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Invited Review

Prognostic Significance of Home and Ambulatory Blood Pressure: Summary of Longitudinal Evidence from the Ohasama Study

Takayoshi Ohkubo[1,2] and Michihiro Satoh[3]

[1]Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan
[2]Tohoku Institute for Management of Blood Pressure, Sendai, Miyagi, Japan
[3]Division of Public Health, Hygiene and Epidemiology, Faculty of Medicine, Tohoku Medical and Pharmaceutical University, Sendai, Miyagi, Japan

The Ohasama Study is a long-term prospective cohort study of the general population in the town of Ohasama (currently, Hanamaki city) in Iwate Prefecture, Japan, that was started in 1986. Ohasama is a typical farming village in the Tohoku region that consists of part-time farming households that cultivate mainly fruit trees. At the start of the study, the prevention of hypertension, a main cause of strokes, was taken to be an important issue in public health activities because of the many people who died or needed care as a result of strokes in Ohasama. A home blood pressure measurement program was then begun with the aim of preventing hypertension while increasing a sense of solidarity among community residents and the awareness that "one must protect one's own health." As a result, this project became the world's first community-based epidemiological study using home blood pressure, as well as 24-hour ambulatory blood pressure, for which measurements were also initiated. In the 1990s, the Ohasama Study reported a linear "the lower, the better" relationship between out-of-office blood pressure and cardiovascular risk. To date, we have accumulated advanced evidence regarding the clinical significance of out-of-office blood pressure. Those have contributed to hypertension management guidelines around the world. This article summarizes the results of representative long-term follow-up studies of the Ohasama Study.

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Introduction

The Ohasama Study is a long-term prospective cohort study of the general population in the town of Ohasama (currently, Hanamaki city) in Iwate Prefecture, Japan, that was started in 1986. Ohasama, located 30 km south of Morioka, is a typical farming village in the Tohoku region that consists of part-time farming households that cultivate mainly fruit trees (Fig. 1). At the start of the study, the prevention of hypertension, a main cause of strokes, was taken to be an important issue in public health activities because of the many people who died or needed care as a result of strokes in Ohasama. A home blood pressure measurement program was then begun with the aim of preventing hypertension while increasing a sense of solidarity among community residents and the awareness that "one must protect one's own health." As a result, this project became the world's first community-based epidemiological study using home blood pressure, as well as 24-hour ambulatory blood pressure, for which measurements were also initiated. This fact allows us to evaluate the long-term prognostic values of out-of-office blood pressure (Asayama et al. 2014a). Statements on the clinical significance of home blood pressure and ambulatory blood pressure based on the results of the Ohasama Study have been included not only in the guidelines of the Japanese Society of Hypertension (JSH) (Ogihara et al. 2009; Shimamoto et al. 2014; Umemura et al. 2019), but also in guidelines in various western and other countries, including the 1997 Joint National Committee (JNC) recommendations (JNC 1997), 1999 World Health Organization-International Society of Hypertension (WHO-ISH) hypertension guidelines (WHO-

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Correspondence: Takayoshi Ohkubo, M.D., Ph.D., Department of Hygiene and Public Health, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan.
e-mail: tohkubo@med.teikyo-u.ac.jp

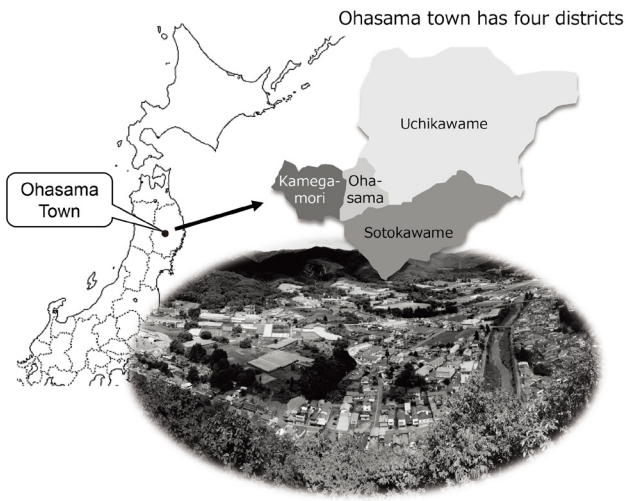

Fig. 1. Ohasama town.

