Original Article

Comparison of the Effects of Telmisartan and Olmesartan on Home Blood Pressure, Glucose, and Lipid Profiles in Patients with Hypertension, Chronic Heart Failure, and Metabolic Syndrome

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We compared the effects of telmisartan and olmesartan in 20 patients with chronic heart failure and metabolic syndrome. The subjects underwent once-daily 40 mg telmisartan for at least 3 months before switching to once-daily 20 mg olmesartan for the next 3 months (post 1). They were then treated with 3 months of once-daily 40 mg telmisartan (post 2). Systolic and diastolic blood pressure in the early morning, plasma B-type natriuretic peptide, serum total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels were increased at post 1 ($p<0.005$, $p<0.05$, $p<0.05$, $p<0.05$, $p<0.05$, and $p<0.005$ *vs.* baseline, respectively) before returning to their baseline values at post 2. The changes in plasma B-type natriuretic peptide levels correlated significantly with the shifts in systolic and diastolic blood pressure in the early morning at posts 1 and 2. Meanwhile, there were no fluctuations in either blood pressure in the late evening or in the outpatient room; nor were there fluctuations in heart rate. Simultaneously, neither serum high-density lipoprotein cholesterol nor fasting blood sugar levels differed significantly between posts. Moreover, telmisartan had more beneficial effects on glucose and lipid profiles in patients with relatively high HbA1c, serum total and low-density lipoprotein cholesterol, and triglyceride levels. Therefore, we concluded that telmisartan was more beneficial than olmesartan for controlling blood pressure in the early morning, as well as for improving glucose and lipid profiles in patients with hypertension, chronic heart failure, and metabolic syndrome. (*Hypertens Res* 2008; 31: 921–929)

***Key Words*: telmisartan, metabolic syndrome, home blood pressure**

Introduction

To judge and control blood pressure, it is important to monitor blood pressure not only in the outpatient room but also at home (*1*–*3*). The proper and continued management of blood pressure is important to achieve the final purpose of antihypertensive therapy: protection of the internal organs. To protect the internal organs against damage, the use of long-acting antihypertensive medication is important for controlling "masked" and "early morning" hypertension, which cannot be observed by measuring blood pressure in only the outpatient room (*1*, *3*, *4*). Telmisartan is a long-acting angiotensin II receptor blocker (ARB), with a half-life ($T_{1/2}$) that is two- to six-fold longer than those of other ARBs (*5*). Telmisartan is more useful for controlling morning hypertension than valsartan when given once daily in the morning (*6*, *7*). Therefore, telmisartan is thought to be more advantageous

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than other ARBs in protecting the internal organs of patients with morning hypertension.

Strategies to prevent cardiovascular disease should include measures for the treatment and prevention of metabolic syndrome, as the morbidity rates of cardiovascular disease are higher in subjects with metabolic syndrome than in those without (*8–10*). The main causes of the syndrome are type-2 diabetes and high blood pressure, which are common background factors in insulin resistance. Therefore, drug therapy should be considered for hypertensive patients with metabolic syndrome to improve insulin resistance, while also regulating lipid and glucose metabolism (*11*, *12*). Telmisartan has recently been reported to have unique activity as a partial agonist of peroxisome proliferator–activated receptor γ (PPAR-γ) (*13–15*), which plays an important role in regulating lipid and glucose metabolism (*16*, *17*).

Therefore, the current study was performed to compare the effects of telmisartan *vs*. olmesartan in controlling home blood pressure and improving lipid and glucose metabolism regulation in patients with chronic heart failure (CHF) and metabolic syndrome.

Methods

This 6-month, open-label study involved 20 outpatients (12 men and 8 women, 66.1±4.7 years old) with chronic, stable, moderate CHF (New York Heart Association [NYHA] class II or III) and metabolic syndrome according to the National Cholesterol Education Program Adult Treatment Panel III classification (*18*) (Table 1). All patients had been taking once-daily 40 mg oral telmisartan for more than 3 months and had home blood pressure of <135/85 mmHg in the early morning (EM) and late evening (LE). The causes of heart failure were old myocardial infarction without current angina pectoris in 8 cases, hypertensive heart disease with left ventricular systolic dysfunction in 10 cases, and aortic valve insufficiency in 2 cases. Patients with complications such as secondary hypertension, hyponatremia (serum Na <135 mEq/L), hypokalemia (serum potassium <3.5 mEq/L), or renal insufficiency (serum creatinine >3.0 mg/dL) were excluded from the study. In addition to the telmisartan or olmesartan, 18 patients (90%) were also given antihypertensive medications, calcium channel blockers, β-receptor blockers, or diuretics; 14 patients (70%) were prescribed antidiabetic medication other than thiazolidinediones; and 18 (90%) received statins (Table 1). Other cardiovascular medications are shown in Table 1. The background cardiovascular medications were given for at least 1 year for β-receptor blockers and at least 3 months for the others, and they were maintained throughout the study period. Patients were instructed to take their antihypertensive medications, including telmisartan and olmesartan, after breakfast. The Institutional Ethics Committee of our hospital approved the protocol, and all patients provided written informed consent prior to participation in the study.

