Original Article

Comparison of Effects of Olmesartan and Telmisartan on Blood Pressure and Metabolic Parameters in Japanese Early-Stage Type-2 Diabetics with Hypertension

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Angiotensin II type-1 receptor blockers (ARBs) are regarded as first-line treatments for type-2 diabetes with hypertension. Despite the availability of various types of ARBs, there are no comparative studies of their effects on patients with diabetes. In this open-label prospective crossover study, we compared the effects of olmesartan (20 mg/day) and telmisartan (40 mg/day). Twenty Japanese early-stage type-2 diabetes patients with hypertension treated with valsartan (80 mg/day) for at least 8 weeks were recruited to this study. At study entry, valsartan was changed to olmesartan (20 mg/day) or telmisartan (40 mg/day) and administered for 8 weeks. The drugs were then switched and treatment was continued for another 8 weeks. We analyzed the blood pressure lowering effects of each drug by 24-h ambulatory blood pressure monitoring at 0, 8, and 16 weeks. Simultaneously, we measured metabolic parameters and inflammation markers. Olmesartan lowered mean systolic and diastolic blood pressure more significantly than did telmisartan. While there were no differences between the groups in metabolic parameters, including HbA1c and adiponectin, the decreases in serum interleukin-6 and highly sensitive C-reactive protein were more significant by olmesartan treatment. Our results indicate that olmesartan has more potent arterial blood pressure lowering and anti-inflammatory effects than telmisartan. (*Hypertens Res* 2008; 31: 7–13)

Key Words: angiotensin, hypertension, type-2 diabetes, inflammation, peroxisome proliferation-activated receptor γ

Introduction

Patients with type-2 diabetes are at high risk for developing cardiovascular diseases, which are also the most common cause of death in these patients. In type-2 diabetes, the prevalence of hypertension is higher than in the general population (1). Hypertension complicated with diabetes increases the incidence of cardiovascular disease (2). Thus, to reduce car-

diovascular events in patients with type-2 diabetes, treatment of hypertension in addition to glycemic control is important (2, 3). The importance of strict blood pressure control in patients with type-2 diabetes was emphasized in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (4). The report recommends a blood pressure target of <140/90 mmHg for most patients with uncomplicated hypertension. On the other hand, the report and the Japanese Soci-

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Fig. 1. Study protocol. The study protocol is shown in this schematic diagram. Blood sampling and ABPM were performed at week 0 for basal data. Blood samples obtained at week 8 or week 16 were used for evaluation of each drug. W, week.

ety of Hypertension (5) also recommends $<130/80$ mmHg for hypertensive patients with diabetes mellitus.

Angiotensin II type-1 receptor blockers (ARB) are widely used for the treatment of hypertension (6). They also have beneficial effects on hypertension-related cardiovascular end-organ damage, at least in part through a reduction of oxidative stress and inflammation (7, 8). In addition, they substantially lower the risk of type-2 diabetes compared with other antihypertensive therapies, probably by regulating insulin sensitivity (9, 10).

Among the several ARBs available in the clinical setting, olmesartan is thought to have a significantly stronger blood pressure lowering effect than losartan or valsartan with their respective starting doses (11, 12). In addition, recent data demonstrated that olmesartan more adequately achieved ambulatory blood pressure monitoring (ABPM) goals during the early morning surge period than did candesartan (13). Considering the importance of strict blood pressure control (14), olmesartan offers certain advantages in clinical use.

With regard to its metabolic effect, telmisartan has the unique property of selective peroxisome proliferation-activated receptor γ (PPAR γ)-modulating activity, at least *in vitro* (15–17). Thus, telmisartan might have clinical effects similar to those of PPAR γ agonists, such as improving insulin resistance and increasing serum adiponectin levels. In fact, a recent study demonstrated that replacement of valsartan with telmisartan reduced serum highly sensitive C-reactive protein (hs-CRP) and increased serum adiponectin (18). Another study revealed that telmisartan has superior effects on metabolic parameters compared to losartan in hypertensive patients with metabolic syndrome (19). In addition, telmisar-

tan's blood pressure lowering effect is reported to last longer than valsartan's (20).

To gain insight into the respective properties of ARB for type-2 diabetic patients with hypertension, an open-label crossover trial was conducted to compare the efficacy of the starting doses of olmesartan and telmisartan on blood pressure, metabolic parameters, and inflammatory parameters.

