ORIGINAL ARTICLE

Morning home blood pressure may be a significant marker of nephropathy in Japanese patients with type 2 diabetes: ADVANCED-J study 1

Yasushi Tanaka¹, Hiroyuki Daida², Yutaka Imai³, Katsumi Miyauchi², Yasukazu Sato⁴, Masao Hiwatari⁵, Akira Kitagawa⁶, Junji Kishimoto⁷, Tsutomu Yamazaki⁸ and Ryuzo Kawamori²

A 3-year multicenter, prospective, randomized, open-label trial (ADVANCED-J) compared the effect of an increased dose of angiotensin-II receptor blocker (ARB) with that of a maintenance dose of ARB plus calcium channel blocker (amlodipine) on blood pressure (BP) control, nephropathy and atherosclerosis in patients with type 2 diabetes and hypertension in whom the usual ARB dose failed to control BP. A cross-sectional analysis using baseline data was conducted. Of 316 patients (recruited between September 2004 and December 2005), 228 patients were evaluated by multiple regression analysis using two models after randomization and exclusions. Model 1 assessed 13 baseline variables (age, sex, estimated diabetes duration, estimated hypertension duration, HbA1c, brain natriuretic peptide (BNP), high-sensitive C-reactive protein (hsCRP), triglycerides (TGs), total cholesterol (TCHO), diabetic retinopathy (DMR), systolic morning home BP (HBP), diastolic morning HBP and brachial-ankle pulse wave velocity (baPWV)) for correlation with the urinary albumin creatinine excretion rate (UACR). In model 2, systolic and diastolic morning HBP was replaced by systolic and diastolic office BP. The systolic morning HBP and systolic office BP or diastolic morning HBP and diastolic office BP correlations were weak, but significant ($r=0.43$ and 0.48 , respectively). BNP, HbA1c, DMR and estimated diabetes duration were significantly correlated with UACR in both models 1 and 2. Although systolic office BP did not show a significant correlation with UACR in model 2, systolic morning HBP showed a significant correlation with UACR in model 1. Morning HBP, but not office BP, may be a significant marker of nephropathy in Japanese patients with type 2 diabetes.

Hypertension Research (2009) **32**, 770–774; doi:10.1038/hr.2009.96; published online 26 June 2009

Keywords: morning home blood pressure; nephropathy; office blood pressure

INTRODUCTION

The combination of hyperglycemia and hypertension markedly increases the risk of diabetic nephropathy in patients with type 2 diabetes.^{1,2} The United Kingdom Prospective Diabetes Study (UKPDS) showed that each 10 mm Hg decrease in systolic blood pressure (SBP) was associated with a 12% reduction in the risk of any diabetes-related complication and with a 13% decrease in microvascular complications, including nephropathy.^{3,4} Thus, to reduce the risk and/or slow the progression of nephropathy, a strict target blood pressure (BP) (<130/80 mm Hg) has been recommended.⁵ As 24-h ambulatory BP monitoring (ABPM) can now be

easily performed with reliable monitoring devices, a number of studies have shown the inadequacy of evaluating BP control from clinical measurements alone.^{6,7} Recent studies have indicated that home BP (HBP) measured in the morning has a stronger predictive power for mortality than does office BP measurement.^{8,9} These reports suggest the importance of monitoring morning HBP, in addition to office BP, to evaluate BP control and to adjust antihypertensive therapy. However, earlier large-scale prospective studies of diabetic complications, such as the UKPDS,^{2–4} only monitored office BP, and the association between morning HBP and nephropathy was not fully evaluated.

¹Department of Medicine, St Marianna University School of Medicine, Kawasaki, Japan; ²Department of Medicine, Juntendo University School of Medicine, Tokyo, Japan;

³Department of Clinical Pharmacology and Therapeutics, Tohoku University Graduate School of Pharmaceutical Sciences and Medicine, Sendai, Japan; ⁴Department of Internal Medicine, Takagi Hospital, Medical Corporation of Kouhoukai, Ohkawa, Japan; ⁵Division of Physical Therapy, Graduate School, University of Health and Welfare, Ohtawara, Japan;

⁶Department of Clinical Trial Management, International University of Health and Welfare Graduate School, Tokyo, Japan; ⁷Digital Medicine Initiative, University of Kyushu, Fukuoka, Japan and ⁸Department of Clinical Epidemiology and Systems, University of Tokyo Graduate School of Medicine, Tokyo, Japan

This work was supported by the Japan Heart Foundation.