Table 1. Patient Profiles

20 outpatients: 12 males, 8 females	
Age (years old)	66.1±4.7 (59–74)
Height (m)	1.63±0.09 (1.50–1.77)
Body weight (kg)	72.8±8.7 (60.0–89.0)
BMI (kg/m^2)	27.4±2.4 (25.9–30.9)
NYHA class II/III	19/1
Treatment for hypertension (n=18 [90%])	
CCB	8 patients
BB	8 patients
Diuretics	10 patients
ACE I	12 patients
Treatment for diabetes (n=14 [70%])	
Sulfonylureas	10 patients
α-Glucosidase inhibitors	5 patients
Biguanides	1 patients
Treatment for dyslipidemia (n=18 [90%])	
Atorvastatin	13 patients
Simvastatin	3 patients
Pravastatin	2 patients
Other cardiovascular medications	
Diuretics	19 patients
Digitalis	6 patients
Pimobendan	2 patients

BMI, body mass index; NYHA, New York Heart Association; CCB, calcium channel blockers; BB, β-blockers, ACE I, angiotensin-converting enzyme inhibitors.

Study Protocol

Patients were enrolled in a 6-month, open-label study and given 20 mg of oral olmesartan once daily in place of 40 mg telmisartan, with comparable antihypertensive efficacy. After 3 months of olmesartan, the medication was switched back to telmisartan at the baseline (40 mg) dose. Outcome parameters evaluated at baseline (pre), after 3 months of olmesartan administration (post 1), and after 3 months of telmisartan re-administration (post 2) included: 1) systolic (SBP) and diastolic blood pressure (DBP) and heart rate at home and in the clinic; 2) plasma B-type natriuretic peptide (BNP) level; 3) lipid profile (serum total cholesterol [TC], low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglyceride [TG] levels); and 4) glucose profile (fasting blood glucose [FBS] and glycosylated hemoglobin [HbA1c]).

Measurements

Blood pressure was measured at home using validated oscillometric Omron HEM-705CP devices (Omron Healthcare, Kyoto, Japan). After 5 min of rest in the sitting position, patients performed 3 successive self-measurements of SBP and DBP twice daily; in the EM between 6 and 9 AM (within

Table 2. Changes in the Parameters

	Pre (T)	Post 1 (O)	Post 2 (T)
Home blood pressure			
SBP in EM (mmHg)	129.0±4.1	130.9±5.3***	129.0±4.7$^{\#\#}$
DBP in EM (mmHg)	75.9±4.5	77.5±4.5*	76.2±3.9$^{\#}$
SBP in LE (mmHg)	127.5±4.1	127.2±5.2	127.2±5.2
DBP in LE (mmHg)	71.1±6.2	70.0±6.1	70.6±5.4
Clinic blood pressure			
SBP (mmHg)	129.9±5.9	129.3±5.0	129.5±5.2
DBP (mmHg)	73.2±6.2	72.1±5.9	72.7±5.3
Heart rate			
EM (/min)	71.0±7.1	70.8±6.0	71.3±6.4
LE (/min)	67.9±4.9	67.0±4.9	68.1±4.9
Outpatients room (/min)	70.7±5.2	69.9±5.0	70.6±5.7
Body weight (kg)	72.8±8.7	72.9±8.2	72.6±8.2
BNP (pg/mL)	191.0±67.9	197.3±75.9*	188.6±68.0$^{\#\#\#}$
Glucose metabolism			
FBS (mg/dL)	111.0±13.2	111.4±14.3	110.7±13.8
HbA1c (%)	6.0±0.7	6.1±0.8*	6.0±0.7$^{\#}$
Lipid metabolism			
TC (mg/dL)	217.7±17.9	220.1±19.3*	218.4±17.9$^{\#}$
LDL cholesterol (mg/dL)	127.8±19.2	130.4±18.3*	127.7±19.0$^{\#}$
HDL cholesterol (mg/dL)	39.9±5.8	39.6±5.4	39.6±4.9
Triglyceride (mg/dL)	218.0±74.3	226.8±82.5***	218.6±75.4$^{\#\#\#}$

T, once-daily telmisartan 40 mg; O, once-daily olmesartan 20 mg; SBP, systolic blood pressure; DBP, diastolic blood pressure; EM, the early morning; LE, the late evening; BNP, B-type natriuretic peptide; FBS, fasting blood sugar; TC, total cholesterol, LDL, low-density lipoprotein; HDL, high-density lipoprotein. *$p<0.05$, ***$p<0.005$ *vs*. pre; $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.005$ *vs*. post 1.

1 h after rising, post-urination, but before breakfast and medication intake) and in the LE between 9 and 11 PM (just prior to sleep). The mean of 3 successive measurements obtained at 1-min intervals was taken as the home blood pressure value. Home blood pressures at baseline, post 1, and post 2 were determined as the average values of each of 3 consecutive days. A physician measured the blood pressure of seated patients at clinic between 9 AM and 2 PM with a conventional mercury sphygomomanometer. The first and fifth Korotkoff sounds were taken to identify SBP and DBP, respectively.

Blood samples were drawn by venipuncture after a 12-h overnight fast and after at least 30 min of rest with the patient in the supine position. Serum FBS, HbA1c, TC, HDL cholesterol, LDL cholesterol, and TG levels were measured immediately using an autoanalyzer (AU 5200; Olympus, Tokyo, Japan). Plasma BNP levels were measured by a subcontract by radioimmunoassay using commercial kits (Shionoria BNP Kit; Shionogi, Osaka, Japan) (FALCO Biosystems, Osaka, Japan). The intra-assay coefficient of variation (2.13% to 7.84%) and inter-assay coefficient of variation (6.81% to 12.15%) increased from high (650.8 pg/mL) to low (18.7 pg/mL) BNP.

