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Comparison of day-to-day blood pressure variability in hypertensive patients with type 2 diabetes mellitus to those without diabetes: Asia BP@Home Study

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Abstract

Blood pressure variability (BPV) has been shown to be independently associated with cardiovascular (CV) mortality and morbidity. Patients with type 2 diabetes mellitus (T2DM) have also been shown to have increased BPV. We aimed to compare BPV in hypertensive patients with diabetes with those without diabetes. A total of 1443 hypertensive patients measured their blood pressure (BP) twice in the morning and twice before bed at home for a week. Demographic data, history of T2DM, and anti-hypertensive use were captured. Clinic BP was measured twice in the clinic. Control of BP was defined as clinic systolic BP (SBP) <140 mm Hg and home SBP < 135 mm Hg. BPV was based on home SBP measurements. A total of 362(25.1%) hypertensives had diabetes and 47.4% were male. Mean age was 62.3 ± 12.1 years. There was no difference in the mean clinic SBP in both groups (139.9 mm Hg vs 138.4 mm Hg P = .188). However, the mean morning home SBP was significantly higher and control rate lower in hypertensives with diabetes than those without (132.3 ± 15 mm Hg vs 129.7 ± 14.4 mm Hg P = .005, 39.4% vs 47.6% P = .007), respectively. Masked uncontrolled morning hypertension was higher in those with diabetes versus those without (12.8% vs 8.4%, respectively). There was no statistically significant difference in BPV between those with and without diabetes. In summary, clinic SBP was similar in hypertensives with or without diabetes. However, control of BP based on both clinic and home SBP thresholds was poorer in hypertensives with diabetes compared to those without. Masked uncontrolled morning hypertension was higher in those with diabetes than those without. There was no difference in BPV between the two groups.

1 | BACKGROUND

Blood pressure variability (BPV) be it short, mid-, or long term has been shown to be independently associated with increased cardiovascular (CV) morbidity and mortality [1-7] as well as renal complications.[8-10]

Type 2 diabetes mellitus (T2DM) has been shown to be associated with an increased risk of CV mortality and morbidity when compared to individuals without diabetes.[11,12]Furthermore, BPV has also been shown to be increased in patients with T2DM [13,14] and to be independently associated with increased CV morbidity and mortality.[14,15] Hypertension has also been shown to be associated with greater BPV.[11,12] In the presence of diabetes in patients with hypertension, it is not surprising nor unexpected that CV morbidity and mortality will be further increased compared to patients with hypertension but without diabetes.[14,15]

Most of the studies on BPV in diabetic patients with hypertension examined short-term BPV using ambulatory blood pressure measurements (ABPM), and indeed, CV morbidity and mortality as well as diabetic nephropathy and macro-albuminuria are increased compared to those diabetic patients without hypertension.[13,15,16] However, not many studies have been done to examine mid-term BPV using home BP measurement (HBPM) in hypertensive patients with diabetes and directly compared them to those hypertensives without diabetes. Hence, we aimed to examine and compare mid-term BPV in hypertensive patients with diabetes to hypertensive patients without diabetes.

2 | METHODOLOGY

This paper is part of the Asia BP at Home study where the methodology has previously been described.[17] Briefly, this study done in 11 Asian countries recruited from specialist clinics, 1443 adult patients aged ≥20 years with hypertension. Included patients may or may not have additional CV risk factors and irrespective of whether they had T2DM or not. These patients were required to do their HBPM using the provided digital BP device (Omron HEM-7130-AP or HEM-7131-E; Omron Healthcare) twice a day, measuring two times within 2 hours of waking in the morning and two times just before going to bed for a week. All demographic data including BP clinic measurements, absence or presence of T2DM, and use of anti-hypertensive drugs were captured.

Diabetes was defined as the diagnosis made by the attending doctor or if patients were on glucose-lowering agents.

2.1 | Blood pressure measurements and definitions

The mean clinic BP was based on the average of the two measurements done at the clinic, and control of clinic BP was defined as a SBP < 140 mm Hg. The mean home BP was derived from the average of the morning home BP readings, and control of home BP was defined as a SBP < 135 mm Hg. We also defined control of clinic BP and HBPM using the new 2017 ACC/AHA guideline thresholds of SBP of 130 mm Hg for morning and clinic BP.

