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Prevention for Micro- and Macro-Vascular Complications in Diabetic Patients

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1. Introduction

One of the goals in long-term cares for patients with diabetes mellitus (DM) is to prevent the development of micro-and macro- vascular complications (The International Diabetes Federation, 2011). To achieve this purpose, an adequate control of blood pressure (BP) as well as a good glycaemic control is crucial (The International Diabetes Federation, 2011). The American Diabetes Association recommended that the BP goal should be lowered to 130/80 mmHg in the daytime of clinic setting (The American Diabetes Association, 2002-2011).

However, in 4733 patients with type 2 DM at high risk for cardiovascular events followed the mean of 4.7 years, targeting a systolic casual/clinic BP (CBP) in the daytime of less than 120 mmHg as compared with less than 140 mmHg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events (ACCORD Study Group, 2010). Further, in 16,893 patient-years of follow-up at 862 sites in 14 countries, a tight control of systolic CBP in the daytime among patients with DM and cardiovascular disease to achieve systolic CBP in the daytime of less than 130 mmHg and diastolic CBP of less than 85 mmHg was not associated with improved cardiovascular outcomes compared with usual control (Cooper-DeHoff et al, 2010). At present, the reasons of difference are not clear.

Recently, a discrepancy between screening BP by CBP measurment and ambulatory BP by ambulatory blood pressure monitaring (ABPM) has been noted. It has also been shown that in patients with essential hypertension, home BP (HBP) measurement in the morning has a stronger predictive power for mortality than CBP measurements in the daytime (Aihara et al, 1998, Ohkubo et al, 1998, Imai et al, 1999). Accordingly, the difference of results (ACCORD Study Group, 2010, Cooper-DeHoff et al, 2010) may be due to be not evaluated BP in the midnight or in the morning by ABPM or HBP measurements.

To evaluate the usefulness of HBP measurement in the morning in patients with DM, we examined whether BP elevations at the awakening-up in the morning detected by HBP were more predictive than those in the daytime detected by CBP for micro- and macro- vascular complications in patients with type 1 or 2 DM, as observed in patients with essential hypertension (Aihara et al, 1998, Ohkubo et al, 1998, Imai et al, 1999).

Our cross-sectional studies have demonstrated that HBP measurements at the awakning-up in the morning offer stronger predictive power for micro- and macro-vascular complications

in patients with type 1 and 2 DM than CBP measurements in the daytime (Kamoi et al, 2002-2003). Further, a study examined which of HBP at the awakning-up in the morning or CBP in the daytime provides the stronger predictive power for outcomes by comparing cumulative events between hypertensive and normotensive patients over 6 years in a prospective and longitudinal study of patients with type 2 DM (Kamoi et al, 2010).

2. Research design and methods

2.1 Subjects

2.1.1 A cross-sectional study

In a cross-sectional study, 10 years ago we studied on 53 Japanese patients with type 1 DM who visited our clinics regularly (Kamoi et al, 2003). The diagnosis of type 1 DM was based on the World Health Organization (WHO) criteria (AlbertiK et al, 1998). Numbers of female patients were twice of male patients. The age was 23 to 81 year old and the duration was 2 to 47 years (Table 1). Of 53 patients, 38 (72%) were treated by multiple daily insulin injections and remaining (28%) by subcutaneous continuous insulin infusion therapy for DM. Twenty two patients (42%) were treated with anti-hypertensive drugs at the beginning of the study (Table 2). Also, we studied on 170 Japanese patients with type 2 DM. They visited our clinic regularly (Kamoi et al, 2002). The diagnosis of type 2 DM was based on the WHO criteria (AlbertiK et al, 1998). The clinical characteriscs are shown in the Table 3. Ratio of numbers in female and male patients was similar. The mean age was middle and the mean BMI was within normal range (Table 3). Of 170 patients, 153 (90%) were treated with oral hypoglycaemic drugs and/or insulin regimens for DM, whereas 80 (47%) were treated with anti-hypertensive drugs at the beginning of the study (Table 4).

2.1.2 A longitudinal study

In a longitudinal study, subjects comprised 400 Japanese patients with type 2 DM enrolled between 1999 and 2005 including the patients participated in the cross-sectional study (Kamoi et al, 2010). After a detailed baseline examination (Table 5), subjects were followed up for all-cause mortality and morbidity.

All participants visited our clinic regularly and were observed until February 28, 2007. Mean survey duration of all patients was 42 ± 20 months (range, 3–72 months). Type 2 DM was diagnosed according to WHO criteria (AlbertiK et al, 1998). No significant difference in the number of patients was noted between females and males. Mean subjects were also middle ages. The mean BMI was within normal range (Table 5). At the beginning of the study, 329 patients (82%) were receiving treatment with oral hypoglycaemic drugs and/or insulin regimens for DM and 196 patients (49%) were receiving treatment with various anti-hypertensive drugs (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blocker, and others) for hypertension (Table 6). For ethical reasons, patients were treated with various anti-hypertensive, anti-diabetic, anti-dyslipidemia, and/or anti-hypercoagulation agents during the course of the study by the patients' own doctors as a part of a continuing standard of medical care.

All patients were fully informed about the purposes and the procedures for study and provided oral consent at enrolment.

	CH group			CN group			
	MH group	MN group	Total	MHgroup	MNgroup	Total	All subjects
Number	6	11	17	8	28	36	53
Age (years)	68 ± 13‡	53 ± 7	58 ± 12	54 ± 15	51 ± 16	52 ± 17	54 ± 15
Sex (female/male)	5/1	8/3	13/4	4/4	19/9	23/13	36/17
BMI (kg/m²)	22 ± 2	23 ± 1	23 ± 2	22 ± 2	22 ± 3	22 ± 3	22 ± 3
Disease duration (yr)	19 ± 11	17 ± 11	18 ± 11	23 ± 12	15 ± 9	17 ± 10	17 ± 10
Blood pressure (mmHg)							
SBP							
Clinic	154 ± 11	160 ± 18	152 ± 9*	120 ± 8	118 ± 11	118 ± 10	129 ± 19
Morning	144 ± 10‡	122 ± 9*	123 ± 14*	151 ± 197‡*	121 ± 13	121 ± 21	124 ± 20
DBP							
Clinic	103 ± 25‡	85 ± 8	91 ± 17†	75 ± 15	71 ± 9	73 ± 11	78 ± 16
Morning	81 ± 11*	74 ± 8*	76 ± 10*	82 ± 10‡*	69 ± 8	72 ± 10	73 ± 10*
HbA1c (JDS%)	6.9 ± 1.2	6.9 ± 0.9	6.9 ± 1.0	7.6 ± 1.3	7.0 ± 0.9	7.2 ± 1.0	7.0 ± 0.9
TG (mg/dl)	65 ± 36	99 ± 47	87 ± 46	116 ± 54	92 ± 34	97 ± 43	94 ± 44
T-CH (mg/dl)	210 ± 30	204 ± 38	206 ± 34	202 ± 20	198 ± 33	199 ± 30	201 ± 32
LDL (mg/dl)	112 ± 27	110 ± 26	111 ± 26	112 ± 20	102 ± 26	105 ± 25	107 ± 25
HDL (mg/dl)	84 ± 8	73 ± 14	77 ± 13	71 ± 16	74 ± 21	73 ± 20	75 ± 18
Serum Cr (mg/dl)	0.9 ± 0.2‡	0.7 ± 0.1	0.7 ± 0.2	1.0 ± 0.6‡	0.7 ± 0.2	0.8 ± 0.3	0.8 ± 0.3
UERA (μg/mg Cr)	107±112‡	6.9±3.7	42±79	324±567‡	7.1±6.9	7.8±287	66±240

Data are means ± SD. The systolic BP (SBP) and the diastolic BP (DBP) levels in all patients were measured at the clinic in the daytime and at the home at the awakening-up in the morning, resepectively. CH; clinic hypertension, CN; clinic normotension, MH; morning hypertension, MN; morning normotension, Cr; creatinine, UERA; urinary excretion rate of albumin. **P<0.01 versus patients with CN;‡P<0.01 versus patients with MN; and †P<0.01 versus patients measured at the clinic in the daytime.

Table 1. Characteristics of patients with type 1 diabetes mellitus in a cross-sectional study

2.2 Method

2.2.1 Blood pressure

2.2.1.1 CBP

CBP levels were measured once in clinical setting of a daytime during each clinic visit. HBP was also measured once each morning, in the sitting position within 10 min after awakening, for every day. For the CBP levels in the daytime, when patients with DM had clinic systolic BP 130 mmHg and/or clinic diastolic BP 85 mmHg, we classified these patients as having clinic hypertension (CH) by the criteria of the WHO and International Society of Hypertension guide lines (Guide lines Subcommittee, 1999).

	CH group			CN group				
	MH group (n=6)	MN group (n=11)	Total (n=17)	MH group (n=8)	MN group (n=26)	Total (n=36)	All subjects (n=53)	Odds ratio (95% CI)
Medical events								
Nephropathy	4	0	4	7	0	7	11	1.3 (0.3 to 5.1)
Microalbuminuria	3	0	3	5	0	5	8	1.3 (0.3 to 6.4)
Clinical albuminuria	1	0	1	2	0	2	3	1.1 (0.1 to 12.6)
Retinopathy	1	4	5	4	4	8	13	1.5 (0.5 to 5.4)
Non-proliferative	0	3	3	0	2	2	5	3.0 (0.5 to 19.7)
Preproliferative	0	1	1	1	1	2	3	1.1 (0.1 to 12.6)
Proliferative	1	0	1	3	1	4	5	0.5 (0.1 to 4.9)
Medical treatment								
Therapy for hypertension								
Oral drugs	5	4	9	6	7	13	22	2.0 (0.6 to 6.4)
Therapy for diabetes mellitus								
MDI	4	8	12	7	19	26	38	0.9 (0.3 to 3.3)
CSII	2	3	5	1	9	10	15	1.0 (0.3 to 3.9)

Data are number. Odds ratio for CH and CN groups was calculated. MDI; multiple daily insulin injections, CSII; subcutaneous continuous insulin infusion, CI; confidence interval.

Table 2. Prevalence of micro- and macro- vascular events and medical treatment in patients shown in the table 1

2.2.1.2 HBP

When the HBP levels at the awakening-up in the morning were systolic HBP 130 mmHg and/or diastolic HBP 85 mmHg, we classified these patients as having morning hypertension (MH). When these values were 130 mmHg of systolic BP and 85 mmHg of diastolic BP, we classified these patients as having clinic normotension (CN) or morning normotension (MN), respectively.

All subjects were divided into two groups: with CH or MH and without CH or MH. Finally, we examined whether CBP in the daytime and HBP at the awakening-up in the morning is more predictive of these events.

2.2.2 Micro- and macro- vascular complications

The microvascular complications detected in this study were nephropathy and retinopathy. Occurrence of nephropathy was evaluated each three months in the clinic setting from beginning of the study based on urinary excretion rate of albumin (UERA), whereas occurrence of retinopathy was evaluated at least once each 6 months during the study. The macrovascular complications defined were coronary heart disease (CHD) and cerebrovascular disease (CVD) assessed by clinical situation. Prevalence of these events was confirmed by medical history at the beginning of the study.

