For nonparametric analyses, HRs of the fifth quintiles (higher than 9,488 mm Hg × beats/min) of the DP for total, CVD, stroke, cardiac, and non-CVD mortalities were all significantly higher than those of the reference quintiles (**Figure 1a**). In the analysis excluding subjects treated with antihypertensive medications, the HR of the fifth quintile of the DP for cardiac mortality was higher than that in the analysis including all subjects (**Figure 1b**).

According these results, we defined DP ≥9,500 mm Hg × beats/min as "high DP" and SBP ≥135 mm Hg as "home systolic hypertension"[18] and compared mortality risks among four groups. The mortality risks of those with high DP and high SBP were significantly higher than those of subjects with normal DP and normal SBP. The risks of those with high DP and normal SBP tended to be higher than those of subjects with normal DP and high SBP (**Supplementary Table S1** online).

For the parametric analyses, the adjusted HRs and percentage increase in risk in the DP are shown in **Figure 2a**. HRs for total, CVD, stroke, cardiac, and non-CVD mortalities were positively and significantly associated with elevated DP. When 47 subjects who died of suicide and injury were censored, the results of analyses of total and non-CVD mortality did not change (data not shown). The adjusted HRs and percentage increase in risk in the SBP are shown in **Figure 2b**. HRs for total, CVD, and stroke mortalities were positively and significantly associated with increased SBP. The adjusted HRs and percentage increase in risk in PR are shown in **Figure 2c**. Significant associations between mortalities and increased PR were observed in the analyses for total and non-CVD mortalities. When evening DP, SBP, or PR were used for HBP data, overall HRs were similar to those obtained using morning measurements (**Supplementary Figures S1** and **S2** online).

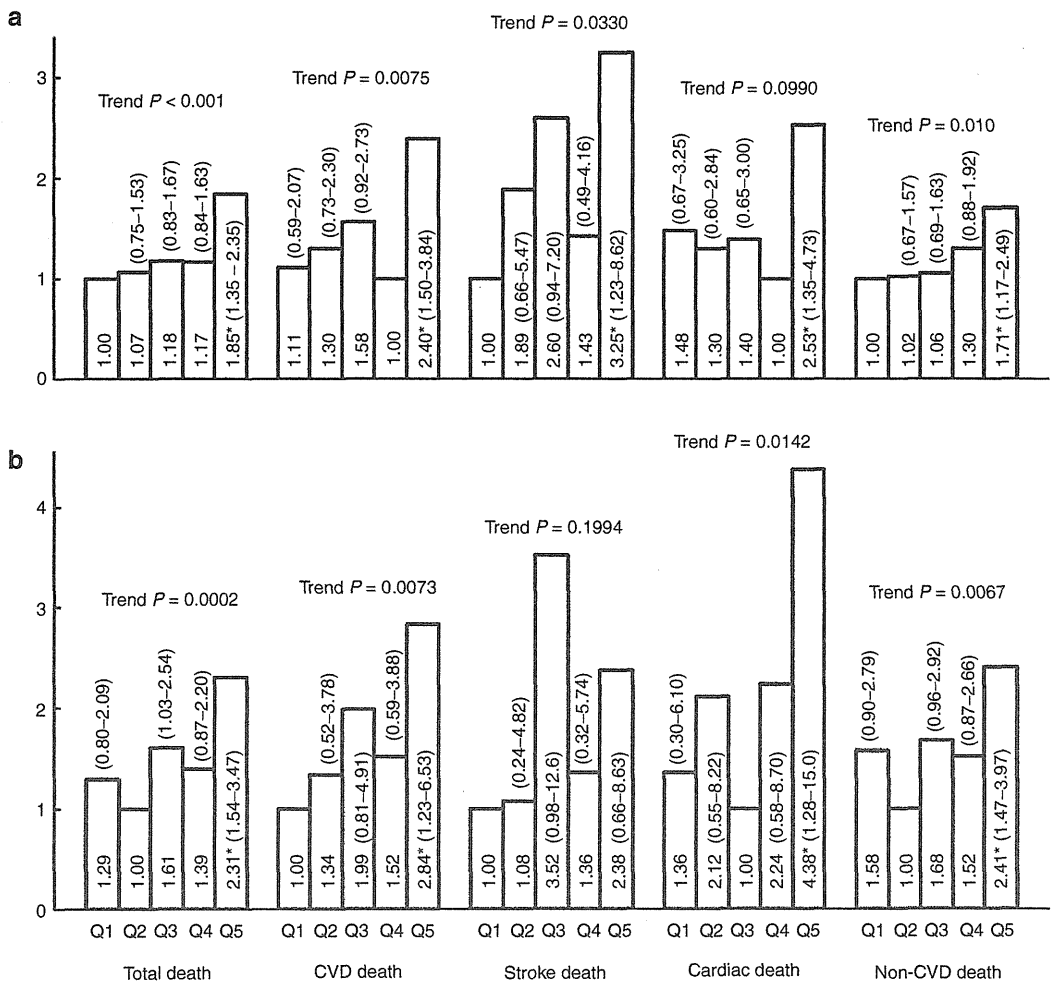


**Figure 1 |** Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the double product. HRs and 95% CIs adjusted for age, sex, smoking status, use of antihypertensive medication, and history of diabetes mellitus or hypercholesterolemia. (**a**) HRs for the analysis with all subjects; (**b**) HRs for the analysis with subjects who did not take antihypertensive medication. The double product quintiles are as follows: Q1: <7,231 mm Hg × beats/min; Q2: 7,231–7,925 mm Hg × beats/min; Q3: 7,926–8,565 mm Hg × beats/min; Q4: 8,566–9,447 mm Hg × beats/min; Q5: ≥9,488 mm Hg × beats/min for **a**, Q1: <7,120 mm Hg × beats/min; Q2: 7,120–7,764 mm Hg × beats/min; Q3: 7,765–8,371 mm Hg × beats/min; Q4: 8,372–9,145 mm Hg × beats/min; Q5: ≥9,145 mm Hg × beats/min for **b**. *$P < 0.05$. CVD, cardiovascular disease.

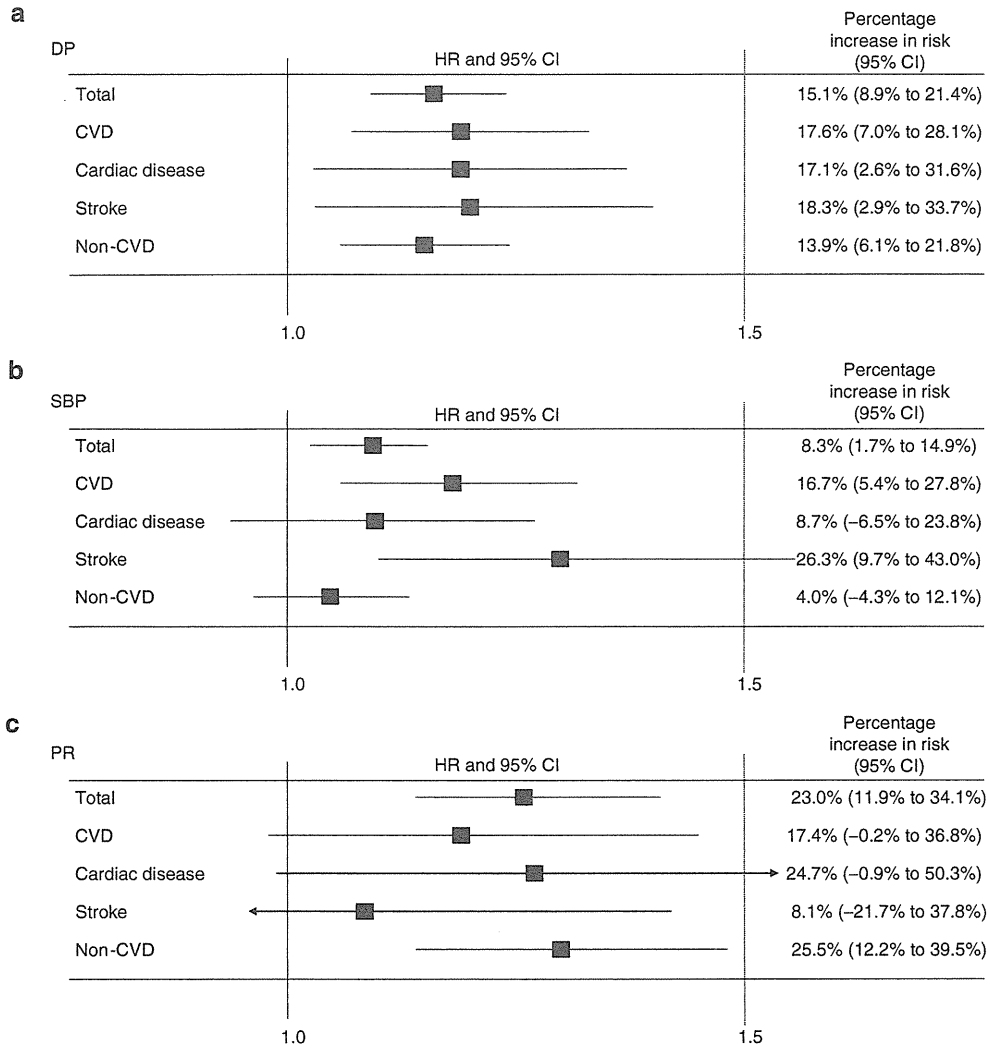


**Figure 2 |** Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the double product (DP), systolic blood pressure (SBP), and pulse rate (PR). The boxes represent the HRs and horizontal lines represent 95% CIs. (**a**) HRs expressed as an increase in the risk of death per 1,000 mm Hg × beats/min elevation of the DP; (**b**) HRs expressed as an increase in the risk of death per 10 mm Hg elevation of SBP; (**c**) HRs expressed as an increase in the risk of death per 10 beats/min elevation of PR. All analyses were adjusted for age, sex, smoking status, use of antihypertensive medication, and history of diabetes mellitus or hypercholesterolemia. CVD, cardiovascular disease.

In the analyses among untreated subjects, the HRs of DP, SBP, and PR were higher than those in the analyses including all subjects, especially HRs for cardiac mortality (**Figure 3**).

In the subgroup analysis including 1,243 subjects with data on serum creatinine, serum creatinine levels were significantly associated with total, CVD, cardiac, and non-CVD mortality. However, DP was still significantly associated with total, CVD, and cardiac mortality (**Supplementary Table S2** online).

In the secondary analyses (**Table 2**), in the analysis for total mortality, the LR $\chi^2$ value of DP significantly improved when the DP was added to the model including SBP or PR. On the other hand, the LR $\chi^2$ values of SBP or PR did not change when they were added to the model including the DP. In the analysis of CVD mortality, the LR $\chi^2$ value of the DP significantly improved when the DP was added to the model with PR and slightly improved when added to the model with SBP. In the analysis of cardiac mortality and non-CVD mortality, the LR $\chi^2$ value of the DP significantly improved when added to the models with SBP. However, in the analysis of stroke mortality, the LR $\chi^2$ value of the DP did not significantly change when added to the model with SBP.