Methods

Subjects

All patients with type-2 diabetes mellitus who visited Jun-tendo University Hospital (Tokyo, Japan) or Secomedic Hospital (Funabashi, Japan) from March 2006 to August 2006 were asked to participate in the study. The inclusion criteria were patients with type-2 diabetes mellitus and hypertension who were being treated with valsartan 80 mg once daily for at least 8 weeks. Patients with HbA1c exceeding 7.0% and/or patients treated with insulin or more than a minimal dose of sulfonylurea agents were excluded from the study. In addition, patients with diabetic microangiopathy, severe renal or hepatic disease, overt cardiovascular disease, or malignancy were excluded. A total of 20 Japanese subjects were recruited for this study. The hospital ethics committee approved this study protocol, and informed consent was obtained from each subject.

Study Design

An open-label crossover design was used. After completion

Table 1. Baseline Characteristics of Study Subjects

Age (years)	63.7±6.9
Gender (male/female)	14/6
Body weight (kg)	66.0±11.4
Body mass index (kg/m ²)	25.6±1.1
Waist (male/female) (cm)	87.8±2.2/85.1±7.5
Mean duration of diabetes (years)	8.1±10.8
Current smokers (<i>n</i>)	11
Presence of metabolic syndrome (<i>n</i>)	13
Medications	
Other antihypertensive medication	
Calcium antagonist (<i>n</i>)	9
Diuretic (<i>n</i>)	3
Hypoglycemic treatment	
Sulfonylurea (<i>n</i>)	8
Glinide (<i>n</i>)	1
α -Glucosidase (<i>n</i>)	4
Thiazolidinedione (<i>n</i>)	1
Statin (<i>n</i>)	2
Aspirin (<i>n</i>)	4

n=20. Data are mean±SD or number of subjects.

of a run-in period consisting of once-daily administration of valsartan 80 mg, blood pressure during a 24-h interval was monitored with ABPM, and fasting blood samples were collected. The participants were then randomized into one of two treatment groups who received either 20 mg olmesartan medoxomil or 40 mg telmisartan once daily in the morning instead of valsartan. After 8 weeks of olmesartan/telmisartan treatment, blood pressure was again monitored with ABPM and fasting blood samples were collected. Then, the subjects on olmesartan were switched to telmisartan and those on telmisartan were switched to olmesartan. This treatment was given for 8 weeks, after which another ABPM was performed with fasting blood sampling (Fig. 1). All subjects were advised to consume their usual diet during the study period. Each patient was reviewed for general health and compliance with medication, which was assessed by tablet counts and checking of blood pressure, body weight, diet, and exercise status at each visit. During this study period the medication was not altered except for ARBs. The clinical characteristics of the study patients are listed in Table 1.

Definition of Metabolic Syndrome

We used the definition proposed by the Japanese Society of Internal Medicine (JSIM). Participants who had obesity (waist: male ≥ 85 cm, female ≥ 90 cm) plus at least two of the following three components were defined as JSIM-MS (metabolic syndrome): 1) high-density lipoprotein (HDL) cholesterol ≤ 1.036 mmol/L or triglyceride ≥ 1.695 mmol/L or medication for hyperlipidemia, 2) fasting glucose ≥ 6.10 mmol/L or medication for diabetes; 3) blood pressure $\geq 130/$

85 mmHg or taking an antihypertensive.

Biochemical Measurements

Blood samples were obtained between 8:00 and 10:00 after overnight fasting. Serum lipids (total cholesterol, HDL cholesterol, low-density lipoprotein [LDL] cholesterol, and triglycerides), glucose, and HbA1c were measured with standard techniques. Insulin, high-sensitivity interleukin (IL)-6, high-sensitivity intercellular adhesion molecule (ICAM)-1, high-sensitivity vascular cell adhesion molecule (VCAM)-1, IL-18, and adiponectin were measured by enzyme immunoassay, and hs-CRP was measured by latex nephelometry, both in a private laboratory (BML Laboratory, Chiba, Japan). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as the product of fasting plasma insulin (μ U/mL) and fasting plasma glucose level (mmol/L) divided by 22.5.