	CH group			CN group			
	MH group	MN group	Total	MH group	MN group	Total	All subjects
Number	74	57	131	23	16	39	170
Age (years)	67 ± 8	64 ± 8	66 ± 9	71 ± 9†	63 ± 9	68 ± 10	66 ± 9
Sex (female/male)	47/27	24/33	74/57	7/16	9/7	16/23	90/80
BMI (kg/m^2)	24 ± 3†	23 ± 2	23 ± 3*	23 ± 3†	22 ± 3	22 ± 3	23 ± 3
Blood pressure (mmHg)							
SBP							
Clinic	167 ± 18†	158 ± 14	163 ± 17*	124 ± 12†	117 ± 9	121 ± 11	153 ± 26
Morning	163 ± 19†	127 ± 7†	147 ± 24‡	166 ± 17†‡	116 ± 10	146 ± 29‡	147 ± 25‡
DBP							
Clinic	97 ± 14†	93 ± 9	95 ± 12*	75 ± 8	73 ± 9	74 ± 9	90 ± 14
Morning	88 ± 11†‡	75 ± 8‡	83 ± 12‡	88 ± 15†‡	69 ± 10	80 ± 16‡	82 ± 13‡
Laboratory variables							
HbA1c (JDS%)	6.5 ± 0.9	6.5 ± 0.9	6.5 ± 0.9	6.7 ± 1.0	6.4 ± 0.7	6.6 ± 0.9	6.5 ± 0.9
TG (mg/dl)	153 ± 77	40 ± 92	148 ± 83	138 ± 74	109 ± 46	126 ± 65	143 ± 80
T-CH (mg/dl)	198 ± 32	96 ± 31	197 ± 3	182 ± 44	204 ± 24	191 ± 38	196 ± 33
LDL (mg/dl)	109 ± 32	01 ± 31	106 ± 31	92 ± 34	122 ± 21	105 ± 33	106 ± 32
HDL (mg/dl)	61 ± 16	66 ± 18	63 ± 17	57 ± 24	59 ± 10	58 ± 20	62 ± 18
Serum Cr (mg/dl)	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2*	1.1 ± 0.4†	0.7 ± 0.2	1.0 ± 0.4	0.9 ± 0.3
UERA (μg/mg Cr)	212±524τ	11±8*	125±405*	1,113±2,449τ	7.5±5.0	660±1,943	248±1,013

Data are means ± SD. The systolic BP (SBP) and the diastolic BP (DBP) levels in all patients were measured at the clinic in the daytime and at the home at the awakening-up in the morning, resepectively. CH; clinic hypertension, CN; clinic normotension, MH; morning hypertension, MN; morning normotension, Cr; creatinine, UERA; urinary excretion rate of albumin. **P<0.01 versus patients with CN ;‡P<0.01 versus patients with MN ; and †P<0.01 versus patients measured at the clinic in the daytime.

Table 3. Characteristics of patients with type 2 diabetes mellitus in a cross-sectional study

2.2.3 Glycaemic control and other variables

Glycaemic control was evaluated by HbA1c values (JDS: normal range 4.5–5.7%) (Kasezawa et al, 1987). Other variables, including serum concentrations of electrolytes and lipids, were also measured (Kamoi et al, 2002). Albumin concentration in random spot urine was measured by the latex agglutinination photometric immunoassay method (Kamoi et al, 2002).

2.2.4 Analytical methods

2.2.4.1 CBP

CBP level was measured by patient's self at the clinic in the daytime in the left arm after a 5-min rest in a sitting position using an automatic device based on the cuff-oscillometric method (FT-200; Parama-Tech, Fukuoka, Japan).

	CH group			CN group				
	MH group (n=74)	MN group (n=57)	Total (n=131)	MH group (n=23)	MN group (n=16)	Total (n=39)	All subjects (n=170)	Odds ratio (95% CI)
Medical events								
Nephropathy	69†	0	39	91†	0	54	43	0.6 (0.3 to 1.1)
Microalbuminuria	67†	0	32	52†	0	31	32	1.0 (0.5 to 2.3)
Clinical albuminuria	12†	0	7	39†	0	24	10	0.2 (0.1 to 0.7)*
Retinopathy	32†	18	28	33†	6	24	26	1.3 (0.5 to 2.9)
Non-proliferative	18	9	15	4	0	3	12	6.4 (0.8 to 50)
Preproliferative	9†	2	6	13	0	8	7	0.8 (0.2 to 3.1)
Proliferative	5	8	7	17†	6	13	8	0.5 (0.2 to 1.6)
CHD	8	11	9	35†	0	20	11	0.5 (0.2 to 1.3)
CVD	23	11	18	35†	0	21	18	0.8 (0.3 to 1.9)
Medical treatment								
Therapy for hypertension								
Oral drugs	61†	15	48	70†	6	44	47	1.2 (0.6 to 2.5)
Therapy for diabetes mellitus								
Oral drugs or insulin	91	86	89	100	88	95	90	0.2 (0.0 to 1.5)

Data are %. The prevalence is a percent ratio of patient with MH, MN, CH, CN, or all patients. Odds ratio for CH and CN groups was calculated. *P<0.01 versus patients with CN, †P<0.01 versus patients with MN. CI: confidence interval.

Table 4. Prevalence of micro- and macro- vascular events and medical treatment in patients shown in the table 3

2.2.4.2 HBP

HBP level was measured at the home in the morning within 10 min after awakening, by a patient's self or a family member, in the left arm in a sitting position. Semiautomatic devices based on the cuff-oscillometric principles that generate a digital display of both systolic BP and diastolic BP were used. All devices met the criteria set by the Association for the Advancement of Medical Instrumentation. A standard arm cuff was used to measure both CBP and HBP levels.

2.2.4.3 Variable parameters

Venous samples were collected during each clinic visit and were analysed for HbA1c levels and concentrations of total cholesterol (TC), low densty lipoprotein cholesterol (LDL), high densty lipoprotein chesterol (HDL), triglyceride (TG), and creatinine without fasting. Microalbuminuria and clinical albuminuria were defined as UERA 30 and 300 μg/mg creatinine, respectively (The American Diabetes Association, 2002).

Variable	MH	MN	CN	CH
n (%)	286 (72*)	114 (28*)	283 (71*)	117 (29*)
Age (years)	66±9†	61±10	65±9	64±10
Sex (F/M)	136/150	52/62	140/143	48/69
Duration (years)	14.1±8.5†	11.2±7.5	13.8±8.2	12.1±8.6
BMI (kg/m^2)	24±3†	23±4	24±3†	23±3
Blood pressure (mmHg)				
Systolic				
Morning	151±19†	117±8**	146±22†	130±20**
Clinic	148±22†	132±20	155±17†	117±9
Diastolic				
Morning	84±11†**	73±10**	82±12†**	77±13**
Clinic	87±16†	78±13	90±14†	71±9
Laboratory variables				
HbA1c (%)	6.7±1.1	6.5±0.8	6.7±1.1	6.6±1.0
TG (mg/dl)	155±122	138±84	154±117	140±100
T-C (mg/dl)	199±33	197±30	198±32	198±32
LDL-C (mg/dl)	109±30	112±27	108±28†	115±31
HDL-C (mg/dl)	60±19	59±17	60±18	60±20
Serum Cr (mg/dl)	0.8±0.3†	0.7±0.2	0.8±0.3	0.8±0.3
UERA (μg/mg Cr)	206±646τ	26±113	141±369	187±854

Data represent mean ± SD. Morning and clinic blood pressures were measured at the home at the wakening-up in the morning and at the clinic in the daytime, respectively. CH; clinic hypertension, CN; clinic normotension, MH; morning hypertension, MN; morning normotension, Cr; creatinine, UERA; urinary excretion rate of albumin. For comparisons of UERA, unpaired *t* test with Welch's correction was used. †P<0.05 versus patients with normotension; **P<0.01 versus patients measured at the clinic in the daytime.

Table 5. Baseline characteristics of patients with type 2 diabetes mellitus on the basis of HBP measurement in a longitudinal study

Variable	MH	MN	Odds ratio (95% CI)	CN	CH	Odds ratio (95% CI)
Medical events (%)						
Microvascular complications	271 (68*)	36 (9.0*)	38 (20 to 75)†	235 (59*)	72 (18*)	3.0 (1.9 to 5.0)†
Nephropathy	157 (39*)	14(3.5*)	8.7 (4.7 to 15.9)†	133 (33*)	38 (10*)	1.8 (1.1 to 2.7)†
Microalbuminuria	121	13	6.3 (3.4 to 11.6)†	105	29	1.7 (1.0 to 2.8)†
Clinical albuminuria	36	1	16.3 (2.0 to 120)†	28	9	1.3 (0.6 to 2.8)
Retinopathy	114 (29*)	22 (5.5*)	2.8 (1.6 to 4.7)†	102 (26*)	34 (8.5*)	1.3 (0.8 to 2.1)
Non-proliferative	66	15	2.0 (0.7 to 3.6)†	61	20	1.3 (0.7 to 2.2)
Pre-proliferative	14	0	12.1 (0.7 to 206)†	11	3	1.3 (0.7 to 2.2)
Proliferative	34	7	2.1 (0.9 to 4.8)†	30	11	1.0 (0.5 to 2.3)
Macrovascular complications	100 (25*)	10 (2.5*)	5.6 (2.8 to 11.1)†	78 (20*)	32 (8.1*)	1.0 (0.6 to 1.6)
Coronary heart disease	36 (9.0*)	4 (1.0*)	4.0 (2.0 to 11.4)†	28 (7.0*)	12 (3.0*)	1.0 (0.5 to 2.0)
Cerebrovascular disease	64 (16*)	6 (1.5*)	5.1 (2.2 to 12.2)†	50 (13*)	20 (5.0*)	1.0 (0.6 to 1.8)
Medical treatment (%)						
Therapy for hypertension	173 (43*)	23 (5.8*)	6.1 (3.6 to 10.1)†	125 (40*)	71 (10*)	2.6 (1.7 to 4.2)†
Therapy for diabetes mellitus						
Oral drugs/or insulin	240 (60*)	89 (22*)	1.5 (0.9 to 2.5)	225 (56*)	104 (26*)	0.5 (0.3 to 0.9)
Therapy for dyslipidemia	71 (18*)	17 (4.3*)	1.9 (1.1 to 3.4)†	71 (18*)	17 (4.3*)	3.5 (1.9 to 6.4)†
Therapy for hypercoagulation	56 (14*)	4 (1.0*)	6.7 (2.4 to 11)†	44 (11*)	6 (1.5*)	3.4 (1.4 to 8.3)†
Therapy for others	4 (1.0*)	3 (0.8*)	0.5 (0.1 to 2.4)	3 (0.8*)	4 (1.0*)	0.3 (0.07 to 1.4)

Data represent means ± SD. Morning and clinic blood pressures were measured at the home at the awkening-up in the morning and in the clinic in the daytime, respectively. *Numbers in parentheses represent a percentage ratio of patients in each type for all subjects. CI: confidence interval. †P<0.05 versus patients with normotension; **P<0.01 versus patients measured at the clinic.

Table 6. Prevalence of micro- and macro- vascular events and medical treatment in patients shown in the table 5

2.3 Statistical analysis

2.3.1 Baseline

All values are presented as means ± SD. Mean values were compared using chi square test or un-paired Student's *t* test. To compare the prevalence of micro- and macro-vascular complications in groups with and without the hypertension, Yates 'continuity corrected x2 test with two-tailed P value was performed and odds ratios were calculated; if prevalence of the events was 0.5 was added to all values before calculating the odds ratio and 95% CIs were provided. Multiple logistic analyses were used to determine the contribution of the variables to the events. Correlation between HBP and CBP levels was calculated. In addition, receiver operating characteristic (ROC) curves for HBP and CBP with various end points were used to examine whether HBP levels in the morning and CBP levels in the daytime behave differently in allowing ascertainment of the true risk or whether the 130/85 mmHg cut points are better for HBP levels in the morning than for CBP levels in the daytime.

	Multivariate-adjusted odds ratio	95% CI
Age (years)	1.03	0.97–1.10
Sex (female/male)	0.85	0.29–2.45
BMI (kg/m^2)	1.29†	1.08–1.55
HbA_{1c} (%)	0.84	0.49–1.45
Clinic blood pressure		
SBP (mmHg)	1.00	0.97–1.04
DBP (mmHg)	0.93†	0.89–0.98
Morning blood pressure		
SBP (mmHg)	1.07†	1.04–1.10
DBP (mmHg)	1.02	0.97–1.07
Triglycerides (mg/dl)	1.00	0.99–1.01
Total cholesterol (mg/dl)	0.98	0.96–1.01
LDL cholesterol (mg/dl)	1.03*	1.00–1.06
HDL cholesterol (mg/dl)	1.02	0.99–1.06
Serum creatinine (mg/dl)	43.2*	1.53–1,225
Anti-hypertensive drugs	5.90*	1.27–9.49
Anti-diabetic drugs	4.89	0.86–27.7

Odds ratio for continuous variables represent a difference of 1 SD. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

Table 7. Multivariate-adjusted odds ratios and 95%CIs of risk factors for nephropathy in patients with type 1 diabetes

2.3.2 Endpoints and outcome measures

Differences in outcomes for each endpoint of death, and new or worsened micro- and macro- vascular complications between hypertensive and normotensive patients on the basis of HBP levels in the morning or CBP levels in the daytime were assessed using survival curves calculated according to Kaplan-Meier methods, then compared by a hazard ratio using the log-rank test. Within the survey time previously defined, a time until censoring or death (or occurrence of the event) was calculated for each endpoint.

