

ORIGINAL ARTICLE

Differences between clinic blood pressure and morning home blood pressure, as shown by Bland–Altman plots, in a large observational study (HONEST study)

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When interpreting home blood pressure (BP) measurements in hypertensive patients, differences between clinic and home BP should be noted. To investigate the differences between clinic and morning home BP in hypertensive patients, we analyzed clinic systolic BP (CSBP) and morning home systolic BP (MHSBP) data from the large-scale observational HONEST (Home BP measurement with Olmesartan Naive patients to Establish Standard Target blood pressure) study ($n = 21\,340$), using BP measurements obtained before starting olmesartan administration. We generated Bland–Altman plots, with the horizontal axis representing mean CSBP and MHSBP ($(\text{CSBP} + \text{MHSBP})/2$) and the vertical axis representing the difference between CSBP and MHSBP ($\text{CSBP} - \text{MHSBP}$). We also did simulation experiments to explore factors affecting the results of the Bland–Altman plots. The difference between CSBP and MHSBP increased as the mean of the two values increased, and when the mean of CSBP and MHSBP was close to 140 mm Hg, the difference was theoretically 0 in average, although large interindividual BP variability existed in this BP range. Results were unaffected by factors such as previous antihypertensive treatment, age and concomitant diabetes or chronic kidney disease. Bland–Altman plots generated from simulated data of normal distribution showed that the slope of the regression line sloped upward, consistent with the results of the HONEST study, when the interindividual BP variability of MHSBP was less than that of CSBP. In conclusion, differences between mean CSBP and MHSBP may be caused by large interindividual variability in CSBP. Therefore, the differences between MHSBP and CSBP may vary between patient groups, which should be noted in the management of hypertension.

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INTRODUCTION

Home blood pressure (BP) measurements are superior to clinic BP measurements in terms of reproducibility^{1–3} and prediction of prognosis.^{4–6} Moreover, because home BP can be easily measured any number of times, it is suitable for long-term observation. Therefore, home BP is useful as an indicator of BP control in clinical practice.

In Japan, the measurement of home BP is relatively well established, and it is used in combination with clinic BP measurements to assess BP control. However, many clinical studies that investigated the effects of antihypertensive treatment on the prevention of cardiovascular events have used only clinic BP as an indicator of the efficacy of treatment,^{7–12} because the use of clinic BP is the gold standard in the evaluation of BP control.

It is well known that there is discrepancy between home and clinic BP values in the same patient, and, in most cases, clinic BP is higher

than home BP because of the white coat effect.¹³ A meta-analysis of 13 studies showed that clinic BP is higher than home BP by an average of 5.3 mm Hg for systolic BP and 3.1 mm Hg for diastolic BP.¹⁴ Moreover, the cutoff values for home BP as diagnostic criteria to define hypertension are lower than those of clinic BP, although they are slightly inconsistent depending on the interpretation of evidence (i.e. 125/80 mm Hg as defined by the World Health Organization¹⁵ and 135/85 mm Hg as defined by the guidelines of Europe and Japan^{16,17}).

As well as the definition of diagnostic criteria for hypertension, physicians are also concerned about the determination of target home BP values. Although the diagnostic criteria might be closely related to the target home BP values, BP values should be considered independently. However, the evidence is even scarcer with regard to target home BP.

The differences between home BP and clinic BP has already been reported using the results of a study that used data from the general

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population and a systematic review of several studies that used data from the general population and/or hypertensive patients.^{6,14} However, few studies have compared them, and current evidence remains limited. Moreover, no reports have examined the differences in detail using data from a large-scale study involving hypertensive patients.

The Home BP measurement with Olmesartan Naive patients to Establish Standard Target blood pressure (HONEST) study was undertaken to investigate the relationship between on-treatment home BP and the occurrence of cardiovascular, renal and other events in patients with essential hypertension who started antihypertensive treatment with olmesartan, including those whose current antihypertensive treatment was supplemented or replaced by olmesartan therapy,¹⁸ and the main results of the HONEST study have been reported.¹⁹ In the present study, we used data from >20 000 patients to evaluate the discrepancy and the relationship between morning home BP and clinic BP in hypertensive patients, neither of which have been fully examined in large-scale studies. We used baseline BP, because it reflects individual differences and is useful to evaluate the effects of previous and concomitant antihypertensive treatment. Although evening home BP was also collected, in this analysis we used only morning home BP, because at enrollment evening home BP was not obligatory.

