Increase Trend in Home Blood Pressure on a Single Occasion Is Associated With B-Type Natriuretic Peptide and the Estimated Glomerular Filtration Rate

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BACKGROUND
Although obtaining multiple home blood pressure (HBP) measurements on a single occasion was recommended in European and Japanese hypertension guidelines, the clinical implications of the differences in BP measurements on a single occasion have been uncertain.

METHODS
Here, 4,149 patients with cardiovascular risk factors were enrolled. We asked the patients to measure their HBP 3 times on a single occasion each day over a 2-week period. We evaluated the target organ damage (TOD) indicators left ventricular mass index (LVMI), urinary albumin creatinine ratio, B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-pro BNP), high-sensitive cardiac troponin, brachial–ankle pulse wave velocity (ba PWV), intima–media thickness, and estimated glomerular filtration rate (eGFR). The associations between TOD and the difference between the first home systolic BP (SBP) value and the average of the second and third home SBP values were assessed by multiple regression analyses with adjustment for covariates.

RESULTS
Compared to the quintile median, the TOD of the first-quintile patients (i.e., those with elevated the second and third home SBP values compared to the first value) were significantly higher BNP, higher NT-pro BNP, higher ba PWV, and lower eGFR. In a univariate analysis of variance, compared to the median quintile, the first-quintile patients had independently and significantly higher BNP, higher NT-pro BNP, and lower eGFR.

CONCLUSION
The patients with elevated the second and third home SBP values compared to the first value taken on a single occasion were likely to have deteriorated BNP, NT-pro BNP, and eGFR.

Keywords: home blood pressure; hypertension; multiple measurements on a single occasion; target organ damage.

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Self-measured home blood pressure (HBP) has been established as providing superior1,2 or equivalent3,4 accuracy in predicting hypertensive target organ damage (TOD) and cardiovascular events compared to in-office and ambulatory measurements. Guidelines issued by both the European Society of Hypertension and the Japanese Society of Hypertension regarding hypertension and HBP measurement recommended that HBP should be measured twice or more on a single occasion.5,6

Rothwell et al.7 reported in 2010 that the within-individual-visit variability obtained at a single clinic visit was lower in patients being treated with a calcium channel blocker compared to those being treated with a beta-blocker, and the lower variability could better prevent stroke events in the calcium channel blocker–treated patients compared to the beta-blocker–treated patients. The clinical implications of multiple BP measurements were thus highlighted. In addition, it has been shown that reading-to-reading BP variability was associated with TOD8 and prognosis.9 These studies suggest that the BP difference in the short term has clinical significance. HBP is also known to have variability in repeated measurements on a single occasion. In most cases, the first HBP reading tends to be higher than the second and third readings.10,11 We thus hypothesized that the differences in BP values measured on a single occasion at home have prognostic significance.

Although compared to clinic BP measurement, the taking of HBP measurements has good reproducibility and excludes the “white coat effect,” the clinical implications of multiple BP measurements on a single occasion at home have not been studied yet. The aim of the present study was to determine whether the differences in BP values measured on a single occasion at home have prognostic significance for hypertensive organ damage.

METHODS
This study was a subanalysis of the Japan Morning Surge-Home Blood Pressure (J-HOP) study, which was

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conducted from 1 April 2005 to 1 June 2010 by 74 doctors at 71 institutions (45 primary practices, 22 hospital-based outpatient clinics, and 4 specialized university hospitals) in Japan. The protocol of the J-HOP study has been registered on the University Hospital Medical Information Network Clinical Trial Registry website under the trial number UMIN000000894. The Ethics Committee of the Internal Review Board of the Jichi Medical University School of Medicine, Japan, approved this study, and written informed consent was obtained from all participants of the J-HOP study.

