Original Article

Ambulatory Blood Pressure Level Rather than Dipper/Nondipper Status Predicts Vascular Events in Type 2 Diabetic Subjects

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To clarify which parameter, diurnal pattern of blood pressure (BP) or level of BP variability, has the stronger predictive value for fatal and nonfatal vascular events, vital status after a mean ($\pm$ SD) follow-up period of 86 ± 46 months was determined in 392 type 2 diabetic subjects without any history of vascular disease, in whom the 24-h BP profile had been monitored between 1988 and 1998. After the exclusion of 28 subjects who died during the follow-up period of causes unrelated to diabetes, 364 subjects were recruited for further analysis. A total of 147 first events, including 50 fatal vascular events and 97 nonfatal vascular events, were recorded during the follow-up period. The rates of various vascular events increased with both reduced nocturnal falls in systolic BP (SBP) and levels of all ambulatory BP parameters. The ambulatory BP parameter showing the largest area under the receiver operating characteristic curve (ROC_{AUC}) for fatal events was the mean 24-h pulse pressure (PP), and that for nonfatal events was the mean nighttime SBP; both exceeded the respective values of nocturnal fall in SBP. Furthermore, when dipper and nondipper diabetic subjects were divided into subgroups based on the 24-h PP (54.3 mmHg) and the nighttime SBP (116.5 mmHg) cut-off points derived from the ROC analyses, Kaplan-Meier plots showed that the diabetic subgroups with high ambulatory BP levels had worse outcomes, independent of dipper/nondipper status. Finally, these parameters were applied to the Cox model with the values of nocturnal fall in SBP and other confounding factors, and results showed that mean 24-h PP and mean nighttime SBP predicted fatal and nonfatal vascular events, respectively, more strongly than nocturnal fall in SBP in type 2 diabetic subjects. These findings therefore suggest that ambulatory BP levels in type 2 diabetic subjects have a higher predictive value for organ damage and death compared with diurnal BP patterns or dipper/nondipper status.

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Key Words: nocturnal blood pressure level, ambulatory pulse pressure, nondippers, prognosis, type 2 diabetes

Introduction

Diabetic subjects show a high incidence of hypertension, which is a major factor for progression of micro- and macroangiopathies. The UK Prospective Diabetes Study (UKPDS) (1, 2) demonstrated that tight blood pressure (BP) control reduced the risk of occurrence and progression of

these complications and deaths related to diabetes in subjects with type 2 diabetes. Many studies have confirmed that ambulatory BP is a better predictor of vascular events and mortality than clinic BP (3–5). In diabetic subjects, Liniger *et al.* (6) first pointed out, in a short follow-up study of a relatively small number of subjects, that nocturnal BP rise in subjects with abnormal cardiovascular reflexes might be associated with a poor outcome. We (7) previously reported that re-

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versed circadian BP rhythm, as determined by the COSINOR (cosine and vector) method, was an independent predictive factor for both fatal and nonfatal vascular events in type 2 diabetic subjects. In support of our observations, Sturrock *et al.* (8) recently demonstrated that the combination of nondipping and subsequent renal impairment led to a higher mortality rate irrespective of diabetes type. These follow-up studies focused on the night-to-day pattern of BP variability, although the nighttime BP levels in diabetic subjects who had a poor outcome were shown to be consistently higher than the daytime BP levels (6–8).

This study aimed to clarify which parameter, diurnal pattern of BP or level of BP variability, is the better predictor of fatal and nonfatal vascular events in type 2 diabetic subjects.