METHODS

Study design

The aims and protocol of the HONEST study have already been reported.¹⁸ HONEST is a large-scale prospective observational study involving patients receiving olmesartan-based treatment with a 2-year follow-up and was registered at <http://www.umin.ac.jp/ctr/index.htm> with the unique trial number UMIN000002567. The study protocol was approved by the Ethical Committee of Daiichi Sankyo and by the review boards of the institutions at their discretion; it conforms with the Pharmaceutical Affairs Laws of Japan and was approved by the Ministry of Health, Labour and Welfare of Japan before commencement. The study was carried out in registered medical institutions, in compliance with Good Post-marketing Study Practice in Japan and internal regulations for clinical studies at each institution. Data were collected through the Internet using a central electronic data-capturing system (PostMaNet; Fujitsu FIP, Tokyo, Japan) that had been validated.

Patients

The HONEST study included patients with essential hypertension who had never been treated with olmesartan (as reported by physicians, with no specific BP range). Patients were excluded if they had a history of recent cardiovascular events or a planned cardiovascular intervention. With the exception of prior use of olmesartan, no restriction was placed on prior or concomitant antihypertensive drugs during the study.

BP measurement

In the present analysis, we used baseline BP to evaluate the effects of previous and concomitant antihypertensive treatment on the differences between the home BP and clinic BP. Home BP was measured by patients using a home BP measuring device with an upper arm cuff. Home BP measuring devices available in Japan are validated and approved by the Ministry of Health, Labour and Welfare of Japan, and they comply with the Association for the Advancement of Medical Instrumentation²⁰ or European standards.²¹ Patients recorded their morning home BP on ≥ 2 days in the 28-day period before starting olmesartan therapy in real-world setting. At each time point, patients measured their BP two times. In the present analysis, we used the mean of two daily morning home BP values (the first measurements). When patients had recorded their BP on more than 2 different days, the two measurements for the days closest to the start of olmesartan therapy were used. Clinic BP was measured according to the usual methods of each institution under daily clinical practice, so as to obtain data in real-world clinical practice. We used one

clinic systolic BP (CSBP) measurement obtained within the 28 days before the start of olmesartan therapy.

Data analysis

To investigate the agreement between CSBP and morning home systolic BP (MHSBP), we performed a Bland–Altman (BA) analysis; this method is used to compare two different measurement techniques.^{22,23} Accordingly, we generated BA plots, with the horizontal axis representing the mean of CSBP and MHSBP ($(\text{CSBP} + \text{MHSBP})/2$) and the vertical axis representing the difference between CSBP and MHSBP ($\text{CSBP} - \text{MHSBP}$). Subsequently, to verify the differences between each BP (CSBP or MHSBP) and the difference between them ($\text{CSBP} - \text{MHSBP}$), we performed additional analyses, with the horizontal axis representing either CSBP or MHSBP alone.

In the BA plots, we plotted the moving averages of the difference between CSBP and MHSBP as the values for the horizontal axis (mean of CSBP and MHSBP) by 5 mm Hg. For instance, for BP 110 mm Hg, the average of the values in a range between 105 and 115 mm Hg was plotted; next, for BP 115 mm Hg, the average of values between 110 and 120 mm Hg was plotted; and so forth.

We also conducted univariate regression analysis of the mean of CSBP and MHSBP on the difference between CSBP and MHSBP. Furthermore, we conducted multivariate regression analysis to explore the effects of various factors (previous antihypertensive treatment, age and concomitant diabetes or chronic kidney disease (CKD)) on the slope of the regression line between difference and the mean of CSBP and MHSBP.

The results of the BA analysis showed a positive correlation between the mean of CSBP and MHSBP ($(\text{CSBP} + \text{MHSBP})/2$) and the difference between CSBP and MHSBP ($\text{CSBP} - \text{MHSBP}$). We hypothesized that this may have been caused by differences in interindividual BP variability between CSBP and MHSBP, thus we conducted simulation experiments using the standard deviation (s.d.) of each BP. Four scenarios, that is, (s.d. of CSBP, s.d. of MHSBP) = (19.0, 16.4), (19.0, 19.0), (16.4, 16.4), and (16.4, 19.0), were used to generate simulation data at random from normal distribution with a single mean value (150 mm Hg).