ABPM

Ambulatory blood pressure monitors (A&D Company, Tokyo, Japan) were used for 24-h ABPM. On the day of ABPM, study medication was administered as close to 8:00 as possible and about 24 h after the previous medication. After the ABPM device was attached, blood pressure was recorded every 60 min. The device was removed after a minimum of 24 h of recording. The daytime (7:00–22:00) and nighttime (0:00–6:00) ABPM were also defined as previously reported (21).

Statistical Analysis

Two-way analysis of variance (ANOVA) was used to compare demographic and laboratory parameters between the olmesartan- and telmisartan-treatment groups. To approximate normal distribution, natural log-transformed values for IL-6 and IL-18 were used in the analysis, and were reported as the geometric means and 95% confidence intervals (CI) for those means. ANOVA was used to analyze the ABPM data of the olmesartan- and telmisartan-treated groups. All statistical tests were two-sided with a 5% significance level. Data are presented as mean±SD.

Results

All enrolled patients (*n*=20) completed the trial. The demographic characteristics and mean baseline data are shown in Tables 1–3. The subjects were relatively obese (body mass index [BMI] 25.6 ± 1.1 kg/m²), and their rate of metabolic syndrome was 65%. Their blood glucose, blood pressure, and lipid data were well controlled.

Figure 2 shows the mean hourly systolic and diastolic blood pressures, and Table 2 shows the mean blood pressure analyzed by 24-h ABPM. The recommended target blood pres-

Table 2. Blood Pressure (mmHg) Recorded by 24-h ABPM during Each Treatment

Variables	Baseline (valsartan)	Olmesartan	Telmisartan	<i>p</i> value*
24 h				
Systolic BP	133.6±12.1	129.4±15.8	132.7±18.3	0.0305
Diastolic BP	75.5±6.3	74.6±7.4	77.3±8.7	0.0087
Mean BP	94.9±7.7	92.7±9.9	95.8±11.6	0.0058
Daytime (7:00–22:00)				
Systolic BP	139.7±14.0	134.1±17.5	136.3±16.7	0.2097
Diastolic BP	78.8±6.4	76.9±8.5	80.1±9.3	0.0215
Mean BP	99.1±8.5	95.7±11.2	98.8±11.4	0.0241
Nighttime (00:00–6:00)				
Systolic BP	121.4±17.9	119.5±20.3	124.9±21.6	0.0281
Diastolic BP	68.9±12.0	69.6±9.6	72.9±10.0	0.0321
Mean BP	86.4±13.5	86.2±12.7	90.2±13.4	0.0212

Data are mean±SD. ABPM, ambulatory blood pressure; BP, blood pressure. **p* values by ANOVA for differences between data of the olmesartan and telmisartan groups.

Table 3. Biochemical Measurements at Baseline, Olmesartan Treatment, and Telmisartan Treatment

	Baseline (valsartan)	Olmesartan	Telmisartan	<i>p</i> value
HbA1c (%)	6.2±0.5	6.3±0.5	6.1±0.3	n.s.
Fasting blood sugar (mmol/L)	7.5±2.2	7.6±2.6	7.5±1.8	n.s.
Insulin (μU/mL)	7.3±5.3	10.4±1.6	9.0±6.8	n.s.
HOMA-IR	2.0±1.1	2.3±1.2	2.4±1.4	n.s.
Total cholesterol (mmol/L)	5.2±0.6	5.2±0.8	5.2±1.0	n.s.
HDL cholesterol (mmol/L)	1.4±0.4	1.4±0.3	1.4±0.4	n.s.
LDL cholesterol (mmol/L)	3.0±0.3	3.0±0.7	3.1±0.6	n.s.
Triglyceride (mmol/L)	14.7±6.6	21.0±25.1	17.8±18.1	n.s.
VCAM-1 (ng/mL)	834±395	864±401	922±404	n.s.
ICAM-1 (ng/mL)	300±75	326±83	316±76	n.s.
Adiponectin (μg/mL)	12.9±10.6	14.0±12.4	13.6±9.8	n.s.
hs-CRP (mg/dL)	0.076±0.063	0.078±0.05	0.144±0.146	0.00418
log interleukin-6 (pg/mL)	1.6±1.7	1.43±1.84	1.9±2.2	0.00133
log interleukin-18 (pg/mL)	183±63	187±68	197±66	n.s.