2.3.3 Risk factor assessment for outcomes

In a longitudinal study, risk factors related to outcomes determined statistically by a log-rank test were assessed using hazard ratios by Cox proportional hazards model. For outcomes of microvascular complications, risk factors were determined in new, worsened, or improved events. Omnibus tests were used to determine the appropriateness of Cox proportional hazards modelling. Confounding factors used in this analysis were variables with MH in the morning or CH in the daytime at baseline and additional therapy for each disease. The analysis was based on the first event of each participant, thereby, allowing each participant to enter once in the Cox proportional hazard models.

These analyses were performed using the GraphPad Prisms of software (version 3.02-5.01; GraphPad Soft-ware, San Diego, CA, USA), the Statistical Package for the Biosciences (SPBS;

Winesteem Institute of Community Medicine, Tokyo, Japan) and the Dr. SPSSII for Windows (SPSS Japan, Tokyo, Japan). A two-tailed value of P< 0.05 was considered statistically significant.

	Multivariate-adjusted odds ratio	95% CI
Age (years)	1.03	0.97–1.10
Sex (female/male)	0.85	0.29–2.45
BMI (kg/m^2)	1.29†	1.08–1.55
HbA_{1c} (%)	0.84	0.49–1.45
Clinic blood pressure		
SBP (mmHg)	1.00	0.97–1.04
DBP (mmHg)	0.93†	0.89–0.98
Morning blood pressure		
SBP (mmHg)	1.07†	1.04–1.10
DBP (mmHg)	1.02	0.97–1.07
Triglycerides (mg/dl)	1.00	0.99–1.01
Total cholesterol (mg/dl)	0.98	0.96–1.01
LDL cholesterol (mg/dl)	1.03*	1.00–1.06
HDL cholesterol (mg/dl)	1.02	0.99–1.06
Serum creatinine (mg/dl)	43.2*	1.53–1,225
Anti-hypertensive drugs	5.90*	1.27–9.49
Anti-diabetic drugs	4.89	0.86–27.7

Odds ratio for continuous variables represent a difference of 1 SD. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

Table 8. Multivariate-adjusted odds ratios and 95%CIs of risk factors for nephropathy in patients with type 2 diabetes

3. Results

3.1 In a cross-sectional study

3.1.1 A type 1 diabetes mellitus

As shown in the figure 1, in type 1 diabetic groups with both CH and CN, the kinds of anti-hypertensive medicines administered after taking breakfast in the groups with MH were greater than in the groups with MN. There were no significant differences in the prevalence of nephropathy and retinopathy between the two groups with CH and CN. In contrast, the prevalence of nephropathy with 8 microalbuminuria and 3 clinical albuminuria in the patients with MH was significantly higher than those with MN (Table 2). The prevalence of proliferative retinopathy in the patients with MH was significantly higher than that in those with MN, although there was no significant difference in all types of retinopathy between two groups. There was no occurrence of CHD or CVD in the two groups. Specifically, systolic MH made a significant (r = 0.66, P = 0.001) contribution to the occurrence of nephropathy by multiple regression analysis, whereas the difference is not related to age, sex, duration of diabetes, BMI, HbA1c, and serum lipid concentrations or use of different methods of insulin therapy and anti-hypertensive drugs. Meanwhile, the duration of diabetes had a significant (r = 0.4, P = 0.001) contribution to the occurrence of retinopathy (Table 7). No relationships

between systolic HBP and diastolic HBP, and systolic CBP and diastolic CBP measurements were observed (morning systolic HBP = 0.28, systolic CBP = 0.07, P = 0.06 and diastolic HBP = 0.25, diastolic CBP = 0.14, P = 0.005). The area under the ROC curve (AUC) of morning systolic HBP (0.99 ± 0.01) was significantly higher (P < 0.001) than that of systolic CBP (0.49 ± 0.10) in nephropathy (Figure 2). There was no statistical difference in AUC between them in other events. In nephropathy, sensitivities of 130 mmHg threshold in morning and clinic systolic BP were 1.0 (95% CI 1.0–1.0) and 0.55 (0.23–0.83), respectively, whereas those of 85 mmHg threshold in morning and clinic diastolic BP were 0.64 (0.31-0.89) and 0.55 (0.23–0.83), respectively. Specificities of 130 mmHg threshold in morning and clinic systolic BP were 0.95 (0.84–0.99) and 0.48 (0.32–0.64) (Figure 3), respectively, whereas those of 85 mmHg threshold in morning and clinic diastolic BP were 0.14 (0.05–0.29) and 0.29 (0.16–0.45), respectively.

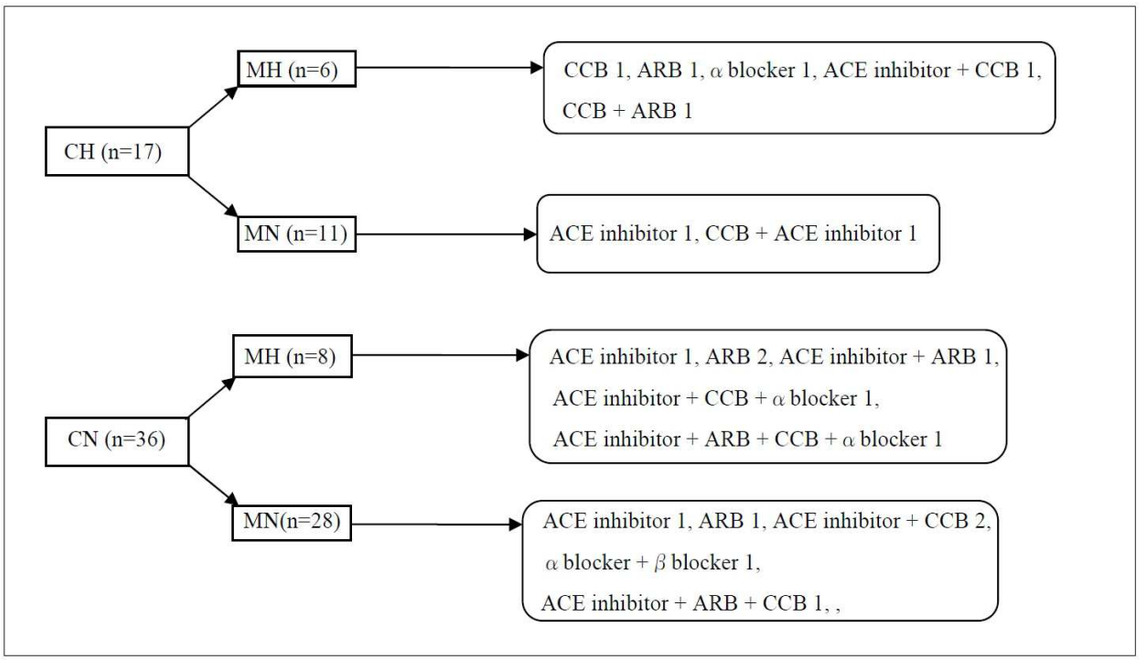

Fig. 1. Various kinds of anti-hypertensive medicines in each group with CH or CN and MH or MN in patients with type 1 diabetes mellitus in a cross-sectional study. These anti-hypertensive medicines were administered after taking a breakfast. CH; clinic hypertension, CN; clinic normotension,MH; morning hypertension, MN; morning normotension, ARB; angiotensin II receptor blocker, CCB; calcium channel blocker , ACE inhibitor; angiotensin converting enzyme inhibitor.

3.1.2 A type 2 diabetes mellitus

As shown in the figure 4, in the type 2 diabetic groups with both CH and CN, the kinds of anti-hypertensive medicines administered after taking breakfast in the groups with MH were also greater than in the groups with MN as those in patients with type 1 diabetes (Table 4). Comparing the characteristics of patients with and without CH, the following trends were noted. The prevalence of CH was four times higher than CN. BMI in CH patients was slightly higher than in CN patients. In contrast, serum creatinine concentration

and UERA in CH patients were significantly lower than in CN patients (Table 3). No significant differences in other variables were noted between the two groups (Tabel 4). A total of 48% of CH patients were being treated with anti- hypertensive drugs, compared with 44% of CN patients (Tabel 4).

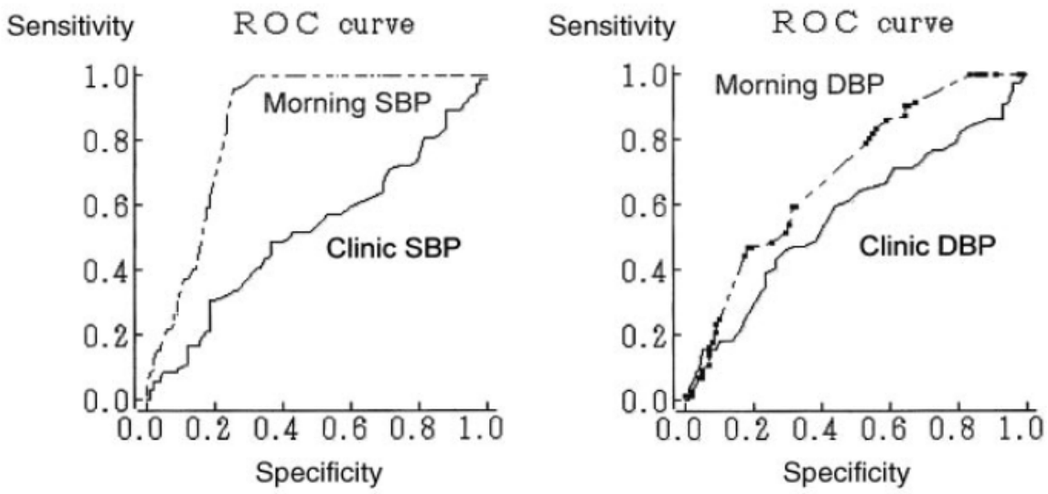

Fig. 2. ROC analysis in nephropathy in patients with type 1 and 2 diabetes mellitus.

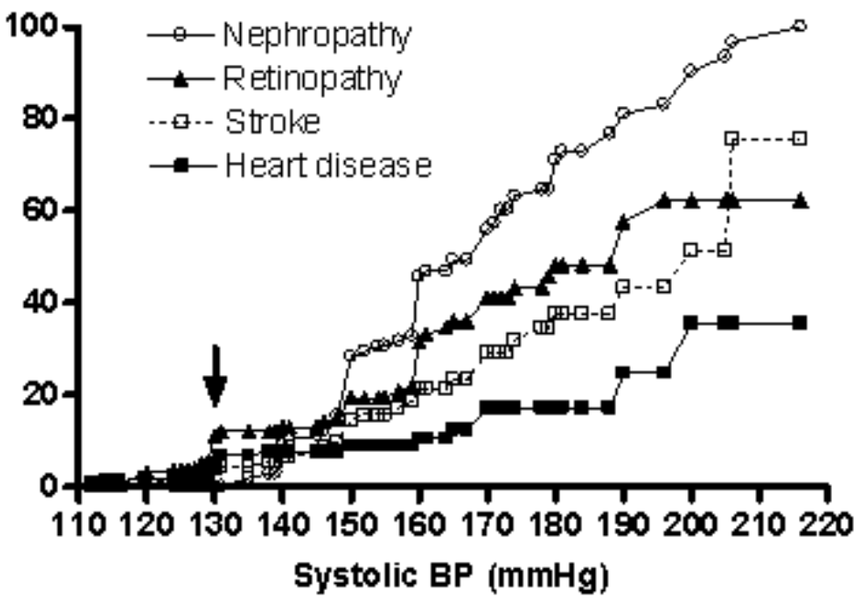

Fig. 3. Threshold of systolic HBP at the wakening-up for prevalence of micro- and macro-vascular events in patients with type 1 and 2 diabetes mellitus. The vertical arrow indicated the value of threshold of systolic HBP.