Correspondence: Dr Y Tanaka, Department of Medicine, Metabolism and Endocrinology, St Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan.

E-mail: y2tanaka@marianna-u.ac.jp

Received 28 April 2009; revised 28 May 2009; accepted 28 May 2009; published online 26 June 2009

The ADVANCED-J study is a 3-year prospective trial designed to compare the effect of increasing the dose of an angiotensin-II receptor blocker (ARB) on BP control, nephropathy and atherosclerosis with that of adding the dihydropyridine calcium channel blocker (DCCB; amlodipine) in hypertensive Japanese patients with type 2 diabetes in whom BP control using the usual ARB dose was inadequate.¹⁰ Both office BP and morning HBP were monitored. A unique point of this study was setting the BP target on the basis of morning HBP, not office BP. Antihypertensive therapy was adjusted to obtain a morning HBP <125/80 mm Hg during the study. In this analysis, to determine the relationship between morning HBP and nephropathy, a cross-sectional assessment of the correlation between the urinary albumin/creatinine ratio (UACR) and morning HBP or office BP was conducted using baseline data from the ADVANCED-J study.

METHODS

Study design and participants

This study was a cross-sectional analysis of the data obtained from the ADVANCED-J study, a multicenter, prospective, randomized, open-label trial conducted over 3 years in 300 patients with type 2 diabetes and ARB-resistant hypertension. The study protocol was approved by the ethics committee of each study site. All patients gave written informed consent to participate. Briefly, 316 patients were recruited during the registration period from 22 centers, whereas office BP was monitored for at least 8 weeks with treatment at the usual single daily dose of an ARB (candesartan 8 mg, losartan 50 mg, telmisartan 40 mg, valsartan 80 mg or olmesartan 20 mg). The final part of the registration period was a control period with ARB alone, lasting for at least 2 weeks, during which time measurement of morning HBP was carried out by patients with a systolic office BP ≥ 135 mm Hg or a diastolic office BP ≥ 85 mm Hg. Treatment was started when the mean morning HBP for the preceding 5 days of the control period on ARB alone was ≥ 130 mm Hg (SBP) or ≥ 80 mm Hg diastolic blood pressure (DBP). A total of 263 eligible patients were allocated to two study groups on the basis of the minimization method, controlling for their urinary albumin level during the control period on ARB alone (<300 vs. ≥ 300 mg per gram creatinine) and for systolic HBP (SHBP) (<135 mm Hg vs. ≥ 135 mm Hg) in the morning after waking, but before starting the study. They either received a higher dose of the same ARB up to the maximum approved dose (candesartan 12 mg, losartan 100 mg, telmisartan 80 mg, valsartan 160 mg or olmesartan 40 mg; ARB group, $n=132$), or continued to receive ARB at the earlier dose plus amlodipine at 5 mg daily (combination group, $n=131$). Primary clinical end points were changes in home BP after arising in the morning and the achievement rate of a home BP level of <125 mm Hg systolic and <80 mm Hg diastolic. The determination of sample size was based on the assumption that treatment differences in change from baseline BP were estimated to be at least 5 ± 15 mm Hg (mean $\pm$ s.d.) for SBP and DBP. It was calculated that, to achieve an 80% or higher power on the primary end point, 142 patients per arm (a total of 284 patients) would be needed to show the superiority of the ARB group using a two-sided test at an α -level of 0.05.

Measurement of variables and analysis

During the control period on ARB alone of at least 2 weeks, morning HBP and evening HBP were measured by patients. HBP data obtained with an electronic home digital BP monitor were transmitted to the central computer server in Tokyo through a portable telemetry device connected to the monitor, and data were automatically input into the software program for analyses (CapTool, a semi-automated electronic data capture system; Mebix, Tokyo, Japan). Patients were instructed to measure their HBP after resting for 5 min in the sitting position, after waking in the morning and before going to bed. Compliance with measurement could be monitored using the software. To exclude the influence of incorrect measurement, SBP >200 mm Hg and DBP <40 mm Hg were defined as errors and rejected by this system. Office BP was also measured at the outpatient clinic at least three times by a physician during this period, that is, at the beginning of the control period on ARB alone, during the study period and at its end. Measurements were obtained after 5 min of rest

in the sitting position. Laboratory tests (fasting blood sample) included testing for HbA1c, plasma glucose, insulin, brain natriuretic peptide (BNP), high-sensitive C-reactive protein (hsCRP), triglycerides (TGs), total cholesterol (TCHO), blood urea nitrogen (BUN) and creatinine. In addition, the urinary albumin creatinine excretion rate (UACR), chest X-ray, ECG, carotid ultrasound, B-mode echocardiography and brachial-ankle pulse wave velocity (baPWV) were examined at least once during the control period on ARB alone of 2 weeks or longer.