CSBP and MHSBP with s.d. in patients with and without a history of cerebro- or cardiovascular disease, concomitant diabetes and CKD were also evaluated.

Data are reported as mean \pm s.d. All tests were two-sided and carried out to the 5% level of significance. SAS release 9.2 software (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

RESULTS

Baseline characteristics

The baseline characteristics of the patients are presented in Table 1. From 3039 medical institutions throughout Japan, 22 373 patients were enrolled in the study. The present analysis included data from 21 340 patients, after excluding patients for reasons such as withdrawal of consent. Patients were divided into those who had been untreated ($n = 10 609$) and those who had been treated ($n = 10 731$) at baseline. Their mean age was 62.8 ± 12.0 and 66.8 ± 11.4 years, respectively. CSBP and MHSBP were 159.2 ± 18.0 and 156.4 ± 15.5 mm Hg in untreated patients and 148.1 ± 18.4 and 146.9 ± 16.0 mm Hg in treated patients, respectively.

Agreement between CSBP and MHSBP

Figures 1a and b show the BA plots for treated and untreated patients. The percentage of patients whose BP was $-5 \leq (\text{CSBP} - \text{MHSBP}) \leq 5$ mm Hg and $-10 \leq (\text{CSBP} - \text{MHSBP}) \leq 10$ mm Hg was 36.7% and 59.5% in untreated patients and 32.5% and 54.5% in treated patients, respectively (Table 1). The slope of the regression line between the difference and the mean of CSBP and MHSBP showed an upward trend. The difference between CSBP and MHSBP was positive ($\text{CSBP} > \text{MHSBP}$) when the mean of CSBP and MHSBP was high, whereas it was negative ($\text{CSBP} < \text{MHSBP}$) when the mean of CSBP and MHSBP was low.

Table 1 Baseline characteristics

No. of subjects (%) or mean \pm s.d.	All (n = 21 340)	Untreated (n = 10 609)	Treated (n = 10 731)	P-value (untreated vs. treated)
Women	10 784 (50.5)	5389 (50.8)	5395 (50.3)	0.4461
Age (years)	64.8 \pm 11.9	62.8 \pm 12.0	66.8 \pm 11.4	<0.0001
Age range (years)	16–100	16–97	25–100	
Body mass index (kg m ⁻²)	24.31 \pm 3.70	24.17 \pm 3.66	24.44 \pm 3.74	<0.0001
Alcohol drinkers	3439 (16.1)	1742 (16.4)	1697 (15.8)	<0.0001
Current smokers	2618 (12.3)	1487 (14.0)	1131 (10.5)	<0.0001
<i>History</i>				
Cerebro- or cardiovascular disease	2241 (10.5)	583 (5.5)	1658 (15.5)	<0.0001
Cerebrovascular disease	1415 (6.6)	411 (3.9)	1004 (9.4)	<0.0001
Cardiovascular disease	966 (4.5)	201 (1.9)	765 (7.1)	<0.0001
<i>Complications</i>				
Dyslipidemia	9484 (44.4)	3937 (37.1)	5547 (51.7)	<0.0001
Diabetes mellitus	4364 (20.4)	1592 (15.0)	2772 (25.8)	<0.0001
Chronic kidney disease	4283 (20.1)	1573 (14.8)	2710 (25.3)	<0.0001
<i>Antihypertensive drugs used</i>				
Calcium channel blocker	7689 (36.0)	0 (0.0)	7689 (71.7)	<0.0001
Angiotensin receptor blocker (except olmesartan)	4535 (21.3)	0 (0.0)	4535 (42.3)	<0.0001
β -Blocker	1336 (6.3)	0 (0.0)	1336 (12.4)	<0.0001
Diuretic	1230 (5.8)	0 (0.0)	1230 (11.5)	<0.0001
Angiotensin-converting enzyme inhibitor	780 (3.7)	0 (0.0)	780 (7.3)	<0.0001
α -Blocker	454 (2.1)	0 (0.0)	454 (4.2)	<0.0001
Others	90 (0.4)	0 (0.0)	90 (0.8)	<0.0001
<i>Clinic measurements</i>				
Systolic blood pressure (mm Hg)	153.6 \pm 19.0	159.2 \pm 18.0	148.1 \pm 18.4	<0.0001
Diastolic blood pressure (mm Hg)	87.1 \pm 13.4	91.4 \pm 12.6	82.9 \pm 12.7	<0.0001
Pulse rate (beats per min)	74.1 \pm 11.2	74.6 \pm 11.0	73.5 \pm 11.4	<0.0001
<i>Home measurements^a</i>				
Systolic blood pressure (mm Hg)	151.6 \pm 16.4	156.4 \pm 15.5	146.9 \pm 16.0	<0.0001
Diastolic blood pressure (mm Hg)	87.1 \pm 11.8	90.7 \pm 11.2	83.5 \pm 11.3	<0.0001
Pulse rate (beats per min)	70.8 \pm 10.0	71.9 \pm 9.8	69.7 \pm 10.0	<0.0001
Patients with blood pressure $-5 \leq$ (CSBP – MHSBP) \leq 5 mm Hg	7384 (34.6)	3893 (36.7)	3491 (32.5)	<0.0001
Patients with blood pressure $-10 \leq$ (CSBP – MHSBP) \leq 10 mm Hg	12 165 (57.0)	6317 (59.5)	5848 (54.5)	<0.0001