Statistical Analysis

All results are expressed as means±SD. Comparisons of baseline and post-study data were performed using the paired *t*-test or Wilcoxon's single-rank test as appropriate. Linear regression analysis was used to test the correlations between continuous variables. Probability values less than 0.05 were regarded as statistically significant.

Results

Serial Changes in Home and Clinic Blood Pressure, BNP, and Parameters of Lipid and Glucose Profiles

Table 2 shows the changes in the parameters examined in this study. SBP and DBP in the EM, plasma BNP levels, serum TC, LDL cholesterol, TG, and HbA1c were increased significantly at post 1 but returned to baseline values at post 2. Meanwhile, SBP and DBP in the LE and at the clinic, as well as heart rate, did not differ significantly. In addition, no changes were observed in serum HDL cholesterol or FBS or in body weight during this study. These results suggested that telmisartan was more beneficial than olmesartan for the management of blood pressure in the EM, heart failure, and both

Table 3. Changes in the Parameters in the Subgroups Divided According to the Baseline BMI

		Pre (T)	Post 1 (O)	Post 2 (T)
Home blood pressure				
SBP in EM (mmHg)	H	129.7±5.4	132.4±5.8*	129.4±5.8$^{\#}$
	L	128.2±5.1	129.3±5.7	128.6±5.9
DBP in EM (mmHg)	H	75.7±4.9	77.4±5.2*	76.0±4.9$^{\#}$
	L	76.5±4.9	77.9±3.0	76.9±2.4
Body weight (kg)	H	76.2±8.3	76.1±8.3	76.0±8.3
	L	69.4±7.7	69.6±7.5	69.4±7.9
BNP (pg/mL)	H	195.8±63.3	207.2±71.4*	194.6±64.5$^{\#\#}$
	L	186.2±58.9	187.4±56.3	182.5±57.9
Glucose metabolism				
FBS (mg/dL)	H	119.2±8.4	120.1±8.3	118.7±9.4
	L	102.8±5.5	102.6±6.2	102.6±5.3
HbA1c (%)	H	6.6±0.5$^{\$}$	6.8±0.5**,$^{\$}$	6.6±0.5$^{\#\#,\$}$
	L	5.5±0.2	5.4±0.2	5.4±0.2
Lipid metabolism				
TC (mg/dL)	H	220.4±23.3	221.7±25.1	219.7±23.6
	L	215.0±14.6	218.6±17.3	217.1±15.4
LDL cholesterol (mg/dL)	H	125.5±21.4	127.1±21.9	125.5±20.6
	L	130.1±15.0	133.7±16.4	129.8±15.8
HDL cholesterol (mg/dL)	H	41.9±5.7	41.2±5.8	41.3±5.2
	L	37.8±6.0	37.9±6.7	37.8±5.5
Triglyceride (mg/dL)	H	232.5±73.4	242.1±82.3*	233.6±75.0$^{\#}$
	L	204.1±58.6	211.5±66.2*	203.6±58.4$^{\#}$

BMI, body mass index; H, patients with high BMI (≥27.0 kg/m^2) at the baseline (n=10); L, patients with low BMI (<27.0 kg/m^2) at the baseline (n=10). Other abbreviasions as in Table 2. *p<0.05, **p<0.01 *vs*. pre; $^{\#}p$<0.05, $^{\#\#}p$<0.01 *vs*. post 1; $^{\$}p$<0.005 *vs*. L.

lipid and glucose metabolism in patients with CHF and metabolic syndrome.

Moreover, these favorable effects of telmisartan, except that on lipid metabolism, were more overt in patients with relatively high body mass index (BMI) (≥27.0 kg/m^2) than in patients with relatively low BMI (<27.0 kg/m^2) (Table 3).

Correlation between Changes in Blood Pressure, BNP, and Parameters of Lipid and Glucose Profiles

Increases in plasma BNP level correlated with the rises in SBP and DBP in the EM at post 1 (Fig. 1A and C), and the decreases in plasma BNP level correlated with the reductions in SBP and DBP in the EM at post 2 (Fig. 1B and D). There were no similar correlations between BNP and SBP or DBP in the LE. Body weight did not change significantly throughout this study and was independent from all parameters, including plasma BNP levels, SBP, and DBP. These observations suggested that it is important to control home blood pressure in the EM for the management of heart failure in patients with CHF and metabolic syndrome.

On the other hand, the trend in lipid and glucose profiles did not seem to correlate with those in SBP or DBP in the EM, LE, or at the clinic. Therefore, the beneficial effects of telmisartan on lipid and glucose profiles were separate from its antihypertensive effect.