Table 1 Clinical characteristics of patients

<i>n=263 (M 162/F 101)</i>		
	<i>Mean $\pm$ s.d.</i>	<i>(n)</i>
Age (years)	65.1 $\pm$ 9.7	263
BMI (kg m ⁻²)	25.3 $\pm$ 3.8	263
Estimated duration of hypertension (years)	6.8 $\pm$ 7.6	247
Estimated duration of diabetes (years)	7.1 $\pm$ 6.8	253
Systolic clinic BP (mm Hg)	151.4 $\pm$ 15.5	263
Diastolic clinic BP (mm Hg)	83.1 $\pm$ 11.2	263
Systolic morning BP (mm Hg)	157.8 $\pm$ 17.9	263
Diastolic morning BP (mm Hg)	83.5 $\pm$ 11.7	263
HbA1c (%)	6.79 $\pm$ 0.97	259
BNP (pg ml ⁻¹)	46.3 $\pm$ 58.1	239
hsCRP (mg per 100 ml)	0.17 $\pm$ 0.24	240
TG (mg per 100 ml)	145.7 $\pm$ 96.4	258
TCHO (mg per 100 ml)	199.1 $\pm$ 33.4	258
Creatinine (mg per 100 ml)	0.81 $\pm$ 0.25	259
UACR (mg per g Cr)	263.7 $\pm$ 676.9	263
EF (%)	68.9 $\pm$ 8.1	248
E/A ratio	0.88 $\pm$ 0.29	226
IVS-d (mm)	11.0 $\pm$ 2.3	248
Right mean IMT (mm)	0.84 $\pm$ 0.20	202
Left mean IMT (mm)	0.88 $\pm$ 0.24	201
PW-d (mm)	10.9 $\pm$ 1.9	248
CTR (%)	49.6 $\pm$ 4.7	243
Right baPWV (cm s ⁻¹)	1820 $\pm$ 377	231
Left baPWV (cm s ⁻¹)	1833 $\pm$ 362	230
Right ABI	1.13 $\pm$ 0.13	231
Left ABI	1.11 $\pm$ 0.13	232

Abbreviations: baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; BNP, brain natriuretic peptide; Cr, creatinine; EF, ejection fraction; F, female; hsCRP, high-sensitive C-reactive protein; M, male; TG, triglyceride; TCHO, total cholesterol; UACR, urinary albumin creatinine excretion rate.

Table 2 Characteristics of patients

<i>n=263 (M 162/F 101)</i>		
	<i>(n)</i>	<i>%</i>
<i>No. of patients with a history of</i>		
Cerebrovascular disease	24	9.1
Coronary heart disease	40	15.2
Cardiac failure	3	1.1
<i>No. of patients using anti-diabetic drugs</i>		
Sulfonylureas	96	36.5
Glinides	14	5.3
Biguanides	37	14.1
Pioglitazone	26	9.9
α -Glucosidase inhibitors	66	25.1
Insulin	54	20.5

Abbreviations: F, female; M, male.

Data analysis

Correlation between morning HBP and office BP was evaluated by a linear regression analysis. To assess the influence of morning HBP on nephropathy, the correlation between UACR and morning HBP or office BP was evaluated by multiple regression analysis using two models. Model 1 examined the association between UACR (objective variable: logarithmic transformation) and 13 variables, baseline hsCRP, BNP, HbA1c, TG, TCHO, diabetic retinopathy (DMR), SBP and DBP for morning HBP (morning SHBP and morning DHBP), baPWV, sex, age, estimated duration of hypertension and estimated duration of diabetes (explanatory variables). In model 2, a correlation with UACR (logarithmic transformation) was assessed using SBP and DBP for office BP (office SBP and office DBP) instead of morning SHBP and morning DHBP. These two models were used to analyze 228 patients, as data for 35 patients were incomplete. All analyses were carried out using SAS statistical software (version 9.1; SAS Institute Inc., Cary, NC, USA), and a *P*-value of <0.05 was considered to be statistically significant.