In the analyses among untreated subjects, the improvement of the LR $\chi^2$ value of the DP became more marked (**Table 2**). In the analysis of CVD mortality, the LR $\chi^2$ value of the DP significantly improved when added to the model including SBP. The improvement of LR $\chi^2$ value of the DP for cardiac mortality became significant when added to the model including PR.

When SBP, PR, and the DP were simultaneously included in the Cox models, the DP was not significantly associated with mortality risk, and there was no significant interaction between SBP and PR (**Supplementary Table S3** online).

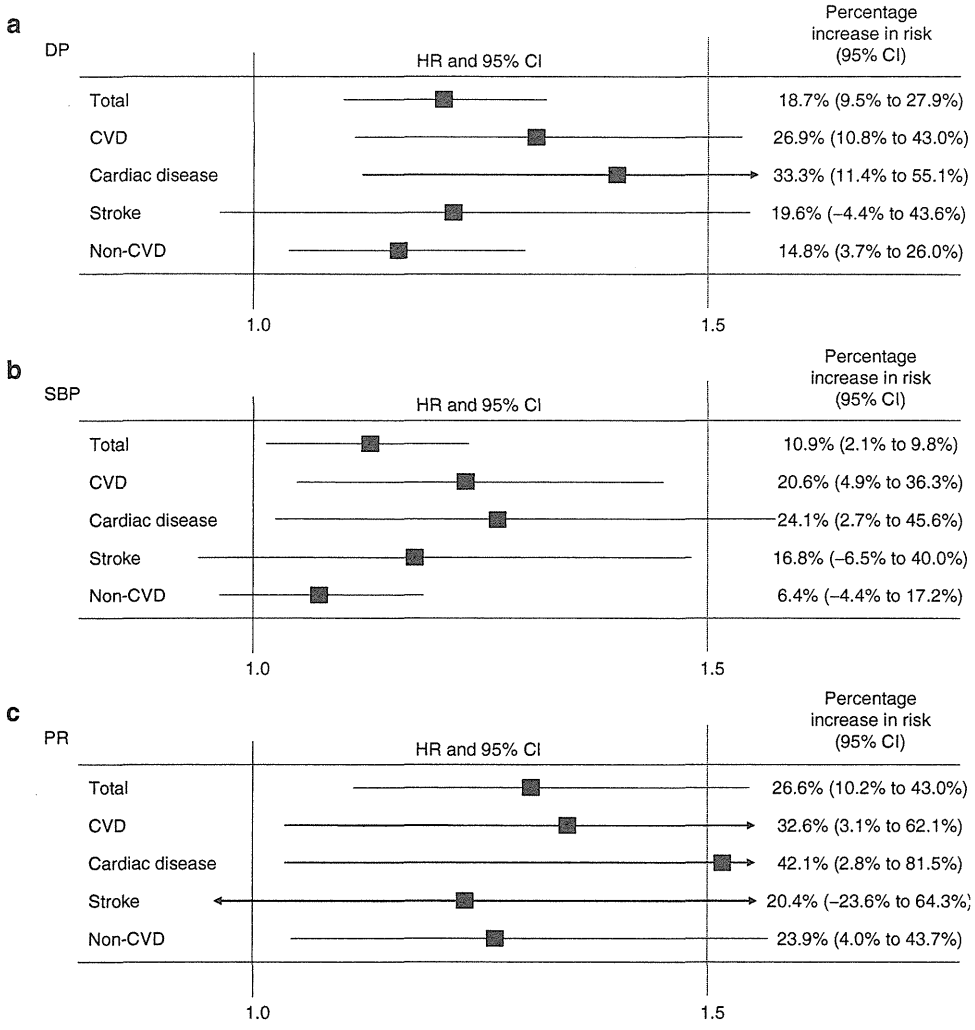


**Figure 3 |** Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the double product (DP), systolic blood pressure (SBP), and pulse rate (PR) (HRs for the analyses with subjects who did not take antihypertensive medication) The boxes represent the HRs and horizontal lines represent 95% CIs. (**a**) HRs expressed as an increase in the risk of death per 1,000 mm Hg × beats/min elevation of the DP; (**b**) HRs expressed as an increase in the risk of death per 10 mm Hg elevation of SBP; (**c**) HRs expressed as an increase in the risk of death per 10 beats/min elevation of PR. All analyses were adjusted for age, sex, smoking status, and history of diabetes mellitus or hypercholesterolemia. CVD, cardiovascular disease.

## DISCUSSION

The present study was based on longitudinal observation of a representative sample of the general population living in a rural Japanese community. The main findings from this study were: (i) the DP measured at rest based on home BP measurement significantly predicted mortality; and (ii) the LR $\chi^2$ value of the DP improved significantly when the DP was added to the models including SBP or PR, especially in the analysis of total mortality, although there was no significant interaction between SBP and PR and the DP did not add any meaningful information to models including both SBP and PR. These associations were essentially similar in a subgroup of untreated participants.

It is well known that high SBP is a strong CVD risk.[1,2] In addition, it was reported that high PR is a risk factor for CVD and non-CVD.[3–7] Although the DP is the product of SBP and PR, it has not been previously investigated whether the DP measured at rest has predictive power for mortality in the general population. In the present study, the DP derived from HBP measurement was shown to have significant predictive powers for all of total, CVD, cardiac, stroke, and non-CVD mortalities. HRs for the DP significantly increased when the DP was higher than 9,488 mm Hg × beats/min. Thus, around 9,500 mm Hg × beats/min would be the cut-off value.

The DP is known as a marker of myocardial oxygen requirement,[8] and elevation of the DP coexists with silent myocardial ischemia.[11] Elevation of the DP at rest may reflect a consistent cardiac load even in a stable condition, which may inversely cause cardiac impairment. Therefore, the DP at rest may be a marker of cardiac dysfunction rather than of systemic arterial load and may be more strongly associated with cardiac disease than other diseases, including stroke.

**Table 2 | Increases in goodness of fit adding the double product, systolic blood pressure, or pulse rate to the Cox model**

| | Total death | | CVD death | | Cardiac disease | | Stroke | | Non-CVD death | |
|---|---|---|---|---|---|---|---|---|---|---|
| | LR$\chi^2$ | *P* | LR$\chi^2$ | *P* | LR$\chi^2$ | *P* | LR$\chi^2$ | *P* | LR$\chi^2$ | *P* |
| All subjects | | | | | | | | | | |
| Adding DP to a model with SBP | 15.6 | <0.0001 | 3.0 | 0.09 | 3.9 | 0.05 | 0.1 | 0.7 | 13.3 | 0.0003 |
| Adding SBP to a model with DP | 0.4 | 0.6 | 1.3 | 0.3 | 0.1 | 0.7 | 4.6 | 0.03 | 2.6 | 0.1 |
| Adding DP to a model with PR | 6.0 | 0.01 | 8.1 | 0.004 | 1.7 | 0.2 | 8.1 | 0.004 | 1.0 | 0.3 |
| Adding PR to a model with DP | 0.6 | 0.4 | 1.0 | 0.3 | 0.06 | 0.8 | 3.3 | 0.07 | 2.7 | 0.1 |
| Adding SBP to a model with PR | 6.2 | 0.01 | 8.5 | 0.004 | 1.4 | 0.2 | 9.4 | 0.002 | 1.0 | 0.3 |
| Adding PR to a model with SBP | 16.0 | <0.0001 | 3.2 | 0.07 | 3.6 | 0.06 | 0.3 | 0.6 | 13.3 | 0.0003 |
| Subjects who did not take antihypertensive medication | | | | | | | | | | |
| Adding DP to a model with SBP | 10.1 | 0.002 | 4.0 | 0.05 | 3.8 | 0.05 | 0.7 | 0.4 | 6.2 | 0.01 |
| Adding SBP to a model with DP | 0.3 | 0.6 | 0.2 | 0.7 | 0.05 | 0.8 | 0.2 | 0.7 | 0.8 | 0.4 |
| Adding DP to a model with PR | 6.0 | 0.01 | 5.8 | 0.02 | 4.4 | 0.04 | 1.8 | 0.2 | 1.7 | 0.2 |
| Adding PR to a model with DP | 0.2 | 0.7 | 0.04 | 0.8 | 0.00 | 1 | 0.1 | 0.8 | 0.5 | 0.5 |
| Adding SBP to a model with PR | 5.7 | 0.01 | 6.4 | 0.01 | 4.8 | 0.03 | 2.0 | 0.2 | 1.3 | 0.3 |
| Adding PR to a model with SBP | 9.7 | 0.002 | 4.5 | 0.03 | 4.2 | 0.04 | 0.8 | 0.4 | 5.4 | 0.02 |

This table shows increases in goodness of fit from adding one of double product (DP), systolic blood pressure (SBP), and pulse rate (PR) to a model including another index (and confounding variables) and vice versa. The greater the likelihood ratio (LR) $\chi^2$, the greater the increase in goodness of fit with the additional value. An LR $\chi^2$ of 3.8 corresponds to a *P* value of 0.05, 6.6–0.01, and 10.8–0.001. Each model was adjusted for all confounding variables (age, sex, smoking status, use of antihypertensive medication, and history of diabetes mellitus, or hypercholesterolemia). CVD, cardiovascular disease.

The association between the DP and stroke was relatively weak compared with that between the DP and cardiac disease, while the DP was significantly associated with stroke mortality. The DP measured in the acute phase of stroke was reported to be associated with poor outcome.[12,13] Severe acute stroke may increase cardiac burden. Thus, the cardiac function of subjects with a high DP before stroke might have been aggravated by the stroke, and strokes that occurred in subjects with a high DP might be fatal.

The DP strongly predicted not only CVD mortality but also non-CVD mortality. DP may reflect poor general health, poor respiratory function, or hypoxia, which may explain why PR is related to non-CVD mortality.[4] In addition, it was reported that CVD risk factors were associated with non-CVD mortality.[28] Thus, the DP would be strongly associated with total mortality.

Predictive values of the DP were more remarkable among subjects who did not take antihypertensive medications. Antihypertensive drugs variously affect BP and PR. Thus, the significance of DP could have been underestimated among those who took antihypertensive medications.

When we compared mortality risks among four groups divided according to DP and SBP, the risks of subjects with high DP and normal SBP tended to be higher than those of subjects with normal DP and high SBP. The mortality risk of patients with high PR and normal SBP appears to be underestimated. Estimation of the DP can provide the mortality risk of both SBP and PR easily, and the DP might be useful to evaluate mortality risk.

Our observational study was unable to resolve the issue of whether DP-lowering treatments such as β-blockers should be implemented for patients with a high DP, or whether there would be more effective treatment for DP than conventional treatments for SBP or PR. Further studies including randomized, controlled trials using DP-lowering therapies are needed to resolve this issue.