Abbreviations: CSBP, clinic systolic blood pressure; MHSBP, morning home blood pressure.
^aMean of two daily morning BP measurements.

In the subsequent analyses with the horizontal axis representing either CSBP (Figures 1c and d) or MHSBP (Figures 1e and f) alone, a similar trend was confirmed; the difference between CSBP and MHSBP was greater when CSBP was high or when MHSBP was low.

In this study, home BP was measured according to each patient's own method. To clarify the effects of this on the results, we used data from approximately 80% of patients who measured home BP according to the methods defined by the Japanese Society Hypertension,¹⁷ and generated BA plots with a regression line (data not shown). The slope of the regression line was almost the same as that of all patients.

Effects of various factors on the slope of the regression line between difference and mean of CSBP and MHSBP

Table 2 shows the results of multiple linear regression analyses using the factors previous antihypertensive treatment, age and concomitant diabetes or CKD, which can affect the differences between CSBP and MHSBP. No significant difference in the slope of the regression line was observed with any of the factors, indicating that no factor affected the differences between CSBP and MHSBP.

Differences between CSBP and MHSBP stratified according to the mean of CSBP and MHSBP

Table 3 shows the differences between CSBP and MHSBP (CSBP–MHSBP) stratified according to the mean of CSBP and MHSBP ($[(\text{CSBP} + \text{MHSBP})/2]$) in three 5-mm Hg ranges (>130 – 135 mm Hg, >135 – 140 mm Hg, and >140 – 145 mm Hg). The differences between CSBP and MHSBP were near 0, indicating that the two values are almost equal, when the mean systolic BP was 135–145 mm Hg in treated patients and 130–140 mm Hg in treated patients with diabetes or CKD.

Differences in the interindividual BP variability of CSBP and MHSBP and their effects on the slope of the regression line

In the present analysis using data from 21 340 patients, the s.d. of CSBP and MHSBP were 19.0 and 16.4 mm Hg, respectively. Although the MHSBP value used in this analysis was the mean MHSBP over 2 days, the s.d. of MHSBP on the first day only (17.3 mm Hg) or the second day only (17.6 mm Hg) was also less than that of CSBP.