Methods

Subjects

The present study was based on the longitudinal observation of subjects participating in our BP monitoring program conducted at the Kanazawa Medical University Hospital, which was begun in 1988. The study comprised 392 consecutive subjects with type 2 diabetes (249 men and 143 women; mean age, 55 ± 14 years [mean $\pm$ SD]) who were initially admitted to our hospital from December 1988 to June 1998 and then followed in our outpatient clinic. Informed consent was obtained from each participant, and the study was approved by the Ethics Committee of our university. Type 2 diabetes was diagnosed according to the criteria of the World Health Organization (9). These diabetic subjects were carefully questioned and examined, and all were determined to have had no history of vascular complications, as described in our earlier study (7). During the follow-up period, a total of 28 subjects died of causes thought to be unrelated to diabetes: cancer ($n = 12$), pneumonia ($n = 5$), a traffic accident ($n = 1$), suicide ($n = 2$), lung tuberculosis ($n = 1$), liver cirrhosis ($n = 1$) and unknown causes ($n = 6$). Thus, of the 392 type 2 diabetic subjects, 364 entered the study.

Methods

Hypertension was defined as systolic BP (SBP) ≥ 140 mmHg, diastolic BP (DBP) ≥ 90 mmHg and/or treatment with hypertensive drugs at the outpatient clinic before admission.

Ambulatory 24-h SBP, DBP and mean arterial pressure (MAP) (oscillometric mode) recordings were performed using an automatic device, ABPM-630 (Nippon Colin Co., Komaki, Japan), under regular hospital conditions as previously described (7). A standard arm cuff was used for all ambulatory BP measurements. The BP measurement device used in this study has been validated previously (10). Pulse pressure (PP) was defined as SBP minus DBP. None of the diabetic subjects took any medication for at least 1 week before the

ambulatory BP monitoring except for oral hypoglycemic agents or insulin. BP readings were taken every 20 min from 0500 to 2200 h and every hour from 2200 to 0500 h. Since all subjects followed the usual inpatient schedules, daytime was defined as from 0600 to 2200 h and nighttime as from 2200 to 0600 h, and adherence to this schedule was confirmed by reference to the diary kept by each subject. In each subject, mean levels of SBP, DBP, MAP and PP in daytime and nighttime and over 24-h were calculated, and the nocturnal fall in SBP was calculated by subtracting the respective mean nighttime from the mean daytime BP readings. Nondippers were defined as those who did not exhibit a reduction in mean SBP of ≥ 10 mmHg from daytime to nighttime, and the remaining subjects were classified as dippers.

After ambulatory 24-h BP measurements, antihypertensive treatment and life-style modifications were initiated when BP exceeded 140/90 mmHg on three consecutive occasions during the admission or after release to our outpatient clinic, as described elsewhere (7). All subjects were then followed-up in our outpatient clinic with the standard therapies for BP and glycemic control.

As end points, various fatal and nonfatal vascular events that were considered to be diabetes-related and that were described in our previous manuscript (7) were determined at the end of January 2003.

Serum concentrations of creatinine and lipids, and HbA1c were measured by the same methods used previously (7).

Statistical Analysis

Data are presented as means $\pm$ SD. Because the data for the comparison of group means were almost normally distributed, ANOVA was applied. For testing of the number of subjects in groups, the χ^2 test was used. Pearson's correlations were performed to determine the association between various mean ambulatory BP parameters and age. Although the analysis included only the first event for subjects who died or experienced nonfatal vascular events, the analysis for nonfatal events was done after the exclusion of the subjects who died. Based on these data, the rates of occurrences of fatal and nonfatal vascular events were expressed as the number of cases per 100 patient-years in diabetic subgroups divided by the degrees of nocturnal fall in SBP, or by the upper and lower limits for the mean $\pm 0.67 \times$ SD of each mean ambulatory BP parameter. In addition, the sensitivity, specificity and accuracy of each BP parameter for predicting various end points were calculated, and receiver operating characteristic (ROC) curves and also the areas under the ROC curves (ROC_{AUC}) for ambulatory BP parameters with various end points were used to investigate whether there was a difference in the level of risk determined by ambulatory BP levels and that determined by a pattern of nocturnal falls in SBP. In the ROC analysis, the optimum cut-off points of each ambulatory BP parameter for both fatal and nonfatal vascular events were determined. Survival and event-free

