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ARTICLE

# Predictive power of home blood pressure indices at baseline and during follow-up in hypertensive patients: HOMED-BP study

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## Abstract

We compared the predictive power for a major adverse cardiovascular event (MACE) of four home blood pressure (BP) indices (systolic BP, diastolic BP, mean BP, and pulse pressure (PP)) obtained at baseline before treatment and during the on-treatment follow-up period in 3147 patients with essential hypertension (women: 50.1%, mean age: 59.5 years). Associations between MACE and each index were determined using Cox proportional hazard models and the likelihood ratio (LR) test. During a median follow-up of 5.4 years, 46 patients experienced MACE, which was a composite of cardiovascular death, non-fatal stroke, and non-fatal myocardial infarction. The LR test showed that systolic, diastolic, and mean BP during follow-up was more closely associated with cardiovascular risk than the corresponding indices at baseline (LR $\chi^2$ for baseline versus follow-up: systolic BP, (6.0, $P = 0.014$) versus (11.3, $P = 0.0008$); diastolic BP, (0.4, $P = 0.53$) versus (12.4, $P = 0.0004$); mean BP, (3.2, $P = 0.074$) versus (15.0, $P = 0.0001$)), whereas neither PP at baseline nor that during follow-up was significantly associated with MACE risk. Among home BP indices during follow-up, mean BP further improved prediction models in which systolic or diastolic BP was already included ($P \le 0.042$), but neither systolic nor diastolic BP improved models with mean BP ($P = 0.80$). In addition to home systolic and diastolic BP, mean BP during follow-up period provides essential information in predicting future cardiovascular diseases, whereas its utilization should be further assessed by an intervention trial targeting mean BP levels.

## Introduction

Observational studies have demonstrated the stronger predictive power of self-measured home blood pressure (BP) over conventional office BP for cardiovascular outcomes [1–6]. In the Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) trial [7], home systolic BP was reported to

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be a better predictor of cardiovascular outcomes than office BP [8]. In HOMED-BP, home systolic BP values measured both at baseline, before initiation of treatment, and during on-treatment follow-up independently predicted cardiovascular outcomes [9].

Several observational studies have reported that systolic BP and calculated mean BP were better predictors of cardiovascular diseases than diastolic BP, whereas the predictive power of pulse pressure (PP) was weak compared with the other three BP indices [10–13]. However, these studies were mainly based on office BP information [10, 11], and available evidence is limited based on out-of-office BP [12, 13]. Furthermore, no studies have examined the difference in the predictive powers of the four indices captured before the initiation of antihypertensive drug treatment and during the treatment period. We aim to compare the prognostic significance for the risk of major adverse cardiovascular event (MACE) of systolic BP, diastolic BP, mean BP, and PP obtained from self-measured home BP at baseline and during follow-up based on the HOMED-BP study.

## Methods

### Study population

The HOMED-BP study was a multicenter clinical trial with a prospective, randomized, open-label, blinded end point evaluation (PROBE) [14] design. The HOMED-BP protocol complies with the Helsinki declaration for the investigation of human subjects [15] and is registered with the UMIN Clinical Trial Registry, number C000000137 (http://www.umin.ac.jp/ctr). The institutional review board of the Tohoku University Graduate School of Medicine approved the study protocol, and all study participants gave written informed consent.

In the HOMED-BP study [7–9], patients with mild-to-moderate hypertension with a minimum age of 40 years were recruited from 457 general practices throughout Japan. Treatment naive patients and previously treated patients whose antihypertensive drug treatment could be discontinued for ≥2 weeks qualified for enrollment. Off treatment, they had to maintain a home BP of 135–79 mmHg systolic or 85–119 mmHg diastolic. Eligible patients should have no contraindication for antihypertensive agents. Randomization was based on a computerized random number function with a minimization algorithm running on a central server at Tohoku University (Sendai, Japan) considering sex, age, and the systolic and diastolic levels of the home BP. In a 2 × 3 design, eligible patients were randomized to usual control (ranging from 125–134 mmHg systolic and from 80–84 mmHg diastolic) versus tight control (<125 mmHg systolic and <80 mmHg diastolic) of home BP and to the initiation of antihypertensive drug treatment with calcium channel blocker, angiotensin converting enzyme inhibitor, or angiotensin receptor blockade. The first patient was randomized on 6 June 2001, and the last patient was randomized on 7 October 2009. The primary outcome of HOMED-BP was then opened based on the last visit, which took place on 30 April 2010 [9].