ISH 1999), and the 2003 European Society of Hypertension-European Society of Cardiology Guidelines Committee (ESH-ESC) hypertension guidelines (ESH-ESC Committee 2003). This is a rare example of epidemiological data from Japan forming the basis for international guidelines. The JSH 2014 guidelines state clearly for the first time that "diagnosis with home blood pressure should be given precedence when there is a difference between office blood pressure and home blood pressure" (Shimamoto et al. 2014). A similar description was also included in JSH 2019 (Umemura et al. 2019). The home blood pressure data collected in the Ohasama Study and other research in Japan have made a significant background contribution to this.

This article summarizes the results of representative long-term follow-up studies of the Ohasama Study. The term "office blood pressure" used in the following is a general term for blood pressure measured in a healthcare environment, such as outpatient settings, medical examinations, and health checkups. The basic findings in the Ohasama Study have been reviewed in the past (Ohkubo 2007). Meanwhile, in the years that followed, we have been accumulating new evidence by varying outcomes and using new blood pressure indices.

Results of Long-Term Follow-up Studies of Home Blood Pressure

a. The predictive ability of home blood pressure is superior to that of office blood pressure for cerebrovascular and cardiovascular mortality

A linear "the lower, the better" relationship was found between home blood pressure and cerebrovascular and cardiovascular mortality risk. When home blood pressure and office blood pressure were simultaneously included in a Cox proportional hazards model as continuous variables, only home blood pressure was significantly related to mortality risk. This high predictive ability of home blood pressure was derived not only from the large number of measurement points (20 times), but it also had a higher predictive ability than office blood pressure even when using only the mean value of two early blood pressure measurements (Ohkubo et al. 1998b).

b. Home blood pressure of ≥ 135/85 mmHg is hypertension

There was a J-shaped relationship between home blood pressure and all-cause mortality. In the high blood pressure range, there were many cerebrovascular and cardiovascular deaths, and in the low blood pressure range there were many non-cerebrocardiovascular deaths. These J-shaped relationships were fitted to a second-degree equation, and standard values were obtained from the point where the relative risk increased significantly parametrically. Values of ≥ 135/85 mmHg were taken as high blood pressure and values below that as normal blood pressure (Tsuji et al. 1997). This suggests that the target for decreasing blood pressure when home blood pressure is used in the control of blood pressure should be ≤ 135/85 mmHg.

c. With home blood pressure, systolic blood pressure is more important than diastolic blood pressure

Using the above reference values, isolated systolic hypertension with home blood pressure was defined as systolic blood pressure of ≥ 135 mmHg and diastolic blood pressure of 85 mmHg. The cerebrovascular and cardiovascular mortality risk in people with isolated systolic hypertension, like that of people with systolic and diastolic hypertension, was about two times higher than that of normotensive people. However, the risk in people with isolated diastolic hypertension was no different from that of normotensive people. This suggested that, when controlling blood pressure using home blood pressure, more weight should be placed on systolic blood pressure (Hozawa et al. 2000).

d. The predictive ability of home blood pressure for stroke is superior to that of office blood pressure

There was a linear "the lower, the better" relationship between home blood pressure and the risk of all strokes, cerebral infarction, and cerebral hemorrhage, and the prognostic ability was superior to that of office blood pressure (Fig. 2) (Ohkubo et al. 2004a, b). While one reason for this high predictive ability of home blood pressure lies in the large number of measurements (Ohkubo et al. 2004a), this was not the only explanation, and even the first measurement value showed superior predictive ability to the mean of two measurements of office blood pressure (Ohkubo et al. 2004a).

e. High home heart rate is a risk for cerebrovascular and cardiovascular mortality

Heart rate was also recorded during home blood pressure measurements, and as for home blood pressure values, home heart rate also had the advantage of being measured