**Study design**

**Entry criteria.** The study protocol and design were described in our recent publication.12,13 The details of the diagnostic criteria for entry and the methods used to evaluate TOD are given in the Supplementary Information. Briefly, the J-HOP study was a prospective observational study designed to evaluate whether HBP values can be used to predict cardiovascular events in Japanese patients with any of the following cardiovascular risk factors: hypertension, hyperlipidemia, diabetes, impaired glucose tolerance, metabolic syndrome, chronic renal disease, history of cardiovascular disease (coronary artery disease, stroke, aortic dissection, peripheral artery disease, congestive heart failure), atrial fibrillation, current smoking, chronic obstructive pulmonary disease, or sleep apnea syndrome. We excluded patients who had a malignancy or chronic inflammatory disease.

**Subject flow.** In the J-HOP study, we enrolled 4,310 ambulant patients who met the above-described entry criteria. In this subanalysis study, to detect and compare the subtle BP differences among BP measurements taken on a single occasion, we excluded 161 atrial fibrillation patients. Our final patient series was thus 4,149 patients.

**BP measurements**

Clinic BP and HBP were measured using a validated upper arm cuff oscillometric BP device (HEM-5001, Medinote, Omron Healthcare, Kyoto, Japan)14 according to the Japanese Society of Hypertension 2004 guidelines.15 This device automatically takes 3 measurements at 15-second intervals after a measurement button is pressed once. All recorded BP parameters were stored along with the time information.

For the measurement of HBP, the patients were instructed to attach the cuff on the same arm throughout the measurements and to measure BP in a sitting position after at least 2 minutes of rest. We instructed the patients to measure their morning HBP and evening HBP in a sitting position each day for a 2-week period. Morning BP was measured within 1 hour after waking, after micturition, and before breakfast and taking any medication, and evening BP was measured before taking antihypertensive medication and just before going to bed. All data in the HBP measurement device were downloaded to a computer and sent to the study control center (Jichi Medical University, Tochigi, Japan).

The clinic BP values were obtained using the average of 6 readings from 2 clinic visits by each patient. The patients were instructed to take their morning medication as usual on the days when they attended the clinic.

**The definition of the single-occasion difference in HBP**

In this study, we defined the single-occasion difference in HBP as the difference between the first HBP value minus the average of the second and third HBP values for the following reasons. The European Society of Hypertension and Japanese Society of Hypertension guidelines regarding hypertension and HBP measurement recommend that HBP should be measured at least twice on a single occasion.5,6 In 2005, Kawabe et al.16 reported that in triplicate measurements of HBP taken on a single occasion, the difference between the second and third values was far smaller than the difference between the first and second values. Additionally, in light of the European Society of Hypertension/Japanese Society of Hypertension guidelines, we investigated the clinical significance of the difference between the first HBP value minus the second value taken on a single occasion.

No prior report demonstrated clinical significance of the differences in BP values measured on a single occasion at home. Thus, there is no standard regarding the differences in BP values. To avoid using an arbitrary definition, we defined the median quintile group (third quintile) as the comparator group.

**Blood examinations**

Blood samples and the biomarker assays are described in the Supplementary Information. Briefly, each patient’s blood sample was collected in the morning in a fasting state at enrollment. All blood samples were measured in a single laboratory (SRL, Tokyo, Japan).

**Cardiac and carotid artery ultrasonography**

Each patient underwent an echocardiography examination at participating institutions. Trained physicians who were unaware of the patient’s laboratory and HBP data performed the cardiac ultrasonography and carotid artery ultrasonography on all patients. Two-dimensional M-mode or B-mode images were obtained using an ultrasound machine according to the guidelines of the American Society of Echocardiology and the European Association of Echocardiography.17 The left ventricular mass index (LVMI) was calculated using the modified American Society of Echocardiography formula indexed to body surface area. The M-mode left ventricular end-diastolic diameter and interventricular septum and posterior left ventricular wall thicknesses at end diastole were measured. The carotid arteries were examined bilaterally at the level of the common carotid artery, bulb, and internal carotid artery, as measured from both transverse and longitudinal orientations. The region with the thickest intima–media thickness was measured, and the values calculated as the mean of the single thickest point in the far wall on both sides were included in our analysis.
Measurement of brachial–ankle pulse wave velocity