Figure 1 Correlation between morning BP and office BP. Abbreviations: BP, blood pressure; UACR, urinary albumin creatinine excretion ratio; CI, confidence interval; *r*, pearson's product-moment correlation coefficient.

RESULTS

The characteristics of eligible patients were randomized as shown in Tables 1 and 2. The 263 patients comprised 162 men and 101 women with a mean age of 65 years (range, 35–85 years). As shown in Figure 1, the correlation between morning SHBP and office SBP or between morning DHBP and office DBP was significant, although weak, with coefficients (*r* values) of 0.43 and 0.48, respectively. Table 3 shows the association between UACR (logarithmic transformation) and other variables in the two models, evaluated by multiple regression analysis. In model 1, BNP, HbA1c, TG, TCHO, DMR, morning SHBP, estimated duration of diabetes and sex were initially selected by stepwise analysis. As a result of re-analysis using these eight variables,

UACR (logarithmic transformation) and Morning home systolic BP plot

UACR (logarithmic transformation) and Office systolic BP plot

Figure 2 Correlation between log[UACR] and systolic BP. Abbreviations: BP, blood pressure; UACR, urinary albumin creatinine excretion ratio; CI, confidence interval; *r*, pearson's product-moment correlation coefficient.

Table 3 Correlation of clinical factors with UACR on multiple regression analysis

Variable	Partial regression coefficient	Standard partial regression coefficient	P-value	95 % CI
Model-1				
BNP (pg ml ⁻¹)	0.004	0.145	0.012	0.001–0.008
HbA1c (%)	0.347	0.198	0.001	0.139–0.555
TG (mg per 100 ml)	0.001	0.079	0.195	–0.001–0.004
TCHO (mg per 100 ml)	0.006	0.120	0.054	0.000–0.012
DMR	0.571	0.149	0.012	0.129–1.013
mSBP (mm Hg)	0.027	0.283	<.0001	0.016–0.038
Estimated duration of diabetes (years)	0.036	0.134	0.023	0.005–0.067
Sex	–0.410	–0.113	0.053	–0.827–0.006
Model-2				
BNP (pg ml ⁻¹)	0.005	0.166	0.007	0.001–0.008
HbA1c (%)	0.324	0.185	0.004	0.104–0.544
TG (mg per 100 ml)	0.002	0.104	0.105	0.000–0.004
TCHO (mg per 100 ml)	0.005	0.104	0.109	0.000–0.004
DMR	0.572	0.151	0.019	0.097–1.047
oSBP (mm Hg)	0.014	0.126	0.056	0.000–0.028
baPWV	0.001	0.146	0.022	0.000–0.001
Estimated duration of diabetes (years)	0.051	0.191	0.003	0.018–0.084
Sex	–0.433	–0.119	0.056	–0.877–0.011

Abbreviations: baPWV, brachial-ankle pulse wave velocity; BNP, brain natriuretic peptide; CI, confidence interval; DMR, diabetic retinopathy; TG, triglyceride; TCHO, total cholesterol. Model 1 examined the association between UACR (objective variable: logarithmic transformation) and 13 variables, baseline hsCRP, BNP, HbA1c, TG, TCHO, DMR, morning SHBP, morning DHBP, baPWV, sex, age, estimated duration of hypertension, and estimated duration of diabetes (explanatory variables). In model 2, correlation with UACR (logarithmic transformation) was assessed using office SBP and office DBP instead of morning SHBP and morning DHBP.

BNP, HbA1c, DMR, morning SHBP, estimated duration of diabetes, and sex showed a significant relationship with UACR. In model 2, BNP, HbA1c, TG, TCHO, DMR, office SBP, baPWV, estimated duration of diabetes and sex were initially selected, and BNP, HbA1c, DMR, baPWV and estimated duration of diabetes showed a significant association with UACR (logarithmic transformation) on re-analysis. In particular, a strong relation ($P < 0.0001$) was observed between UACR (logarithmic transformation) and morning SHBP in model 1. The correlation coefficient between UACR (logarithmic transformation) and morning SHBP was $r = 0.32$, and the correlation coefficient between UACR (logarithmic transformation) and office SHBP was $r = 0.18$ in Figure 2. Log transformation was used to reduce right skewness in the distribution for UACR before statistical analyses in Table 3 and Figure 2.

DISCUSSION

This study showed weak, but significant, correlations between morning SHBP and office SBP or between morning DBP and office DBP, whereas BNP, HbA1c, DMR and morning SHBP (but not office SBP) were significantly correlated with UACR in diabetic patients who had hypertension resistant to the standard ARB therapy.