The present study also had some limitations. The analyses were based on data obtained from HBP measurement. No data on the DP, BP, and PR based on conventional BP measurement were available. Thus, we cannot investigate the predictive power of the DP based on conventional BP. Second, we did not have detailed data of antihypertensive medication use, including use of β-blockers. Third, although the DP reflects cardiac function, we did not have any data of left ventricular function measured with ultrasonic cardiography. However, participants with history of CVD including symptomatic systolic dysfunction or heart failure were excluded from the study. Furthermore, the sensitivity analysis that excluded subjects treated with antihypertensive medication revealed consistent results. Thus, the study results would unlikely be affected by absence of data on β-blocker use or left ventricular function. Lastly, because the study population was all Japanese, the present results might not be representative of non-Japanese populations.

In conclusion, the present study provides new evidence from an observational study that, in Japanese populations, the DP at rest based on HBP measurement was significantly associated with not only CVD mortality but also non-CVD mortality. The LR $\chi^2$ value of the DP improved significantly when the DP was added to the models including SBP or PR. These findings are preliminary, and further study is needed to confirm the usefulness of the DP in risk stratification.

Supplementary material is linked to the online version of the paper at http://www.nature.com/ajh

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# Pre-hypertension as a significant predictor of chronic kidney disease in a general population: the Ohasama Study

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**Abstract**

**Background.** Hypertension is associated with an increased risk of development of chronic kidney disease (CKD). However, it is unclear whether pre-hypertension is related to the incidence of CKD.

**Methods.** The incidence of CKD defined as positive proteinuria or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 $m^2$ was examined in 2150 inhabitants without pre-existing CKD from the general Japanese population. The association of blood pressure and CKD incidence was examined using a Cox regression model adjusted for age, sex, habitual smoking and drinking, obesity, history of cardiovascular disease, diabetes mellitus or hypercholesterolemia, eGFR at baseline, number of follow-up examinations and year of baseline examination. Participants were categorized according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.

**Results.** Participants were categorized into normotension ($n = 586$, 27.3 %), pre-hypertension ($n = 815$, 37.9 %), Stage 1 hypertension ($n = 386$, 18.0 %) and Stage 2 hypertension ($n = 363$, 16.9 %). During a mean follow-up of 6.5 years (14 023 person-years), 461 incidences of CKD were recorded. Compared to normotension, adjusted hazard ratios of CKD were significantly higher for pre-hypertension (1.49, $P < 0.003$), Stage 1 (1.83, $P < 0.001$) and Stage 2 (2.55, $P < 0.001$) hypertension. The population-attributable fraction of pre-hypertension (12.1 %) was considered to be compatible to that of Stage 1 (8.6 %) and Stage 2 (14.9 %) hypertension.

**Conclusion.** This was the first study to demonstrate that pre-hypertension was significantly associated with an increased risk of CKD and was one of the considerable causes of CKD in the general population.

**Keywords:** chronic kidney disease; epidemiology; population-attributable fraction; pre-hypertension; risk factors

## Introduction

Pre-hypertension, defined in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) [1], is reported to be associated with a risk for developing hypertension [2] and is related to the morbidity and mortality of cardiovascular disease (CVD) [2, 3]. Therefore, identification of individuals with pre-hypertension is an important strategy to inhibit progression to hypertension and thereby reduce the risk of CVD in the general population.

The high prevalence of chronic kidney disease (CKD) is now considered a major public health issue. In fact, the number of patients with end-stage renal disease (ESRD) on chronic hemodialysis in 2008 exceeded 283 421 in Japan [4]. Both early detection and appropriate intervention during the initial stages of CKD are necessary for prevention of a further increase in the number of patients with ESRD. Hypertension is a critical risk factor for progression of CKD [3, 5, 6] and a predictor of development to ESRD [7]. On the other hand, in previous studies, it has not been definitely shown that pre-hypertension based on the JNC7 criteria is significantly associated with progression to CKD [8–10]; therefore, its relationship remains controversial.

In the present study, the risk of CKD was investigated among people with pre-hypertension, and the impact of the burden of pre-hypertension in the general population was examined.

## Materials and methods

*Design*

The present study was based on longitudinal observation of individuals who had been participating in a survey on CVD in Ohasama, Iwate Prefecture, Japan. This project was approved by the Institutional Review Board of Tohoku University School of Medicine and by the Department of Health of the Ohasama Town Government. All of the participants provided written informed consent. The socioeconomic and demographic characteristics of this region and the details of this project have been previously described [11].

*Study cohort*

In Japan, annual health check-ups are available for farmers, the self-employed, pensioners and dependents aged at least 40 years. Ohasama, a rural community, in 1992 had a total population of 7496, and 3076 residents were eligible for annual health check-ups. Among them, subjects who did not undergo the examinations at all from 1993 to 2007 ($n$ = 549), those who did not provide an informed consent ($n$ = 55) and those diagnosed with CKD including each of positive proteinuria ($n$ = 91) and estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 $m^2$ ($n$ = 231) at baseline were excluded. Thus, the number of subjects who were included in the present statistical analysis totaled 2150.

*Measurement of eGFR and proteinuria*

Serum creatinine (Scr) was measured using the Jaffé method during annual check-ups before 2002 and by the enzymatic method subsequently. Renal function was estimated by calculated glomerular filtration rate (GFR) using a modified Japanese equation based on inulin clearance as follows: eGFR (mL/min/1.73 $m^2$) = 194 × (Scr in enzymatic method)$^{-1.094}$ × age$^{-0.287}$ (× 0.739, if female) [12]. The following equation was used to convert the level of Scr from the Jaffé method to that for the enzymatic method (Scr in enzymatic method = Scr in Jaffé method − 0.2) [13]. Diagnosis of proteinuria was made using a urine dipstick test (Urohemabonbix 5G08C; Bayer Medical, Tokyo, Japan). Positive proteinuria was considered to be present for a dipstick result of ≥ 1 +, corresponding to a urinary protein level > 30 mg/dL [14]. CKD was defined as positive proteinuria or eGFR < 60 mL/min/1.73 $m^2$.

*Blood pressure measurement*

Blood pressure (BP) was measured twice by nurses at local medical centers using a semi-automatic BP-measuring device (USM-700F; UEDA Electronic Works, Tokyo, Japan) based on the microphone method with subjects in a seated position after resting for at least 2 min. The average of the two readings was used in this analysis. The devices have been validated previously [15] and meet the criteria of the Association for the Advancement of Medical Instrumentation [16].

*Diagnostic criteria for hypertension and BP category*

Participants were categorized according to the JNC7 [1] as having normotension (systolic BP < 120 mmHg and diastolic BP < 80 mmHg), pre-hypertension (systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg), Stage 1 hypertension (systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg) and Stage 2 hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg). Treated participants were categorized as having Stage 2 hypertension.

*Data collection and diagnostic criteria on other variables*

Information on smoking status, habitual drinking, use of anti-hypertensive medications at baseline, as well as a history of CVD, diabetes mellitus or hypercholesterolemia were verified on the basis of information recorded in medical charts at the Ohasama Hospital and a questionnaire administrated during annual health check-ups as we described previously [17]. The history of CVD was derived from a disease of the circulatory system (ICD-10: I00–I99) or transient ischemia attack. Subjects treated with lipid-lowering drugs or displaying serum cholesterol levels ≥ 220 mg/dL were considered to have hypercholesterolemia. Subjects with fasting serum glucose levels ≥ 126 mg/dL or non-fasting glucose levels ≥ 200 mg/dL or who used insulin or oral anti-hyperglycemic agents were defined as having diabetes mellitus. Body mass index (BMI) was calculated as weight (kg) divided by height squared ($m^2$). The presence of obesity was diagnosed with BMI levels ≥ 25 kg/$m^2$.

*Follow-up and outcomes*

Primary outcomes were defined as the onset of CKD at the time of the annual check-up from 2002 to 2010. If a participant experienced more than one CKD event during follow-up, only the first outcome for the individual contributed to the outcome analysis. The date of onset of CKD was defined as the midpoint between the last date when the subjects did not have CKD and the first date when the subject was diagnosed with CKD. The follow-up period was defined as the number of days from the date of observation to the date of CKD diagnosis or to the date of the final check-up. Similarly, an eGFR < 60 mL/min/1.73 $m^2$ or an isolated positive proteinuria were analyzed as individual primary outcomes. Secondary outcomes were defined as a composite of CKD or death from all causes.

*Statistical analysis*

For statistical analysis, SAS software, version 9.1 (SAS Institute, Cary, NC) was used. Statistically significant differences were compared by means of one-way analysis of variance. The association between baseline BP and the incidence of CKD, eGFR < 60 mL/min/1.73 $m^2$ and positive proteinuria was examined using the Cox proportional hazard regression model adjusted for age, sex, habitual smoking and drinking, obesity, CVD, diabetes mellitus, hypercholesterolemia, anti-hypertensive treatment, eGFR at baseline, the number of follow-up examinations and year of baseline examination. In subgroup analysis, participants were stratified according to age (≥ 60, < 60 years), sex, number of follow-up examinations (≥ 3, < 3) and length of follow-up period (≥ 6, < 6 years).

The incidence rates of CKD were examined for participants among BP groups using Kaplan–Meier survival function estimates and the log-rank test. To evaluate the impact of pre-hypertension and hypertension on the onset of CKD, the adjusted population attributable fraction (adjusted PAF) was calculated as Pe × [adjusted hazard ratio (HR) − 1], in which Pe is the proportion of exposed subjects in each BP categories and adjusted HR is the multiple-adjusted HR for CKD in reference to normotension. The PAF is an index of how much of the scale of the disease burden in a population could be eliminated if the effects of certain causal factors were eliminated from the population [18, 19].

## Results

*Baseline subject characteristics*

The 2150 study participants consisted of 1364 (63.4 %) women, 815 (37.9 %) patients with pre-hypertension, 386 (18.0 %) patients with Stage 1 hypertension and 363 (16.9 %) with Stage 2 hypertension which included 274 (12.7 %) patients who were treated with anti-hypertensive drugs. The overall mean value ± SD was 60.3 ± 9.6 years for age. Characteristics of the study population across BP groups are shown in Table 1. After conversion of the level of Scr from the Jaffe method to that for the enzymatic method, baseline Scr was 0.65 ± 0.12 mg/dL and eGFR was 82.3 ± 14.7 mL/min/1.73 $m^2$.