Effects of Telmisartan on Parameters of Lipid and Glucose Metabolism

To investigate the effects of telmisartan on lipid and glucose metabolism parameters, we compared serial changes in these parameters between the 2 groups, stratified according to the mean serum TC, LDL cholesterol, TG, and HbA1c levels at post 2. Figure 2A shows the serial changes in TC in patients with relatively high TC (≥220.1 mg/dL at post 2; mean value, 232.3 mg/dL) and low TC (<220.1 mg/dL at post 2; mean value, 197.4 mg/dL). In comparison with olmesartan, telmisartan decreased TC concentrations in patients with relatively high TC, whereas patients with relatively low TC showed no difference between the groups. Similarly, telmisartan had more beneficial effects than olmesartan on serum LDL cholesterol in patients with relatively high serum LDL cholesterol (≥130.4 mg/dL at post 2; mean, 146.5 mg/dL) (Fig. 2B) and on TG levels (≥226.8 mg/dL at post 2; mean, 297.4 mg/dL) (Fig. 3A) and HbA1c (≥6.1% at post 2; mean, 6.9%) (Fig. 3B) at post 2. However, no differences were observed between the medications for patients with relatively low LDL cholesterol (<130.4 mg/dL; mean, 114.3 mg/dL) (Fig. 2B),

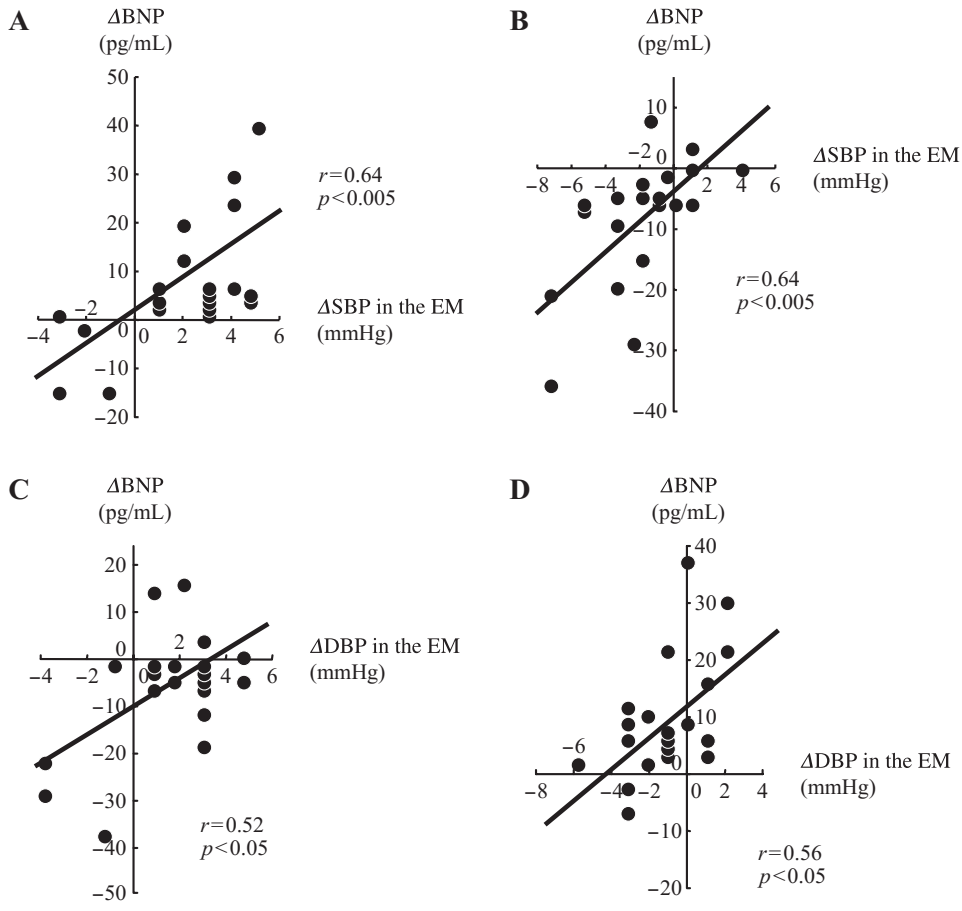

Fig. 1. *Correlation between ΔBNP and ΔSBP in the EM. BNP, B-type natriuretic peptide; SBP, systolic blood pressure; DBP, systolic blood pressure; EM, early morning. A: Correlation between ΔBNP and ΔSBP in the EM from pre to post 1. B: Correlation between ΔBNP and ΔSBP in the EM from post 1 to post 2. C: Correlation between ΔBNP and ΔDBP in the EM from pre to post 1. D: Correlation between ΔBNP and ΔDBP in the EM from post 1 to post 2.*

TG (<226.8 mg/dL; mean, 169.0 mg/dL) (Fig. 3A) or HbA1c (<6.1%; mean, 5.6%) at post 2 (Fig. 3B). Consequently, telmisartan showed marked effects on lipid and glucose profiles only in patients with serious dysfunction in lipid or glucose metabolism.

Discussion

This is the first direct comparison of the effects of telmisartan and olmesartan on home blood pressure and both lipid and glucose profiles in hypertensive patients with CHF and metabolic syndrome. Our findings indicated that once-daily telmisartan at a dose of 40 mg reduced morning blood pressure and improved lipid and glucose metabolism as compared with once-daily 20 mg olmesartan, suggesting that telmisartan may be more beneficial than olmesartan in the management of hypertension, CHF, and metabolic syndrome.

Internal Organ Protection by Long-Acting Antihypertensive Medication

Telmisartan's antihypertensive action consistently shows a longer half-life than those of other ARBs and amlodipine (*6*, *7*, *19*, *20*). In the present study, after the switch from telmisartan (once daily, 40 mg) to olmesartan (once daily, 20 mg), EM blood pressure was elevated at approximately 24 h post-administration, while there was little variation in LE at approximately 12 h or approximately 3–5 h after administration at our clinic (Table 2). These results indicated that telmisartan's antihypertensive action lasts longer than olmesartan's.