Based on our previous report indicating that the risks of cardiovascular outcomes were similar in the randomized groups (tight versus usual BP control, and a comparison of drug classes to initiate treatment) because of the small BP difference between the groups [9], we combined all 3518 participants in the present study. We excluded 371 patients because home BP during follow-up was not available. Therefore, the number of participants statistically analyzed totaled 3147 in the present analysis.

### Measurement of home blood pressures

Patients enrolled in HOMED-BP were asked to measure BP at home every morning throughout the study period. Home BP was measured in accordance with the Japanese Guidelines for home BP monitoring [16]: after ≥2 min rest in a sitting position, within an hour of waking, before breakfast, and before taking antihypertensive medications. Validated [17] oscillometric OMRON HEM-747IC-N monitors (Omron Healthcare, Kyoto, Japan), which store up to 350 readings in their memory, were supplied to patients for self-measurement of BP at home. Home BP was used for determining eligibility, and treatment adjustments at each visit were the average of the morning readings available over 5 days immediately preceding the visit. Home BP at baseline was defined as an average of the 5-day morning home BP measured just before randomization and before the initiation of antihypertensive drug treatment. Home BP during follow-up was defined as an average of the last available 5-day morning home BP values in patients without an event or the corresponding home BP values recorded 6 months before an event; this 6-month interval minimizes bias due to the fall or rise in the follow-up BP as a forerunner of an event [18]. The PP and mean BP were calculated according to the formulae: PP = systolic BP − diastolic BP, and mean BP = (systolic BP + 2 × [diastolic BP])/3, respectively.

### Definition of events and co-morbidity

We coded end points according to the International Classification of Diseases, 10th revision (ICD-10). We defined a composite of cardiovascular death (ICD-10 codes I00 to I99), non-fatal myocardial infarction (I21), and non-fatal stroke (I60, I61, and I63) [9] as MACE, and used this

composite in the present study. The end point committee, which was unaware of the patients' randomization, adjudicated all events. We used the outcome results considering only the first event in an individual.

Body mass index was calculated as body weight in kilograms divided by height in meters squared. Diabetes mellitus was defined as a fasting plasma glucose of 7.0 mmol/l (126 mg/dl) or more, $HbA_{1c}$ of 6.5% or more [19], or treatment with antidiabetic agents. Hypercholesterolemia was defined as a total cholesterol of 5.69 mmol/l (220 mg/dl) or more, a documented history of hypercholesterolemia, or taking lipid-lowering drug treatment.

### Statistical analysis

For database management and statistical analysis, we used SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina). Statistical significance was defined as an alpha-level <0.05 on two-sided tests. All data are expressed as the mean ± SD unless otherwise stated.

We applied a Cox proportional hazard model adjusted for sex, age, body mass index, smoking and drinking, diabetes mellitus, hypercholesterolemia, and a history of cardiovascular disease. To compare the association of different home BP indices with MACE, relative hazard (RH) and 95% confidence interval (CI) was estimated for a 1-SD difference in each index. This value is a "standardized" comparison of RH and is necessary because each BP index is measured on a different scale.

The likelihood ratio (LR) $\chi^2$ statistic for the risk of MACE was used as a measure of the improvement of goodness of fit [12, 13, 20] or "informativeness" when changing a model that contained only the confounders but no BP index (the "base model") into a model containing each BP index (and the confounders). The LR $\chi^2$ test between one model containing a single home BP index with covariables and a similar model but further containing another home BP index was used to assess whether the additional home BP index significantly improved the adequacy of the model. A significant LR $\chi^2$ indicates that the regression coefficient of the additional index is significant compared with 0 [20]; that is, the index provides significantly more information. The degrees of freedom for LR $\chi^2$ are all 1; therefore, an LR $\chi^2$ of 3.8 corresponds approximately to a $P$ value of 0.05, 6.6 to 0.01, and 10.8 to 0.001.