The brachial–ankle pulse wave velocity (ba PWV) was measured with a volume-plethysmographic device, the AT-form PWV/ABI (Omron Healthcare). The details of the measurements and the reproducibility of this automatic method have been described. Briefly, this device simultaneously records right and left brachial and tibial arterial pressure wave forms. Occlusion cuffs connected to both plethysmographic and oscillometric sensors were placed around both arms and ankles of the patient for the pulse wave analysis and BP measurements. The time difference between the brachial and ankle arterial pressure wave (ΔT) was determined using the wave front velocity theory. Finally, the ba PWV was calculated as (the distance between the arm and ankle)/ΔT. The ba PWV was measured by trained investigators who did not know the patients’ characteristics, in a quiet and temperature-controlled laboratory after a 5-minute rest by the patient in the supine position. The means of the right and left ba PWV values were used for the analyses.

Statistical analysis

All primary analyses were performed for all patients. Data are expressed as the means (±SD) or percentages. Since the values of the urinary albumin creatinine ratio, B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-pro BNP), and high-sensitive cardiac troponin were highly skewed, these data are expressed as the median (25% value, 75% value) and logarithmically transformed before the statistical analysis. Logarithmically transformed factors were assessed, and we confirmed that they showed a normal distribution by Kolmogorov–Smirnov test. In addition, we assessed the homogeneity of variance by Levene test in interquintiles. In LVMI, log urinary albumin creatinine ratio, log BNP, log NT-pro BNP, log high-sensitive cardiac troponin, and ba PWV, the P values were over 0.05, respectively. A 1-way analysis of variance (ANOVA) was performed to detect differences among quintile groups, and the Bonferroni was employed for multiple pairwise comparisons among quintile groups. The chi-square test was used to evaluate differences in prevalence rates. Residual analyses were performed after the chi-square test. A univariate ANOVA (UNIANOVA) was carried out to adjust the results of the ANOVA. Factors significantly different among quintile groups were selected as covariates for the confounding effects in the UNIANOVA, and the Bonferroni was used for the multiple pairwise comparisons compared with the median quintile group. Associations/differences with a P value less than 0.05 (2-tailed) were considered significant. All statistical analyses were performed with SPSS version 21 software (SPSS, Chicago, IL).

RESULTS

Baseline characteristics

Table 1 shows the baseline characteristics of all patients divided into quintile groups according to the differences between their first home systolic BP (SBP) values and the average of the second and third home SBP values. Compared to the median quintile group (group 3), the patients in the first quintile group (i.e., those with elevated the second and third home SBP values compared to the first value) were significantly older, significantly more likely to be male, and had significantly lower body mass index values, a significantly higher percentage of alpha-blocker medication, a significantly higher rate of smoking, a significantly higher rate of diabetes mellitus, and a significantly higher average of the second and third home SBP values.

Compared to the quintile median, the fifth quintile patients (i.e., those with the greatest differences between their first home SBP values and the average of the second and third home SBP values) were significantly older, significantly more likely to be female, and had a significantly higher rate of hypertension, significantly lower rate of smoking, and significantly higher average home SBP.

Supplementary Table S1 also shows the baseline characteristics of all patients divided into quintile according to the difference between the first and second home SBP values. The only result that differed from those in Table 1 was that there was no significant difference in current smoking among the quintile groups.

Association of TOD with the quintiles according to the difference between the first and the average of the second and third SBP values

Compared to the quintile median values, the TODs of the first-quintile patients were significantly higher BNP, significantly higher NT-pro BNP, significantly higher ba PWV, and significantly lower estimated glomerular filtration rate (eGFR) values (Table 1). There were no significant differences among the quintile groups according to the difference between the first and the average of the second and third home SBP values in LVMI, urinary albumin creatinine ratio, high-sensitive cardiac troponin, or intima–media thickness.