For CHF patients with hypertension, it is important to control blood pressure continuously throughout the day (*1*, *21*, *22*). Therefore, it is recommended to monitor their home blood pressure both at home and in the outpatient room (*1–3*). Insufficient EM hypertension management is responsible for difficulty in preventing and recovering from hypertensive

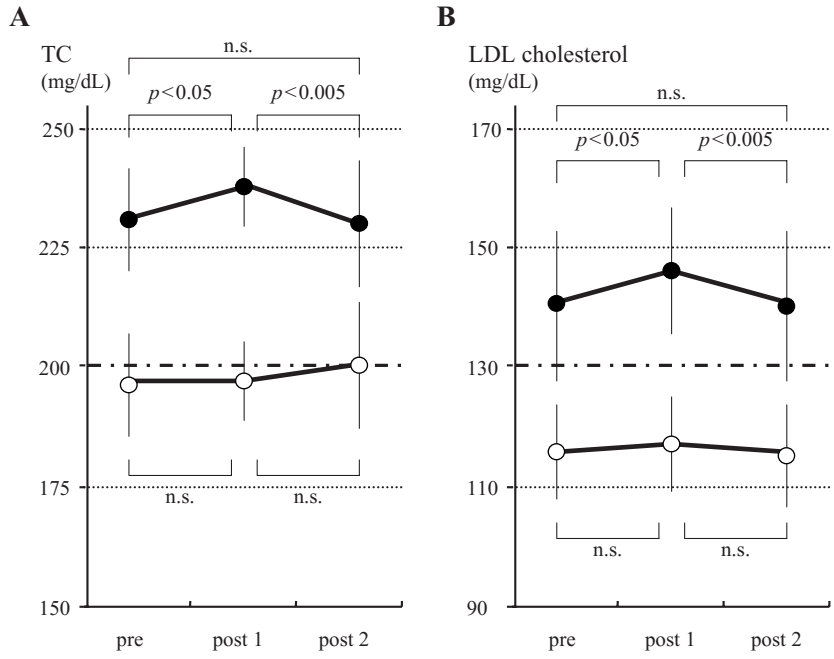

Fig. 2. *Serial changes in TC and LDL cholesterol. A: TC, total cholesterol. ●, patients with TC ≥220.1 mg/dL at post 2 (mean: 232.3 mg/dL; n=13); ○, patients with TC <220.1 mg/dL at post 2 (mean: 197.4 mg/dL; n=7). B: LDL cholesterol, low-density lipoprotein cholesterol. ●, patients with LDL cholesterol ≥130.4 mg/dL at post 2 (mean: 146.5 mg/dL; n=10); ○, patients with LDL cholesterol <130.4 mg/dL at post 2 (mean: 114.3 mg/dL; n=10). Note that telmisartan had significant effects on serum TC or LDL cholesterol levels in patients with TC ≥220.1 mg/dL (A) or LDL cholesterol ≥130.4 mg/dL (B) at post 2.*

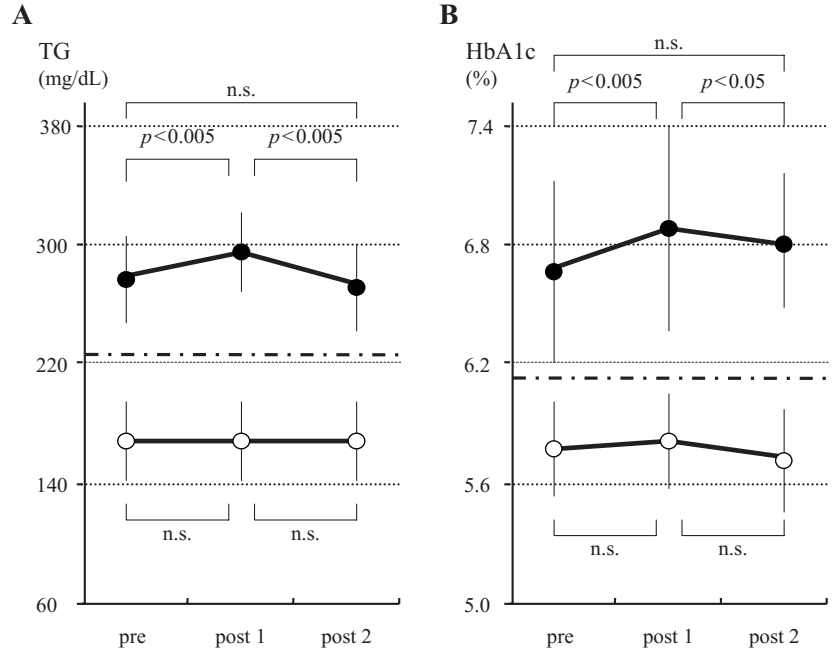

Fig. 3. *Serial changes in TG and HbA1c. A: TG, triglyceride. ●, patients with TG ≥226.8 mg/dL at post 2 (mean: 297.4 mg/dL; n=9); ○, patients with TG <226.8 mg/dL at post 2 (mean: 169.0 mg/dL; n=11). B: HbA1c, glycosylated hemoglobin. ●, patients with HbA1c ≥6.1% at post 2 (mean: 6.9%; n=8); ○, patients with HbA1c <6.1% at post 2 (mean: 5.6%; n=12). Note that telmisartan had significant effects on serum TG or HbA1c levels in patients with TG ≥226.8 mg/dL (A) or HbA1c ≥6.1% (B) at post 2.*