## Results

### Baseline characteristics

The baseline characteristics of the study population are shown in Table 1. Of the 3147 patients, 1577 (50.1%) were women, 658 (20.9%) were current smokers, 1514 (48.1%) drank alcohol, 485 (15.4%) had diabetes, 1051 (33.4%) had hypercholesterolemia, and 98 (3.1%) had a history of cardiovascular disease. Age and body mass index averaged 59.5 ± 10.0 years and 24.4 ± 3.4 kg/m$^2$, respectively.

### Incidence of events

Over a median follow-up of 5.4 years (interquartile range, 3.2–7.0; maximum 8.9 years), a first MACE occurred in 46 patients, including cardiovascular death in 6, non-fatal stroke in 32, and non-fatal myocardial infarction in 8.

### Predictive powers of home BP indices at baseline and during follow-up

Adjusted RHs of each BP index with LR $\chi^2$ values compared with the base model are shown in Fig. 1. Of the home BP indices at baseline before treatment initiation, all except PP ($P = 0.060$) produced positive and significant changes for predicting the risk of MACE when compared with the base model ($P \le 0.020$); systolic BP and mean BP were strongly associated with MACE risk, followed by diastolic

**Table 1** Baseline characteristics of the study population

| | Total ($n = 3147$) |
|---|---|
| Age, years | 59.5 (10.0) |
| Women, % | 50.1 |
| Body mass index, kg/m$^2$ | 24.4 (3.4) |
| Current smoking, % | 20.9 |
| Current habitual drinking, % | 48.1 |
| Diabetes mellitus, % | 15.4 |
| Hypercholesterolemia, % | 33.4 |
| Previous cardiovascular disease, % | 3.1 |
| *Home blood pressure at baseline* | |
| Systolic pressure, mmHg | 151.7 (12.6) |
| Diastolic pressure, mmHg | 89.9 (10.1) |
| Mean pressure, mmHg | 110.5 (9.3) |
| Pulse pressure, mmHg | 61.8 (12.5) |
| Heart rate, beat per min | 68.8 (9.5) |
| *Home blood pressure during follow-up* | |
| Systolic pressure, mmHg | 129.8 (13.2) |
| Diastolic pressure, mmHg | 76.5 (9.6) |
| Mean pressure, mmHg | 94.2 (9.5) |
| Pulse pressure, mmHg | 53.3 (11.5) |
| Heart rate, beat per min | 67.1 (9.9) |

Values are arithmetic mean (SD) or proportions, appropriately. Diabetes mellitus is a fasting plasma glucose of 7.0 mmol/l (126 mg/dl) or more, or an $HbA_{1c}$ of 6.5% or more, or treatment with oral antidiabetic drugs or insulin. Hypercholesterolemia is total serum cholesterol of 5.69 mmol/l (220 mg/dl) or more, a history of hypercholesterolemia, or taking lipid-lowering drugs