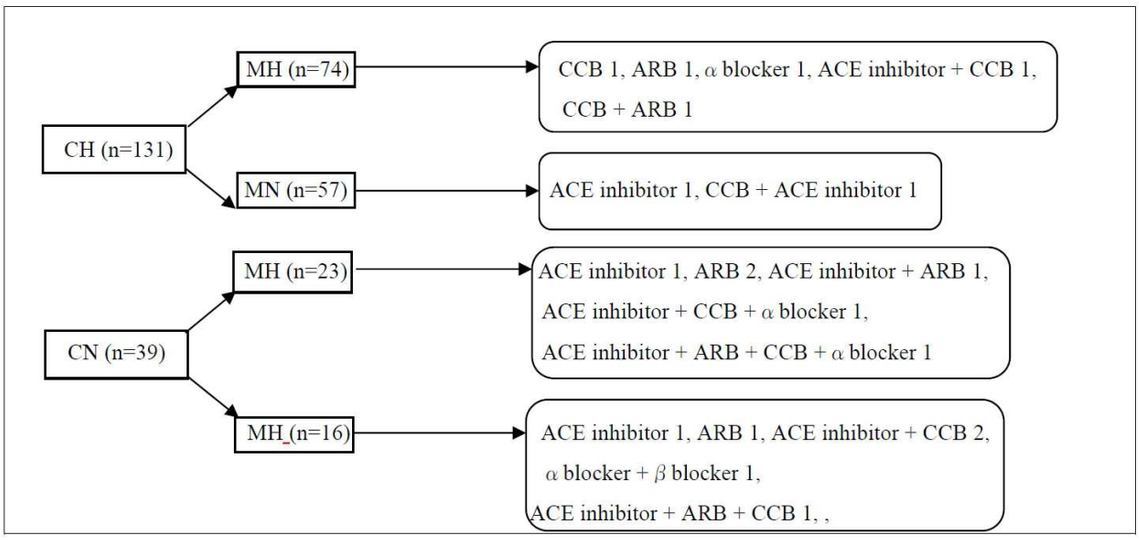

Fig. 4. Various kinds of anti-hypertensive medicines in each group with CH or CN and MH or MN in patients with type 2 diabetes mellitus in a cross-sectional study. CH; clinic hypertension, CN; clinic normotension, MH; morning hypertension, MN; morning normotension, ARB; angiotensin Ⅱ receptor blocker, CCB; calcium channel blocker , ACE inhibitor; angiotensin converting enzyme inhibitor

When we compared the prevalence of diabetic complications in the two groups, there were no significant differences in the prevalence of nephropathy, retinopathy, CHD, and CVD between the two groups. However, the prevalence of clinical albuminuria in CH patients was lower than in CN patients (Table 2).

The CH patients were further divided into two groups: with and without MH (Table 3). BMI in MH patients was slightly higher than in MN patients. Systolic BP, diastolic BP, and UAER in MH patients were significantly higher than those in MN patients. There were no significant differences in other variables between the two groups. Nephropathy was observed in 69% of MH patients, whereas there was no nephropathy in MN patients. The prevalences of retinopathy and CVD in MH patients were also significantly higher than in MN patients (Table 4). The prevalence of treatment with anti- hypertensive drugs was higher in MH than in MN (Table 4).

The CN patients were also divided into two groups: with and without MH (Table 3). The means of age, BMI, systolic HBP, and diastolic HBP in MH patients were significantly higher than those in MN patients. Serum creatinine concentration and UAER were also higher in MH than in MN. No significant differences in other variables were shown between the two groups. However, the prevalence of nephropathy in MH patients was high (91%), whereas no nephropathy was observed in MN patients. The prevalences of retinopathy, CHD, and CVD in MH patients were also higher than in MN patients. More MH patients than MN patients were being treated with anti- hypertensive drugs (Table 4).

Comparing the characteristics of the two patient groups with and without MH, the following trends were noted (Table 3). The means of age, sex, HbA1c levels, and lipid concentrations were not different between the two groups. However, systolic BP and diastolic BP, based on HBP in the morning, in MH patients were significantly higher than in MN patients. Serum creatinine concentration and UAER were also higher in MH patients

(Table 3). The prevalences of treatment with anti-hypertensive and anti-diabetic drugs were 3 and 1.5 times higher, respectively, in MH patients compared with MN patients (Table 4). The prevalence of nephropathy in MH patients was 75%, whereas no nephropathy was noted in MN patients. The prevalence of retinopathy in MH patients was twice that found in MN patients, although there was no difference in the prevalences of non-proliferative and proliferative retinopathies between the two groups (Table 4). The prevalences of CHD and CVD in MH patients were four and six times higher, respectively, than in MN patients.

Specifically, the prevalence of nephropathy in all subjects was highly associated ($P < 0.001$) with systolic MH, but not with age, sex, HbA1c, serum lipid concentrations without LDL, and use of anti-diabetic drugs by multiple logistic analysis. However, prevalence of nephropathy was associated with BMI, LDL concentration, serum creatinine concentration, and use of anti-hypertensive drugs and was negatively associated with diastolic CBP (Table 8).

The relationships between systolic HBP and diastolic HBP in morning and clinic measurements were described by regression equations of morning systolic HBP = 0.23 systolic CBP + 111 and morning diastolic HBP = 0.26 diastolic CBP + 58, respectively. The correlations were poor (morning versus clinic systolic BP, $r = 0.05$, $P = 0.004$; morning versus clinic diastolic BP, $r = 0.09$, $P = 0.0001$). In comparison of ROC curves for HBP and CBP with the events, the areas under ROC curves of morning systolic HBP (0.86 ± 0.39) and morning diastolic HBP (0.70 ± 0.52) were significantly higher ($P < 0.001$ and $P = 0.035$, respectively) than those of systolic CBP (0.52 ± 0.60) and diastolic CBP (0.57 ± 0.59) in nephropathy, indicating that HBP has a higher predictive value than CBP (Figure 2). In contrast, there were no statistical differences between them in other events. In nephropathy (Figure 2), sensitivities of the 130 mmHg threshold in morning and clinic systolic BP were 1.00 (1.00–1.00 95% CI) and 0.18 (0.10–0.29), respectively, whereas those of the 85 mmHg threshold in morning and clinic diastolic BP were 0.49 (0.37–0.61) and 0.43 (0.31–0.55), respectively. Specificities of the 130 mmHg threshold in morning and clinic systolic BP were 0.68 (0.58–0.77) and 0.85 (0.76–0.91) (Figure 3), respectively, whereas those of the 85 mmHg threshold in morning and clinic diastolic BP were 0.75 (0.65–0.83) and 0.73 (0.64–0.82), respectively.

3.2 In a longitudinal study

3.2.1 Baseline characteristics of patients

In the patients with a type 2 DM, baseline characteristics of patients classified as hypertensive or normotensive on the basis of HBP and CBP are shown in Tables 5, respectively. Based on HBP, prevalence of MH was double that of MN. Mean age, duration of disease, BMI, systolic BP and diastolic BP in both HBP and CBP, serum creatinine concentration and UAER were also significantly higher with MH than with MN (Table 5). In MH patients, morning diastolic HBP was significantly lower than diastolic CBP. In MN patients, morning systolic and diastolic HBP were significantly lower than systolic and diastolic CBP, respectively. No significant differences were noted in other laboratory variables between the two groups. Prevalence of microvascular complications was significantly great higher with MH than with MN, and prevalence of nephropathy was about 9-fold higher with MH than with MN (Table 6), although there was no dialysis. Prevalence of macrovascular complications was also significantly higher with MH than with MN. Most patients showing MH received anti-hypertensive and anti-diabetic drugs. The prevalence of patients receiving anti-hypertensive drugs was 6-fold higher for MH than for MN. The prevalence of patients receiving anti-diabetic drugs appeared 1.5-fold higher with MH than with MN, although no significant difference was evident. Prevalences of using anti-dyslipidemia and anti-hypercoagulation

agents were also significantly higher with MH than with MN (Table 6), but prevalences were lower than those for anti-hypertensive and anti-diabetic drugs.
On the basis of CBP, most characteristics of CH and CN patients at baseline were similar to those of MH and MN patients, respectively (Table 5). However, no significant differences in mean age, duration of disease, serum creatinine concentration or UAER or in prevalences of retinopathy and macrovascular complications were noted between these patients. Meanwhile, mean LDL was significantly lower with CH than with CN. In patients with CN, morning systolic and diastolic HBP were significantly higher than systolic and diastolic CBP, respectively (Table 5).

3.2.2 Endpoints and outcome measures

Nine cumulative events (2.3%) of death were observed for 6 years (Figure 6). They were with sustained MH, whereas none occurred in patients with sustained MN (Table 9). The hazard ratio was significantly (5-fold) higher with sustained MH than with sustained MN.

Outcome	Patient Status on the Basis of HBP Measurement (n = 400)				Patient Status on the Basis of CBP Measurement (n = 400)			
	Hypertension (n=286)	Normotension (n = 114)	Hazard Ratio (95% CI)	P	Hypertension (n=283)	Normotension (n = 117)	Hazard Ratio (95% CI)	P
Primary outcome								
Death	9	0	4.87 (1.23–19.3)	0.02*	6	3	0.62 (0.13–2.87)	0.54
Secondary outcome								
Microvascular complications	55	17	2.06 (1.25–3.38)	0.01*	50	22	0.89 (0.53–1.51)	0.67
Macrovascular complications	20	1	3.85 (1.56–9.47)	0.01*	20	1	3.11 (1.16–8.30)	0.02*

Characteristics of patients at baseline on the basis of HBP and CBP measurement are shown in Tables 1 and 2, respectively. The 400 patients in each group were classified as having hypertension or normotension according to values of blood pressure measured at home or in the clinic at the start of this study, respectively. Differences in outcomes for new or worsened events of each endpoint between sustained hypertensive patients and sustained normotensive patients in each group were assessed using survival curves from the Kaplan-Meier method and comparisons were analyzed using hazard ratios by the log-rank test.
*Significant difference between hypertensive and normotensive patients.

Table 9. Primary and secondary outcomes in a longitudinal study.

On the causes of death, 3, 3, 2 and 1 patients in the MH group were due to cancer with brain, breast or pancreas, CVD, CHD and unknown cause, respectively. while 3, 1, 1 and 1 patients in the CH group were due to cancer with brain, breast or pancreas, CVD, CHD and unknown cause, respectively, and 2 and 1 patients in the CN group were due to CVD and CHD, respectively (Kamoi et al, 2010). As shown in figure 7, new or worsened events of microvascular complications were observed in 72 patients (18%) included 36 with retinopathy and 59 with nephropathy, while improved events of microvascular complications were shown in 102 patients (25.5%) included 27 with retinopathy and 79 with nephropathy. New or worsened events of macrovascular complications were shown in 21 patients (5.3%) included 8 patients with myocardial infarction, 3 with heart failure, 1 with atrial fibrillation, 7 with cerebral infarction and 2 with cerebral bleeding. These new or worsened cumulative events were also significantly higher with sustained MH than with sustained MN, whereas no significant difference was seen between sustained CH and CN.

In terms of macrovascular complications, cumulative events also occurred significantly with sustained CH (Table 9).

On the outcome of each group with normotension, white coat hypertension, masked hypertension or sustained hypertension, we were not able to survey their outcomes with statistics as a cohort study, because that each number participated in this study was small.

3.2.3 Risk factor assessment for outcomes

In terms of death, macrovascular complications at baseline represented a significant risk factor for patients with sustained MH, as determined by a Cox proportional hazard model that was significantly (P<0.001) appropriate according to Omnibus tests. Serum creatinine and UAER at baseline levels also represented significant confounding factors. However, as hazard ratios for these parameters were 0.01 and 1.00, respectively, these represented negative or small associated risk (Table 10).

In terms of microvascular complications, MH at baseline on the basis of HBP was a significant risk factor related to new, worsened or improved events of events according to a Cox proportional hazard model that was significantly (P<0.001) appropriate by Omnibus tests. Additional therapies for hypertension and DM also represented significantly confounding factors, but displayed negative associations with this outcome (Table 10).