organ damage and can lead to deterioration of cardiac function in CHF patients with hypertension (*1*, *3*, *4*). Cardiologists usually evaluate the management state of CHF patients by monitoring their plasma BNP levels (*23*, *24*). Plasma BNP level is a useful indicator for screening the heart failure state. ARBs have been reported to decrease plasma BNP levels *via* the effects of the reduction of afterload and preload and, more importantly, *via* myocardial protection through their suppressive action on the renin-angiotensin-aldosterone system (*25*–*29*). In the present study, the transition of plasma BNP levels correlated with the transition of SBP and DBP in the EM (Fig. 1). On the other hand, it is believed that the changes in both SBP and DBP in the LE (less than 0.3 mmHg and 1.1 mmHg, respectively) were not significant and did not influence plasma BNP level. These observations suggested that control of morning blood pressure is important and that telmisartan is more effective than olmesartan in managing CHF patients with hypertension, partially due to its longer antihypertensive action.

Effects of ARBs on Glucose Metabolism

Although ARBs improve insulin resistance as a class through their inhibitory effects on AT1 receptors (*30*), telmisartan also has a PPAR-γ–activating effect that acts synergistically to further improve insulin resistance (*13*, *16*, *31*). It has been reported that this action of telmisartan is about 1/2 titer per mol/L of the thiazolidinedione, pioglitazone (*15*). Indeed, telmisartan's effect on improving glucose metabolism has been reported to be superior to those of other ARBs, losartan (*32*), candesartan, and valsartan (*33*, *34*), due to its effects that improve insulin resistance (*13*, *27*, *35*, *36*). In the current study, HbA1c rose when the treatment regimen was switched from telmisartan to olmesartan but decreased after the return to telmisartan (Fig. 3B). Meanwhile, there were no changes in FBS throughout the study. These observations did not directly demonstrate that telmisartan improved insulin resistance in the present study, since the transition of the insulin value and resistance were not measured directly. The discrepancy in the effects of telmisartan on FBS and HbA1c in our study may have been caused by the prescription of oral anti-diabetic medicine, sulfonylureas, and others for most patients, and their FBSs were controlled under relatively low values. Further studies are needed to investigate the effects of telmisartan *vs*. olmesartan on FBS and HbA1c in diabetic patients who are not being treated by such medicine.

A previous study indicated HbA1c reduction after telmisartan treatment (*32*), although others noted no such effect (*35*, *37*, *38*). These reports were difficult to compare because the baseline characteristics of the subjects and the telmisartan dose differed from study to study. When differences in physical characteristics due to race are taken into consideration, the BMIs were relatively high in both the former study (*32*) and the present study, while they were relatively low in the latter reports, except in Nagel *et al*. (*38*). Therefore, telmisartan may reduce HbA1c only in obese patients, in whom insulin resistance will be remarkable. In the present study, telmisartan had more additive beneficial effects on HbA1c in patients with relatively high HbA1c (≥6.1%) or BMI (≥27.0 kg/m^2), but patients with relatively low HbA1c (<6.1%) or BMI (<27.0 kg/m^2) showed no such effects between telmisartan and olmesartan (Fig. 3 and Table 3). These observations suggested that the reduction in HbA1c induced by telmisartan was striking only in cases with marked glucose metabolism dysfunction. This may explain why there were no HbA1c fluctuations after telmisartan treatment in the report by Nagel *et al*. (*38*), in which baseline HbA1c was as low as 5.5%.

Effects of ARBs on Lipid Metabolism

PPAR-γ, activated by telmisartan, affects fat cell differentiation (*39*). Telmisartan shows excellent effects in controlling body weight and fat accumulation in the internal organs and reduces adipose cell size better than valsartan (*34*). Moreover, telmisartan has also been reported to increase low serum adiponectin levels (*40*–*42*) in patients with metabolic syndrome. In the present study, serum TC, LDL cholesterol, and TG levels increased after the switch from telmisartan to olmesartan, and dropped once more after the return to telmisartan (Figs. 2A, B, and 3A). Previous studies indicated reduced TC, LDL cholesterol, and TG levels after treatment with telmisartan (*37*, *43*, *44*), while other studies noted no such findings (*35*, *42*, *45*). Although these reports were difficult to compare because the baseline lipid profiles of the subjects and telmisartan doses differed among the studies, the baseline TC, LDL cholesterol, and TG were higher in the former than in the latter reports. In the present study, telmisartan had more beneficial effects on lipid profiles in patients with relatively high TC (≥220.1 mg/dL), LDL cholesterol (≥130.4 mg/dL), and TG (≥226.8 mg/dL) levels and showed no additive effects on lipid profiles in patients with relatively low TC (<220.1 mg/dL), LDL cholesterol (<130.4 mg/dL), and TG (<226.8 mg/dL) levels. These results suggest that the molecular mechanism underlying the favorable effects of telmisartan on lipid disorder may differ from those of statins, and that the lipid metabolism improvement is a unique effect of telmisartan not shared by other ARBs. These results were mostly in agreement with a recent report, which stated that severely altered baseline lipid parameters are necessary to see an improvement in lipid metabolism with telmisartan treatment (*44*). This mechanism of action of telmisartan remains unclear, but could perhaps be explained by the high lipophilicity of this agent as compared with other ARBs, including olmesartan (*46*), by PPAR-α–activating effects but not PPAR-γ–activating effects (*13*), or by unknown molecular effects to fat cells.