Fig. 1. Age-related trends in mean 24-h SBP, DBP, MAP and PP at entry in 8 groups divided according to 5-year age strata from <40 years to ≥ 70 years. Data are the means $\pm$ SD. Numbers of subjects in each group are shown in bar graphs of the PPs. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

survival curves were estimated using the Kaplan-Meier product-limit method and compared by the log-rank test. The effects of prognostic factors on survival and the occurrence of various vascular events were evaluated by the Cox proportional-hazards model after adjusting for potentially confounding factors at $p < 0.05$ in the comparison of baseline characteristics. In this model, the mean 24-h SBP and serum creatinine were selected from hypertension- and renal function-related parameters, respectively. Relative risks adjusting for 24-h SBP, age, duration of diabetes, serum creatinine, 24-h PP and nocturnal fall in SBP for fatal events, and after adjusting for 24-h SBP, body mass index (BMI), smoking status (yes or no), duration of diabetes, serum creatinine, nighttime SBP, and nocturnal fall in SBP for nonfatal vascular events, and their 95% confidence intervals (CI) in the Cox's model were calculated as previously described (7). The statistical significance was defined as a two-tailed p value less than $p < 0.05$.

Results

The study population consisted of 364 subjects (mean age, 54 ± 14 years; 232 men and 132 women) for whom follow-up data were available. A total of 147 first events were recorded during a mean follow-up period of 86 ± 46 months (range, 2–168 months), including 50 fatal vascular events and 97 nonfatal vascular events. The fatal events consisted of 16 cerebral infarctions, 5 cerebral hemorrhages, 4 cardiac

infarctions, 18 cardiac failures and 7 sudden deaths; and the nonfatal vascular events consisted of 20 cerebral infarctions, 4 cerebral hemorrhages, 9 cases of angina pectoris, 5 cardiac infarctions, 5 cardiac failures, 4 cases of diabetic gangrenes, 17 severe retinal lesions, and 33 introductions of hemodialysis.

Relationship between Age and Mean 24-h BP Levels in Diabetic Subjects

Aging is one of the major factors promoting arteriosclerosis. Figure 1 shows the trends of mean 24-h SBP, DBP, MAP and PP at entry in 8 groups divided according to 5-year age strata from <40 years to ≥ 70 years. SBP, MAP and PP gradually increased with age, while DBP reached a plateau at 50 to 60 years, with a gradual fall thereafter. As a continuous variable, age was strongly correlated with PP ($r = 0.394$; $p < 0.001$) and SBP ($r = 0.251$; $p < 0.001$), was weakly correlated with MAP ($r = 0.123$; $p = 0.015$), and bore no relationship to DBP.

Comparison of Demographic Characteristics at Entry in the Diabetic Subgroups with and without Vascular Events

As shown in Table 1, as expected, the mean follow-up period was shorter in the diabetic subgroup with fatal and nonfatal vascular events than in that without them. The prevalence

Table 1. Comparison of Demographic Characteristics at Entry in Diabetic Subgroups with and without Vascular Events