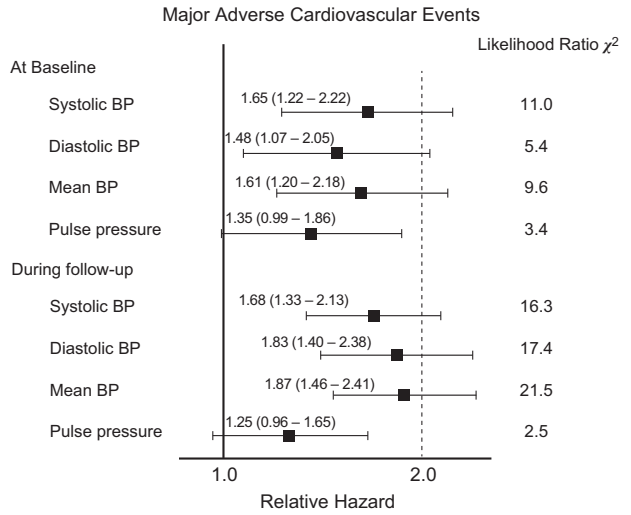


**Fig. 1** Multivariable-adjusted relative hazards (RHs) for home blood pressure (BP) indices at baseline and during follow-up. Filled squares represent the RHs of major adverse cardiovascular events associated with 1-SD increment of home BP indices individually, adjusted for sex, age, body mass index, smoking and drinking, diabetes mellitus, hypercholesterolemia, and history of cardiovascular disease. Horizontal lines represent 95% confidence intervals. Likelihood ratio $\chi^2$ statistics for cardiovascular events have been calculated by comparing a Cox model with a single BP index (and confounding variables) to the base model (which included confounders but no BP index)

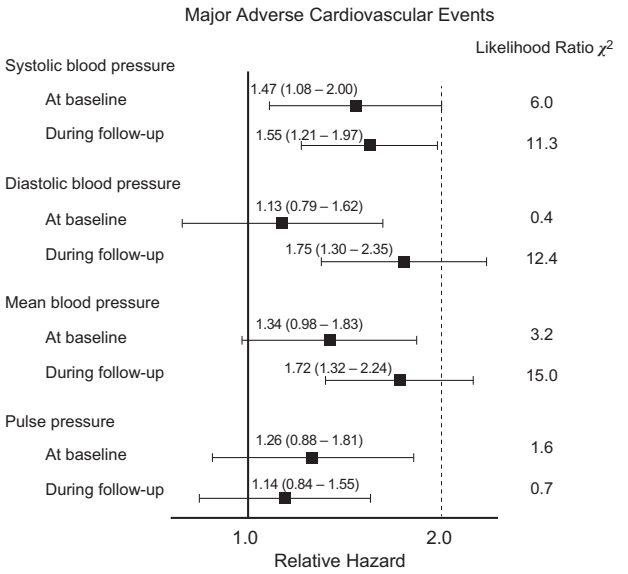


**Fig. 2** Multivariable-adjusted relative hazards (RHs) for home blood pressure (BP) indices when baseline and follow-up BP of the same index were simultaneously included. Filled squares represent the RHs of major adverse cardiovascular events associated with 1-SD increment of home BP indices, adjusted for sex, age, body mass index, smoking and drinking, diabetes mellitus, hypercholesterolemia, and history of cardiovascular disease. Horizontal lines represent 95% confidence intervals. Likelihood ratio $\chi^2$ statistics for cardiovascular events reflect increases in the goodness of fit from adding one home BP index at baseline to a model with the corresponding home BP index during follow-up and vice versa

BP. Similar associations were observed during on-treatment follow-up between the risk of MACE and home BP indices, in particular, diastolic BP and mean BP marked larger LR $\chi^2$ values.

## Baseline versus follow-up home BP indices as predictors of cardiovascular events

Figure 2 indicates the MACE risk in each home BP index when both baseline and follow-up BP were simultaneously included in the model (Fig. 2). Regarding systolic BP, baseline and follow-up values were both significantly and independently associated with the risk of MACE ($P \le 0.014$). The predictive power of diastolic BP and mean BP at baseline were not significant when further adjusted by the corresponding follow-up index ($P \ge 0.071$), whereas the values captured during the follow-up period had stronger predictive power ($P \le 0.0002$). Neither PP at baseline nor during the follow-up period predicted the risk of MACE ($P \ge 0.060$).

## Comparison of predictive power among home BP indices during follow-up

Table 2 shows increases in goodness of fit by adding home BP indices during follow-up. Systolic BP produced significant changes in the LR $\chi^2$ statistic when it was added to the PP-alone model ($P < 0.0001$). Although comparison of the combined systolic BP and PP model to the systolic BP-alone model also produced significant changes in the LR $\chi^2$ statistic ($P = 0.022$), the magnitude of changes in the LR $\chi^2$ statistic was greater for systolic BP (19.0) than for PP (5.21). A similar association was observed between diastolic BP and PP ($P < 0.0001$ when diastolic BP was added to the PP-alone model and $P = 0.042$ when PP was added to the diastolic BP-alone model). When mean BP and PP were simultaneously included in the model, PP had no additional information ($P = 0.80$ when PP was added to the mean BP-alone model), whereas mean BP was more informative ($P < 0.0001$ when mean BP was added to the PP-alone model).