Data are mean±SD. **p* values by ANOVA for differences between data of the olmesartan and telmisartan groups. HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; VCAM-1, vascular cell adhesion molecule; ICAM-1, intercellular adhesion molecule-1; hs-CRP, highly sensitive C-reactive protein; n.s., not significant.

sure level (<130/80 mmHg) was achieved in 8, 9, and 7 cases during valsartan, olmesartan, and telmisartan treatment, respectively. Olmesartan reduced systolic, diastolic, and mean blood pressure by 3.3, 2.7, and 3.1 mmHg more than did telmisartan, respectively; these were statistically significant differences. Similarly, olmesartan significantly reduced diastolic and mean blood pressure during the daytime by 3.2 and 3.1 mmHg, and reduced systolic, diastolic, and mean blood pressure during the nighttime by 5.4, 3.3, and 4.0 mmHg, respectively, more than telmisartan did; these differences between treatments were statistically significant. The metabolic markers, including HbA1c, HOMA-IR, and serum adiponectin, were comparable between the two treatments. On the other hand, among the inflammation markers investi-

gated in the present study, IL-6 and hs-CRP were reduced by olmesartan significantly more than the reduction by telmisartan.

Discussion

Our data demonstrated that olmesartan at 20 mg/day had more potent blood pressure lowering and anti-inflammatory effects than telmisartan at 40 mg/day. Although recent data demonstrated that telmisartan has unique PPARγ-modulating activity (15–17), the metabolic parameters during each treatment were comparable.

In this study, we compared the blood pressure lowering effects of each ARB by 24-h ABPM. With regard to mean

Fig. 2. Changes in mean profiles of hourly systolic (a) and diastolic (b) blood pressure in each treatment.

blood pressure on a particular day, olmesartan was significantly more effective than telmisartan at reducing systolic, diastolic, and mean blood pressure. Recently, several large trials showed that strict blood pressure control could reduce the onset of cardiovascular disease in patients with type-2 diabetes (2, 3, 22). For example, a 4 mmHg fall in diastolic blood pressure in the Hypertension Optimal Treatment (HOT) study was equated with a 51% decrease in the onset of cardiovascular disease (2). Similarly, a 1.92 mmHg decrease in systolic blood pressure in the Heart Outcomes Prevention Evaluation (HOPE) study was equated with a 25% reduction in cardiovascular mortality in type-2 diabetic patients (3, 22). Therefore, the fall in arterial pressure recorded in our study was more than a subtle change. In addition, olmesartan therapy reduced mean systolic and diastolic blood pressure to below 130/80 mmHg, which is recommended by JNC 7 (4) and ESH/ESC (23).

After adjustment for classic risk factors, the increases in 24-h daytime (8:00–20:00) and nighttime (0:00–6:00) ambulatory blood pressure were associated with cardiovascular events (24). While olmesartan and telmisartan are regarded as

ARBs with a longer duration of action (13, 25), olmesartan significantly reduced both daytime and nighttime mean blood pressure levels compared with telmisartan. These results suggest that the superiority of olmesartan's blood pressure lowering effect might depend on its strength rather than on the duration of its pharmacological action.

In addition to their beneficial effects on lowering blood pressure, ARBs have anti-atherogenic effects by blocking angiotensin II, which promotes oxidative stress, inflammation, vasoconstriction, and thrombosis (7, 8), as well as anti-diabetic effects by regulating insulin sensitivity (9, 10, 26). In this study, we evaluated the effects of olmesartan and telmisartan on inflammatory markers. Several recent studies have demonstrated that olmesartan, but not telmisartan, reduces serum IL-6 level (27–29). In agreement with these data, we also found that serum hs-CRP and IL-6 levels were significantly lower by olmesartan than by telmisartan treatment. Angiotensin II is known as one of the main effector peptides inducing IL-6 expression in vascular smooth muscle cells (30, 31). In addition, it is well known that IL-6 induces CRP expression. Because ARB's blood pressure lowering effect seems to parallel the effect of angiotensin II blocking, it is conceivable that olmesartan, a stronger ARB, can reduce serum IL-6 level more efficiently than telmisartan.