	Fatal vascular events		Nonfatal vascular events	
	No events	Events	No events	Events
<i>n</i>	314	50	217	97
Follow-up period (months)	94 ± 44	55 ± 46 ^{***}	111 ± 36	57 ± 37 ^{***}
Age at entry (years)	52 ± 13	64 ± 12 ^{***}	52 ± 14	54 ± 12
Sex (male/female)	204/110	28/22	142/75	62/35
Body mass index (kg/m ²)	24.0 ± 4.3	23.4 ± 4.3	24.6 ± 4.3	23.1 ± 4.0 ^{**}
Hypertensive subjects (<i>n</i> (%))	116 (36.9)	31 (62.0) ^{**}	66 (30.4)	50 (51.5) ^{***}
Antihypertensive medication (<i>n</i> (%))				
Prior history at baseline	101 (32.2)	30 (60.0) ^{***}	53 (24.9)	48 (49.5) ^{***}
At time of final follow-up	128 (40.8)	35 (70.0) ^{***}	71 (32.7)	57 (58.8) ^{***}
Calcium antagonist	100 (31.9)	21 (42.0)	55 (25.3)	45 (46.4)
ACE inhibitor or ARB	48 (15.3)	11 (22.0)	22 (10.1)	26 (26.8)
α -Blocker	7 (2.2)	3 (6.0)	6 (2.8)	1 (1.0)
Diuretic	28 (8.9)	10 (20.0)	6 (2.8)	22 (22.7)
Others	3 (1.0)	1 (2.0)	2 (0.9)	1 (1.0)
Unknown	12 (3.8)	1 (2.0)	7 (3.2)	5 (5.2)
Current smokers (<i>n</i> (%))	123 (39.2)	24 (48.0)	74 (34.1)	49 (50.5) ^{**}
Duration of diabetes (years)	7 ± 6	11 ± 7 ^{***}	5 ± 5	10 ± 7 ^{***}
Insulin use (<i>n</i> (%))	88 (28.0)	23 (46.0)	50 (23.0)	38 (39.2)
HbA1c (%)	8.9 ± 2.5	8.5 ± 2.5	8.7 ± 2.4	9.2 ± 2.5
Serum total cholesterol (mmol/l)	5.12 ± 1.14	5.30 ± 1.71	5.04 ± 1.06	5.30 ± 1.34
Serum triglyceride (mmol/l)	1.76 ± 0.98	2.28 ± 1.47	1.68 ± 1.06	1.94 ± 1.14
Serum HDL cholesterol (mmol/l)	1.09 ± 0.34	1.06 ± 0.26	1.11 ± 0.31	1.09 ± 0.39
Serum creatinine (μ mol/l)	75.1 ± 30.9	96.4 ± 59.2 ^{**}	69.8 ± 20.3	88.4 ± 44.2 ^{***}
Persistent proteinuria (<i>n</i> (%))	50 (15.9)	21 (42.0) ^{***}	12 (5.5)	38 (39.2) ^{***}
Glomerular filtration rate (ml/s)	1.47 ± 0.44	1.25 ± 0.48 [*]	1.53 ± 0.43	1.32 ± 0.43

Data are means ± SD, *n*, or *n* (%). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; HDL, high-density lipoprotein. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. diabetic subjects without events.

of hypertension was higher, the durations of diabetes longer, and the serum creatinine levels higher in the diabetic subgroup with fatal and nonfatal vascular events than in that without them. Age was higher and glomerular filtration rate was lower in only the diabetic subgroup with fatal vascular events than in that without them. Otherwise, body mass index was lower, and prevalence of current smokers was higher in only the diabetic subgroup with nonfatal vascular events than in that without them. However, there were no significant differences in sex, prevalence of antihypertensive medication use at the final follow-up, HbA1c, insulin use, or serum lipid levels between the diabetic subgroup with and that without fatal and nonfatal vascular events.

Comparison of Ambulatory BP Parameters in the Diabetic Subgroups with and without Vascular Events

As shown in Table 2, mean 24-h, daytime and nighttime SBP levels were significantly higher in the diabetic subgroups with fatal and also nonfatal vascular events than in that without them, and mean ambulatory MAP and PP levels showed the same tendency. However, mean ambulatory DBP

levels were similar between the diabetic subgroup with and that without vascular events. On the other hand, there was a smaller mean nocturnal fall in SBP and a greater proportion of nondippers in the diabetic subgroup with nonfatal, but not in that with fatal, vascular events compared with the diabetic subgroups without any vascular events.

Mean daytime levels of SBP, DBP and MAP in diabetic subjects without fatal or nonfatal vascular events were higher than the respective mean nighttime levels, although these differences in diabetic subjects with fatal or nonfatal vascular events were consistently small because of the increased proportion of nondippers. With regard to PP, there was little difference between mean daytime and nighttime levels irrespective of the presence of fatal or nonfatal vascular events.