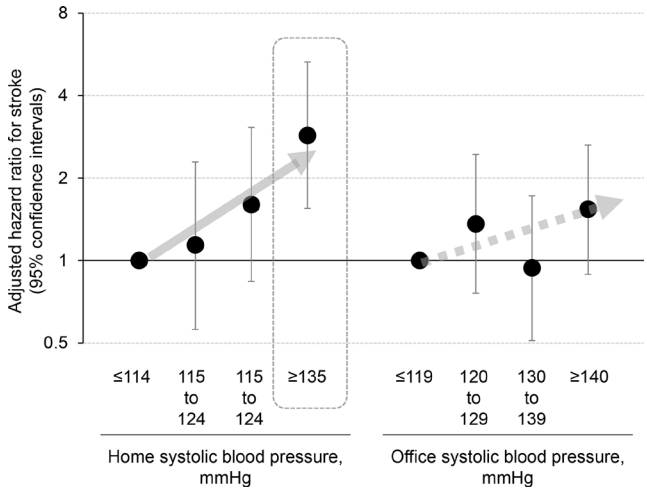

Fig. 2. Home or office blood pressure and stroke risks.
The data in the Ohasama report (Ohkubo et al. 2004a) was used. The hazard ratios were adjusted for age, sex, smoking status, the use of antihypertensive medication, history of heart disease, hypercholesterolemia, and diabetes.

over the long-term under stable conditions. In fact, this home heart rate was a predictor of cerebrovascular and cardiovascular mortality independent of home blood pressure (Hozawa et al. 2004).

f. The accuracy of stroke prediction is increased by combining home blood pressure and hypertension severity classification

The accuracy of stroke risk predictions was improved by combining the hypertension severity classifications advocated in the JNC-7, 2003 ESH-ESC and 2004 JSH guidelines with home blood pressure (Asayama et al. 2004, 2005, 2008). That accuracy was improved even more when the more detailed ESH-ESC classifications were used (Asayama et al. 2005).

g. People with white-coat hypertension have a higher risk of developing true hypertension after eight years than people with true normotension

Follow-up of people with white-coat hypertension, that is, normal home blood pressure and high office blood pressure, showed that nearly half (47%) developed true hypertension over a mean observation period of eight years. This was significantly higher than the rate in those who had true normotension at the start of the survey (22%) (Ugajin et al. 2005). Recent findings also showed that office blood pressure, as a continuous variable, was associated with the risk of developing hypertension as detected by home blood pressure measurements among normotensive participants (Satoh et al. 2022; Nakayama et al. 2023).

h. Both morning home blood pressure and evening home blood pressure have a higher predictive ability for stroke than office blood pressure, but morning blood pressure has superior predictive ability in people taking antihypertensives

Like morning home blood pressure, the indicators of both evening home blood pressure and morning-evening mean home blood pressure showed higher predictive abilities for stroke than did office blood pressure (Asayama et al. 2006). However, in an analysis of people taking antihypertensive medication, the risk of stroke was very high in the morning hypertension group, which suggested that an insufficient decline in blood pressure in the morning is a risk factor for stroke. Morning home blood pressure based classification showed a linear increase in stroke risk even among treated individuals whereas a linear association was not observed when based on office blood pressure (Yasui et al. 2010).

i. Great day-to-day variability in blood pressure and heart rate indicates a high risk for death from cerebrovascular and cardiovascular disease

When the standard deviation (SD) of home blood pressure and heart rate measured a total of 20 times, once each morning, for an average of 20 days was taken as an indicator of day-to-day variability, increases in both day-to-day variability in blood pressure and day-to-day variability in heart rate were related to risk of death from cerebrovascular or cardiovascular disease independently of blood pressure and heart rate levels (Kikuya et al. 2008). Among men, the association between day-to-day variability and stroke risk was clearer in ever smokers than in never smokers (Hashimoto et al. 2012).

j. Home systolic blood pressure has a better predictive ability for stroke than pulse pressure