Recent studies suggest that telmisartan, but not other ARBs, could act as a partial PPAR γ agonist (15–17). Since PPAR γ plays an important role in the regulation of insulin sensitivity, at least in part by increasing serum adiponectin level (32, 33), telmisartan might have a preferable effect on patients with diabetes. In a 3-month study comparing telmisartan 80 mg and losartan 50 mg in hypertensive patients with metabolic syndrome, only telmisartan improved blood glucose level and insulin sensitivity (19). Here, we compared the effects of olmesartan and telmisartan on various metabolic parameters. However, our results showed no differences in metabolic parameters, including serum adiponectin level, between telmisartan and olmesartan. It is not clear why telmisartan did not change metabolic parameters in our study. We used a starting dose of telmisartan (40 mg/day) for 8 weeks. It is possible that a higher dose and/or longer administration may be required to observe the unique metabolic effect of telmisartan. In addition, baseline HOMA-IR in the present study was smaller than in the previous study that showed telmisartan's clinical effect on insulin sensitivity (19). It might be difficult to observe the metabolic effect of telmisartan in subjects with low insulin resistance. In fact, recent data demonstrated that telmisartan has a neutral effect on insulin resistance in hypertensive metabolic syndrome with relatively low HOMA-IR (34). However, the gold standard of insulin sensitivity measurement is the hyperinsulinemic euglycemic glucose clamp method. Further studies are needed to assess the effect of telmisartan on insulin resistance by hyperinsulinemic euglycemic glucose clamp. It is noteworthy that other studies reported that telmisartan improves glycemic control and insulin sensitivity without affecting serum adi-

ponectin levels (35–37). In rats fed a high-fat, high-carbohydrate diet, telmisartan treatment promoted increases in caloric expenditure and protected against dietary-induced weight gain (38). They demonstrated that these findings may be due to the increased expression of genes for regulating mitochondrial function and energy metabolism (17) in skeletal muscle, suggesting that this effect does not necessarily depend on adiponectin's effect. Thus, it is possible that telmisartan improves insulin sensitivity without affecting serum adiponectin level also in the clinical setting.

In conclusion, at clinical doses in patients with type-2 diabetes, olmesartan seems to have more potent blood pressure lowering and anti-inflammatory effects than telmisartan, but similar effects on metabolic parameters. Our results suggest that olmesartan can be considered an ideal agent to prevent future onset of cardiovascular disease in type-2 diabetic patients with hypertension.

References

1. Hypertension in Diabetes Study (HDS): I. Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. *J Hypertens* 1993; **11**: 309–317.
2. Hansson L, Zanchetti A, Carruthers SG, *et al*, HOT Study Group: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998; **351**: 1755–1762.
3. UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; **317**: 703–713.
4. Chobanian AV, Bakris GL, Black HR, *et al*: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; **289**: 2560–2572.
5. Japanese Society of Hypertension: Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2004). *Hypertens Res* 2006; **29** (Suppl): S1–S105.
6. Hirose H, Saito I: Trends in blood pressure control in hypertensive patients with diabetes mellitus in Japan. *Hypertens Res* 2003; **26**: 717–722.
7. Dzau VJ: Theodore Cooper Lecture: tissue angiotensin and pathobiology of vascular disease: a unifying hypothesis. *Hypertension* 2001; **37**: 1047–1052.
8. Zhang C, Hein TW, Wang W, Kuo L: Divergent roles of angiotensin II AT1 and AT2 receptors in modulating coronary microvascular function. *Circ Res* 2003; **92**: 322–329.
9. Pfeffer MA, Swedberg K, Granger CB, *et al*: Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003; **362**: 759–766.
10. Dahlöf B, Devereux RB, Kjeldsen SE, *et al*: Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 2002; **359**: 995–1003.
11. Oparil S, Williams D, Chrysant SG, Marbury TC, Neutel J: Comparative efficacy of olmesartan, losartan, valsartan, and irbesartan in the control of essential hypertension. *J Clin Hypertens (Greenwich)* 2001; **3**: 283–291, 318.
12. Smith DH, Dubiel R, Jones M: Use of 24-hour ambulatory blood pressure monitoring to assess antihypertensive efficacy: a comparison of olmesartan medoxomil, losartan potassium, valsartan, and irbesartan. *Am J Cardiovasc Drugs* 2005; **5**: 41–50.
13. Brunner HR, Arakawa K: Antihypertensive efficacy of olmesartan medoxomil and candesartan cilexetil in achieving 24-hour blood pressure reductions and ambulatory blood pressure goals. *Clin Drug Investig* 2006; **26**: 185–193.
14. Kario K, Pickering TG, Umeda Y, *et al*: Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation* 2003; **107**: 1401–1406.
15. 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.
16. Schupp M, Janke J, Clasen R, Unger T, Kintscher U: Angiotensin type 1 receptor blockers induce peroxisome proliferator-activated receptor-gamma activity. *Circulation* 2004; **109**: 2054–2057.
17. Schupp M, Clemenz M, Gineste R, *et al*: Molecular characterization of new selective peroxisome proliferator-activated receptor gamma modulators with angiotensin receptor blocking activity. *Diabetes* 2005; **54**: 3442–3452.
18. 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.
19. 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.
20. Lacourciere Y, Krzesinski JM, White WB, Davidai G, Schumacher H: Sustained antihypertensive activity of telmisartan compared with valsartan. *Blood Press Monit* 2004; **9**: 203–210.
21. Inaba M, Noguchi Y, Yamamoto T, *et al*: Effects of a low dose of indapamide, a diuretic, given daily or every-other-day on blood pressure and metabolic parameters. *Hypertens Res* 2004; **27**: 141–145.
22. Heart Outcomes Prevention Evaluation Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; **355**: 253–259.
23. 2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens* 2003; **21**: 1011–1053.
24. Clement DL, De Buyzere ML, De Bacquer DA, *et al*: Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. *N Engl J Med* 2003; **348**: 2407–2415.
25. Neutel J, Smith DH: Evaluation of angiotensin II receptor blockers for 24-hour blood pressure control: meta-analysis of a clinical database. *J Clin Hypertens (Greenwich)* 2003;