Comparison of the Rates of Occurrence of Fatal and Nonfatal Vascular Events in the Diabetic Subgroups

Figure 2 shows the rates of occurrence of fatal and nonfatal vascular events expressed in cases per 100 patient-years in the diabetic subgroups divided by the degree of nocturnal fall in SBP. The reduction in the nocturnal SBP fall in dia-

Table 2. Comparison of Ambulatory BP Parameters in Diabetic Subgroups with and without Vascular Events

Ambulatory BP parameters	Fatal vascular events		Nonfatal vascular events	
	No events (n = 314)	Events (n = 50)	No events (n = 217)	Events (n = 97)
Systolic BP				
24-h (mmHg)	123 ± 18	136 ± 24***	120 ± 16	131 ± 20***
Daytime (mmHg)	125 ± 18	137 ± 24**	123 ± 17	131 ± 20***
Nighttime (mmHg)	119 ± 20	135 ± 25***	115 ± 17	129 ± 22***
Diastolic BP				
24-h (mmHg)	73 ± 10	73 ± 11	72 ± 10	76 ± 11**
Daytime (mmHg)	75 ± 11	74 ± 11	74 ± 10	77 ± 11
Nighttime (mmHg)	70 ± 11	72 ± 11	68 ± 10	75 ± 11
Mean arterial pressure				
24-h (mmHg)	90 ± 12	94 ± 14*	88 ± 12	94 ± 13***
Daytime (mmHg)	92 ± 13	95 ± 15	90 ± 12	95 ± 13***
Nighttime (mmHg)	87 ± 13	93 ± 15**	84 ± 12	93 ± 14***
Pulse pressure				
24-h (mmHg)	50 ± 11	63 ± 17***	48 ± 10	55 ± 13***
Daytime (mmHg)	50 ± 11	63 ± 17***	49 ± 10	54 ± 13***
Nighttime (mmHg)	49 ± 12	63 ± 17***	47 ± 11	55 ± 14
Nocturnal fall in systolic BP (mmHg)	- 6 ± 11	- 2 ± 12*	- 8 ± 10	- 2 ± 12***
Nondipper (n (%))	232 (74)	42 (84)	148 (68)	84 (87)†

Data are means ± SD, or n (%). * $p<0.05$, ** $p<0.01$, *** $p<0.001$ vs. the diabetic subgroup without vascular events. † $p<0.001$ vs. the diabetic subgroup without vascular events (χ^2 test). BP, blood pressure.

Fig. 2. The rates of occurrence for fatal (right panel) and nonfatal (left panel) vascular events expressed in cases per 100 patient-years in diabetic subjects divided by the degree of nocturnal fall in SBP.

betic subjects was clearly related to the increases in the occurrence of both fatal and nonfatal vascular events. On the other hand, when each mean ambulatory BP parameter was divided into 3 levels as shown in Fig. 3, the higher the ambulatory BP level in 24-h, daytime and nighttime of all ambulatory BP parameters, the more frequent was the occurrence of both fatal and nonfatal vascular events, suggesting that not only the nocturnal fall in SBP but also the ambulatory BP level contributes to the occurrence of both fatal and nonfatal

vascular events.

To identify the most predictive factor for fatal and nonfatal vascular events, the accuracy and ROC_{AUC} values of 24-h, daytime and nighttime measurements of ambulatory BP parameters were compared with those of nocturnal fall in SBP (Table 3). The highest value for ROC_{AUC} predicting fatal and nonfatal vascular events among ambulatory BP parameters was 0.739 of 24-h PP and 0.695 of nighttime SBP, respectively. These values were higher than the values of 0.618 and 0.667 for nocturnal fall in SBP for fatal and nonfatal vascular events, respectively. Furthermore, as optimum cut-off points, a value of 54.3 mmHg for 24-h PP for fatal events, and a value of 116.5 mmHg for nighttime SBP for nonfatal events were obtained from the ROC analysis.