We performed a UNIANOVA to confirm these TOD indicators independently of their association with the difference between the first and the average of the second and third home SBP values (Table 2). Model 1 was adjusted by the factors that showed a significant difference among quintile groups: age, gender, body mass index, hypertension, alpha-blocker use, current smokers, diabetes or impaired glucose tolerance, and average of all home SBP measurements. Model 2 was adjusted by model 1 cofactors plus the factors with a propensity to show a significant difference among groups in which the P values were 0.05 < P < 0.1: calcium channel blocker use, regular alcohol drinkers, and chronic renal disease. With this adjustment, we found that the difference between the first and the average of the second and third SBP values were significantly and independently associated with BNP, NT-pro BNP, and eGFR in both model 1 and model 2. This association did not remain for ba PWV. In the post hoc test, compared to the quintile median, the first-quintile patients had independently and significantly higher BNP, higher NT-pro BNP, and lower eGFR values (Table 2).

We performed similar analyses for all patients divided into quintile groups according to the difference between...
### Table 1. Clinical characteristics of the patients by quintiles according to the difference between the first and the average of the second and third home SBP

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quintile groups: the difference between the first and average of second and third SBP values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Difference between the first and average of the second and third home SBP, mm Hg</td>
<td>$-1.6 \pm 1.6$ ($-13.08$–$0.15$)</td>
</tr>
<tr>
<td>Patients, n</td>
<td>826</td>
</tr>
<tr>
<td>Age, years</td>
<td>$66.6 \pm 10.3^{**}$</td>
</tr>
<tr>
<td>Male, %</td>
<td>$50.5^{††}$</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>$23.8 \pm 3.3^{*}$</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>$86.9$</td>
</tr>
<tr>
<td>Medicated hypertension, %</td>
<td>$79.1$</td>
</tr>
<tr>
<td>Calcium channel blocker use, %</td>
<td>$54.0$</td>
</tr>
<tr>
<td>Angiotensin II receptor blocker use, %</td>
<td>$50.6$</td>
</tr>
<tr>
<td>ACE blocker use, %</td>
<td>$6.4$</td>
</tr>
<tr>
<td>Alpha-blocker use, %</td>
<td>$7.5^{††}$</td>
</tr>
<tr>
<td>Beta-blocker use, %</td>
<td>$14.5$</td>
</tr>
<tr>
<td>Diuretics use, %</td>
<td>$25.9$</td>
</tr>
<tr>
<td>Regular alcohol drinkers, %</td>
<td>$26.5$</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>$14.8^{†}$</td>
</tr>
<tr>
<td>Diabetes or impaired glucose tolerance, %</td>
<td>$27.6^{††}$</td>
</tr>
<tr>
<td>Dyslipidemia, %</td>
<td>$40.9$</td>
</tr>
<tr>
<td>Chronic renal disease, %</td>
<td>$5.2$</td>
</tr>
<tr>
<td>Sleep apnea syndrome, %</td>
<td>$3.1$</td>
</tr>
<tr>
<td>Mets, %</td>
<td>$20.8$</td>
</tr>
<tr>
<td>First home SBP, mm Hg</td>
<td>$133 \pm 15$</td>
</tr>
<tr>
<td>Average of second and third home SBP, mm Hg</td>
<td>$135 \pm 15^{**}$</td>
</tr>
<tr>
<td>Average of first and second home SBP, mm Hg</td>
<td>$134 \pm 15$</td>
</tr>
<tr>
<td>Average of all home SBP, mm Hg</td>
<td>$134 \pm 15$</td>
</tr>
</tbody>
</table>