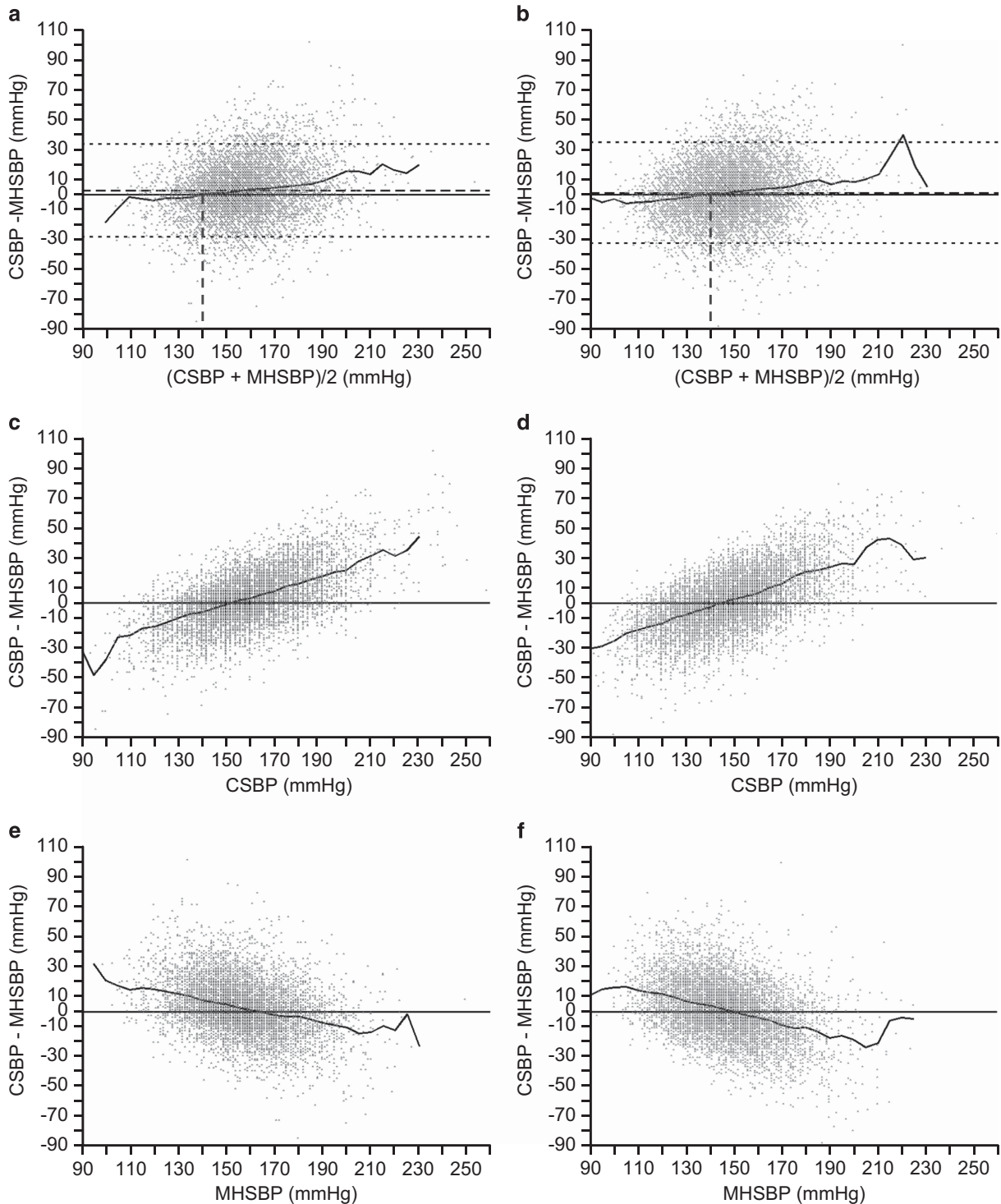


Figure 1 Bland–Altman (BA) plots showing the differences between the mean of clinic systolic blood pressure (CSBP) and morning home systolic blood pressure (MHSBP) and the difference between CSBP and MHSBP at baseline. (a) untreated patients ($n=10\,609$) and (b) treated patients ($n=10\,731$). $P=0.826$ for the interaction between $(\text{CSBP}+\text{MHSBP})/2$ for untreated patients and $(\text{CSBP}+\text{MHSBP})/2$ for treated patients. Calculated moving averages of the difference between CSBP and MHSBP as the values in the horizontal axis (mean of CSBP and MHSBP) increased by 5 mmHg, and plotted these continuously in the BA plots. Results of subsequent analyses, with the horizontal axis representing CSBP (c, untreated patients; d, treated patients) and MHSBP (e, untreated patients; f, treated patients).