Kaplan-Meier Survival Analysis

Figures 4 and 5 illustrate the findings of the Kaplan-Meier survival curve analysis in the dipper and the nondipper diabetic subgroups divided by 54.3 mmHg of the 24-h PP cut-off point for fatal vascular events (Fig. 4), and 116.5 mmHg of the nighttime SBP cut-off point for nonfatal vascular events (Fig. 5). In both fatal and nonfatal vascular events, the survival and event-free survival rates were lower in the diabetic subgroups with high ambulatory BP levels than in those with low ones, irrespective of diurnal BP patterns or dipper/nondipper status ($p<0.001$ for each, log-rank test).

Fig. 3. The rates of occurrence for fatal (left panel) and nonfatal (right panel) vascular events expressed in cases per 100 patient-years in diabetic subjects divided by 3 levels (upper and lower limits of $0.67 \times SD$ of each mean value) for 24-h, daytime and nighttime of each ambulatory BP parameter. The middle subgroups contain approximately 50% of the participants, and the higher and the lower subgroups each contain about 25% of the participants.

Table 3. ROC Analyses in Fatal and Nonfatal Vascular Events in Diabetic Subjects

Ambulatory BP parameters	Fatal vascular events		Nonfatal vascular events	
	Accuracy	ROC _{AUC}	Accuracy	ROC _{AUC}
Systolic BP				
24-h	0.725	0.664	0.663	0.652
Daytime	0.687	0.647	0.622	0.621
Nighttime	0.626	0.686	0.625	0.695
Diastolic BP				
24-h	0.478	0.508	0.590	0.608
Daytime	0.607	0.533	0.603	0.571
Nighttime	0.451	0.538	0.616	0.665
Mean arterial pressure				
24-h	0.602	0.587	0.644	0.637
Daytime	0.571	0.563	0.603	0.598
Nighttime	0.563	0.620	0.625	0.689
Pulse pressure				
24-h	0.714	0.739	0.590	0.654
Daytime	0.725	0.734	0.565	0.631
Nighttime	0.780	0.736	0.632	0.685
Nocturnal fall in systolic BP	0.613	0.618	0.632	0.667

ROC, receiver operating characteristic curve; ROC_{AUC}, area of under curve in ROC analysis; BP, blood pressure.

Fig. 4. The Kaplan-Meier survival curve analysis in the dipper and nondipper diabetic subgroups divided by 54.3 mmHg of the 24-h PP cut-off point for fatal vascular events ($p<0.001$, log-rank test).

Fig. 5. The Kaplan-Meier event-free survival curve analysis in the dipper and nondipper diabetic subgroups divided by 116.5 mmHg of the nighttime SBP cut-off point for nonfatal vascular events ($p<0.001$, log-rank test).

Table 4. Adjusted RR for Fatal and Nonfatal Vascular Events in Diabetic Subjects Evaluated by the Cox Proportional-Hazards Model

	Fatal vascular events		Nonfatal vascular events	
	Adjusted RR (95% CI)	<i>p</i>	Adjusted RR (95% CI)	<i>p</i>
24-h systolic BP	0.99 (0.96–1.03)	0.818	1.01 (0.99–1.03)	0.191
Age	1.03 (0.99–1.07)	0.081		
Body mass index			0.98 (0.92–1.04)	0.480
Duration of diabetes	1.05 (1.00–1.10)	0.036	1.06 (1.03–1.10)	<0.001
Current smoker			1.00 (0.99–1.02)	0.325
Serum creatinine	1.86 (1.09–3.15)	0.019	1.53 (0.97–2.40)	0.063
Nighttime systolic BP			1.03 (1.01–1.06)	0.041
24-h pulse pressure	1.07 (1.01–1.13)	0.022		
Nocturnal fall in systolic BP	1.01 (0.98–1.04)	0.392	1.01 (0.98–1.05)	0.231

RR, relative risk; CI, confidence interval; BP, blood pressure.