In conclusion, the results of our study demonstrated that the antihypertensive effect of once-daily telmisartan continued to the next morning and before the next administration, resulting in more favorable management of CHF than occurs with olm-

esartan treatment. In addition, telmisartan showed more beneficial effects on lipid and glucose metabolism than olmesartan, especially in patients with relatively severe disorders in lipid and glucose profiles. Further studies with larger numbers of patients should compare the effects of telmisartan and olmesartan in controlling home blood pressure and improving the regulation of lipid and glucose metabolism. Moreover, further studies are needed also to investigate the effects of telmisartan *vs*. olmesartan on FBS and HbA1c in diabetic patients who are not being treated with oral anti-diabetic medicine. Furthermore, additional investigations of the molecular mechanisms of the favorable effects of telmisartan on lipid disorder are required.

References

1. Mancia G, De Backer G, Dominiczak A, *et al*, 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.
2. Tislér A, Dunai A, Keszei A, *et al*: Primary-care physicians' views about the use of home/self blood pressure monitoring: nationwide survey in Hungary. *J Hypertens* 2006; **24**: 1729–1735.
3. Shimizu M, Shibasaki S, Kario K: The value of home blood pressure monitoring. *Curr Hypertens Rep* 2006; **8**: 363–367.
4. Chrysant SG, Chrysant GS, Desai A: Current status of angiotensin receptor blockers for the treatment of cardiovascular diseases: focus on telmisartan. *J Hum Hypertens* 2005; **19**: 173–183.
5. Kakuta H, Sudoh K, Sasamata M, Yamagishi S: Telmisartan has the strongest binding affinity to angiotensin II type 1 receptor: comparison with other angiotensin II type 1 receptor blockers. *Int J Clin Pharmacol Res* 2005; **25**: 41–46.
6. Lacourcière Y, Krzesinski JM, White WB, Davidai G, Schumacher H: Sustained antihypertensive activity of telmisartan compared with valsartan. *Blood Press Monit* 2004; **9**: 203–210.
7. White WB, Lacourciere Y, Davidai G: Effects of the angiotensin II receptor blockers telmisartan *versus* valsartan on the circadian variation of blood pressure: impact on the early morning period. *Am J Hypertens* 2004; **17**: 347–353.
8. Ford ES: Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. *Diabetes Care* 2005; **28**: 1769–1778.
9. Lorenzo C, Williams K, Hunt KJ, Haffner SM: The National Cholesterol Education Program—Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. *Diabetes Care* 2007; **30**: 8–13.
10. Galassi A, Reynolds K, He J: Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. *Am J Med* 2006; **119**: 812–819.
11. Nelson MR: Managing 'metabolic syndrome' and multiple risk factors. *Aust Fam Physician* 2004; **33**: 201–205.
12. Kurtz TW: New treatment strategies for patients with hypertension and insulin resistance. *Am J Med* 2006; **119** (Suppl 1): S24–S30.
13. Benson SC, Pershadsingh HA, Ho CI, *et al*: Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARgamma-modulating activity. *Hypertension* 2004; **43**: 993–1002.
14. Kurtz TW, Pravenec M: Antidiabetic mechanisms of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists: beyond the renin-angiotensin system. *J Hypertens* 2004; **22**: 2253–2261.
15. Schupp M, Janke J, Clasen R, Unger T, Kintsher U: Angiotensin type 1 receptor blockers induce peroxisome proliferators–activated receptor-gamma activity. *Circulation* 2004; **109**: 2054–2057.
16. Lehman JM, Moore JB, Smith-Oliver TA, Wilkinson WO, Willson TM, Kliewer SA: An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferators–activated receptor γ (PPAR γ). *J Biol Chem* 1995; **270**: 12953–12956.
17. Schiffrin EL, Amiri F, Benkirane K, Igralz M, Diep QN: Peroxisome proliferators–activated receptors: vascular and cardiac effects in hypertension. *Hypertension* 2003; **42**: 664–668.
18. National Cholesterol Education Program: Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; **285**: 2486–2497.
19. Mallion J, Siche J, Lacourcière Y: ABPM comparison of the antihypertensive profiles of the selective angiotensin II receptor antagonists telmisartan and losartan in patients with mild-to-moderate hypertension. *Hum Hypertens* 1999; **13**: 657–664.
20. Littlejohn T, Mroczek W, Marbury T, VanderMaelen CP, Dubiel RF: A prospective, randomized, open-label trial comparing telmisartan 80 mg with valsartan 80 mg in patients with mild to moderate hypertension using ambulatory blood pressure monitoring. *Can J Cardiol* 2000; **16**: 1123–1132.
21. VA Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. *JAMA* 1970; **213**: 1143–1152.
22. Diez J, Gonzalez A, Lopez B, Ravassa S, Fortuno MA: Effects of antihypertensive agents on the left ventricle: clinical implications. *Am J Cardiovasc Drugs* 2001; **1**: 263–279.
23. Inomata T, Nishii M, Takehara H, *et al*: Brain natriuretic peptide-guided treatment reduces cardiovascular events of heart failure in outpatient management. *Circulation* 2003; **108** (Suppl): IV-446 (Abstract).
24. Wang TJ, Larson MG, Levy D, *et al*: Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004; **350**: 655–663.
25. Latini R, Masson S, Anand I, *et al*, for the Val-HeFT Inves-