Using the threshold of clinic systolic BP (SBP) of 140 mm Hg and morning home SBP of 135 mm Hg, the proportion of patients with well-controlled hypertension (clinic SBP < 140 mm Hg and mean of measurements of morning home SBP < 135 mm Hg), white-coat effect (clinic SBP > 140 mm Hg but mean of home morning SBP of <135 mm Hg), masked uncontrolled hypertension (clinic SBP < 140 mm Hg but mean of home morning SBP > 135 mm Hg), and sustained morning hypertension (clinic SBP > 140 mm Hg and mean of home morning SBP > 135 mm Hg) was determined.

2.2 | Blood pressure variability

BPV for each patient was calculated using standard deviation (SD), coefficient of variation (CV), variation independent of the mean (VIM), and average real variability (ARV) for morning and evening SBP based on the patients' home BP readings during the study period. The BPV for the average of the morning and evening SBP was also calculated.

Average real variability (ARV) is the average absolute difference between successive BP measurements and, in contrast to CV, takes the order of the BP measurements into account. Both CV and ARV are partially dependent on the overall mean BP levels over time, and this issue may not be resolved even if mean BP level over time is used as an adjustment factor. Therefore, we also used BP variability independent of the mean (VIM), another BP variability measure that has no correlation with mean BP levels. These variability measures have been used in previously reported BP variability studies.

TABLE 1 Comparison of baseline characteristics in hypertensive patients with T2DM to those without diabetes

	DM (N = 362)	Non-DM (N = 1081)	*P*
Age, years (mean ± SD)	64.8 ± 10.3	61.5 ± 12.6	<.001
Male, %	48.5	47.0	.670
BMI, kg/m^2	27.0 ± 4.7	25.7 ± 4.3	<.001
Habitual drinking	12.7	9.9	.139
Current smoking	11.3	7.4	.028
Shift worker	3.3	3.1	.861
Current disease			
Hyperlipidemia, %	65.8	47.4	<.001
Carotid artery disease, %	16.9	10.6	<.001
Thoracic aortic aneurysm, %	0.8	0.5	<.001
Chronic kidney disease, %	8.6	4.6	.008
Atrial fibrillation, %	5.0	3.3	.153
Past history			
Angina pectoris, %	12.2	9.5	.160
Myocardial infarction, %	4.7	3.0	.131
Aortic dissection, %	0.3	0.1	.439
Heart failure, %	5.8	3.2	.039
Peripheral artery disease, %	1.7	0.4	<.000
Stroke, %	6.9	6.3	.711
Use of anti-hypertensives:			
ARB	206 (56.9)	507 (46.9)	.001
ACE	58 (16.0)	110 (10.2)	.004
CCB	227 (62.7)	726 (67.2)	.120
β-blocker	126 (34.8)	302 (27.9)	.014
Diuretics	65 (17.9)	189 (17.5)	.870
α-blocker	17 (4.7)	37 (3.4)	.260
Others	4 (1.1)	11 (1.0)	1

2.3 | Statistical analysis

All statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc) at Super Circulation Monitoring with High Technology R&D Center, Jichi Medical University COE Cardiovascular Research and Development Center (JCARD; Tochigi, Japan). Mean was used for normally distributed variable and median for those not normally distributed. *t* test was used to compare continuous variables between hypertensive patients with diabetes with those without diabetes, and chi-square test was used to compare categorical variables between the two groups. A *P*-value of < .05 was considered as significant.

3 | RESULTS

A total of 362 (25.1%) hypertensive patients had diabetes and 47.4% were male. The mean age of the group as a whole was 62.3 ± 12.1 years, and mean BMI was 26.0 ± 4.5 kg/m^2. Table 1 shows the comparison of demographic and CV risk factors between those with and those without diabetes. Those hypertensive patients who also had T2DM were older, were more overweight/obese, and had more CV risk factors and organ damage. Use of angiotensin receptor blockers and β-blockers was higher in those with diabetes compared to those without diabetes (56.9% vs 46.9%, *P* = .001 and 34.8% versus 27.9%, *P* = .014, respectively) but use of CCBs (62.7% vs 67.2% *P* = .12) and diuretics (17.9% vs 17.5%, *P* = .87) between the two groups was not significantly different.

