2	15	18.7 ± 13.8	0.122
	Evening admin	13	66.1 ± 146.2	13	71.5 ± 164.1	0.619
Urinary 8-OHdG (ng mg^{-1} Cr)						
	Total	25	9.7 ± 3.7	25	9.6 ± 3.7	0.841
	Morning admin	13	10.3 ± 4.0	13	10.1 ± 3.8	0.868
	Evening admin	12	9.1 ± 3.4	12	9.0 ± 3.6	0.916

Abbreviations: Cr, creatinine; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HDL, high-density lipoprotein; HOMA-R, homeo- stasis model insulin resistance; LDL, low-density lipoprotein; NGSP, national glycohemoglobin standardization program; 8-OHdG, 8-hydroxy-20-deoxyguanosine.
[a]Analysis of covariance (ANCOVA).

Table 5 ABPM Value (compared between subjects with and without metabolic syndrome)

			Baseline	*8 weeks*	*Change from baseline to 8 weeks*	*95% confidence interval*		
Variable	*Group*	n	*Mean ± s.d.*	*Mean ± s.d.*	*Mean ± s.d.*	*Lower*	*Upper*	P-value[a]
24 h (mm Hg)								
SBP	Non-Mets	9	131.1 ± 16.6	123.8 ± 15.6	−7.3 ± 7.4	−13.0	−1.6	0.587
	Mets	24	130.2 ± 9.3	121.1 ± 12.5	−9.2 ± 10.4	−13.6	−4.8	
DBP	Non-Mets	9	81.1 ± 14.1	76.9 ± 10.2	−4.3 ± 6.0	−8.9	0.3	0.361
	Mets	24	80.0 ± 9.4	74.1 ± 9.1	−6.0 ± 6.5	−8.7	−3.2	
Daytime (mm Hg)								
SBP	Non-Mets	9	136.7 ± 13.9	127.7 ± 13.4	−9.1 ± 9.1	−16.1	−2.1	0.930
	Mets	29	133.7 ± 10.5	125.0 ± 13.4	−8.7 ± 11.2	−12.9	−4.4	
DBP	Non-Mets	9	84.4 ± 12.7	80.0 ± 8.6	−4.4 ± 7.7	−10.3	1.6	0.280
	Mets	29	82.6 ± 9.3	76.2 ± 9.1	−6.4 ± 7.4	−9.3	−3.6	
Nighttime (mm Hg)								
SBP	Non-Mets	10	124.1 ± 21.9	119.4 ± 19.9	−4.8 ± 11.3	−12.8	3.3	0.378
	Mets	25	123.3 ± 9.1	114.8 ± 14.8	−8.4 ± 11.3	−13.1	−3.8	
DBP	Non-Mets	10	76.2 ± 15.6	71.7 ± 11.8	−4.5 ± 6.1	−8.9	−0.2	0.485
	Mets	25	74.6 ± 10.4	68.6 ± 10.7	−6.0 ± 9.2	−9.8	−2.2	
Early morning (mm Hg)								
SBP	Non-Mets	10	136.7 ± 12.3	127.7 ± 14.2	−9.0 ± 5.4	−12.8	−5.1	0.728
	Mets	29	134.7 ± 12.0	127.3 ± 14.8	−7.3 ± 11.6	−11.8	−2.9	
DBP	Non-Mets	10	83.9 ± 15.0	80.0 ± 10.1	−4.0 ± 12.6	−13.0	5.0	0.535
	Mets	29	85.1 ± 11.7	78.3 ± 9.9	−6.8 ± 11.9	−11.3	−2.3	

Abbreviations: ABPM, ambulatory BP monitoring; DBP, diastolic blood pressure; Mets, metabolic syndrome; SBP, systolic blood pressure.
[a]Analysis of covariance (ANCOVA).

administration group. However, subjects in the morning administration group had significantly lower serum adrenaline levels (27.6 ± 20.4 *vs.* 34.8 ± 22.5 mg dl^{-1}, $P = 0.032$) and subjects in the evening administration group had significantly lower fasting plasma insulin level (6.1 ± 2.2 *vs.* 8.7 ± 2.2 mg dl^{-1}, $P = 0.025$) at 8 weeks compared with baseline.

Finally, we compared BP profiles between subjects with or without metabolic syndrome or potential metabolic syndrome. There was no significant difference in the mean BP change (24 h, daytime, nighttime and early morning) from baseline to 8 weeks between subjects with or without metabolic syndrome (Table 5).