tigators: The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT. *Eur Heart J* 2004; **25**: 292–299.
26. Kasama S, Toyama T, Kumakura H, *et al*: Effects of candesartan on cardiac sympathetic nerve activity in patients with congestive heart failure and preserved left ventricular ejection fraction. *J Am Coll Cardiol* 2005; **45**: 661–667.
27. Shimada H, Kitamura K, Anraku M, *et al*: Effect of telmisartan on ambulatory blood pressure monitoring, plasma brain natriuretic peptide, and oxidative status of serum albumin in hemodialysis patients. *Hypertens Res* 2005; **28**: 987–994.
28. Masson S, Latini R, Anand IS, *et al*, Val-HeFT Investigators: Direct comparison of B-type natriuretic peptide (BNP) and amino-terminal proBNP in a large population of patients with chronic and symptomatic heart failure: the Valsartan Heart Failure (Val-HeFT) data. *Clin Chem* 2006; **52**: 1528–1538.
29. Kasama S, Toyama T, Hatori T, *et al*: Comparative effects of valsartan and enalapril on cardiac sympathetic nerve activity and plasma brain natriuretic peptide in patients with congestive heart failure. *Heart* 2006; **92**: 625–630.
30. Jandeleit-Dahm KA, Tikellis C, Reid CM, Johnston CI, Cooper ME: Why blockade of the renin-angiotensin system reduces the incidence of new-onset diabetes. *J Hypertens* 2005; **23**: 463–473.
31. Pershadsingh HA, Kurtz TW: Insulin-sensitizing effects of telmisartan: implications for treating insulin-resistant hypertension and cardiovascular disease. *Diabetes Care* 2004; **27**: 1015.
32. Vitale C, Mercuro G, Castiglioni C, *et al*: Metabolic effect of telmisartan and losartan in hypertensive patients with metabolic syndrome. *Cardiovasc Diabetol* 2005; **4**: 6.
33. Miura Y, Yamamoto N, Tsunekawa S, *et al*: Replacement of valsartan and candesartan by telmisartan in hypertensive patients with type 2 diabetes: metabolic and antiatherogenic consequences. *Diabetes Care* 2005; **28**: 757–758.
34. Sugimoto K, Qi NR, Kazdova L, Pravenec M, Ogihara T, Kurtz TW: Telmisartan but not valsartan increases caloric expenditure and protects against weight gain and hepatic steatosis. *Hypertension* 2006; **47**: 1003–1009.
35. Usui I, Fujisaka S, Yamazaki K, *et al*: Telmisartan reduced blood pressure and HOMA-IR with increasing plasma leptin level in hypertensive and type 2 diabetic patients. *Diabetes Res Clin Pract* 2007; **77**: 210–214.
36. Benndorf RA, Rudolph T, Appel D, *et al*: Telmisartan improves insulin sensitivity in nondiabetic patients with essential hypertension. *Metabolism* 2006; **55**: 1159–1164.
37. Derosa G, Ragonesi PD, Mugellini A, Ciccarelli L, Fogari R: Effects of telmisartan compared with eprosartan on blood pressure control, glucose metabolism and lipid profile in hypertensive, type 2 diabetic patients: a randomized, double-blind, placebo-controlled 12-month study. *Hypertens Res* 2004; **27**: 457–464.
38. Nagel JM, Tietz AB, Göke B, Parhofer KG: The effect of telmisartan on glucose and lipid metabolism in nondiabetic, insulin-resistant subjects. *Metabolism* 2006; **55**: 1149–1154.
39. Janke J, Schupp M, Engeli S, *et al*: Angiotensin type 1 receptor antagonists induce human *in-vitro* adipogenesis through peroxisome proliferator–activated receptor-gamma activation. *J Hypertens* 2006; **24**: 1809–1816.
40. Clasen R, Schupp M, Foryst-Ludwig A, *et al*: PPAR-gamma–activating angiotensin type-1 receptor blockers induce adiponectin. *Hypertension* 2005; **46**: 137–143.
41. Moriuchi A, Yamasaki H, Shimamura M, *et al*: Induction of human adiponectin gene transcription by telmisartan, angiotensin receptor blocker, independently on PPAR-gamma activation. *Biochem Biophys Res Commun* 2007; **356**: 1024–1030.
42. Negro R, Formoso G, Hassan H: The effects of irbesartan and telmisartan on metabolic parameters and blood pressure in obese, insulin resistant, hypertensive patients. *J Endocrinol Invest* 2006; **29**: 957–961.
43. Derosa G, Cicero AF, Bertone G, *et al*: Comparison of the effects of telmisartan and nifedipine gastrointestinal therapeutic system on blood pressure control, glucose metabolism, and the lipid profile in patients with type 2 diabetes mellitus and mild hypertension: a 12-month, randomized, double-blind study. *Clin Ther* 2004; **26**: 1228–1236.
44. Inoue T, Morooka T, Moroe K, Ikeda H, Node K: Effect of telmisartan on cholesterol levels in patients with hypertension—Saga Telmisartan Aggressive Research (STAR). *Horm Metab Res* 2007; **39**: 372–376.
45. Koulouris S, Symeonides P, Triantafyllou K, *et al*: Comparison of the effects of ramipril *versus* telmisartan in reducing serum levels of high-sensitivity C-reactive protein and oxidized low-density lipoprotein cholesterol in patients with type 2 diabetes mellitus. *Am J Cardiol* 2005; **95**: 1386–1388.
46. Wienen W, Entzeroth M, van Meel JCA, *et al*: A review on telmisartan: a novel, long-acting angiotensin II–receptor antagonist. *Cardiovasc Drug Rev* 2000; **18**: 127–156.