Factors Predicting Fatal and Nonfatal Vascular Events in Diabetic Subjects

In the Cox proportional-hazards model, the adjusted relative risks of confounding factors for fatal and nonfatal vascular events are shown in Table 4. Although there was a significant difference in each of the confounding factors between the diabetic subgroup with and that without vascular events at baseline, the mean 24-h PP, duration of diabetes and serum creatinine for fatal vascular events, and the mean nighttime SBP and duration of diabetes for nonfatal vascular events exhibited statistically significant adjusted relative risks ($p<0.05$ for each).

Discussion

In this study, we clearly showed that mean 24-h PP and mean nighttime SBP predicted fatal and nonfatal vascular

events, respectively, more strongly than nocturnal fall in SBP in the type 2 diabetic subjects studied. These findings suggest that ambulatory BP levels have a higher predictive value for organ damage and death compared with diurnal BP patterns or dipper/nondipper status. In addition to the ambulatory BP levels, duration of diabetes was an independent predictor for both fatal and nonfatal vascular events, and serum creatinine was an independent predictor only for fatal vascular events. On the other hand, age, BMI, and smoking habits were less useful in predicting vascular events.

As shown in Fig. 1, changes in ambulatory SBP, DBP, MAP and PP levels with age in the diabetic subjects studied tended to be similar to observations of the Framingham heart study (11), probably reflecting large artery stiffness. Furthermore, that study (12) demonstrated that, with increasing age, there was a gradual shift from DBP to SBP in subjects 50–60 years of age, and then to PP in subjects over 60 years of age as predictors of coronary heart disease risk. Taken to-

gether with our data, these findings indicate that age should be considered when prognosis is evaluated. In the present study, diabetic subjects with fatal vascular events were older (mean age of over 60 years at entry) than those without them, while diabetic subjects with nonfatal vascular events were similar in age (mean age of about 50 years at entry) to those without them. These facts may account for the difference in the predictive factors—*i.e.*, 24-h PP was most predictive for fatal vascular events and nighttime SBP for nonfatal vascular events—because the subjects who died were of course excluded from the analysis for nonfatal vascular events. However, in this study age was not an independent predictive factor in the Cox model. Although the reason for this is not clear, differences in the methods used to measure BP may have played the role: conventional BP measurements were used in the Framingham heart study, while we used ambulatory 24-h BP recordings during hospitalization. Alternatively, the finding may have been related to diabetes-specific microvascular complications. In fact, some diabetic subjects in this study had various degrees of microvascular complications, although they were not severe. We previously reported that autonomic dysfunction, especially orthostatic hypotension, and/or diabetic nephropathy were related to the reversal of diurnal BP rhythm (13), and were even independent predictive factors for nonfatal vascular events (7). Thus, our data suggest that diabetes-specific factors such as duration of diabetes and serum creatinine are stronger predictors than age or sex.

Since O'Brien *et al.* (14) first pointed out the relationship between nondippers status and the high risk of cerebrovascular complications in nondiabetic subjects, the altered diurnal BP pattern had been considered in relation to various organ damages and outcomes in various populations. Verdecchia *et al.* (15) showed that nondippers with essential hypertension had a poor prognosis for cardiovascular events. Furthermore, Ohkubo *et al.* (16) recently demonstrated that a diminished nocturnal decline in BP was a risk factor for cardiovascular mortality, independent of the overall BP load during a 24-h period, in the general population of the Ohasama Study. On the other hand, other investigators (17, 18) have reported that insufficient control of nighttime BP in subjects with essential hypertension was associated with the development of cardiovascular complications. In fact, Staessen *et al.* (4) demonstrated that the nighttime SBP more accurately predicted end points than the daytime SBP level. Thus, it is not clear which measures of ambulatory BPs, level or pattern, are the most important when predicting prognosis in nondiabetic subjects. Although the terms “dipper” and “nondipper” do not refer to the levels of diurnal BP variability, nondippers generally show higher mean 24-h ambulatory BPs than dippers when daytime BP levels are similar between them, leading to BP overload throughout the day.