Earlier studies have shown an elevation of BNP level in type 2 diabetic patients with microalbuminuria or macroalbuminuria compared with that in patients with normoalbuminuria, and results from this study are consistent with these findings.^{11,12} However, those studies and current study data included patients with coronary heart disease (CHD). Recently, Igarashi *et al.*¹³ reported similar results for type 2 diabetic patients, but they observed no difference between patients with normoalbuminuria and those with microalbuminuria/macroalbuminuria after excluding patients with CHD. Thus, in this study, multiple regression analysis was performed after excluding patients with CHD and cerebrovascular disease. HbA1c, DMR and

morning SHBP still showed a significant correlation with UACR, but not BNP. This result suggests that BNP may be associated with progression of macrovascular disease, such as CHD or cerebrovascular disease, but not with albuminuria.

To date, most large-scale studies addressing the effect of antihypertensive therapy on morbidity and mortality have been based on office BP,^{2,14,15} and the role of HBP monitoring in managing hypertension remains unclear. Against this background, results from this study suggest the importance of home-based BP monitoring for detection and/or control of nephropathy, and that reliance on clinic-based BP measurement alone may hamper the timely identification of patients with incipient nephropathy. These findings are consistent with those of an earlier study of the significance of hypertension assessed by morning HBP measurement for the development of nephropathy and atherosclerosis in diabetic patients. Kamoi *et al.*¹⁶ measured clinic BP once during each visit and once each morning at home for 1 month in 170 type 2 diabetic patients receiving antidiabetic and antihypertensive therapy. They defined clinic and home morning hypertension (MH) as SBP ≥ 130 mm Hg and/or DBP ≥ 85 mm Hg. Although there were no significant differences in the prevalence of nephropathy, retinopathy, CHD and cerebrovascular disease between groups with ($n = 131$) and without clinic hypertension ($n = 39$), the prevalence of these complications was significantly higher ($P < 0.05$) in patients with ($n = 97$) than in those without ($n = 73$) MH. In particular, nephropathy was strongly associated with systolic MH.

Interestingly, Nielsen *et al.*¹⁷ reported that the prevalence of white-coat hypertension (clinical hypertension with a normal BP at home on 24-h ABPM) was significantly higher in diabetic patients with normoalbuminuria (urinary albumin excretion (UAE) < 30 mg per day) than in those with microalbuminuria (UAE; 30–300 mg per day) or macroalbuminuria (UAE > 300 mg per day), that is, 23 vs. 8% and 9%, respectively. These reports suggest that office BP may not exactly

reflect the state of 24-h BP in diabetic patients, and that it may be difficult to detect patients with incipient nephropathy by monitoring office BP alone. Recently, Leitão *et al.*¹⁸ reported that type 2 diabetic patients with masked hypertension (normal office BP and elevated HBP detected by 24-h ABPM) have a higher UAE than those without masked hypertension. Taken together, these findings suggest that office BP may not be related to HBP, and HBP monitoring may be more useful for evaluating the risk of nephropathy than is office BP. However, these studies included many patients without antihypertensive therapy, whereas all patients in this study were resistant to the standard ARB therapy. Thus, it is difficult to compare these studies directly with the current study, and it remains unclear why the correlation between morning HBP and office BP was weak or why morning HBP, but not office BP, was correlated with UACR in this study. Further investigation will be required to clarify these issues.

There are several weaknesses in this study, including the fact that it was a cross-sectional study, and that an HBP monitor, not a 24-h ABPM system, was used. Also, UACR was only measured once during the control period on ARB alone. As the ADVANCED-J study involves 265 patients and is a unique prospective trial focusing on morning BP adjusted with antihypertensive therapy to obtain a target morning HBP <125/80 mmHg, an ordinary HBP monitor, rather than an ABPM system, was used. The data transfer system and CapTool allowed measured precise BP data to be exactly transmitted to the central server, and major system problems have not occurred to date. The ADVANCED-J study is still in progress, therefore the relationship between UAE and morning HBP, plus the significance of normalizing morning BP to prevent the development and/or progression of nephropathy, may be clarified further by future data.

In conclusion, a significant association of UACR with morning SHBP in diabetic patients with hypertension refractory to conventional ARB therapy was identified, whereas no association was found with office BP. Thus, morning BP may be a significant marker of nephropathy in Japanese patients with type 2 diabetes.

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