The systolic BP and diastolic BP model compared with the systolic BP-alone model produced significant changes in the LR $\chi^2$ statistic ($P = 0.022$). Similarly, a comparison of the combined systolic BP and diastolic BP model to the diastolic BP-alone model also produced significant changes in the LR $\chi^2$ statistic ($P = 0.042$). Whereas the LR $\chi^2$ value of mean BP was significantly greater than that of systolic BP and diastolic BP when mean BP was compared with systolic BP and diastolic BP, respectively ($P \le 0.042$).

**Table 2** Increases in goodness of fit adding home BP indices during follow-up

| Comparison | LR $\chi^2$ | *P* for LR |
|---|---|---|
| *Systolic BP versus PP* | | |
| Adding systolic BP to a model with PP | 19.0 | <0.0001 |
| Adding PP to a model with systolic BP | 5.21 | 0.022 |
| *Diastolic BP versus PP* | | |
| Adding diastolic BP to a model with PP | 19.0 | <0.0001 |
| Adding PP to a model with diastolic BP | 4.14 | 0.042 |
| *Mean BP versus PP* | | |
| Adding mean BP to a model with PP | 19.0 | <0.0001 |
| Adding PP to a model with mean BP | 0.06 | 0.80 |
| *Systolic BP versus diastolic BP* | | |
| Adding systolic BP to a model with diastolic BP | 4.14 | 0.042 |
| Adding diastolic BP to a model with systolic BP | 5.21 | 0.022 |
| *Mean BP versus systolic BP* | | |
| Adding mean BP to a model with systolic BP | 5.21 | 0.022 |
| Adding systolic BP to a model with mean BP | 0.06 | 0.80 |
| *Mean BP versus diastolic BP* | | |
| Adding mean BP to a model with diastolic BP | 4.14 | 0.042 |
| Adding diastolic BP to a model with mean BP | 0.06 | 0.80 |

Likelihood ratio (LR) $\chi^2$ reflects increase in goodness of fit from adding one blood pressure (BP) index to a model including another index (and confounding variables), and vice versa. The greater LR $\chi^2$, the greater the increase in goodness of fit or "informativeness" with the additional BP index. The degrees of freedom for LR $\chi^2$ are all 1, and an LR $\chi^2$ of 3.8 corresponds to a *P* value of 0.05, 6.6 to 0.01, and 10.8 to 0.001, respectively. Because information of systolic and diastolic BP are used for the calculation of mean BP as well as pulse pressure (PP), some statistics show the same value

## Discussion

In the present study, we compared the predictive values of four BP indices (systolic BP, diastolic BP, mean BP, and PP) obtained from home BP measurement at baseline and during follow-up for the risk of cardiovascular events using data from the HOMED-BP study. We found that (1) systolic, diastolic, and mean BP at baseline and during follow-up were significant predictors of MACE, whereas no PP values showed significant associations; (2) systolic, diastolic, and mean BP values during follow-up were more closely associated with the risk of MACE than the values at baseline; and (3) mean BP values during follow-up were the strongest predictor of the risk of MACE among all BP indices examined in the present study.

The present findings were consistent with previous studies based on conventional office BP [10, 11], ambulatory BP [12], and home BP [13] in that systolic, diastolic, and mean BP were significant predictors of cardiovascular outcome, but PP was not. However, unlike previous studies [10–13] in which BP information was captured on one occasion, we evaluated the prognostic significance of BPs both measured at baseline, before the start of antihypertensive treatment, and during the follow-up on-treatment period. We emphasize that the present study first revealed that home systolic, diastolic, and mean BP during follow-up was associated with a risk of cardiovascular outcomes independent of corresponding home BP indices at baseline. Furthermore, home diastolic and mean BP at baseline did not have any significant prognostic power when the corresponding BP captured during follow-up were further adjusted in the model. These findings support the importance of achieving lower levels of home systolic, diastolic, and mean BP for the prevention of cardiovascular disease under antihypertensive drug treatment. As shown in Fig. 2, home systolic BP both at baseline and during follow-up significantly and independently predicted MACE. These results further indicate the importance of considering the residual risk of home systolic BP at baseline before treatment initiation to improve the prevention of future cardiovascular diseases.