*Follow-up and outcomes*

The mean duration of follow-up was 6.5 ± 4.7 years (maximum 14.9 years). The numbers of follow-up visits were 1, 2, 3, 4 or 5 + in 480, 526, 206, 259 and 679 participants, respectively. Of the 2150 participants, the number of patients with onset of CKD was 461 subjects, which included solely an eGFR < 60 mL/min/1.73 $m^2$ in 360 (78.1 %) subjects, isolated positive proteinuria in 149 (32.3 %) subjects and both criteria in 48 (10.4 %) subjects. Additionally, a total of 290 deaths during the follow-up period were recorded and consisted of 54 (18.6 %), 96 (33.1 %) and 140 (48.3 %) subjects with

**Table 1.** Clinical characteristics in the three BP groups[a]

| Variable | BP groups | | | | |
|---|---|---|---|---|---|
| | Normal ($N=586$) | Pre-HT ($N=815$) | HT-1 ($N=386$) | HT-2 ($N=363$) | P[b] |
| Age, years | 56.8 ± 10.5 | 59.8 ± 9.4[c] | 62.4 ± 8.6[c,d] | 64.8 ± 6.9[c,d,e] | < 0.001 |
| Female, % | 75.8 | 61.2[c] | 51.3[c,d] | 61.4[c,e] | < 0.001 |
| Current smoker, % | 8.2 | 11.4 | 12.2 | 9.9 | 0.15 |
| Current drinker, % | 11.3 | 16.3 | 20.0[c] | 21.5[c] | < 0.001 |
| BMI, kg/m$^2$ | 22.5 ± 3.0 | 23.5 ± 3.1[c] | 24.1 ± 3.1[c,d] | 24.2 ± 3.2[c,d] | < 0.001 |
| History of CVD, % | 0.6 | 1.6 | 1.0 | 8.0[c,d,e] | < 0.001 |
| Diabetes mellitus, % | 4.8 | 6.6 | 6.0 | 11.6[c,d,e] | 0.006 |
| Hypercholesterolemia, % | 19.6 | 25.9 | 31.3[c] | 38.6[c,d] | < 0.001 |
| Anti-hypertensive treatment, % | 0 | 0 | 0 | 75.5[c,d,e] | < 0.001 |
| Serum creatinine, mg/dL | 0.63 ± 0.11 | 0.65 ± 0.13 | 0.67 ± 0.12[c,d] | 0.66 ± 0.12[c] | < 0.001 |
| eGFR, mL/min/1.73 m$^2$ | 82.6 ± 14.6 | 83.6 ± 22.6 | 81.7 ± 13.7 | 79.4 ± 14.0[c,d] | < 0.001 |
| No. of follow-up exams | 3.6 ± 2.2 | 3.5 ± 2.1 | 2.9 ± 1.9[c,d] | 3.3 ± 2.0 | < 0.001 |
| Follow-up period, years | 7.2 ± 5.0 | 6.8 ± 4.7 | 5.5 ± 4.3[c,d] | 5.7 ± 4.6[c,d] | < 0.001 |
| Systolic BP, mmHg | 109.4 ± 7.6 | 129.3 ± 5.9[c] | 146.2 ± 5.5[c,d] | 143.1 ± 19.6[c,d,e] | < 0.001 |
| Diastolic BP, mmHg | 63.3 ± 7.1 | 73.1 ± 7.1[c] | 81.4 ± 9.1[c,d] | 78.3 ± 12.6[c,d,e] | < 0.001 |

[a]Values are expressed as percentage or mean ± SD. HT, hypertension; Normal, normotension; Pre-HT, pre-hypertension; Scr, serum creatinine.
[b]Analysis of variance and $\chi^2$ tests were used to compare continuous and categorical variables across BP groups, respectively.
[c]$P < 0.05$ for comparison used Scheffe's multiple comparison test between each BP groups and normotension.
[d]$P < 0.05$ for comparison between each BP groups and pre-hypertension.
[e]$P < 0.05$ for comparison between each BP groups and Stage 1 hypertension.

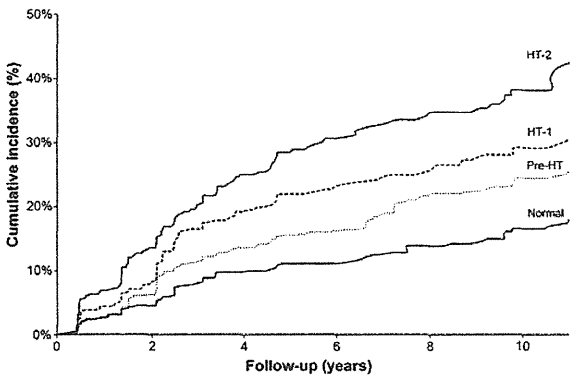


**Fig. 1.** Kaplan–Meier curves for the cumulative incident of CKD for normotension, pre-hypertension (Pre-HT) and Stage 1 hypertension (HT-1) and Stage 2 hypertension (HT-2).

normotension, pre-hypertension and hypertension, respectively. Kaplan–Meier curves for the cumulative incident of CKD are shown in Figure 1. There was a significant difference in the cumulative incidence of CKD between normal, pre-hypertension and hypertension categories (log-rank test, $P < 0.001$).

### *Risk factors associated with CKD*

Independent association was investigated between the incidence of CKD and confounding factors in a multivariate model containing systolic and diastolic BP (Table 2). Significant determinants for the incidence of CKD were age, eGFR, systolic BP and diastolic BP. Associations between the incidence of eGFR < 60 mL/min/1.73 m$^2$ and confounding factors were similar to associations between confounding factors and the incidence of CKD (Supplemental Table S1). Significant determinants for the incidence of eGFR < 60 mL/min/1.73 m$^2$ were age, eGFR, smoking, systolic BP and diastolic BP.

Only systolic BP was a significant determinant of the incidence of proteinuria (HR 1.12 per 10 mmHg increase in systolic BP, $P = 0.04$) (Supplemental Table S2). On the other hand, in the model, if diastolic BP was added instead of systolic BP, age (HR 1.28 per 10 years of age, $P = 0.03$) and the use of anti-hypertensive medication (HR 1.52, $P = 0.04$) were significantly related to the incidence of proteinuria (Supplemental Table S2). All subgroup analyses for age, sex, number of follow-up examinations and length of follow-up period were confirmatory (Supplemental Table S3). None of the interaction terms reached significance ($P \geq 0.14$).

### *Adjusted HR and PAF of CKD for pre-hypertension and hypertension*

Adjusted HR and adjusted PAF for CKD incidence in pre-hypertension and hypertension compared to normotension are demonstrated in Figure 2A. The HR of a composite end point of CKD or death from all causes in pre-hypertension and hypertension were evaluated and similar results were revealed (Figure 2B).

## Discussion

The present study demonstrated that the risk for CKD in pre-hypertension was significantly higher compared to normotension in the general population. The PAF for CKD in pre-hypertension was comparable to that of Stage 1 and Stage 2 hypertension. In previous studies, whether pre-hypertension was associated with the onset of ESRD as a hard outcome has been examined; however, there

**Table 2.** HRs for incidence of CKD[a]

| Variable | Multivariate model with systolic BP | | Multivariate model with diastolic BP | |
|---|---|---|---|---|
| | HR (95 % CI) | P | HR (95 % CI) | P |
| Age (per 10 year increase) | 1.30 (1.13–1.48) | < 0.001 | 1.36 (1.19–1.55) | < 0.001 |
| Female | 0.88 (0.68–1.13) | 0.31 | 0.87 (0.68–1.12) | 0.29 |
| Obesity (BMI > 25 kg/m$^2$) | 1.02 (0.83–1.25) | 0.85 | 1.03 (0.83–1.26) | 0.82 |
| Current smoking | 1.36 (0.98–1.88) | 0.07 | 1.34 (0.97–1.85) | 0.08 |
| Current drinking | 0.81 (0.60–1.08) | 0.15 | 0.81 (0.60–1.08) | 0.14 |
| Diabetes mellitus | 0.80 (0.56–1.14) | 0.22 | 0.83 (0.58–1.19) | 0.31 |
| Hypercholesterolemia | 1.08 (0.88–1.33) | 0.47 | 1.08 (0.87–1.33) | 0.49 |
| History of CVD | 1.22 (0.71–2.09) | 0.47 | 1.20 (0.70–2.05) | 0.51 |
| Anti-hypertensive therapy | 1.24 (0.96–1.60) | 0.096 | 1.31 (1.02–1.68) | 0.04 |
| eGFR (per mL/min/1.73 m$^2$ decrease) | 1.06 (1.05–1.07) | < 0.001 | 1.06 (1.05–1.07) | < 0.001 |
| Systolic BP (per 10 mmHg increase) | 1.12 (1.06–1.19) | < 0.001 | | |
| Diastolic BP (per 10 mmHg increase) | | | 1.15 (1.05–1.26) | 0.002 |

[a]CI, confidence interval.

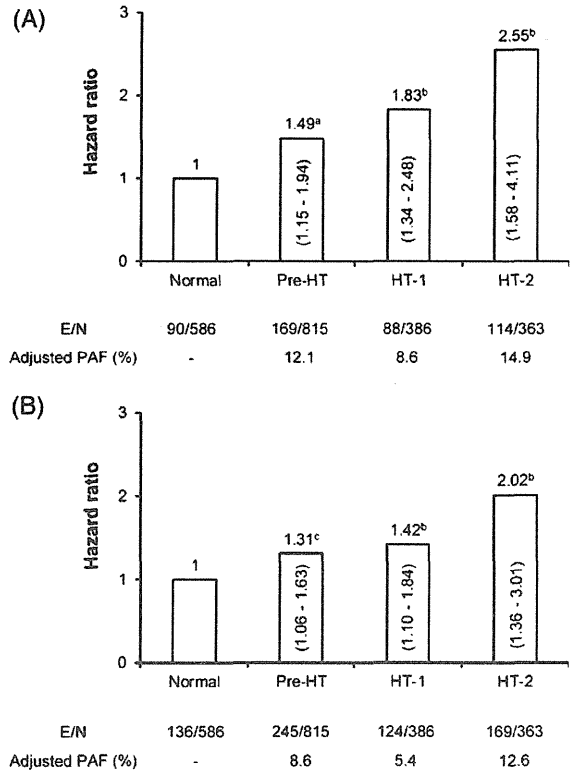


**Fig. 2.** HRs and 95 % confidence intervals of (A) CKD and (B) a composite end point of CKD or death from all causes for normotension, pre-hypertension (Pre-HT), Stage 1 hypertension (HT-1) and Stage 2 hypertension (HT-2) adjusted for confounding factors in reference to normotension. E/N, number of events/number of participants. [a]P < 0.01 versus reference. [b]P < 0.001 versus reference. [c]P < 0.03 versus reference.

was no strong statistical significance [20, 21]. Independent significance was shown only in a younger population (mean age 37 ± 13 years) [22]. Concerning prospective studies of pre-hypertension and CKD in the general population, there have only been a few studies [8–10], all of which have failed to clearly demonstrate the prognostic significance of pre-hypertension for CKD. A study of 17 375 healthy volunteers from the general Viennese population showed an increased risk for CKD in pre-hypertension, but this was not statistically significant (P = 0.35) [8]. In a 12-year follow-up study of 8093 men, a systolic BP of 120–129 mmHg did not predict CKD [9]. In a prospective study of 23 534 subjects, normal or high-normal BP was also not significantly associated with the risk of CKD (P ≥ 0.07) [10]. Thus, the present study is the first report to demonstrate a significant association between individuals with pre-hypertension and the development of CKD in a general population. One of the reasons for the differences in the results of the present study compared to past studies is that participants in the present study were mainly elderly (mean age 60 years in this study versus 41–51 years in previous studies [8–10]). Elderly people are more susceptible to various stresses such as dehydration, chronic inflammation and malnutrition; therefore, there is a possibility that levels of eGFR in elderly participants might easily deteriorate. Secondly, the definition of CKD used in the present study was either positive proteinuria or eGFR < 60 mL/min/1.73 m$^2$, whereas decreased eGFR alone was used as the definition of CKD in previous studies [8, 9]. Thirdly, in statistical analysis, a Cox proportional hazard regression was used to examine the association between pre-hypertension and the risk of CKD. In previous studies, multivariate logistic regressions were performed [8, 9], but the censored subjects were not fully considered. These factors could have led to the novel significant association in the present study.