TABLE 2 Comparison of mean clinic and home BP and pulse rate in those hypertensive with T2DM and those without diabetes

	DM (N = 362)	Non-DM (N = 1081)	*P*
Clinic blood pressure			
Systolic blood pressure, mm Hg	139.9 ± 17.5	138.4 ± 18.6	.188
Diastolic blood pressure, mm Hg	80.3 ± 10.4	82.8 ± 11.2	.002
Pulse rate, bpm	76.0 ± 12.4	73.7 ± 11.6	.003
Self-measured blood pressure at home			
1) Morning measurement			
Systolic blood pressure, mm Hg	132.3 ± 15.0	129.7 ± 14.4	.005
Diastolic blood pressure, mmHg	78.9 ± 9.4	81.1 ± 9.5	.001
Pulse rate, bpm	71.4 ± 10.3	69.9 ± 9.3	.010
2) Evening measurement			
Systolic blood pressure, mm Hg	132.1 ± 15.9	128.1 ± 15.2	<.001
Diastolic blood pressure, mm Hg	78.4 ± 9.8	77.1 ± 9.5	.022
Pulse rate, bpm	72.5 ± 10.2	74.6 ± 11.2	.002

The mean morning home SBP was significantly higher in hypertensive with diabetes compared to those without (132.3 ± 15 mm Hg vs 129.7 ± 14.4 mm Hg, *P* = .005, respectively), while there was no difference in the mean clinic SBP between the two groups (139.9 ± 17.5 vs 138.4 ± 18.6, *P* = .188, respectively; Table 2).

Control of clinic SBP (OBP) based on the conventional threshold of SBP < 140 mm Hg was lower at 52.2% in hypertensives with diabetes (vertical black line Panel B Figure 1) compared to 56.0% in those without diabetes (vertical black line Panel A Figure 1). Control of home morning SBP (HBP) based on the conventional home threshold of SBP < 135 mm Hg was achieved in 63.6% in those with diabetes (horizontal black line Panel B Figure 1) and 69.7% in those without diabetes (horizontal black line Panel A Figure 1).

Combining control based on control of both clinic SBP of < 140 mm Hg together with morning home SBP of < 135 mm Hg, the control in those with diabetes was significantly lower than those without diabetes (39.4% vs 47.6%, *P* = .007, respectively; Table 3). Masked morning uncontrolled hypertension was also greater in those with diabetes (12.8% vs 8.4%, *P* = .02; Table 3).

When using the lower ACC-AHA threshold of SBP of 130 mm Hg, the proportion of BP control was nearly halved and conversely uncontrolled was doubled. The prevalence of masked morning uncontrolled hypertension was also halved in those with T2DM when the lower AHA threshold of SBP < 130 mm Hg was used (Table 3 and Figure 1).

There was no statistically significant difference in all the indices of BPV of the morning, evening, and morning-evening SBP between those with and without diabetes (Table 4).

4 | DISCUSSION

In our study, based on the clinic SBP, half of our patients regardless of whether they had diabetes or not achieved the BP target of SBP < 140 mm Hg (52.3% versus 56%, respectively). Similarly, based on HBPM, the SBP target of home SPB < 135 mm Hg was achieved in more than half of the patients regardless of whether they had diabetes or not (63.6% vs 69.7%, respectively). These findings are reflected in the main paper where 55.1% of all hypertensive patients had well-controlled clinic SBP and 68.2% well-controlled home morning SBP.[18]

However, although half of the patients regardless of their diabetes status were controlled based both on clinic and home BP, the mean home SBP was significantly lower in those without diabetes. This is consistent with other studies which showed that BP is more difficult to control in hypertensive patients with diabetes than those hypertensive without diabetes.[19,20]

HBPM is useful to detect masked hypertension. Masked hypertension is also associated with increased CV risk. We found that masked morning uncontrolled hypertension was 50% more common in hypertensive patients with diabetes than those without (12.8% vs 8.4%, *P* = .06, respectively, Figure 1). Detecting masked hypertension