In terms of macrovascular complications, HbA1c and presence of micro- and macrovascular complications at baseline in patients with sustained MH were significantly associated with this outcome, as determined by a Cox proportional hazard model that was significantly (P<0.001) appropriate by Omnibus tests. Additional therapy for hypertension represented a negative confounding factor significantly (Table 4). In patients with sustained CH on the basis of CBP, a Cox proportional hazard model was found to be significantly (P<0.001) appropriate by Omnibus tests, and additional therapies for hypercoagulation and others represented a significant confounding factor (P=0.025; Hazard ratio 5.71). No other significant risk factors were identified other than serum TG level at baseline (P=0.025), for which the hazard ratio was 1.00. Additional therapy for hypertension also represented significantly confounding factors, but displayed negative associations with this outcome (P=0.001; Hazard ratio 0.10) (data not shown in the table).

4. Discussion

4.1 Blood pressure (BP)

Over the past 100 years, BP has been measured in the clinic of daytime, which has been called casual or clinic BP (CBP). As hypertension research and treatment methodologies have substantially advanced since the development of CBP, the gold standard of BP measurement for practice and research has been CBP (Imai et al, 2004). Namely, an evaluation for BP is based on the value of CBP. However, an alternative to the CBP was proposed soon after the introduction of BP measurements. Recent studies show that a discrepancy between CBP and ABPM has been noted. It has also been shown that in patients with essential hypertension, HBP measurement in the morning has a stronger predictive power for mortality than CBP measurements in the daytime (Aihara et al, 1998, Ohkubo et al, 1998, Imai et al, 1999). Further, BP measurements by using ABPM or HBP revealed that there is a white hypertension that BP by CBP in the daytime is high, whereas

BP byHBP in the daytime is normal or a masked hypertension that BP in the daytime is normal but BP in the night or in the morning is high in peoples (Pickering, 1992), whch has worsend outcomes for complications in patients, is paied attention to many researchers.

Variable	Death		Microvascular Events		Macrovascular Events	
	Hazard Ratio	P	Hazard Ratio	P	Hazard Ratio	P
Baseline						
Age (years)	1.22	0.13	1.00	0.21	1.10	0.20
Sex	5.61	0.28	1.02	0.86	2.59	0.24
Duration (years)	1.12	0.10	0.99	0.94	0.94	0.11
BMI (kg/m^2)	0.97	0.84	1.00	0.85	1.16	0.10
Blood pressure (mmHg)						
Morning hypertension	0.01	0.95	2.10	0.01*	4.16	0.25
Clinic hypertension	0.11	0.15	0.87	0.27	4.22	0.08
Laboratory variables						
HbA1c (%)	0.73	0.68	1.07	0.22	1.90	0.01*
Triglycerides (mg/dl)	1.00	0.79	1.00	0.95	1.00	0.28
Total cholesterol (mg/dl)	1.01	0.71	1.00	0.83	1.01	0.38
LDL-cholesterol (mg/dl)	1.00	0.91	1.00	0.84	0.99	0.63
HDL-cholesterol (mg/dl)	1.07	0.28	1.00	0.64	1.03	0.10
Serum creatinine (mg/dl)	0.01	0.01*	0.90	0.69	0.53	0.58
Urinary albumin excretion (mg/g creatinine)	1.00	0.03*	1.00	0.98	1.00	0.72
Medical events						
Microvascular complications	0.24	0.78	1.07	0.16	1.67	0.04*
Macrovascular complications	46.0	0.02*	1.08	0.57	3.87	0.01*
Medical treatment						
Therapy for hypertension						
Baseline	0.01	0.07	0.96	0.71	0.99	0.98
Additional	1.18	0.93	0.39	0.01*	0.02	0.01*
Therapy for diabetes mellitus						
Baseline	0.82	0.81	1.04	0.54	1.21	0.50
Additional	0.04	0.07	0.38	0.01*	1.21	0.46
Therapy for dyslipidemia						
Baseline	0.19	0.35	1.14	0.35	0.36	0.19
Additional	0.01	0.99	1.09	0.84	0.01	0.98
Therapy for hypercoagulation and others						
Baseline	26.3	0.21	1.05	0.79	4.43	0.07
Additional	0.01	0.99	0.38	0.07	0.77	0.86

macro- vascular

Each outcome of death, and new, worsened or improved micro- and new or worsened macrovascular events was determined in patients with sustained morning hypertension on the basis of home blood pressure (HBP), which was determined by the log-rank test. Confounding factors were variables at baseline and additional therapy for each disease. Associated risk factors among the confounding factors were assessed using hazard ratio by Cox proportional hazards modeling.
*P value was significant for each risk factor.

Table 10. Risk factors for each outcome of events in patients with sustained morning hypertension on the basis of HBP

4.1.1 Method for blood pressure

4.1.1.1 Clinic Blood Pressure (CBP)

In 1896, Riva-Rocci developed an indirect arm-cuff method for the BP measurement, and in 1905, Korotkoff introduced the use of auscultation. Since then, the method for BP measurement with sphygmomanometers has remained essentially unchanged for 100 years. Nowadays, the oscillometric method takes the plase of sphygmomanometers for having a favorable environment.

4.1.1.2 Home Blood Pressure (HBP)

4.1.1.2.1 ABPM by automated BP measurements

However, alternative methods to the CBP are proposed as HBP. To evaluate the HBP, many methods have developed in the world. One of the methods is ABPM. There are many reports on the results using ABPM for several decades (Imai et al, 2004). Clinically, Sokolow M and his colleagues developed the initial semiautomatic ABPM device in 1962. It consisted of a BP cuff that was manually inflated by the subject and of a tape recorder on which the Korotkoff sounds were recorded. Now, ABPM provides automated measurements of arterial BP for 24 hours or longer. Most modern ABPM monitors use the oscillometric technique. The monitors are programmed to take readings at desired intervals, usually every 15 to 30 minutes, throughout the day and night. At the end of recording, the readings are downloaded onto a computer.

ABPM demonstrated the variability of BP during the daytime and its relatively poor correlation with CBP and first showed that ABPM correlates more closely than CBP with damage to heart and arteries caused by hypertension. They also provided that ABPM improves the ability to predict risk. Nowadays, ABPM is reliable and quiet, and can be programmed to be fully automatic and be worn with little discomfort. Rrecordings by ABPM demonstrate the well-known diurnal pattern of BP, with the higher pressures in the afternoon, with the lower readings in the evening, with the nadir during sleep, and the well-reported early morning surge starting. The BP measurement by ABPM showed there is a white coat hypertension or a masked hypertension (Pickering, 1992). Thus, the ABPM provides BP information in relation to time.

4.1.1.2.2 HBP by self-BP measurement

Another method is self-BP measurement. In 1940, Ayman and Goldshine first reported the concept of "self-BP measurement" and demonstrated an apparent difference between the CBP and the self measured BP. Initially, self-measurement was done using the auscultation method. In the 1970s, an electric device based on the microphone method was marketed, but not widely distributed because of high price, mechanical difficulties, and the issue of auscultation gap. Explosive distribution of HBP measurement devices since the 1980s is mediated by the development of devices based on the cuffoscillometric principle. The basic algorithm of the principle has been improved by procedures to correctly approximate the characteristic changes during phase I and phase V Korotkoff sounds owing to electronic development. Recently, the accuracy of the automatic device is determined by comparison with the auscultation method and no other standard method is currently available for this purpose. At present, three types of electrical devices for HBP measurements are commercially available: the arm-cuff device, the wrist-cuff device, and the finger-cuff device. Ten million such electrical devices are produced each year in the Far East (including

Japan, Korea, Taiwan and China), which represents 85% of the world production. Of those, 35% are wrist-cuff devices. Finger-cuff devices commanded a considerable portion of the market share owing to their convenience and ease-of-use. Nowdays, manufacturers have decreased production of finger-cuff devices owing to technical problems and extensively increased production of wrist-cuff devices. In Japan, wrist-cuff devices possess 30% of the market share. Wrist-cuff devices are much easier to handle and more portable, but include serious shortcomings (Imai et al., 2004). The reference level for BP measurement is the right atrium. When the measurement site is 10 cm below (above) the right atrium, systolic BP and diastolic BP are measured 7 mmHg higher (lower) than those at the level of the right atrium. Even after appropriate correction of the hydrostatic pressure, another issue remains concerning the anatomy of the wrist. At the wrist, the radial and ulnar arteries are surrounded by the radial bone, the ulnar bone and several long tendons, including the palmaris longus tendon. Therefore, even a sufficient amount of cuff pressure over the arterial area does not necessarily occlude these arteries completely. As a result, wrist-cuff devices sometime provide erroneous readings, especially for systolic BP. Therefore, arm-cuff devices based on the cuff-oscillometric method are recommended for HBP measurement (Imai et al, 2004), which is recommended by guidline of many societies for hypertension (the European Society of Hypertension and the European Society of Cardiology, 2007, the American Heart Association, American Society of Hypertension and Preventive Nurses Association, 2008, the Japanese Society of Hypertension , 2009).

4.1.1.1.3 Differences between ABPM by automated-BP measurement and HBP by self-BP measurement

It is very important to know the characteristcs of the difference between ABPM and HBP. ABPM is measured under several psychological and physiological conditions by automated BP measuremnt, while HBP is measured under relatively stable conditions by self-BP measurment. Although both ABPM and HBP are able to evaluate BP in the night-time, an estimation of BP in the short-time by HBP is inadequate. Meanwhile, an estimation of BP in the long-time for more than 24 hours including the drug effect by ABPM is inadequate and occasionally insufficient due to regression to the mean, and reproducibility owing to measure BP under psychological and physiological conditions by ABPM is poor (Imai et al, 2004). Further, the costs for ABPM by automated BP measurement including devices are higher than those for HBP by self-BP measurement. However, we confirmed that ABPM is sometimes better to check the accuracy of HBP measurement method.

4.1.2 Variation

4.1.2.1 Variation of BP by HBP in healthy subjects

There is no difference in BP by HBP using Omron device between left and right arms for a day and for one month. Further, there is no difference in BP using left arm- cuff by HBP between summer and winter.

4.1.2.2 Variation of BP by HBP in diabetic patients

As mentioned in above, the variation of BP by HBP at the awakening-up using wrist-cuff in a diabetic patient is sometimes higher than that using arm-cuff. In diabetic patients, BP by HBP at the wakening-up is also increased sometimes by stress for a month. In them, more than 10% of day-by-day coefficient variation (CV) in HBP at the wakening-up for a month

leads to have more occurences of complications with micro- and macro-vascular disturbences than less than 10% of CV (Figure 5) as shown in a diabetic patient who had acute myocardial infarction. These findings were demonstrated by Ohasma study (Imai et al, 2004). Short-term BP variability is a risk factor for cardiovascular diseases (Imai et al, 2004). Although short-term information is available from ABPM, the information on day-by-day variability is obtained only with home BP measurements. The Ohasama study demonstrated that day-by-day variability reflects the risk of cardiovascular diseases. Thus, home BP measurements can now replace ABPM (Imai et al , 2004).

4.1.3 Threshold

Subjects from the Ohasama population aged 40 years and over were followed up for an average of 10.6 years. In the study, when the relationship between BP level and stroke incidence being analyzed by a Cox regression model was adjusted for age, sex, and drug treatment, the study suggested that there is higher predictability of HBP when compared with CBP. The linear regression analysis deduced that 140/90 mmHg for CBP corresponds to 125/80 mmHg for HBP, suggesting that the normative value of HBP is less than 125/80 mmHg (Imai et al, 2004)

In our study, we used thresholds of once HBP value at the awakening-up in the morning and those of CBP in the daytime as <130/85 mmHg value based on the criteria of CH owing to the 1999 WHO-International Society of Hypertension guidelines (Guide lines Subcommittee, 1999). This studies showed the threshold of 130 mmHg of systolic BP at the awakening-up in the morning for micro- and macro-vasclualr complications is significant (Figure 3), while diastolic BP of HBP at the wakening-up is persistently referred to assement the BP for the complications.