DISCUSSION

Although telmisartan is known to have long-lasting effects on lowering BP, previous reports have suggested that high-dose (80 mg per day) telmisartan monotherapy administered at bedtime may achieve significantly better nocturnal BP regulation than morning administration.[12] Previous reports have shown that drug adherence rates are generally higher for morning administration than for evening administration.[16] Although the present study was conducted in a university medical hospital and subjects showed good adherence to drug administration, such differences in adherence rate could influence the observed effect of T40/A5 FDC on the patients' general clinical condition. In fact, in the present study we found that in patients whose hypertension was uncontrolled by 5 mg of amlodipine per day, T40/A5 FDC therapy achieved optimal mean BP during the day and night regardless of the time of administration. We also revealed that both morning administration and evening administration of T40/A5 FDC could safely reduce BP equally in subjects with dipper type and non-dipper type hypertension. In addition to both telmisartan and amlodipine having strong efficacy and a long half-life, these two agents likely have complementary effects on reducing BP; telmisartan inhibits vasoconstriction caused by angiotensin II, while amlodipine leads to vasodilation by blocking the transmembrane calcium influx into vascular smooth muscle cells. The 24-h BP profile as measured by ABPM is known to correlate with the development of cardiovascular disease and prognosis more accurately than office BP;[17–20] in addition, nighttime BP was recently shown to be a better predictor of outcome than other BP profiles evaluated by ABPM.[21,22] Our study suggests that T40/A5 FDC therapy may prevent cardiovascular disease and improve prognosis independent of the time of administration.

The relationship between metabolic syndrome and diurnal BP changes remains controversial, although pooled data suggest that patients with metabolic syndrome are more likely to have a nondipping pattern in their 24-h BP profile.[23] Telmisartan is known to act as a partial agonist of peroxisome proliferator-activated receptor gamma, which regulates fatty acid storage and glucose metabolism, and it is reported to have positive effects on glucose and lipid metabolism.[24,25] Therefore, we investigated the changes in glucose and lipid metabolism after 8 weeks of treatment withT40/A5 and found that there were no significant changes. We also investigated whether there were significant differences in the efficacy of T40/A5 FDC therapy between patients with and without metabolic syndrome and found that T40/A5 FDC therapy was associated with optimal BP in patients with and without metabolic syndrome with no significant differences.

Morning administration of T40/A5 was associated with a significant reduction in serum adrenaline from baseline values, but evening administration had no impact on serum adrenaline. CCB causes reflex activation of the sympathetic nervous system and increases

catecholamine.[26,27] On the other hand, activation of the AT1 receptor by angiotensin II could cause sympathetic overactivity[28,29] and, although the effects of ARBs on catecholamine secretion is still controversial, several studies have shown that renin–angiotensin–aldosterone system blockade by ARBs could decrease the excess sympathetic responses to chronic stress and reduce serum catecholamine.[30] The elimination half-life of telmisartan is ~24 h and that of amlodipine is 30–50 h;[4–6] as we drew blood samples from all of our patients in the daytime, it is possible that only when T40/A5 was administered in the morning were blood concentrations of telmisartan high enough to reduce serum catecholamine levels at the time of the blood draw. However, further investigations are needed to clarify the mechanisms of action of T40/A5 therapy.

The present study has several limitations. First, the sample size was relatively small and the follow-up period was relatively short; larger and longer studies could better reflect the clinical efficacy or impact on prognosis of T40/A5 FDC therapy. Second, several study subjects had already taken various orally administered drugs for dyslipidemia and diabetes mellitus at baseline; these agents might have affected several parameters, such as glucose levels and lipid profile. Third, although all blood samples were obtained during the daytime, the time of blood sampling varied (morning or afternoon); therefore, the circadian variation in catecholamine might have affected our results. Finally, more-frequent BP measurement (for example, 15–20-min intervals) or 48-h periods of ABPM might have revealed the clinical effects of T40/A5 FDC therapy on the diurnal BP profile more accurately.

In conclusion, we showed that combination therapy with 40 mg of telmisartan and 5 mg of amlodipine significantly decreased the 24-h mean BP and clinical BP in patients whose hypertension was uncontrolled by 5 mg of amlodipine per day, independent of administration time (morning or evening).

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