Table 1. Continued

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>value</th>
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</tr>
</thead>
<tbody>
<tr>
<td>LVMI, g/m² (n = 1,176)</td>
<td>96 ± 24</td>
<td>92 ± 26</td>
<td>12.4 (7.0, 26.9)</td>
<td>12.4 (7.1, 26.2)</td>
<td>14.6 (8.0, 35.5)</td>
<td>106 ± 32</td>
<td>0.22</td>
<td>0.76</td>
<td>0.003</td>
<td>0.003</td>
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</tr>
<tr>
<td>BNP, pg/mL (n = 3,493)</td>
<td>3.5 (4.3, 23.3)</td>
<td>3.5 (4.3, 23.3)</td>
<td>4.0 (2.9, 8.5)</td>
<td>4.0 (2.9, 8.5)</td>
<td>4.0 (2.9, 8.5)</td>
<td>5.2 (2.6, 9.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>hs-TnT, ng/mL (n = 3,493)</td>
<td>0.003 (0.003, 0.006)</td>
<td>0.003 (0.003, 0.006)</td>
<td>0.003 (0.003, 0.006)</td>
<td>0.003 (0.003, 0.006)</td>
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<td>0.003 (0.003, 0.006)</td>
<td>0.003 (0.003, 0.006)</td>
</tr>
<tr>
<td>ba PWV, cm/s (n = 2,583)</td>
<td>73.8 ± 23.3</td>
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<tr>
<td>IMT, mm (n = 1,338)</td>
<td>17.1 ± 3.6</td>
<td>17.1 ± 3.6</td>
<td>17.1 ± 3.6</td>
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<td>17.1 ± 3.6</td>
<td>17.1 ± 3.6</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m² (n = 526)</td>
<td>110 ± 18</td>
<td>110 ± 18</td>
<td>110 ± 18</td>
<td>110 ± 18</td>
<td>110 ± 18</td>
<td>110 ± 18</td>
<td>110 ± 18</td>
<td>110 ± 18</td>
<td>110 ± 18</td>
<td>110 ± 18</td>
<td>110 ± 18</td>
</tr>
<tr>
<td>UAR and BNP values are expressed as the median (25% value, 75% value). UAR, BNP, NT-pro BNP, and hs-TnT were logarithmically transformed before the statistical analysis. Post hoc tests were performed comparing the quintile groups with only the quintile median (group 3). **P &lt; 0.01 after residual analyses in chi-square test.</td>
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</tbody>
</table>

**DISCUSSION**

In the present study of patients with cardiovascular risk factors, we first examined the associations between the BP difference obtained on a single occasion and the extent of TOD. We found that the patients with elevated SBP in their second and third measurements compared to the first time on a single occasion were more likely to have indicators of deteriorated hypertensive TOD, i.e., increased BNP, increased NT-pro BNP, and decreased eGFR. The results of the present study suggest that the difference in SBP readings taken on a single occasion could be associated with hypertensive TOD.

**The changes in BP values at single-occasion measurement**

In this study, approximately 20% of the patients' home SBPs were increased by repeated measurement on a single occasion. In addition, 20% of the patients' home SBPs were decreased by >5 mm Hg with repeated measurement.

Several studies have shown that SBP has a tendency to decrease with repeated measurement after the first reading; the reported differences between the first and second measurements were the averaged values 2.3-26 and 3.5 mm Hg.21 These differences have been consistently observed for 7 days10 and 6 days.21 However, these results were calculated from mass data. When the focus was on individual subjects' SBP changes over repeated (triplicate) measurement, decreased SBP was seen in 60% of the subjects, increased SBP was observed in 30%, and no change was seen in 10%.16 These reports do not conflict with our present results. Thus, it is important to keep in mind that with repeated measurements, many individuals will show increased HBP.

**The mechanisms by which the increase in the second and third values would result in adverse outcomes**

Several studies have noted that sympathetic nerve hyperactivity was associated with deteriorated BNP and chronic kidney disease.34 Easy sympathetic nerve hyperactivation due to astonishment by recognizing their own first BP values causes an elevation of SBP in their second and third...
Table 2. The target organ damage in the first-quintile patients compared to the quintile median, adjusted by cofactors

<table>
<thead>
<tr>
<th>Target organ damage</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td>Adjusted R²</td>
</tr>
<tr>
<td>BNP, pg/mL</td>
<td>4.16</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>NT-pro BNP, pg/mL</td>
<td>3.37</td>
<td>0.01</td>
</tr>
<tr>
<td>ba PWV, cm/s</td>
<td>2.11</td>
<td>0.08</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>5.72</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BNP and NT-pro BNP were logarithmically transformed before the statistical analysis. Model 1 was adjusted by the factors that showed a significant difference among quintile groups: age, gender, BMI, hypertension, alpha-blocker use, current smokers, diabetes or impaired glucose tolerance, and average of all home SBP measurements. Model 2 was adjusted by model 1 cofactors plus the factors with a propensity to show a significant difference among groups in which the P values were 0.05 < P < 0.1: calcium channel blocker use, regular alcohol drinkers, and chronic renal disease.