Mean BP during follow-up, calculated by systolic and diastolic BP, had greater predictive power than the other BP indices examined in the present study, which suggests a possibility that the utilization of mean BP could be beneficial for reducing the risk of cardiovascular disease events when antihypertensive treatment is implemented. From a physiological viewpoint, mean arterial pressure (MAP) is regulated by changes in cardiac output and systemic vascular resistance, and calculated mean BP is an approximate measure of MAP [21]. Increased mean BP, which reflects steady pressure stress imposed on the heart, would be therefore the key predictor of cardiovascular risk, i.e., persistent decreases in pressure load appear to be important for antihypertensive treatment. However, mean BP was not directly measured; rather, it was calculated with a formula using systolic and diastolic BP. Furthermore, no guidelines for hypertension mention the diagnosis and treatment thresholds of mean BP level. The use of mean BP may not currently be practical in clinical settings. Rather, the use of systolic and diastolic BP would be more practical and relevant, even though mean BP might be a pathophysiologically informative parameter with different properties than systolic and diastolic BP.

PP remains an elusive cardiovascular risk factor as related findings are inconsistent between studies [22]. Recently, our research group assessed the predictive value of home PP in 6470 people from five populations enrolled in the International Database of home blood pressure in relation to cardiovascular outcome (IDHOCO) [23] and found that home PP adds a significant contribution but little information in predicting cardiovascular outcomes. Although home PP level in the elderly below 68 mmHg was proposed as probably being innocuous [23], the use of this threshold in clinical practice might be of little value because

home PP does not substantially enhance risk stratification over and beyond the steady component of the BP level and other cardiovascular risk factors [23]. The direct comparison between conventional PP and other BP indices provided confirmatory results [10, 11], and PP based on ambulatory monitoring [12] and home self-measurement [13] were also less informative based on our cohort study.

Our current study must be interpreted within the context of potential limitations. First, although our results are representative for health care provided to middle-aged and older Japanese individuals, they might not be applicable to other settings or ethnic groups with a different distribution of risk factors. Second, we did not compare the predictive power of cardiovascular disease risk for home and clinic BPs because the literature proving this point is overwhelming [1–3, 8]. Previous studies based on clinic BP have showed that systolic BP and mean BP were superior to other BP measurements in predicting cardiovascular events [10, 11]. We have reported the higher predictive power of self-measured systolic home BP than office BP [8]. Thus, the present finding based on home BP further reveals the usefulness of mean BP regarding cardiovascular risk prediction. Third, we could not preform sensitivity analysis according to event subtypes, e.g., stroke incidence, because of the small number of events. In general, Cox models should be used with at least 10 events per variable and are acceptable with five to nine events per variable [24]. Finally, although we used a validated automated home device [17] to capture BP indices, the values measured by an oscillometric technique might be different than those measured by the auscultation method, particularly for calculating mean BP and PP. However, because BPs were self-measured at home under the guidelines for home BP monitoring [16], and because home BP data were automatically recorded and transferred via a secured web-based system, at least the internal validity of the measured values was highly guaranteed.

In conclusion, the present study demonstrated that in addition to systolic and diastolic home BP, mean BP at baseline and, more closely, during the antihypertensive treatment period provide essential information in predicting MACE. Strict home BP-lowering therapy would reduce cardiovascular risk in patients with mild-to-moderate hypertension, and long-term management of hypertension by antihypertensive drug treatment should be based on self-measured home BP [6]. However, the utilization of home mean BP should be clarified by an intervention trial that targets mean BP levels.

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## Compliance with ethical standards

**Conflict of interest** T.H. is a full-time employee of GlaxoSmithKline but has contributed to this study independently of GlaxoSmithKline. Omron Healthcare provided research support to K.A., Y.I., H.M., and T.O. Pfizer and Astellas Pharma, Inc., provided research grants to H.M. The remaining authors declare that they have no conflict of interest.

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