Figure 2 shows BA plots generated from the simulation experiments, with estimated regression lines. As shown in Figure 2a, when the s.d. of MHSBP is less than that of CSBP, the regression line has an upward slope, which is consistent with the results of the

present analysis. On the other hand, when the s.d. are equal, the slope of the line is 0 (Figures 2b and c), and when the s.d. of CSBP is less than that of MHSBP, the line has a downward slope (Figure 2d).

Effects of previous or concomitant diseases on s.d. of CSBP and MHSBP

Table 4 shows mean CSBP and MHSBP with s.d. in patients with and without a history of cerebro- or cardiovascular disease, concomitant diabetes and CKD. In all subgroups, mean CSBP and MHSBP were similar, and there was no substantial difference in s.d.

DISCUSSION

We consider that this report provides abundant information on the differences between CSBP and MHSBP. The results of the BA analysis showed a tendency for the difference between CSBP and MHSBP to increase when the mean of CSBP and MHSBP was high. Moreover, when the mean of CSBP and MHSBP was close to 140 mm Hg, the difference was theoretically 0 in average, although there was large interindividual BP variability. The slope of the regression line was unaffected by factors such as previous antihypertensive treatment, age and concomitant diabetes or CKD.

In the present analysis, we hypothesized that there is one BP (true value) that can predict cardiovascular events, and clinic BP and morning home BP measurements are methods to identify the true value. Therefore, we used BA plots, which are visual representations of the agreement between two different measurement techniques. If both clinic BP and morning home BP measurements were the true value, there should be no difference between the two measurements. However, the results of the analysis showed that the two measurements do not always agree, and the regression line indicates a positive correlation. We assumed that this may be the result of interindividual BP variability between CSBP and MHSBP, thus we conducted simulation analyses. We also confirmed that the differences were unaffected by factors such as a history of cerebro- or cardiovascular disease and concomitant diseases.

Table 2 Effects of various factors on the slope of the regression line between the difference and the mean of clinic systolic blood pressure and morning home systolic blood pressure

Factor	n	Slope of regression line (95% CI)	P-value
Untreated	10 609	0.19 (0.17–0.21)	0.8260
Treated	10 731	0.18 (0.16–0.20)	
Age <65 years	9817	0.17 (0.15–0.18)	0.0688
Age ≥65 years	11 523	0.19 (0.17–0.21)	
No diabetes	16 976	0.19 (0.17–0.20)	0.0633
Diabetes	4364	0.16 (0.12–0.20)	
No CKD	16 901	0.18 (0.17–0.20)	0.4998
CKD	4238	0.17 (0.14–0.20)	

Abbreviations: CI, confidence interval; CKD, chronic kidney disease.

Table 3 Differences between CSBP and MHSBP stratified according to mean of CSBP and MHSBP in three ranges (> 130–135, > 135–140, > 140–145 mm Hg)

Mean of CSBP and MHSBP	All		Untreated		Treated		Treated and DM		Treated and CKD	
	n	Difference ^a	n	Difference ^a	n	Difference ^a	n	Difference ^a	n	Difference ^a
> 130–135	1077	–1.6	249	–2.4	828	–1.4	237	–2.7	225	–0.5
> 135–140	1621	–0.6	453	–1.9	1168	–0.1	304	0.5	285	0.6
> 140–145	2258	0.4	806	1.2	1452	0.0	413	0.4	336	1.4

Abbreviations: CKD, chronic kidney disease; CSBP, clinic systolic blood pressure; DM, diabetes mellitus; MHSBP, morning home systolic blood pressure.

^aMean of the difference between CSBP and MHSBP.

In a meta-analysis of several studies, BA analysis of the differences between home systolic BP and CSBP has shown a significant correlation between (clinic BP+home BP)/2 and clinic BP–home BP in untreated hypertensive patients, and that the difference in BP increases as mean BP increases.¹⁴ In the Finn-HOME study, which involved 2051 individuals from the general adult population, BA analysis was also performed for clinic BP and home BP: a slight but significant positive correlation was found between (clinic BP+home BP)/2 and clinic BP–home BP, for both systolic and diastolic BP, and the difference in BP became greater as mean BP increased.²⁴ Although these studies aimed to clarify the discrepancy between clinic and home BP, the results are almost consistent with those of the present study, in respect that CSBP is higher than MHSBP when mean BP is high, whereas MHSBP is higher than CSBP when mean BP is low. In addition, the previous studies of the differences between clinic BP and home BP were mostly carried out in the general population.^{5,24} These studies provide valuable information; however, clinicians want to know the level of discrepancy between clinic and home BP in patients with hypertension who need treatment too. In this respect, the present study provides unique and sound evidence that differs from the findings of previous studies involving subjects from the general population.