In the present study, participants were mainly elderly subjects. In the elderly, CKD is associated with clinical and subclinical vascular pathology, atherosclerosis [23, 24] and age-related decline in renal function (which may be a consequence of atherosclerosis). In morphological analysis, as a result of renal biopsy, pre-hypertension was associated independently with renal arteriosclerosis and arteriolar hyalinosis. The association was present even after adjustment for traditional cardiovascular risk factors such as total cholesterol, glucose intolerance, BMI, habitual smoking and alcohol intake in Japanese population-based autopsy samples [25]. In a similar study for IgA

nephropathy based on renal biopsy, pre-hypertension was significantly related to the severity of mesangial proliferation and arteriolar sclerosis, including intimal thickening and hyalinosis [26]. Prolonged systemic high BP might induce pathological changes such as atherosclerosis, which can cause a disturbance in renal perfusion and renal ischemia, resulting in a subsequent decline in renal function [27, 28].

The prevalence of subjects with pre-hypertension was 37.9 % in the present study, comparable to results of the Japanese National Health and Nutrition Examination Survey in 2006 (39.7 %) [29]. In the present study population, due to the high prevalence of pre-hypertension compared to that of Stage 1 (18.0 %) and Stage 2 (16.9 %) hypertension, the PAF for CKD in pre-hypertension was considerably high (12.1 %) and comparable to that of Stage 1 (8.6 %) and Stage 2 (14.9 %) hypertension. Therefore, it is preferable to consider earlier interventions for pre-hypertension in order to prevent the progression of CKD among the general population. In practice, it is supposed that lifestyle intervention is the mainstay of treatment for pre-hypertension for the general population. Lifestyle modifications such as weight reduction for maintaining a normal body weight, improving dietary habits, reducing sodium intake, increasing physical activity and restricting alcohol consumption have all been shown both to lower BP effectively and have a beneficial effect on cardiovascular risks [30–32]. Such lifestyle changes are also recommended for patients with pre-hypertension. Essentially, the definition of the pre-hypertension according to JNC7 was intended to emphasize the importance of identification of individuals who could lower their BP in order to prevent progression to hypertension and cardiovascular events through adoption of a healthier lifestyle [1]. Population strategies such as a public health and social and policy reforms, not high-risk strategies limited to hypertension, might be necessary in order to attain a better BP target.

In line with previous studies [33, 34], the present study confirmed a weak, but significant, relationship between systolic BP and the development of proteinuria. In relation to diastolic BP, it remains controversial whether diastolic BP is an independent predictor of CKD [9, 35, 36]. In the present study, however, when diastolic BP was added into the model for prediction of CKD instead of systolic BP, the results were not statistically different from when systolic BP was used, excluding the onset of proteinuria.

In patients with hypertensive CKD, it was recently reported that intensive BP control had no favorable effect on the progression of decreased renal function [37]. Additionally, it was suggested that even strict control of BP is ineffective for the treatment of full-blown hypertension. Therefore, early intervention for pre-hypertension is essential to prevent declines in renal function in the general population.

The present study has some limitations. Firstly, the subjects in the present study were participants of an annual health check-up. Thus, the present population had a tendency to be health conscious, and, as a result, there is a possibility that a selection bias exists. However, the prevalence of pre-hypertension in the present study is at least similar to that of Japan as a whole. Secondly, the diagnosis of CKD in the present study depended on the value of creatinine or positive proteinuria on only one occasion. In 2002, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) provided guidelines that include a clear definition and classification for CKD. It defined CKD as the presence of kidney damage or GFR of $< 60$ mL/min/1.73 $m^2$ for $\geq 3$ months [38]. In previous epidemiological studies [6, 8, 23, 39], diagnosis of CKD had been determined in the same manner as in the present study. Thirdly, the analysis focused exclusively on Japanese residents and therefore might not be representative of non-Asian or non-Japanese subjects. There are several reports that have referred to a comparison of the epidemiology of CKD between Japanese and other ethnicities [40, 41], and its interpretation remains controversial. Thus, further research in other ethnic and cultural groups is needed to confirm the generalizability of the present findings. Finally, serum creatinine was measured in some cases using the Jaffe method and in those cases, the values were corrected in order to obtain an equivalent value for the enzymatic method using a modified equation, which may have altered the results of the present study.

In conclusion, pre-hypertension was significantly associated with an increased risk of CKD in a general Japanese population. The PAF for CKD in pre-hypertension was found to be comparable to that in Stages 1 and 2 hypertension. These results suggest that a public health strategy solely based on hypertension might be inappropriate, and that it is valuable to pay more attention to pre-hypertension in order to improve primary prevention of CKD.

## Supplementary data

Supplementary data is available online at http://ndt.oxfordjournals.org.

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# Evaluating home blood pressure in treated hypertensives in comparison with the referential value of casual screening of blood pressure: the Ohasama study

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***Objective*** **The target home blood pressure (BP) levels for antihypertensive treatment have not been fully investigated. We estimated home BP values that corresponded to the referential values of casual screening of BP using reduced major axis (RMA) regression for data from untreated and treated individuals in a general population.**

***Methods*** **The study included 2651 participants (778 treated) aged 20 years or above. The relationships between casual BP and home BP were examined using RMA regression to consider measurement errors. We calculated estimated home BP values that corresponded to casual BP using the regression equations.**

***Results*** **Although casual BPs and home BPs were significantly correlated (all: $P<0.0001$), the coefficients of determination in multiple regression were higher in untreated individuals than those in treated ones. When RMA regression was applied between casual BP ($x$) and morning home BP ($y$), the equations were expressed as $y=0.78x+26.55$ (systolic BP) and $y=0.84x+14.34$ (diastolic BP) in treated individuals and $y=0.79x+19.29$ (systolic BP) and $y=0.85x+9.94$ (diastolic BP) in untreated ones. The estimated home BPs corresponded to 140/90 mmHg of casual BP: 135.8/89.8 mmHg (morning), 132.2/86.6 mmHg (evening), and 133.9/87.8 mmHg (average) in treated individuals and 129.2/86.7 mmHg (morning), 127.8/84.8 mmHg (evening), and 128.2/85.2 mmHg (average) in untreated individuals.**

***Conclusion*** **We estimated the referential values of home BP in treated hypertensives using a regression model; however, further intervention studies on home BP are needed to clarify the target treatment goals of home BP.** *Blood Press Monit* **17:89–95 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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**Keywords: antihypertensive drugs, corresponding criteria, general population, home blood pressure monitoring, reduced major axis regression**

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## Introduction

Self-measurement of blood pressure (BP) at home (home BP) is highly reproducible and reliable and is known to be a useful clinical tool [1–4]. Home BP of at least 135/85 mmHg as the criterion for hypertension used in the guidelines [1,2,4–7] is being increasingly recognized, whereas the target home BP levels for antihypertensive treatment have not been fully investigated. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2009) [4] proposed provisional target control levels on the basis of home BP. The proposed target level was determined by simply applying the 5 mmHg difference between casual screening BP (casual BP) and home BP. In other words, the reference value of hypertension on the basis of casual BP is 140/90 mmHg and that for home BP is 135/85 mmHg. However, we previously reported that the relationships between casual BP and home BP in treated individuals were different from those in untreated ones [8]. Moreover, we could not avoid measurement errors of casual BP as well as home BP *per se* because BP fluctuates continuously. Previous reports [8,9] had used the least

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square regression to determine home BP, which corresponded to referential casual BP cutoff values; this model assumed that the independent variable had no errors. It is important that the analysis incorporates equal weighting of measurement errors to accurately determine target home BP values.

In this study, we aimed to identify the relationship between casual BP and home BP in treated hypertensives as well as in untreated individuals, and to estimate home BP values to correspond with the referential values of casual BP in treated hypertensives using a regression model that considers measurement errors. Information on BP was obtained from a general population in northern Japan.

## Methods

### Design and study population

The present study was a part of a study of a home BP measurement program in Ohasama, which is a rural community in Japan. The socioeconomic and demographic characteristics of this region [8] and the details of the selection of the study participants have been previously described [10]. From 1988 to 1995, we contacted all 5858 participants, 20 years or above, who lived in the four districts of Ohasama town. Individuals who were not at home during the normal working hours of the data collection nurses and those hospitalized or incapacitated were ineligible. Home BP data were obtained from 3047 individuals who collected their own data more than three times during the 4-week study period. This criterion was based on our previous observation that the average BP value obtained during the first 3 days was not significantly different from the values obtained for the entire study period [11]. Casual BPs were not obtained for 396 individuals who did not participate in annual health checkups. Therefore, the study population comprised 2651 individuals, including 1873 untreated individuals and 778 treated individuals. The study protocol was approved by the institutional review board of Tohoku University School of Medicine and by the Department of Health of the Ohasama Town Government. Informed consent was obtained from each individual.

### Blood Pressure measurement

Individuals were seated at rest for at least 2 min, and then casual BP was measured by well-trained nurses or technicians. In Ohasama, BPs were measured twice consecutively during the health checkup, using a semiautomatic BP measuring device (USM700F; Ueda Electronic Work Co. Ltd, Tokyo, Japan) on the basis of the microphone method [12].

We used the following procedure to determine the accuracy of home BP. Briefly, health education classes were conducted by physicians and well-trained public health nurses to inform the population of the significance of home BP recording and to teach them how to measure their own BP. Approximately 80% of household members living in Ohasama town attended the classes; public health nurses visited all of the remaining households to provide instructions on home BP measurement. After their ability to measure home BP was verified, individuals were asked to measure their own home BP in a sitting position every morning within 1 h after waking and after at least 2 min of rest, and to record the measurements for 4 weeks. If individuals were taking antihypertensive drugs, home BP was measured before medication was taken. Individuals were also asked to measure their BP every evening just before going to bed. These procedures have been described in detail in our previous report [13], and were developed according to the guidelines for self-monitoring of home BP [2]. Home BP was measured using a semiautomatic BP measuring device (HEM401C; Omron Healthcare Co. Ltd, Kyoto, Japan) on the basis of the cuff-oscillometric principle, which generates a digital display of systolic and diastolic BP [12].