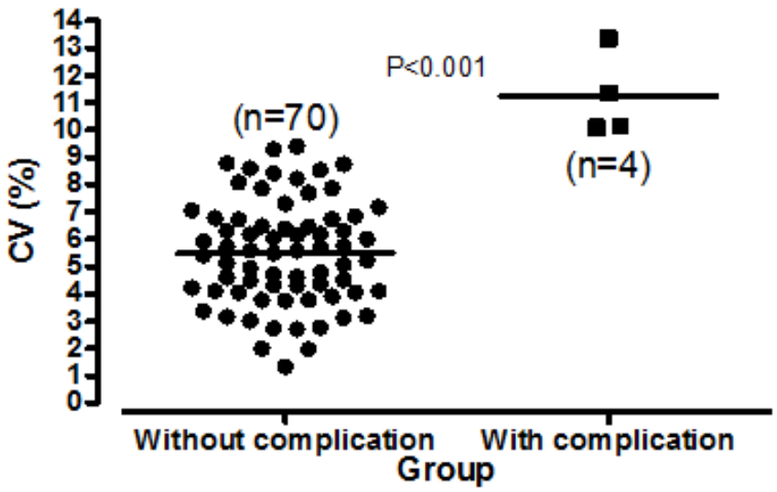

Fig. 5. Relationship between variations of BP by HBP measured at the awakening-up in the morning and vascular comlications in diabetic patients in comparison with those of less than 10% and more than 10% of CV for a month. In diabetic patients, the mean of more than of 10% for CV has demonstrated that there were more complications than that of less than 10% for CV.

Recently, all guidelines recommended a threshold for HBP by 5-10 mmHg is lower than for CBP (Mancia et al, 2007, Pickering et al, 2008, Ogihara et al, 2009). The guidelines indicated that the target HBP goal for treatment is <130–135/85 mmHg in the morning (Mancia et al, 2007) and <135/85 mmHg or <130/80 mmHg in the morning in high-risk patients (Pickering et al, 2008). The Japanese Society of Hypertension defined the threshold of controlled BP is < 135 /85 mmHg of HBP in the morning (Ogihara et al,2009).

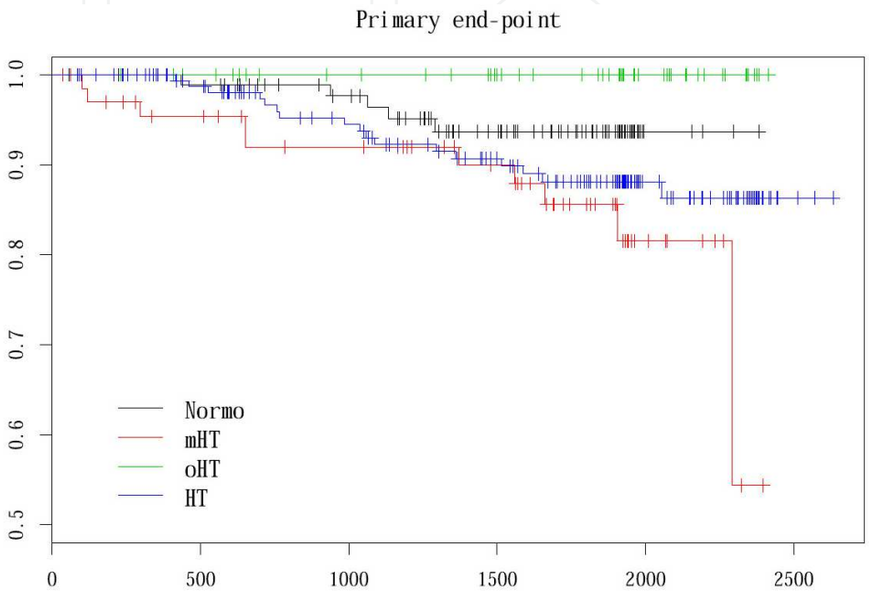

Fig. 6. Event-free survival curve of primary endpoints in patients with type 2 diabetes in a longitudinal study. Normo; MN and CN, mHT; MH, oHT; CH, HT; MH and CH

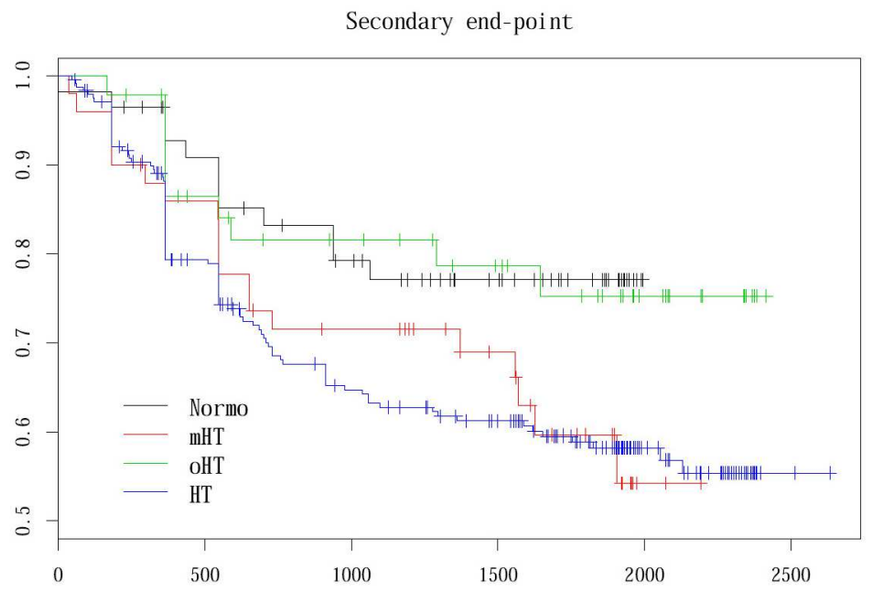

Fig. 7. Event-free survival curve of secondary endpoints in patients with type 2 diabetes in a longitudinal study. Normo; MN and CN, mHT; MH, oHT; CH, HT; MH and CH

4.2 In a cross-sectional study

4.2.1 In a type 1 diabetes mellitus

As shown in the figure 1, in the type 1 diabetic groups with CH or CN, the anti-hypertensive medicines in the groups with MH were larger number than in the groups with MN. The prevalence of nephropathy in the patients with MH was significantly higher than in those without MH, even though they had CN (Table 2). In contrast, the occurrence was not observed in those without MH, even though they had CH. Specifically, nephropathy, including clinical albuminuria, was observed in patients with systolic MH but not in patients without MH. Analysis by ROC curves also indicates that home BP in the morning has a stronger predictive power than clinic BP, especially in nephropathy (Figure 2). The cut point of 130-mmHg morning systolic BP has higher sensitivity and higher specificity than that of clinic systolic BP (Figure 3). This finding indicates that nephropathy in type 1 diabetic patients may be strongly related to morning home BP rather than clinic BP (Kamoi et al, 2003). The reason may be explained by several factors, such as white coat hypertension, nondipper hypertension, and morning surge. Particularly, an increase in nocturnal BP, as detected by ABPM, in type 1 diabetes is related to the development of microalbuminuria (Moore et al, 1992, Lurbe et al, 2003). These phenomena are thought to be caused by many neuroendocrine and hematological factors, especially autonomic neuropathy (Spallone et al, 1993, Lafferty et al, 2000, Torbjornsdotter et al, 2001). Although we did not measure 24-h ambulatory BP, the greater range in the relation of morning home BP and clinic BP may be partially explained by true and white coat hypertension, reverse-dipping hypertension, and the effects of treatment with anti- hypertensive drugs. In contrast, the prevalence of retinopathy in type 1 diabetic patients did not relate to BP, including morning home BP, although the degree of retinopathy was strengthened by MH. The duration of diabetes contributed to retinopathy significantly. They support the hypothesis that sustained long-term hyperglycaemia is the strongest predictor for developing retinopathy and that high morning home BP accelerates retinopathy as well as nephropathy.

4.2.2 In a type 2 diabetes mellitus

In the type 2 diabetic patients who were regularly treated with diet and exercise or medications for hyperglycaemia and hypertension, we found that one half of CH patients had MN, whereas two thirds of CN patients had MH. The prevalences of nephropathy, retinopathy, CHD, and CVD in patients with MH were significantly higher than in patients without MH, even though they had CN. In contrast, the prevalence of these vascular disturbances was significantly lower in patients without MH than in patients with MH, even though they had CH. Specifically, nephropathy, including clinical albuminuria, was observed in patients with systolic MH but not in any patients without MH. The difference is not related to age, sex, BMI, HbA1c, serum lipid concentrations, or use of anti-diabetic and anti-hypertensive drugs. The finding in the present cross-sectional study indicates that micro- and macro- vascular complications of type 2 diabetic patients may be strongly related to HBP in the morning rather than CBP.

The reason for the underlying relation of high HBP in the morning rather than high CBP to the vascular complications is not clearly determined by this study. However, several possibilities are postulated. First, type 2 diabetic patients have high prevalence of increased CBP but normal HBP in the morning (white coat hypertension) (Burgess et al, 1991, Puig et al, 1995). White coat hypertension seems to be a low risk for vascular complications

(Pickering, 1996, Nielson et al, 1997). Second, O'Brien et al (O'Brien et al, 1988) and Imai et al (Imai et al, 1990) reported that nocturnal decline in BP in patients with essential hypertension is often diminished (non-dipper hypertension) and sometimes inverts to become a nocturnal elevation (inverted dipper hypertension). Non-dipper hypertension, particularly inverted dipper hypertension, accelerates vascular disturbances (Shimada et al, 1990, Okubo et al, 1997), including microalbuminuria (Opsahl et al, 1988). Many studies have reported that type 2 diabetic patients have non-dipper hypertension (Forgari et al, 1994, Spalone et al, 1993, Farmer et al, 1998, Sturrock et al, 2000, White, 2001, Aronson, 2001). Therefore, it seems that blunted nocturnal and/or inverted dipper hypertension may cause micro- and macro- vascular complications in type 2 diabetic patients. Third, a morning surge in BP may be related to these events. A number of reports indicate that the early morning surge in BP acts as a trigger for vascular events (White, 2001, Aronson, 2001). Most diabetic patients have the morning surge (Aronson, 2001). These phenomena in diabetic patients are considered to be caused by many neuroendocrine and haematological factors, including autonomic neuropathy, which may result in glomerular hyperfiltration, hypercoagulability, and hypofibrinolysis, promoting micro- and macro- vascular disturbances. In fact, a high prevalence of these phenomena was observed in MH but not in MN. In addition, the severity of MH in CN patients tended to be greater than in CH patients. Moreover, the relation of MBP and CBP levels was a greater range, indicating true and white coat hypertension, and MBP level in some patients was higher than the corresponding CBP level, indicating that reverse dipping hypertension might occur, although we did not measure 24-h ambulatory BP. It is hypothesized that treatment with anti- hypertensive drugs reduced daytime BP but did not restore blunted nocturnal hypertension, did not decrease nocturnal hypertension, and could not attenuate the morning surge in BP (Spalone et al, 1993, Imai et al, 1999). The greater range in relation of MBP and CBP, and the negative association between events of nephropathy and clinic DBP may be partially explained by the effect of treatment with anti- hypertensive drugs, as hypothesized above.

Analysis by ROC curves also indicates that HBP has a stronger predictive power than CBP, especially in nephropathy. The cut points of 130/85 mmHg have higher sensitivity in morning measurement than in clinic measurement (Figure 2), although specificity in the cut point of 130 mmHg SBP in the morning measurement was lower than in the clinic measurement. Accordingly, measurement of HBP in the morning is a useful method of determining these phenomena, as indicated by the Ohasama study (Imai et al, 1990-2004, Okubo et al, 1995-1998), and high HBP levels at the awakening-up in the morning in type 2 diabetic patients may be related to micro- and macro- vascular complications of diabetes.

All findings indicate that high BP levels at the awakening-up in the morning, obtained by means of self-measurement in type 2 diabetic patients, should be treated as hypertension.

4.3 In a longitudinal study

4.3.1 General

We analysed the influence of HBP at the awakening-up in the morning and of CBP in the daytime on outcomes of events including death, microvascular complications as nephropathy and retinopathy, and macrovascular complications as CHD and CVD for data obtained over 6 years in a prospective, longitudinal study of type 2 diabetic patients. To clarify which of HBP or CBP provides the stronger predictive power for the outcomes, the

400 patients were classified as with or without hypertension based on HBP and CBP measurements at baseline, because that although the cross-sectional studies have demonstrated that HBP measurements at the awakening-up in the morning offer stronger predictive power for micro- and macro-vascular complications in patients with type 1 and 2 DM than CBP measurements in the daytime (Kamoi et al, 2002-2003) and the MH may be caused by micro- and macro-vascular complications.