In the J-HOME study, which involved 3308 patients with hypertension, BA plots were generated with the horizontal axis representing either CSBP or MHSBP alone, instead of their average. The observed tendency of the discrepancy between CSBP and MHSBP was similar to the results of the present study. In addition, the results of the J-HOME study showed that the difference between CSBP and MHSBP is increased in older patients.²⁵

It should be noted that the above simulation is based on the assumption that average values of the CSBP and MHSBP are similar. In the present study, there was only a slight difference between CSBP and MHSBP values. However, several previous studies have reported that clinic BP is higher than home BP, whereas some studies in Japan showed that there was only a small difference (Supplementary Table). Similarly, the finding that s.d. of clinic BP is greater than that of home BP is consistent with many studies in Japan, whereas the results were opposite in Western studies (Supplementary Table). This may be because of the difference in regions, types of devices used and methods of BP measurement, which reflect real-world clinical practice. Further studies are necessary to clarify this issue.

The present study has several limitations. First, we used baseline BP that was measured before start of the study treatment. Therefore, home BP measured by patients may not fully comply with the study protocol. The reason we used baseline BP is because it reflects individual differences and is useful to evaluate the effects of previous and concomitant antihypertensive treatment, as compared with BP during the follow-up period. After the study completion, we confirmed that about 80% of patients complied with the BP measuring