The devices for the measurement of casual BP and home BP were calibrated before the start of the study [12,13]. All devices fulfilled the criteria set by the Association for the Advancement of Medical Instrumentation [14].

### Status of the use of antihypertensive medication

Individuals' characteristics including age, sex, BMI, smoking status, drinking status, use of antihypertensive medication, history of cardiovascular disease, diabetes mellitus, and hypercholesterolemia were obtained from the initial questionnaire survey and regular checkup results. We reviewed the medical records of Ohasama Hospital to confirm the treatment status of antihypertensive medication.

### Data analysis

Casual BP of each individual was the average of two consecutive casual BP readings. Morning home BP of each individual and evening home BP were separately averaged to reflect morning and evening home measurements. The average home BP of each individual was the average of the entire period of morning and evening home measurements.

Normotension was defined as casual BP < 140/90 mmHg and average home BP < 135/85 mmHg. White-coat hypertension was defined as casual BP ≥ 140/90 mmHg and average home BP < 135/85 mmHg. Masked hypertension was defined as casual BP < 140/90 mmHg and average home BP ≥ 135/85 mmHg. Sustained hypertension was defined as casual BP ≥ 140/90 mmHg and average home BP ≥ 135/85 mmHg. The definitions were based purely on individual's BP levels; we did not consider the treatment status in these definitions.

The correlations between casual BP and home BP were analyzed using Pearson's correlation coefficients. Untreated and treated individuals were analyzed separately.

**Table 1 Clinical characteristics of the participants**

| Variables | All participants | AHM | | *P* values |
|---|---|---|---|---|
| | | Untreated | Treated | |
| Number of participants (*n*, %) | 2651 | 1873, 70.7 | 778, 29.3 | |
| Age (years) | 57.6 ± 14.1 | 54.0 ± 14.0 | 66.4 ± 9.8 | <0.0001 |
| Male (%) | 1034, 39.0 | 722, 38.5 | 312, 40.1 | 0.5 |
| BMI (kg/m$^2$) | 23.5 ± 3.1 | 23.2 ± 3.0 | 24.1 ± 3.4 | <0.0001 |
| Past history of CVD (*n*, %) | 124, 4.7 | 27, 1.4 | 97, 12.5 | <0.0001 |
| Diabetes mellitus (*n*, %) | 239, 9.0 | 136, 7.3 | 103, 13.2 | <0.0001 |
| Hypercholesterolemia (*n*, %) | 700, 26.4 | 409, 21.8 | 291, 37.4 | <0.0001 |
| Current smoking (*n*, %) | 538, 20.3 | 406, 21.7 | 132, 17.0 | 0.006 |
| Current drinking (*n*, %) | 729, 27.5 | 520, 27.8 | 209, 26.8 | 0.7 |
| Systolic CBP (mmHg) | 130.6 ± 18.0 | 127.2 ± 17.0 | 138.8 ± 17.8 | <0.0001 |
| Diastolic CBP (mmHg) | 74.3 ± 11.3 | 73.0 ± 10.8 | 77.5 ± 11.9 | <0.0001 |
| Morning systolic HBP (mmHg) | 123.7 ± 15.2 | 119.1 ± 13.3 | 134.8 ± 13.9 | <0.0001 |
| Morning diastolic HBP (mmHg) | 74.3 ± 10.0 | 72.1 ± 9.2 | 79.4 ± 9.9 | <0.0001 |
| Evening systolic HBP (mmHg) | 121.7 ± 14.7 | 117.7 ± 13.4 | 131.3 ± 13.2 | <0.0001 |
| Evening diastolic HBP (mmHg) | 72.4 ± 9.6 | 70.5 ± 9.2 | 77.0 ± 9.1 | <0.0001 |
| Average systolic HBP (mmHg) | 122.7 ± 14.6 | 118.4 ± 13.0 | 133.0 ± 12.8 | <0.0001 |
| Average diastolic HBP (mmHg) | 73.3 ± 9.5 | 71.3 ± 8.9 | 78.2 ± 9.2 | <0.0001 |
| Normotension (*n*, %) | 1595, 60.2 | 1361, 72.7 | 234, 30.1 | <0.0001 |
| White coat hypertension (*n*, %) | 373, 14.1 | 239, 12.8 | 134, 17.2 | |
| Masked hypertension (*n*, %) | 300, 11.3 | 118, 6.3 | 182, 23.4 | |
| Sustained hypertension (*n*, %) | 383, 14.4 | 155, 8.3 | 228, 29.3 | |

Values are expressed as mean ± SD.
*P* values are calculated using Student's *t*-test (continuous variables) or Fisher's exact test (categorical variables).
The definitions of normotension, white-coat hypertension, masked hypertension, and sustained hypertension have been provided in the text.
AHM, antihypertensive medication; CBP, casual-screening blood pressure; CVD, cardiovascular disease; HBP, self-measurement of home blood pressure.

To compare the coefficients of determination, multivariable linear regression was performed to adjust for possible confounding factors: age, sex, obesity, smoking status, drinking status, diabetes mellitus, hypercholesterolemia, and past history of cardiovascular disease. To estimate home BP values from the relationships between casual and home BP using regression equations, the reduced major axis (RMA) regression, also known as standardized major axis [15,16], was applied (Web Appendix and Web Fig. 1, *http://www.cpt.med.tohoku.ac.jp/paper/supl/MBP200404*). RMA was preferred over the linear regression model because the mean values of both dependent ($y$) and independent ($x$) variables include any existing error – not only the equation error but also the measurement error. Consequently, there was no reason to preferentially weight deviations from the line in either the $y$ or the $x$ direction. RMA achieved equal weighting of these deviations because the major axis of the distribution of $x$ and $y$ variables was calculated using standardized data and then rescaled to the original axes. To compare the RMA estimates between treated individuals and untreated ones, differences in common slope were determined using a permutation test. Tests for differences in elevation were carried out using analysis of variance.

All data were expressed as mean (SD) unless otherwise stated. $P$ value less than 0.05 (two-sided test) was considered statistically significant. RMA analysis was applied using SMATR version 2.0 software (New South Wales, Australia) [16]. All other regression, variance, and mean comparison functions were performed using the SAS system (version 9.2; SAS Institute, Cary, North Carolina, USA).

## Results

The characteristics of individuals including BP information are shown in Table 1. For home BP among the study individuals, the mean number of measurements was 22.7 (7.3) in the morning and 23.6 (6.7) in the evening. The distribution of BP values for casual BP and home BP in treated individuals was significantly higher than that in untreated individuals. When individuals were classified into four groups on the basis of their average home BP and casual BP levels, normotension, white coat hypertension, masked hypertension, and sustained hypertension, the proportion in each group was significantly different between treated and untreated individuals.

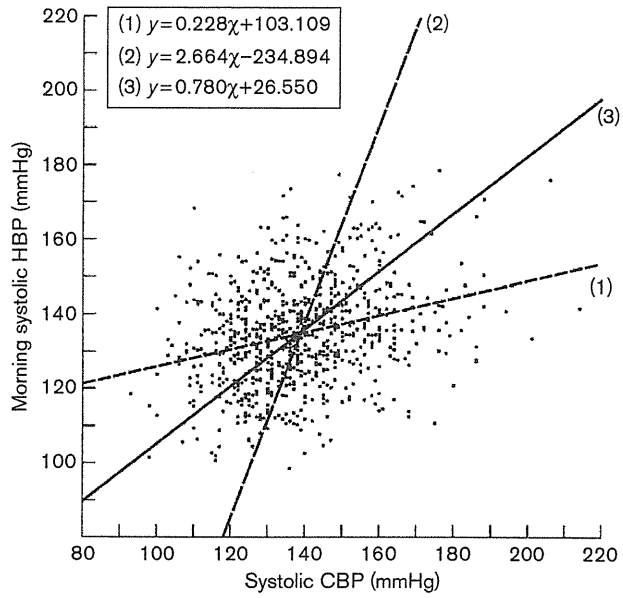
Casual BPs and home BPs were significantly correlated (all: $P < 0.0001$), and the correlations ($r$) with casual BP in untreated individuals were higher than those in treated ones (morning systolic BP: $r = 0.554$ vs. 0.293, evening systolic BP: $r = 0.536$ vs. 0.279, average systolic BP: $r = 0.561$ vs. 0.303, morning diastolic BP: $r = 0.497$ vs. 0.381, evening diastolic BP: $r = 0.477$ vs. 0.378, average diastolic BP: $r = 0.504$ vs. 0.396). As shown in Table 2, the coefficients of determination in the multiple regression model adjusted for possible confounding factors were also higher in untreated individuals than those in treated ones, and the strongest coefficient of determination ($R^2 = 0.435$) was observed between the casual systolic BP and morning home systolic BP.

**Table 2 Relationships between home blood pressure and casual blood pressure in treated or untreated individuals using multiple regression analysis**

| | $\beta$ | 95% CI | SE | $R^2$ |
|---|---|---|---|---|
| Morning HBP | | | | |
| Systolic | | | | |
| All participants | 0.331 | 0.305–0.357 | 0.013 | 0.445 |
| Treated | 0.202 | 0.151–0.253 | 0.026 | 0.178 |
| Untreated | 0.343 | 0.314–0.371 | 0.015 | 0.435 |
| Diastolic | | | | |
| All participants | 0.353 | 0.325–0.381 | 0.014 | 0.355 |
| Treated | 0.251 | 0.198–0.305 | 0.027 | 0.248 |
| Untreated | 0.350 | 0.318–0.382 | 0.016 | 0.367 |
| Evening HBP | | | | |
| Systolic | | | | |
| All participants | 0.320 | 0.294–0.346 | 0.013 | 0.397 |
| Treated | 0.194 | 0.145–0.244 | 0.025 | 0.132 |
| Untreated | 0.342 | 0.312–0.372 | 0.015 | 0.385 |
| Diastolic | | | | |
| All participants | 0.340 | 0.312–0.368 | 0.014 | 0.316 |
| Treated | 0.250 | 0.199–0.301 | 0.026 | 0.192 |
| Untreated | 0.341 | 0.308–0.375 | 0.017 | 0.314 |
| Average HBP | | | | |
| Systolic | | | | |
| All participants | 0.326 | 0.301–0.351 | 0.013 | 0.444 |
| Treated | 0.198 | 0.151–0.246 | 0.024 | 0.164 |
| Untreated | 0.343 | 0.315–0.371 | 0.014 | 0.433 |
| Diastolic | | | | |
| All participants | 0.346 | 0.320–0.373 | 0.014 | 0.358 |
| Treated | 0.250 | 0.201–0.300 | 0.025 | 0.236 |
| Untreated | 0.345 | 0.314–0.376 | 0.016 | 0.364 |

Adjusted factors: age, sex, obesity, smoking status, drinking status, diabetes mellitus, hypercholesterolemia, and past history of cardiovascular disease.
Dependent variables are home blood pressure (BP), independent variables are casual BP.
CI, confidence interval; HBP, self-measurement of home BP; $R^2$, coefficient of determination; $\beta$, regression coefficient.