All subjects were Japanese patients with type 2 diabetes. Subject characteristics were broadly similar to those described previously (Kamoi et al, 2002), except that patients with CH showed a higher prevalence of nephropathy than patients with CN.

Recently, all guidelines recommended a threshold for HBP by 5-10 mmHg lower than for CBP (Mancia et al, 2007, Pickering et al, 2008, Ogihara et al, 2009) as mention. In this study, the use of the same thresholds based on the criteria of CH owing to the 1999 WHO-International Society of Hypertension guidelines (WHO, 1999) for both methods resulted to MN patients with higher threshold and more severe MH patients selected with HBP. Nevertheless, the cumulative event of death was observed in sustained MH patients, but not in sustained MN patients. United Kingdom Prospective Diabetes Study (UKPDS) reported that the cumulative incidence of death was 12.4 % (597 of 4801 patients with type 2 diabetes) for ten years (Adler et al, 2000). In the study, the incidence was 2.3 % for 6 years. Although the reason is unclear why the incidence in this study is lower than in UKPDS, the hazard ratio was significantly (5-fold) higher in sustained MH patients than in sustained MN patients, while no significant difference was seen between sustained CH and CN patients. In addition, cumulative events of new or worsened microvascular complications were significantly (2-fold) higher in sustained MH patients than in sustained MN patients, while no significant difference was seen between sustained CH and CN patients. The incidence of the events is about 50% higher in the MH patients as compared to the MN patients (19.2% vs. 14.9%), while the hazard ratio indicates that the risk of an event in the MH patients is about twice as high as the risk of an event in the MN patients. This may be explained by that the follow-up time in the MH patients is much shorter than the follow-up time in the MN patients. Furthermore, UKPDS reported that the cumulative incidence of CHD was 12.5 % (600 of 4801 patients with type 2 diabetes) for ten years. In the study, the incidence was 5.3 % for 6 years. Also, although the reason is unclear why the incidence in this study is lower than in UKPDS (Adler et al, 2000), cumulative events of new or worsened macrovascular complications were significantly higher in sustained MH patients than in sustained MN patients, and significantly higher in sustained CH patients than in sustained CN patients.

The present results indicate that cumulative events of death and new or worsened micro- and macro- vascular complications are more strongly related to sustain MH, although sustained CH is also related to them,

In terms of death among sustained MH patients, the finding that presence of macrovascular complications at baseline was a significant risk factor indicates that sustained MH may be a trigger for death among patients with macrovascular complications. In the event of new or worsened microvascular complications, the fact that MH at baseline was the only associated risk factor indicates that sustained MH also represents a strong contributor to new or worsened microvascular complications. The finding that additional therapy for hypertension suppressed occurrence of new or worsened microvascular complications supports this view. In the event of new or worsened macrovascular complications, the identification of glycaemic control and presence of micro- and macro- vascular

complications at baseline among patients with sustained MH as associated risk factors indicates that sustained MH, as along with glycaemic control and presence of micro- and macro-vascular complications (American Diabetes Association, 2009), is important risk factor. It is supported this view that age, sex, serum creatinine, LDL and proteinuria were not risk factors. Moreover, additional therapy for hypertension improved or prevented the macrovascular events, supporting this idea. Meanwhile, the finding that sustained CH was related to the macrovascular events is consistent with the findings of a previous report (Aldler et al, 2000). Accordingly, not only sustained CH but also sustained MH is related to the new or worsened macrovascular events.

All findings indicated that events of death and new or worsened micro- and macro-vascular complications in type 2 diabetic patients are strongly related to sustained MH, irrespective of sustained CH as demonstrated in a cross-sectional study (Kamoi et al, 2002-2003) and in the Ohasama study (Okubo et al, 1998), and support the view that the available evidence suggests that HBP has strong prognostic value, which appears to be superior to that of the conventional CBP measurements. The reasons of differencnt results by studies of ACCORD and Cooper-DeHoff et al may be obtained by evaluation of BP by HBP measurement at the wakening-up.

4.3.2 Limitations of this study

In a longitudinal study, this study was that the numbers of patients participating and events occurring over the 6 years of the study were heterogeneous and small, so we were unable to survey outcomes and compare differences among baseline groups of patients with MH, MN, CH and CN as a cohort study. Further, there were no evening measurements as well as 24 hours BP monitoring to compare them. Instead, we classified the 400 patients into patients with or without hypertension based on HBP and CBP measurements and compared differences in cumulative events between sustained hypertensive and normotensive patients in each group. These patients' classifications obviously overlapped. Accordingly, the censoring date depends on whether HT and NT are defined according to CBP or HBP and the same censoring time was not used in the 2 analyses. Furthermore, for ethical reasons, most patients received treatment with various anti-hypertensive agents and other medications during follow-up. Therefore, we were unable to examine outcomes without changing treatments from baseline over the 6 years of the study and whether these drugs would thus have influenced the outcomes of events in this study. At baseline 49% of the subjects received anti- hypertensive treatment. Anti-hypertensive drugs are most likely prescribed on the basis of CBP. Therefore, somebody argues that it is not appropriate to classify patients taking anti- hypertensive drugs and having a normal BP as normotension, and the untreated CBP in most of these patients may be probably in the hypertensive range. This may introduce a bias in the comparison between CBP and HBP.

Particularly, it is clinically more informative to evaluate the prognostic value of both white coat hypertension and masked hypertension based on CBP and HBP among subjects with diabetes. However, we were not able to survey their outcomes with statistics as a cohort study, because that each number participated in this study was small.

Someone may indicate that the prognostic values of CBP and HBP should be assessed as not only categorical data, but also continuous variables. The analysis using continuous variables

may give more significant meaning, but in this study, BP as continuous variables showed high fluctuation and the numbers participated were small. Accordingly, as the analysis with statistics is complex, we did not examine it in this study.

By meta-analysis, compared with clinic BP monitoring alone, systolic BP at daytime by home BP monitoring has the potential to overcome therapeutic inertia and lead to a small but significant reduction in systolic and diastolic BP. Hypertension control with home BP monitoring can be enhanced further when accompanied by plans to monitor and treat elevated BP, although there is not a systematic review on the morning BP by home BP measurement (Agarwal et al, 2011).

4.3.3 A mechanism undering awakening-up hypertension related to vascular complications in patients with diabetes mellitus

As shown in Figure 8, when subjects had awakening-up from sleeping, their parasympathic activity changed to sympathic activity. Such changes at the awakening-up have most increase in activiation of renin-angiotenin-aldosteron-vasopressin system, coaglulation system and oxidant stress, and most decreases in activation of plasminogen activator inhibitor and fibilinolytic system. The alterations have companied with most conctriction of blood vessel owing to most decreased endothelial function in the day (Figure 9) (Otto et al, 2004). In the states, hypertension may lead to have a vascular injury, resulting in vascular disturbances. Most patients with diabetes have hypertension when we used measurement of BP by HBP at the awkening-up as well as CBP in the daytime.

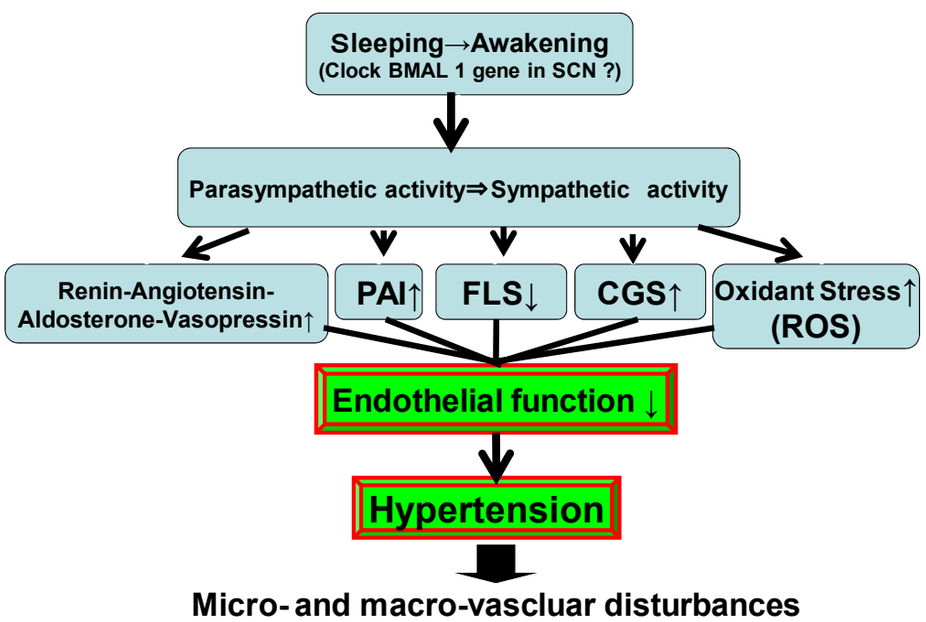

Fig. 8. Scheme of mechanism underling awakening-up hypertension related vascular disturbences in diabetic patients. BMAL ; Brain-Muscle-Arnt-Like-protein, SCN ; supra optic nucleus, PAI; plasminogen activator inhibitor, FLS ; fibilinolytic system, CGS; coaglulation system

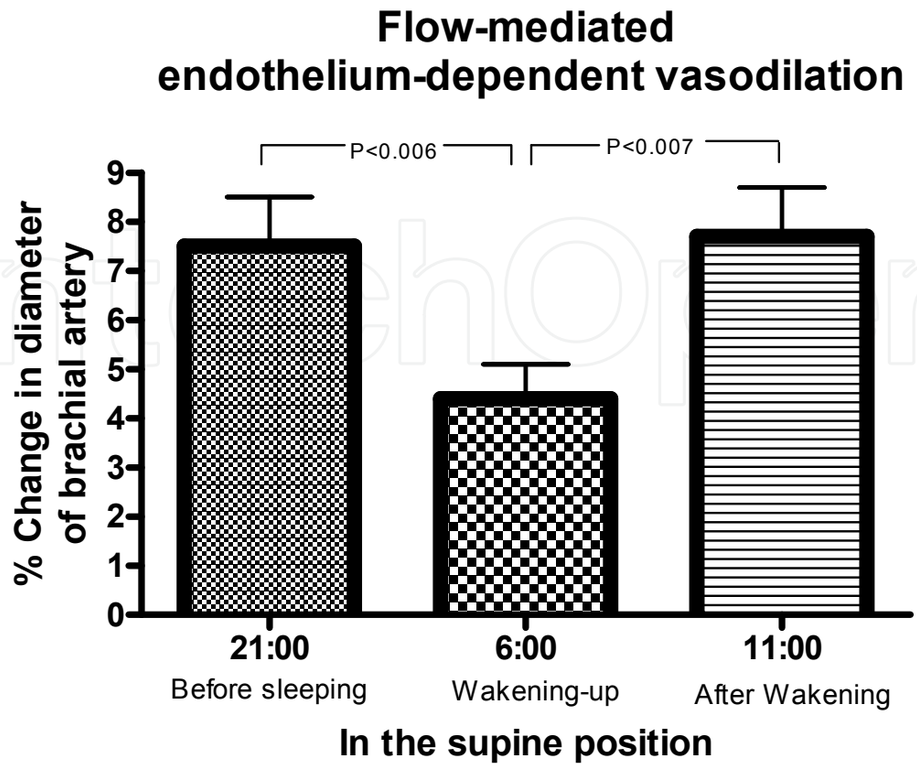

Fig. 9. Change in diameter of brachial artery at the awakening-up, after the wakening and before sleeping in the supine postion of healthy subjects by evaluation using flow-mediated echogram.

4.3.4 A reason why we measure BP at the wakening-up by HBP

There were more occurrences of CVD and CHD in the morning and in the evening in Japanese peoples in 1994 (Sato et al, 1994). However, the reason was unclear. Also, Stergiou GS et al in 2002 showed that the incidences of vascular complications in patients with hypertension at the awakening-up in Siesta were greater number than those in patients with normotension at the awakening-up (Stergious et al, 2002) (Figure 10). Our previous studies demonstrated that secretions of hormones related to BP in the upright position are higher than in the recumbent position (Kamoi et al, 1988). These findings indicated that the differences may be related to the difference of parasymapthic- and sympathic-nerves activities. Further, the increased hormones have decresded immediately after bias by various factors including own or other helps. In fact, HBP at the morning has been decreased immediately after awakening-up and second or third measurement of HBP is more decreased than first measurement of BP. Therefore, we chosed first HBP measurement once at the awakening-up except another points of BP in a day, although someone thinks that the once mesurment may be strict, because that many reseachers have a mean of BP for several mesuremnts of BP becasuse that most patients desire to pass urine after awakening. When they are unbearable to pass it, I recommend once measurement of BP after passing the urine. Most patients have awakening-up in the eary morning, but some patients who have worked in midnight have awakening-up in the late morning. Therefore, I recommend patients to measure BP at awakening-up in the day. The method is simple and accurate to assess HBP.