Abbreviations: ba PWV, brachial-ankle pulse wave velocity; BMI, body mass index; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; UNIANOVA, univariate analysis of variance.

The difference in predicting power between the first and second HBP measurements

In this study, the patients whose BP increased with repeated measurement had greater degrees of TOD. No prior report demonstrated the same results as the present study, but several studies compared the predictive power of the first with second HBP readings. In the Didima study, the average systolic HBP of all the first readings was higher than that of all the second readings, and the SBP difference was 3.5 ± 4.3 mm Hg. However, the predictive prognostic implication value was similar between the first and second readings. Similarly, it has been reported that the correlations between LVMI or urine microalbumin and the first or second HBP values were equally strong. There thus appears to be no significant difference in prognostic predicting power among the absolute values of multiple measurements taken on a single occasion. However, our results suggest that the difference in HBP values obtained on a single occasion could be associated with TOD, which could not be detected only by once measurement on a single occasion.

Study limitations

A limitation of the present study bears mentioning. Because this study was conducted by only our study group, other studies of other samples should be examined to test our hypothesis regarding the association between the difference in BP values obtained on a single occasion and TOD. Despite this limitation, the results have important implications for the management of patients with hypertension shown by HBP measurements, and they provide informative data regarding multiple BP measurements obtained on a single occasion.

It is difficult to determine whether the association between the BP difference and the logarithmically transformed factors and the association with the raw factor were exactly the same since the mean of the transformed data was a geometric mean and that of the raw data was an arithmetic mean. However, the geometric mean was equal to or less than the arithmetic mean; therefore, the significant association between the BP difference and logarithmically transformed factor has adequate meaning.

Certainly, there was a finding that compared to 10-second intervals, 1-minute intervals gave average HBP values that were closer to the ambulatory BP values when the HBP values were obtained on a single occasion. However, in that study, both 10-second and 1-minute intervals between 3 successive HBP values showed good correlations with the ambulatory BP measurements on a single occasion. Thus, the patients who easily develop sympathetic nerve hyperactivation may be likely to have deteriorated hypertensive TOD values, i.e., increased BNP, increased NT-pro BNP, and decreased eGFR.

It is speculated that peripheral vasodilatation could be induced by nitric oxide, which was activated with manchette compression in patients with normal endothelial function. Therefore, the BP would be unlikely to decrease in patients with endothelial dysfunction.
values. In addition, there is evidence that a 15-second interval may be as accurate as the conventional 1-minute interval. Shorter intervals may influence the blunting trend of HBP decline, but they did not increase that trend. Additionally, since all patients were divided into quintile groups according to the differences between their first home SBP values and the average of the second and third home SBP values, the results could not be influenced by the 15-second intervals.

It is uncontrollable that the sample size of over 4,000 participants makes it easy to obtain statistically significant results. However, the appropriate sample size is difficult to calculate because there is no study that demonstrates the association between the differences in BP values measured on a single occasion at home and the TOD, and thus the effect size in the power analysis was unpredictable. This point is to be discussed in further studies.

Conclusion

The patients with elevated second and third SBP values compared to their first readings on a single occasion were likely to have deteriorated hypertension TOD. The present findings suggest a hypothesis that the difference in the SBP measured on a single occasion could be used to predict hypertension TOD. Such a hypothesis would need to be examined prospectively and in other samples.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at American Journal of Hypertension (http://ajh.oxfordjournals.org).

DISCLOSURE

The authors declared no conflict of interest.

REFERENCES