**Fig. 1**




Regression lines for three different methods; relationships between casual systolic blood pressure (BP) and morning home systolic BP in 778 treated individuals. (1) Linear regression model using casual BP as an independent variable; (2) linear regression model using home BP as an independent variable; (3) reduced major axis regression model. CBP, casual-screening BP; HBP, self-measurement of home BP.

The regression lines among treated individuals on the basis of (a) the linear regression model using casual BP as an independent variable, (b) the linear regression model using morning home BP as an independent variable, and (c) the RMA model are demonstrated in Figure 1 and the Web in Figure 2 (*http://www.cpt.med.tohoku.ac.jp/paper/supl/MBP200404*). Each of the three regression slopes was significantly different from the others ($P < 0.0001$). These significant differences ($P < 0.0001$) were also observed irrespective of BP information, that is, systolic and diastolic BP or morning, evening, and average home BP, and of treatment status.

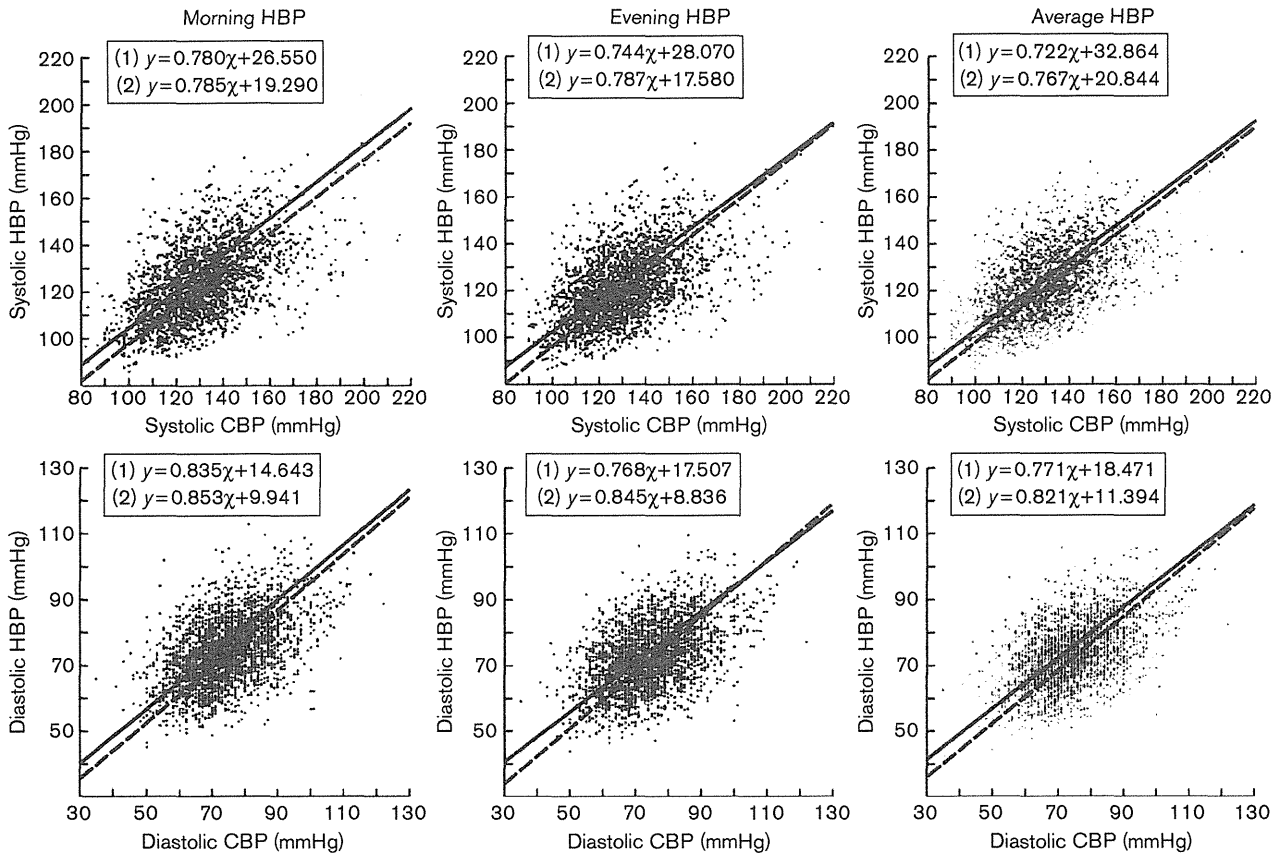
The distributions and results of RMA regression analysis between casual BP and each home BP in treated individuals as well as untreated ones are shown in Table 3 and Figure 2. Regression slopes determined using the RMA method for the relation between casual BP and home BP in treated individuals were not significantly different from the slopes in untreated ones for systolic and diastolic BP, except for evening diastolic BP. In the comparison of adjusted intercept, the values for treated individuals were markedly higher (morning systolic BP: 6.6 mmHg, evening systolic BP: 4.6 mmHg, average systolic BP: 5.9 mmHg, morning diastolic BP: 3.4 mmHg, average diastolic BP: 3.3 mmHg) than those for untreated ones.

**Table 3 Relationships between casual blood pressure and home blood pressure in treated or untreated individuals using reduced major axis regression analysis**

| | Untreated | | Treated | | |
|---|---|---|---|---|---|
| | | 95% CI | | 95% CI | *P* values |
| Morning HBP | | | | | |
| Systolic BP | | | | | |
| Slope | 0.785 | 0.756–0.815 | 0.780 | 0.729–0.835 | 0.9 |
| Intercept | 19.29 | 15.48–23.10 | 26.55 | 19.17–33.94 | <0.001 |
| Diastolic BP | | | | | |
| Slope | 0.853 | 0.820–0.887 | 0.835 | 0.783–0.891 | 0.6 |
| Intercept | 9.94 | 7.46–12.42 | 14.64 | 10.36–18.93 | <0.001 |
| Evening HBP | | | | | |
| Systolic BP | | | | | |
| Slope | 0.787 | 0.758–0.818 | 0.744 | 0.695–0.796 | 0.2 |
| Intercept | 17.58 | 13.70–21.45 | 28.07 | 21.00–35.14 | <0.001 |
| Diastolic BP | | | | | |
| Slope | 0.845 | 0.812–0.879 | 0.768 | 0.720–0.820 | 0.02 |
| Intercept | 8.84 | 6.34–11.33 | 17.51 | 13.56–21.46 | <0.001 |
| Average HBP | | | | | |
| Systolic BP | | | | | |
| Slope | 0.767 | 0.738–0.796 | 0.722 | 0.673–0.770 | 0.1 |
| Intercept | 20.84 | 17.15–24.54 | 32.86 | 26.09–39.64 | <0.001 |
| Diastolic BP | | | | | |
| Slope | 0.821 | 0.788–0.853 | 0.771 | 0.721–0.820 | 0.09 |
| Intercept | 11.39 | 9.024–13.76 | 18.47 | 14.57–22.38 | <0.001 |

Dependent variables are home blood pressure (BP) and independent variables are casual BP. *P* values were calculated using the permutation test (slope) or analysis of variance (intercept).
CI, confidence interval; HBP, self-measurement of home BP.

**Fig. 2**




Relationships between casual BP and home BP in treated or untreated individuals; results of reduced major axis (RMA) regression analysis. (1) The solid line indicates the RMA regression line in the treated group; (2) dotted line indicates the RMA regression line in the untreated group. *x*-axis: casual BP, *y*-axis: home BP. CBP, casual-screening BP; HBP, self-measurement of home BP.

On the basis of RMA regression analysis, estimated home BP values in untreated individuals that corresponded to the cutoff value of casual BP hypertension (140/90 mmHg) were 129.2/86.7 [95% confidence interval (95% CI): 128.5/86.2–129.8/87.1] mmHg for morning home BP, 127.8/84.8 (95% CI: 127.2/84.4–128.4/85.3) mmHg for evening home BP, and 128.2/85.2 (95% CI: 127.6/84.8–128.8/85.7) mmHg for average home BP. Estimated home BP values in treated hypertensives, which corresponded to the control levels of casual BP (140/90 mmHg) proposed in ESH-ESC 2007 [3], were 135.8/89.8 (95% CI: 134.5/88.9–137.1/90.7) mmHg for morning home BP, 132.2/86.6 (95% CI: 131.0/85.8–133.5/87.5) mmHg for evening home BP, and 133.9/87.8 (95% CI: 132.6/87.0–135.2/88.7) mmHg for average home BP.

According to the ESH-ESC 2007 Guidelines [3], we further carried out analyses using home BP values measured in the initial 7 days (Web Tables 1–3, *http://www.cpt.med.tohoku.ac.jp/paper/supl/MBP200404*). The levels of casual BP and home BP in the initial 7 days are higher than those in the entire period, although the relationships between them were essentially the same.

## Discussion

In the present study, we estimated home BP values using casual BP values in treated hypertensives using the RMA regression model.

The regression slopes between casual BP and home BP using casual BP for the independent variable are significantly different from the slopes using home BP for the independent variable when calculated using the least square linear regression model as shown in Figure 1 in the current study. BP fluctuates continuously in a 24-h period, and the variability is influenced by neural, mechanical, and humoral factors [17]. Casual BP readings tend to reflect the patient's status at a particular time point and may include measurement errors. Moreover, although home BP has superior reproducibility and reliability [18,19], home BP measurement is still prone to measurement errors. We have previously reported [11] long-term fluctuation in home BP measurements over an average of 14 times (SD of systolic BP = 8.8 ± 3.1 mmHg, and SD of diastolic BP = 6.6 ± 2.3 mmHg). Because both casual BP and home BP show natural variations and

measurement errors, RMA regression would be appropriate for the estimation of home BP values corresponding to casual BP values.

Home BP was significantly related to casual BP irrespective of treatment status, similar to previous reports [11,20]. In addition, casual BP and home BP values in treated individuals were more similar than those in untreated ones. One of the possible reasons for this is the duration of action of antihypertensive drugs used in 1992 (< 12 h for a twice-a-day prescription and <24 h for a once-a-day prescription) [21]. The proportion of masked hypertension in treated individuals is higher than that in untreated ones. This factor would also be influential along with an insufficient duration of action of antihypertensive drugs.

Another possibility is that treated hypertensives are accustomed to medical settings and may show less reaction, or in other words, a lower BP in a medical setting [22].

The increased variability [23,24] in vasomotor activity because of atherosclerosis and arteriosclerosis and the diminished baroreflex sensitivity associated with increased arterial stiffness may also be a reasonable possibility. Antihypertensive treatment *per se* is a kind of marker for greater severity of hypertension. Hypertensive patients are exposed to the risk of atherosclerosis for long periods of time both before and during therapy.