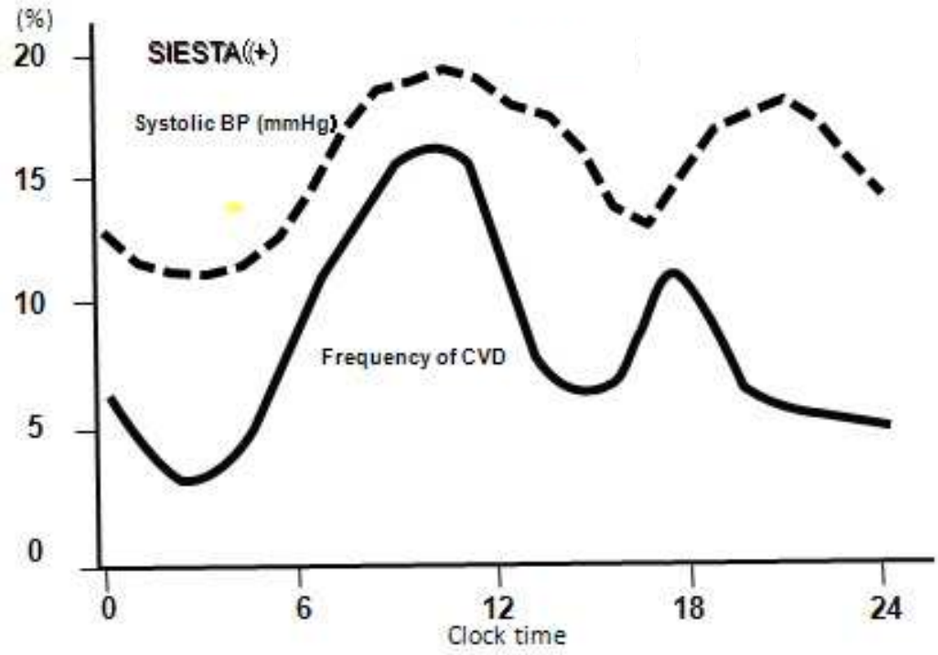

Fig. 10. Relationship between systolic blood pressure at the awkening-up in Siesta of Greece and cerebral vascular diseases (CVD).

4.3.5 An usefulness of BP by HBP in the disaster

First, Kario et al observed that there were more occurences CVD or CHD in patients with MH, which increased after several days after Hanshin-Awaji earthquake using ABPM in 1994 (Kario et al, 2002). The mechanism may be due to activity of sympathic nerve, which was supported by administration of α blockers. They proposed if peoples have the MH by HBP or ABPM, α blockers administration into the peoples have been recommended, which needs few weeks post the disaster. To evaluate MH in the morning, BP must be measured by a device of measurements HBP or ABPM. However, in Japan, nowadays, peoples in the public refuge houses have BP measurement in the daytime, but not upon awakening in the morning.

Our experices in the 2004 Mid-Niigata Prefecture Earthquake in 2004 (Kamoi et al, 2006) are same as Kario et al. The patients measured HBP in the awkening-up in his own house showed an increased HBP within a few weeks afer earthquake and the patients suppressed HBP in the awalening-up by taking anti-hypertensive medicines for MH before the earthquake had no vascular complications (Figure 12), whereas peoples without measured HBP had many CHD, CVD or dialysis during 6 months after the earthquake (Kamoi et al, 2006). These findings suggest that it is important to control MH

as we11 as CH during a disaster to prevent vascular complications, particularly such as nephrophaty. However, our study showed only one-third of patients measured their HBP within three months after the shock. Although the reasons why they did not measure their HBP were not clarified by the study, it is known that some patients lost their HBP measurement equipment, some had their equipment destroyed, and some suffered from anxiety, in particular sleep disturbance, as result of the devastation caused by the strong earthquake. In the public refuge houses, all patients have BP measurements in the daytime as the report by Kario et al, but not upon awakening in the morning. Therefore, we recommend strongly that there is need to develop a procedure of BP measurement upon awakening in the morning during a disaster in the public refuge houses as well as in their homes and to educate individuals about appropriate adaptation mechanisms following a disaster such as taking special care of themselves during the initial three months following a disaster. Appropriate information about morning hypertension should be provided to all affected people using all possible means, including the mass media, to decrease the potential for adverse consequences.

4.3.6 Treatment methods for awakening-up hypertension, by HBP in patients with diabetes melitus

First, restriction of salt ingestion in diabetic patients is necessary to have better BP by HBP at the awakening-up as patients with hypertension in the daytime. As hyperglycaemia causes increased urinary excretion of glucose via convoluted tubule, reabsorption of sodium cloride from the convoluted tubule into blood is increased. Hence, volume expansion in the blood and activation of sympathic nerve occure in them. They lead to occure MH in the morning as CH in the daytime. Therefore, restriction of salt ingestion (less than 7.0 g/day) is usefull to control MH.

Second, howeve, the treatment is not effective in most diabetic patients. Some patients have MN in the admission of hospital, but have MH in their homes. Probably, the sympathic activity of them may increase in the daily life, which shows the MH at the awakening-up but CN in the daytime as masked hypertension. Further, some patients have orthostatic hypotension by nerve disturbenes, which shows that BP are hypotension by CBP in the daytime, whereas they are MH by HBP at the awakening-up in the morning. In such patients, switched bedtime adminstration of α blockers is effective (Figure 11) (Kamoi et al, 2006).

Third, when the patients have CH in the daytime and MH at the awakening-up, administration of long active anti-hypertensive medicines after taking breakfast as a conventinal method for hypertension is usfull. Sometimes, such adminstraton is not effective in the patients with MH. In that case, switched bedtime administration is effective (Kamoi et al, 2006). In the world, many studies by researchers on administration methods of them are proceeding.

Fourth, we meet many patients who had albeit such treatments, the therapy had no effective for MH. In such diabetic patients, clock time disturbed may be accompanied (Figure 8). As it is difficult to treat such patients, the treatment methods remain to be not resolved completely.

Any way, controlling high BP at the wakening-up by using various methods prevents for micro- and macro- vascluar complications.

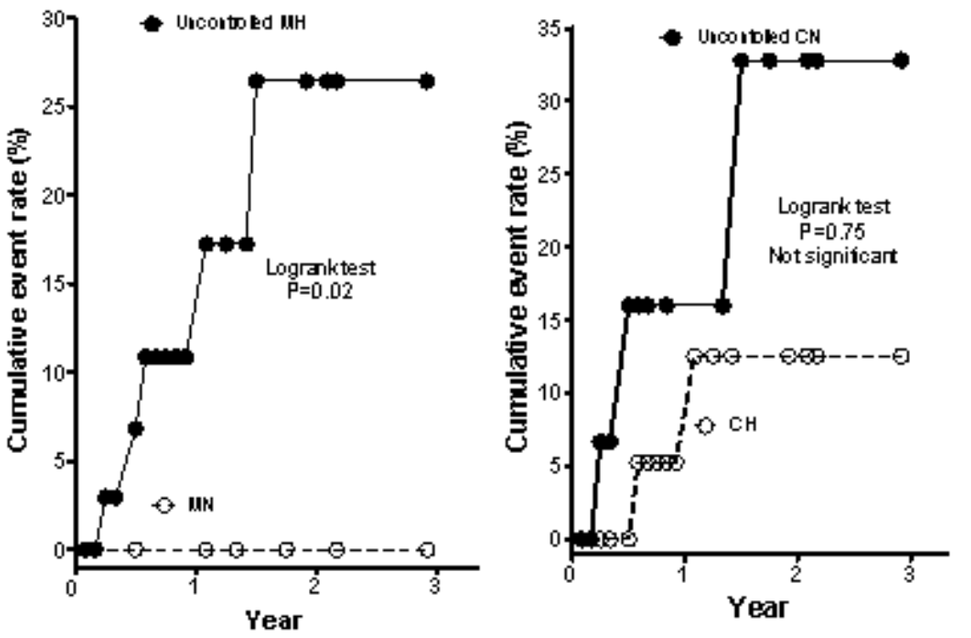

Fig. 11. Effect of α blocker administration at bedtime in type 2 diabetic patients on nephropathy. The patients were treated with doxosine received at bedtime for 3 years for MH.

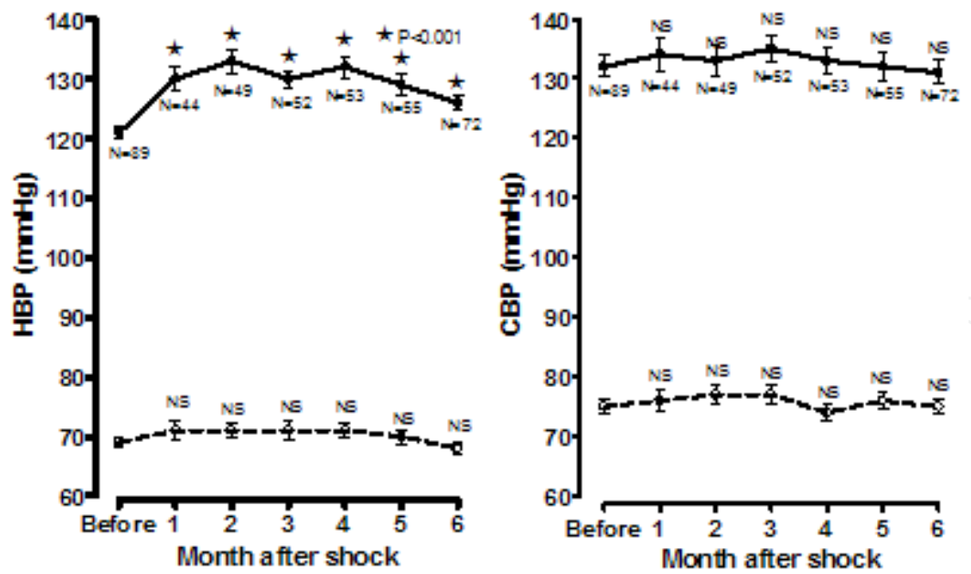

Fig. 12. Effect of earthquake (magnitude 7.0) on HBP and CBP at the awakening-up in type 2 diabetic patients for 6 months. Increased BP at the awakening-up in the morning owing to devastation by earthquake continued for several months, whereas CBP was not changed, eventhough the patient had received anti-hypertensive medicines before occuring earthquake.

5. Conclusion

In conclusion, elevations of blood pressure on self-measurement at the awakening-up in the morning as well as clinical blood pressure measurement in the daytime in type 1 and 2 diabetic patients are strongly related to microvascular complications, especially nephropathy, and the control of morning hypertension may prevent to have a development of micro- and macro-vascular complications in patients with diabetes mellitus.

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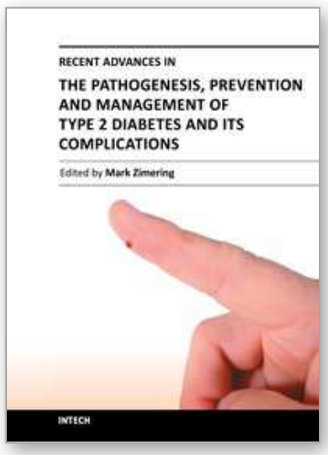

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Type 2 diabetes â€œmellitusâ€ affects nearly 120 million persons worldwide- and according to the World Health Organization this number is expected to double by the year 2030. Owing to a rapidly increasing disease prevalence, the medical, social and economic burdens associated with the microvascular and macrovascular complications of type 2 diabetes are likely to increase dramatically in the coming decades. In this volume, leading contributors to the field review the pathogenesis, treatment and management of type 2 diabetes and its complications. They provide invaluable insight and share their discoveries about potentially important new techniques for the diagnosis, treatment and prevention of diabetic complications.

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