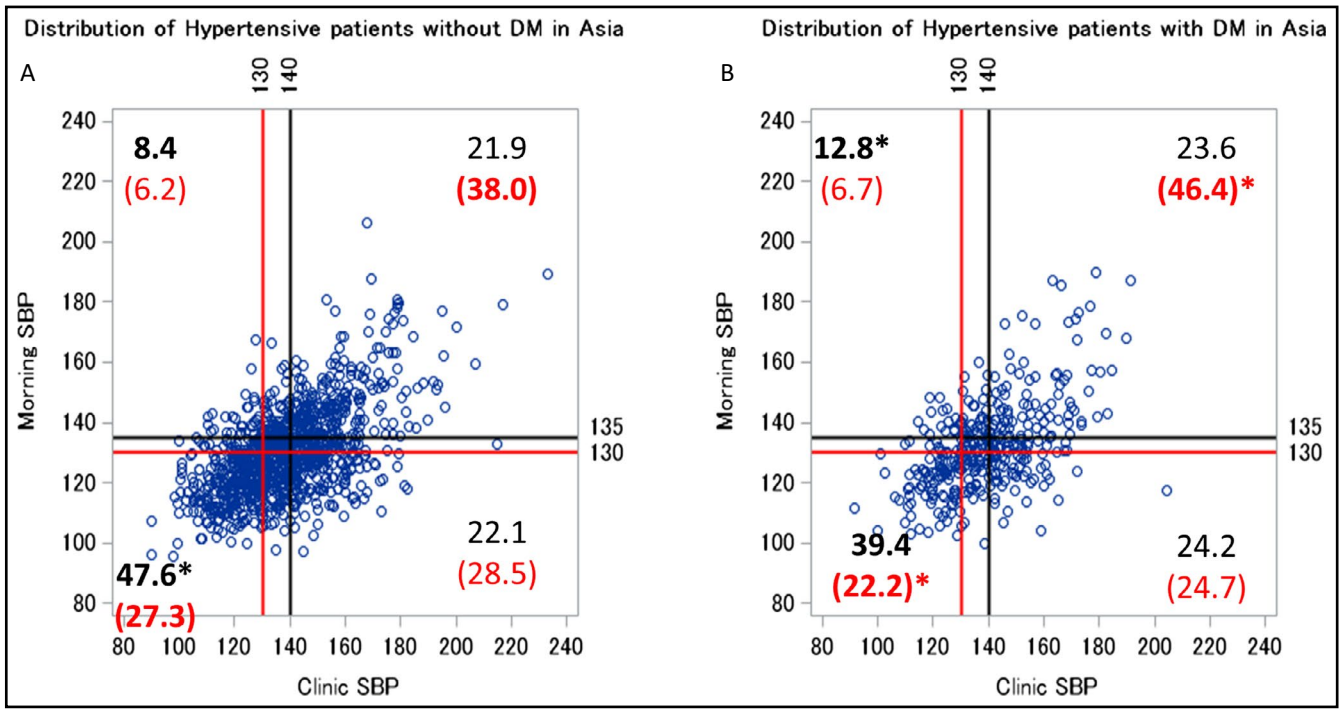

FIGURE 1 Comparison of BP control and type between those with and without T2DM

TABLE 3 Comparison of SBP control status (controlled, white-coat effect, masked, and uncontrolled hypertension) between hypertensive with T2DM and those without by conventional and ACC-AHA* BP threshold

	DM (N = 362)	Non-DM (N = 1081)	*P*
Controlled %	39.4	47.6	.007
White coat %	24.2	22.1	.424
Masked %	12.8	8.4	.017
Uncontrolled %	23.6	21.9	.511
AHA threshold (OBP < 130 mm Hg and HBP < 130 mm Hg)			
Controlled %	22.2	27.3	.061
White coat %	24.7	28.5	.173
Masked %	6.7	6.2	.803
Uncontrolled %	46.4	37.9	.005

*ACC-AHA: American College of Cardiology-American Heart Association Guidelines on Management of Hypertension 2017.

is of particular importance as otherwise the increased CV risk of hypertensive patients with diabetes will be under-estimated. Hence, HBPM should be strongly encouraged particularly in hypertensive patients with diabetes.

This recommendation is supported by another study that also showed masked hypertension to be higher in diabetes with hypertension.[21] Although masked hypertension is much lower in our study than the afore-mentioned study, which showed it to be as high as 42.5% in treated hypertensive patients with diabetes vs 32.5% in those without diabetes,[22] it is nevertheless still very important to encourage HBPM especially in hypertensive patients with diabetes.

Furthermore, based on a clinic SBP of < 140 mm Hg and home SBP of <135 mm Hg, the control rate in those with diabetes was significantly lower than those without diabetes (39.4% vs 47.6%, *P* = .007, respectively, Table 3). Again this is consistent as BP is usually more difficult to control in those with diabetes.[19,20]

Our study found that day-to-day BPV was not different in hypertensive patients with diabetes compared to those without diabetes, whether it was the morning, evening, or morning-evening SBP. This is a surprise finding as many studies have shown that BPV particularly the 24-hour and nighttime is higher in patients with diabetes because of increased arterial stiffness and autonomic dysfunction which may induce significant impairment in baroreflex sensitivity.[13,14,23,24]

Several factors may explain the lack of difference seen in our study. Firstly, the BPV in our study was much lower in our hypertensive patients with diabetes than what was found in other studies. For example in one study, the CV of morning/daytime BPV of HBPM was 7.26%, while ours was 5.2% on a background of a higher HBPM mean SBP of 136.8 mm Hg in their study, while ours was 132.3 mm Hg.[9] The lower mean SBP may be an important reason for our lower BPV as BPV is very dependent on age and the mean BP [25,26] and here in our study both the mean clinic and home BP in the diabetics are not only low but below the target of 140/90 and 135/80 mm Hg, respectively. Thus, the BPV in diabetics is consequently also lower. This highlights that effort should be made to lower mean BP and this will also lower the BPV.