- 5: 58–63.
26. Julius S, Kjeldsen SE, Weber M, et al: Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004; **363**: 2022–2031.
 27. Fliser D, Buchholz K, Haller H: Antiinflammatory effects of angiotensin II subtype 1 receptor blockade in hypertensive patients with microinflammation. *Circulation* 2004; **110**: 1103–1107.
 28. Link A, Lenz M, Legner D, Bohm M, Nickenig G: Telmisartan inhibits beta2-integrin MAC-1 expression in human T-lymphocytes. *J Hypertens* 2006; **24**: 1891–1898.
 29. Nagel JM, Tietz AB, Goke B, Parhofer KG: The effect of telmisartan on glucose and lipid metabolism in nondiabetic, insulin-resistant subjects. *Metabolism* 2006; **55**: 1149–1154.
 30. Han Y, Runge MS, Brasier AR: Angiotensin II induces interleukin-6 transcription in vascular smooth muscle cells through pleiotropic activation of nuclear factor-kappa B transcription factors. *Circ Res* 1999; **84**: 695–703.
 31. Schieffer B, Schieffer E, Hilfiker-Kleiner D, et al: Expression of angiotensin II and interleukin 6 in human coronary atherosclerotic plaques: potential implications for inflammation and plaque instability. *Circulation* 2000; **101**: 1372–1378.
 32. Picard F, Auwerx J: PPAR(gamma) and glucose homeostasis. *Annu Rev Nutr* 2002; **22**: 167–197.
 33. Staels B, Fruchart JC: Therapeutic roles of peroxisome proliferator-activated receptor agonists. *Diabetes* 2005; **54**: 2460–2470.
 34. Bahadir O, Uzunlulu M, Oguz A, Bahadir MA: Effects of telmisartan and losartan on insulin resistance in hypertensive patients with metabolic syndrome. *Hypertens Res* 2007; **30**: 49–53.
 35. Benndorf RA, Rudolph T, Appel D, et al: Telmisartan improves insulin sensitivity in nondiabetic patients with essential hypertension. *Metabolism* 2006; **55**: 1159–1164.
 36. 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.
 37. Derosa G, Cicero AF, D'Angelo A, et al: Telmisartan and irbesartan therapy in type 2 diabetic patients treated with rosiglitazone: effects on insulin-resistance, leptin and tumor necrosis factor- α . *Hypertens Res* 2006; **29**: 849–856.
 38. 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.