According to several guidelines [1,2,4–7], the home BP value of 135/85 mmHg is adopted as a criterion for the diagnosis of hypertension on the basis of worldwide cross-sectional studies [9,25] and the prospective study in Ohasama [26]. In contrast, the ESH-ESC 2007 [3] proposes 130–135/85 mmHg as the criterion for hypertension on the basis of home BP, with a 5 mmHg range in the systolic BP. In the present study, home BP values that corresponded to casual BP values for hypertension (140/90 mmHg) were lower than 140/90 mmHg irrespective of antihypertensive treatment status; however, home BP values that corresponded to casual BP (140/90 mmHg) were different by their treatment status. The previous studies cited in guidelines included untreated individuals [9,26] or both untreated and treated individuals [25]. The estimated home BP values in untreated individuals corresponded to the cutoff value of hypertension in casual BP (140/90 mmHg) in the present study (morning BP: 129.2/86.7 mmHg, evening BP: 127.8/84.8 mmHg, and average home BP: 128.2/85.2 mmHg). These values are similar to those of previous studies [27–30] and recent guidelines. Moreover, this study demonstrated that the estimated home BP values in treated individuals corresponded to the general target BP values for casual BP in ESH-ESC 2007 [3].

This study must be interpreted within the context of potential limitations. First, we measured casual BP and home BP using the auscultatory USM700F and the oscillometric HEM401C, respectively [12]. The casual and home BPs were therefore recorded using different techniques when consensus on formal and standardized validation of devices for BP measurement was still growing [31]. Second, several guidelines proposed treatment target BP values by classifying individuals on the basis of factors such as age, comorbidities, and past history; however, the number was not sufficient, especially among treated individuals in this study, to provide reliable cutoff values using such a classification. Third, our results were not based on the evidence of prognosis such as morbidity of cardiovascular diseases and cardiovascular mortality. In our study, the correlations between casual BP and home BP were comparably low in treated hypertensives. The results of an intervention study based on home BP, which will be available in the near future, should help to establish target control levels of home BP in treated hypertensives [32]. Fourth, the usage of antihypertensive medications in 1992 may have influenced our results. Recently, new long-acting calcium channel blockers and new kinds of antihypertensive drugs such as angiotensin II receptor blockers and direct renin inhibitors have been marketed. The relationships between casual BP and home BP on the basis of these new antihypertensive agents should be investigated in the future.

In conclusion, we estimated the reference values of home BP in treated hypertensives in the present study. However, the relationships between casual BP and home BP in treated individuals are lower than those in untreated individuals according to the statistical analysis ($r$-values). Further prospective studies and interventional trials specifically designed to compare the predictive power between home BP and casual BP are needed to clarify the reference values of home BP in treated individuals.

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### Conflicts of interest

There are no conflicts of interest.

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ORIGINAL CONTRIBUTIONS

# Aldosterone-to-Renin Ratio as a Predictor of Stroke Under Conditions of High Sodium Intake: The Ohasama Study

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**BACKGROUND**

Aldosterone is thought to have deleterious effects on the cardiovascular system. The aldosterone-to-renin ratio (ARR) is more reproducible than aldosterone levels alone and could be an index for inappropriate aldosterone secretion or activity. We previously reported the apparent relation between ARR and hypertension in subjects with high sodium intake. This prospective study investigated the risk of ARR for a first stroke in a general population stratified by sodium intake.

**METHODS**

We obtained plasma renin activity (PRA) and plasma aldosterone concentrations (PAC) for 883 participants aged ≥35 years not receiving antihypertensive treatment in the general population of Ohasama (mean age: 59.0 ± 11.3 years; 65.6% women).

**RESULTS**

Over a mean of 10.9 follow-up years, 45 strokes occurred. The median PRA, PAC, and ARR were 1.2 ng/ml/h, 6.4 ng/dl, and 5.3 ng/dl per ng/ml/h, respectively. Using Cox regression, we computed hazard ratios adjusted for sex, age, body mass index (BMI), and systolic blood pressure. No association between logARR and stroke was observed in subjects overall. However, in subjects with high sodium intake (≥median of 4,058 mg/day (salt equivalent, 10.5 g/day)), each 1 s.d. increase in logARR was associated with an increased hazard ratio for stroke (hazard ratio: 1.49, $P = 0.04$). No significant association was observed in subjects with low sodium intake ($P = 0.7$). When we repeated all the analyses using logPRA or logPAC, no significant associations were found.

**CONCLUSION**

These results suggest that high ARR, that is, relative aldosterone excess, is a predictor for stroke under conditions of high sodium intake.

***Keywords:*** *aldosterone-to-renin ratio; blood pressure; hypertension; relative aldosterone excess; salt-sensitive hypertension; sodium intake; stroke*

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Aldosterone is thought to have deleterious effects on the cardiovascular system through several mechanisms, including cardiovascular remodeling, endothelial dysfunction, vascular inflammation, and atherosclerosis.[1,2] In fact, patients with primary aldosteronism have an increased prevalence of stroke compared with those with essential hypertension.[3] Recently, Tomashitz *et al.*[4] showed that, even in the absence of primary aldosteronism, a higher plasma aldosterone concentration (PAC) is strongly associated with an increased risk for stroke mortality. However, their study[4] was conducted only in a special population (patients referred for coronary angiography).

The aldosterone-to-renin ratio (ARR) is believed to be more reproducible than aldosterone levels alone and could be an index for inappropriate aldosterone secretion or activity and salt sensitivity.[5,6] Previously, we reported that not PAC but ARR was significantly associated with a high prevalence of hypertension.[7] Furthermore, the relation between

ARR and hypertension was strengthened for subjects with high sodium intake.[7] Therefore, it could be hypothesized that ARR may be a more accurate predictor of stroke than PAC and that the association between ARR and stroke risk may be more remarkable under conditions of high sodium intake.

The objective of this prospective study was to investigate the risk of ARR for stroke in a general population stratified by sodium intake.

## METHODS

*Design.* This investigation was a part of the Ohasama study. Socioeconomic and demographic characteristics of this region and details of the study project have been described previously.[8,9] The institutional review boards of Tohoku University School of Medicine and the Department of Health of the Ohasama Municipal Government approved the study.

*Study population.* In Japan, annual health checkups are available for farmers, the self-employed, pensioners, and dependents aged >35 years. In 1997, the population of Ohasama included 7,318 subjects. Of those, 4,992 were ≥35 years, and 2,719 were eligible for a health checkup that year. Subjects ($n$ = 888) who did not undergo a health checkup were ineligible. Of the 1,831 eligible individuals, 1,346 subjects (74%, mean age: 61.5 ± 11.2 years; 65% women) gave informed consent and participated in the present study. For the current analysis, we excluded 34 subjects due to insufficient data on nutrient intake and 42 subjects due to a previous history of stroke at entry. Furthermore, we excluded 339 subjects treated with antihypertensive drugs because of the effects of antihypertensive medications on the renin–angiotensin system.[10] To eliminate patients with primary aldosteronism completely, we further excluded 48 subjects who had ARR ≥20 ng/dl per ng/ml/h.[11] The remaining 883 subjects were followed.

*Data collection.* Blood for measurement of PRA (ng/ml/h) and PAC (ng/dl) was drawn with subjects in a sitting position after ~30 min rest, between 9 and 11 AM or between 1 and 3 PM; most subjects had not fasted. Blood was collected in chilled EDTA tubes, and measured by radioimmunoassay (SRL, Tokyo, Japan) with the SPAC-S Aldosterone Kit (TFB, Tokyo, Japan) for PAC and with the plasma renin activity (PRA) "TFB" (TFB) for PRA. The interassay coefficients of variation were 10.5% at 1.5 ng/ml/h for PRA and 4.55% at 8.98 ng/dl for PAC. The intra-assay coefficients of variation were 7.78% at 1.25 ng/ml/h for PRA and 4.81% at 8.95 ng/dl for PAC. The lower limits of detections were 0.1 ng/ml/h for PRA and 1.0 ng/dl for PAC. If the values were less than the lower limits, PRA and PAC were considered equal to 0.1 ng/ml/h and 1.0 ng/dl, respectively. Hypercholesterolemia was defined as total cholesterol ≥5.68 mmol/l (≥220 mg/dl), use of medication for hypercholesterolemia, and/or a history of hypercholesterolemia. Diabetes mellitus was defined as a fasting blood glucose level ≥7.0 mmol/l (≥126 mg/dl), random blood glucose level ≥11.11 mmol/l (≥200 mg/dl), hemoglobin $A_{1c}$ level ≥6.5%, use of medication for diabetes, and/or a history of diabetes mellitus. Blood pressure was measured twice consecutively during the health checkup. Measurements were taken by nurses or technicians at local medical centers using an automatic USM-700F sphygmomanometer[12] (UEDA Electronic Works, Tokyo, Japan) based on the Korotkoff sound technique. All measurements were taken with subjects in the sitting position, after a minimum 2-min rest. The mean of the two readings was defined as the blood pressure. Estimated glomerular filtration rate was estimated from the serum creatinine using a Japanese equation.[13]

*Sodium and potassium intakes.* A standardized method was used to calculate food consumption and related nutrients from data obtained in a Japanese version of the food-frequency questionnaire, which asked about the average frequency of consumption of each food during the previous year.[14] We previously confirmed that the food-frequency questionnaire is reasonably reproducible and comparable with diet records, taking into account seasonal variations in food consumption.[14,15] We then estimated sodium and potassium intakes, which were adjusted for total energy intake using the residual method. Sodium or potassium intakes were regressed on total energy, and residuals from the regression line were defined as sodium or potassium intakes adjusted by the residual method.[16] To assess the reproducibility of the food-frequency questionnaire in a previous study, we calculated correlation coefficients between two food-frequency questionnaires completed with a 1-year interval.[14] The correlation coefficient between the two assessments of sodium chloride was 0.70 after adjustment for age, gender, and total energy.[14]

*Follow-up and outcome.* Residence in Ohasama (as of 30 November 2010) was confirmed by the residents' registration cards. In Japan, these cards are considered accurate and reliable, because they are used for pensions and social security benefits. The incidence of stroke until 30 November 2010, was determined by reviewing the Stroke Registration System of Iwate Prefecture, death certificates, National Health Insurance receipts, and questionnaires sent to each household at the time of health-checkup. This information was then confirmed by checking the medical charts of Ohasama Hospital, which is the only hospital in the town and where ≥90% of subjects had regular checkups. Almost all stroke cases were admitted to Ohasama Hospital, where the diagnosis was confirmed by computed tomography and/or magnetic resonance imaging of the brain. The diagnostic criteria of stroke subtypes were based on the Classification of Cerebrovascular Disease III of the National Institute of Neurological Disorders and Stroke.[17] We defined "cerebral infarction" as ischemic stroke and defined "intracerebral hemorrhage" and "subarachnoid hemorrhage" as hemorrhagic stroke. Transient ischemic attacks were not included in stroke.

*Statistical analysis.* To analyze the relationship between tertiles of ARR and subjects characteristics, we compared means and proportions using analysis of variance and the $\chi^2$ test for uni-