BPV is also influenced by the type of anti-hypertensive drugs used. Calcium channel blockers (CCBs) and diuretics have been found

TABLE 4 Comparison of day-to-day BPV of in hypertensives with T2DM and those without T2DM

Self-measured blood pressure at home	DM (N = 362)	Non-DM (N = 1073)	*P*
Morning measurement			
SD	6.9 ± 3.3	6.8 ± 3.2	.621
CV	5.2 ± 2.4	5.3 ± 2.4	.778
VIM	6.8 ± 3.1	6.8 ± 3.1	.857
ARV	7.5 ± 4.2	7.2 ± 3.6	.205
Evening measurement			
SD	7.6 ± 3.6	7.6 ± 3.5	.706
CV	5.8 ± 2.7	6.0 ± 2.7	.418
VIM	7.6 ± 3.5	7.6 ± 3.4	.978
ARV	8.4 ± 4.4	8.2 ± 4.1	.562
ME average			
SD	5.8 ± 2.6	5.6 ± 2.7	.284
CV	4.4 ± 1.9	4.3 ± 2.0	.934
VIM	5.7 ± 2.5	5.6 ± 2.6	.767
ARV	6.0 ± 3.0	5.7 ± 2.8	.069

Abbreviations: ARV, average real variation; CV, cofficient of variation; ME, morning-evening; SD, standard deviation; VIM, variation independent of the mean.

to be associated with a lower BPV than the renin-angiotensin inhibitors (RAS).[27,28] In our study, the use of CCBs was high but there was no difference in their use in both the groups (62.7% in those with T2DM and 67.2 in non-T2DM, *P* = 012). Similarly, there was no difference in the use of diuretics (17.9% in those with diabetes and 17.5% in those without, *P* = .87) and these could have accounted to some extent the lower and similar BPV in those with and without diabetes.

5 | CONCLUSION

BPV in our patients with hypertension and diabetes is comparable to those hypertensives without diabetes. Although lowering BP in hypertensive patients with diabetes is more difficult, it is still achievable in over half the patients. Masked hypertension is higher in hypertensives with diabetes than those without. While HBPM is very important in the overall management of hypertension, it is more so in the case of hypertensive with diabetes. Hence, HBPM should be further encouraged in such patients. Furthermore, every effort should be made to lower BP to target, particularly in those hypertensive patients with diabetes as this will reduce their CV risk substantially.

5.1 | Strengths and limitations

This is one of the few studies that used HBPM to do a direct comparison of BPV in hypertensive patients with diabetes to those without and done concurrently in many centers in Asia. HBPM is becoming more widely used to complement better management of hypertension and it can help identify diabetic patients who may have masked hypertension.

Another strength is that this study was done in a pragmatic manner, similar to routine clinical practice and it supports that lower BPs can be achieved even in more difficult to treat patients like hypertensives with diabetes.

This study did not examine short-term BPV using ABPM, which may be different from mid-term BPV as the mechanism of BPV is different. Whether there will be any difference in short-term BPV between these two groups remains unknown. Furthermore, other parameters like fasting glucose which is associated with BPV was not done.

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CONFLICTS OF INTEREST

All other authors report no potential conflicts of interest in relation to this article.

AUTHORS CONTRIBUTION

K Kario conceptualized the main Asia BP@Home study. The authors collected the data. YC Chia conceptualized this paper and wrote the manuscript. Naoko Tomitani did the analysis of the data. K Kario reviewed the manuscript. All other authors read and contributed to the manuscript.

DISCLOSURES

YC Chia has received honoraria and sponsorship to attend conferences and CME seminars from Abbott, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Menarini, Merck Sharp & Dohme, Novartis, Orient Europharma, Pfizer, and Sanofi; and a research grant from Pfizer. K Kario received research grants from Omron Healthcare, Fukuda Denshi, A&D, Pfizer Japan, and honoraria from Omron Healthcare. S Park has received research grants and honoraria from Pfizer. S Siddique has received honoraria from Bayer, Novartis, Pfizer, ICI, and Servier; and travel, accommodation, and conference registration support from Atco Pharmaceutical, Highnoon Laboratories, Horizon Pharma, ICI, Pfizer and CCL. J Shin has received honoraria

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