With regard to subjects with type 2 diabetes, it is known that a reduced nocturnal fall in BP is related to an increased urinary albumin excretion rate (19, 20), and nighttime SBP

levels positively correlate with urinary albumin excretion rate (21, 22). These relationships have been confirmed in longitudinal studies by ourselves (23) and others (24). Moreover, Knudsen *et al.* (25) recently reported that nighttime SBP was higher in diabetic subjects with macrovascular diseases and advanced microvascular complications than in those without them, suggesting that altered ambulatory BPs in type 2 diabetic subjects are associated with progression of not only micro- but also macrovascular complications. However, it is still unresolved which parameter of ambulatory BPs is more important as a predictor of vascular event risk in type 2 diabetic subjects. This is the first report showing that the ambulatory BP level is more important as an independent predictor for various vascular events than the pattern of 24-h BP variability, independent of age and sex, in type 2 diabetic subjects. In this study, we determined the cut-off points to be 54.3 mmHg of the 24-h PP, and 116.5 mmHg of the nighttime SBP. The normal asleep SBP/DBP levels recommended by the Joint National Committee 7th Report (26) are less than 120/75 mmHg, while the European Society of Hypertension (27) recommended less than 115/65 mmHg as an optimal level and less than 120/70 mmHg as a normal level. Thus, although our cut-off point for the nighttime SBP level is similar to these recommendations, the cut-off point for the 24-h PP level, which is closely related to fatal vascular events, is shown for the first time in this study.

An important mechanism underlying the rise of PP with age is progressive arterial stiffening of the aorta and large arteries (11, 28). Miyagi *et al.* reported that the presence of diabetes substantially contributes to the increase in PP (29). Schram *et al.* (30) recently reported that PP was associated with cardiovascular mortality among the diabetic, but not among the nondiabetic individuals who participated in the cohort of the Hoorn Study, suggesting that the presence of diabetes, per se, allows PP to be an independent predictor of cardiovascular events, strokes and deaths. Furthermore, although Staessen *et al.* (31) found that the 24-h and the nighttime ambulatory PPs predict cardiovascular outcome in older subjects with systolic hypertension, in this study the 24-h PP as a confounding factor was selected based on the ROC analysis. However, the mean 24-h, daytime and nighttime PP levels were similar to each other in the diabetic subgroups irrespective of the presence of fatal vascular events. In addition, the ROC_{AUC} values for 24-h, daytime and nighttime PPs were consistently higher than the others. Accordingly, these findings suggest that 24-h, daytime and nighttime levels of ambulatory PPs can be considered to be almost equivalent as predictive factors for fatal vascular events, supporting the observations of Perk *et al.* (32), who showed that ambulatory PP was a relatively sleep-independent variable in both diabetic and nondiabetic subjects.

The main limitation of our study is the lack of information on the degree of BP and glycemic control during the follow-up periods in all participants, and on the effect of antihypertensive drugs on BP pattern as well as protection from organ

damage in the long term. However, we did make efforts to obtain excellent BP and glycemic control in each individual during the whole follow-up period as described in the Methods section. Another limitation is that our data were obtained from diabetic subjects during hospitalization, so that the values of ambulatory BP measurements may not have been equal to those during daily life.

In conclusion, this study clearly showed that the 24-h PP and the nighttime SBP levels as ambulatory BP parameters were very good predictors of fatal and nonfatal vascular events in hospitalized type 2 diabetic subjects, respectively, and either was a better predictor than the degree of nocturnal SBP fall, thus demonstrating that the ambulatory BP level more powerfully predicts vascular events than the diurnal BP pattern. Moreover, this study suggests that diabetic subjects who have a long duration of diabetes or microvascular complications, irrespective of age or sex, should measure their ambulatory BPs. Further study is needed to establish adequate methods of 24-h BP control to prevent various vascular complications in type 2 diabetic subjects.

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