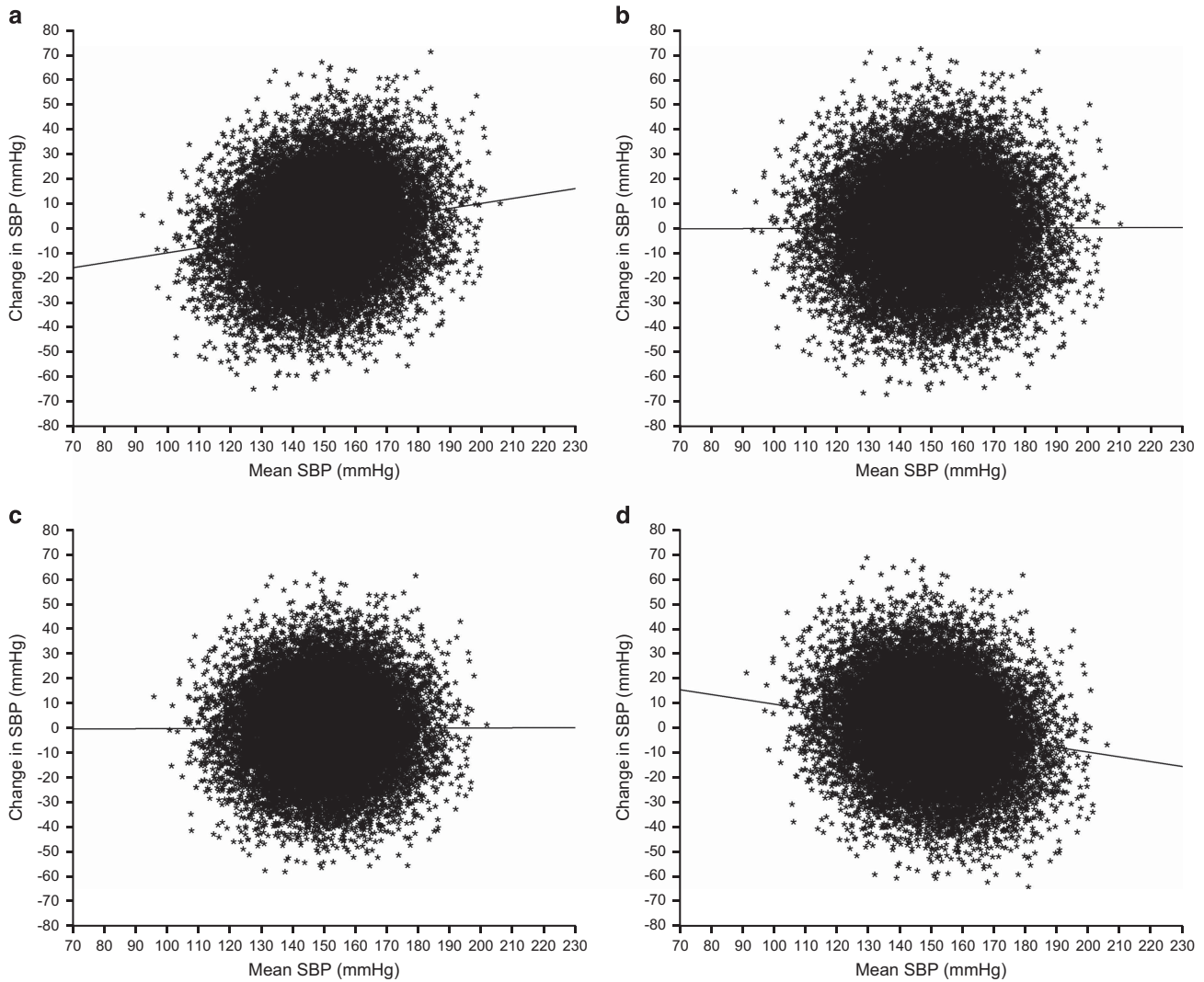


Figure 2 Bland–Altman (BA) plots generated from simulation data with three scenarios for the differences between the s.d. of clinic systolic blood pressure (CSBP) and the s.d. of morning home systolic blood pressure (MHSBP). (a) s.d. of CSBP > s.d. of MHSBP (19.0, 16.4); (b) and (c) s.d. are equal (19.0, 19.0 and 16.4, 16.4, respectively); (d) s.d. of CSBP < s.d. of MHSBP (16.4, 19.0). —, regression line by univariate regression analysis of the mean of CSBP and MHSBP on the difference between CSBP and MHSBP.

Table 4 Mean CSBP and MHSBP with s.d. in patients with and without a history of cerebro- or cardiovascular disease, concomitant diabetes and CKD

	Cerebro- or cardiovascular disease			Concomitant diabetes			CKD		
	n	Mean (mm Hg)	s.d. (mm Hg)	n	Mean (mm Hg)	s.d. (mm Hg)	n	Mean (mm Hg)	s.d. (mm Hg)
<i>MHSBP</i>									
No	18 828	152.1	16.4	16 976	152.2	16.4	16 901	152.0	16.1
Yes	2241	147.0	15.9	4364	149.3	16.3	4283	150.0	17.3
Unknown	271	153.2	19.2				156	148.4	19.6
<i>CSBP</i>									
No	18 828	154.5	18.9	16 976	154.2	19.1	16 901	154.2	18.7
Yes	2241	146.4	17.8	4364	151.2	18.4	4283	151.6	19.9
Unknown	271	153.5	23.0				156	147.4	22.9

Abbreviations: CKD, chronic kidney disease; CSBP, clinic systolic blood pressure; MHSBP, morning home systolic blood pressure.

methods recommended by JSH2009. We did not collect information regarding the home BP device models used by patients. However, the study protocol required use of a home BP measuring device with an upper arm cuff, which are deemed validated and approved by the Ministry of Health, Labour and Welfare of Japan, and meet the standards of United States or European countries. Another limitation is that clinic BP was measured according to the usual methods of each institution under daily clinical practice, and thus not fully standardized. Nevertheless, we consider the influence of those issues to be limited because of the large sample size of the present study. In conclusion, the present analysis clarified the differences between MHSBP and CSBP (i.e. in patients with the mean of CSBP and MHSBP close to 140 mm Hg, MHSBP was similar to CSBP) in real-world clinical practice. However, the results may vary in different geographic areas, which should be noted in the management of hypertension.

CONFLICT OF INTEREST

KS, KK, TK, ST and IS have received honoraria from Daiichi Sankyo. KK has received research funding from Daiichi Sankyo. YI is employee of Daiichi Sankyo Co., Ltd. FK is employee of Daiichi Sankyo Development Ltd.

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