Systolic blood pressure in home blood pressure measurements was shown to have a higher predictive value for stroke than pulse pressure (Inoue et al. 2009). This suggested that, when using home blood pressure in the control of blood pressure, greater weight should be placed on systolic blood pressure.

k. High home double product levels predict mortality risk

A high home double product, which is the product of home systolic blood pressure and heart rate, significantly predicted mortality risk (Inoue et al. 2012).

l. Home blood pressure level is a better prognostic factor than day-to-day variability in home blood pressure

A blood pressure variability index based on home blood pressure represented the risk of stroke or cardiovascular disease mortality, but its effectiveness did not exceed that of home blood pressure level (Asayama et al. 2013) (Fig. 3).

m. An increase in day-to-day home blood pressure variability predicts future cognitive decline

Day-to-day variability in home blood pressure predicted future cognitive decline independent of home blood pressure (Matsumoto et al. 2014). This association was independent from home blood pressure levels (Fig. 4).

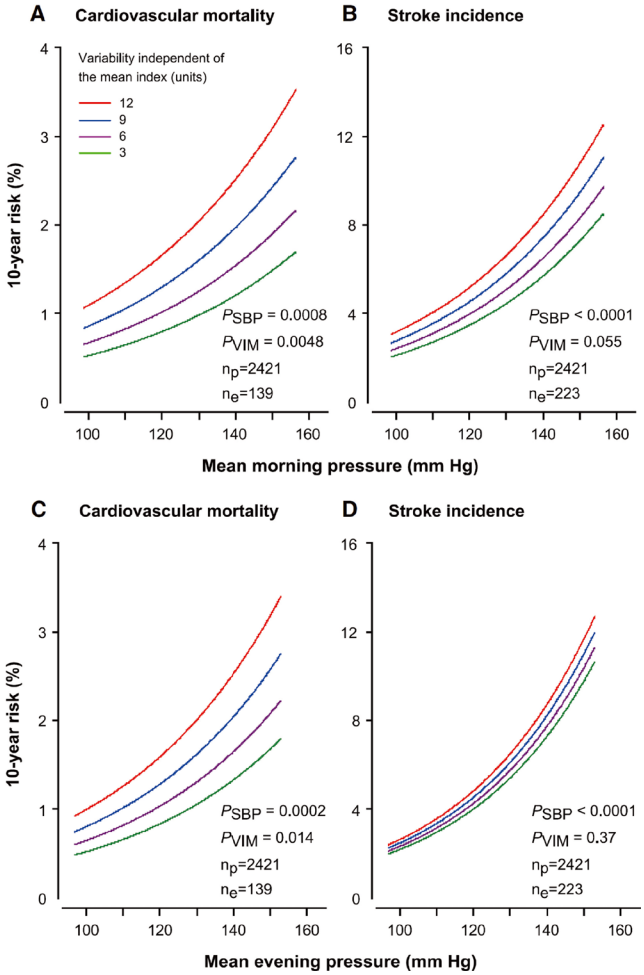

Fig. 3. Absolute 10-year risk of cardiovascular mortality (A and C) and stroke incidence (B and D) in relation to the mean level of systolic blood pressure measured at home in the morning (A and B) or evening (C and D) in 2421 participants.
The analyses were standardized to the distributions (mean or ratio) of sex, age, body mass index, heart rate, smoking and drinking, total cholesterol, diabetes mellitus, history of cardiovascular diseases, and treatment with antihypertensive drugs. In each panel, mean systolic blood pressure along the horizontal axis (SBP) covers the 2.5th to 97.5th percentile interval. Four continuous lines represent the risk independently associated with variability independent of the mean (VIM) equal to 3, 6, 9, and 12 units. *P* values are for the independent effect of SBP (P_{SBP}) and VIM (P_{VIM}). n_p and n_e indicate the number of participants at risk and the number of events.
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n. The predictive ability for stroke of home blood pressure is high regardless of impaired physical function

In older adults aged 60 years or more, home blood pressure had a higher predictive ability for stroke than office blood pressure regardless of whether or not the individual had impaired physical function (Murakami et al. 2017).

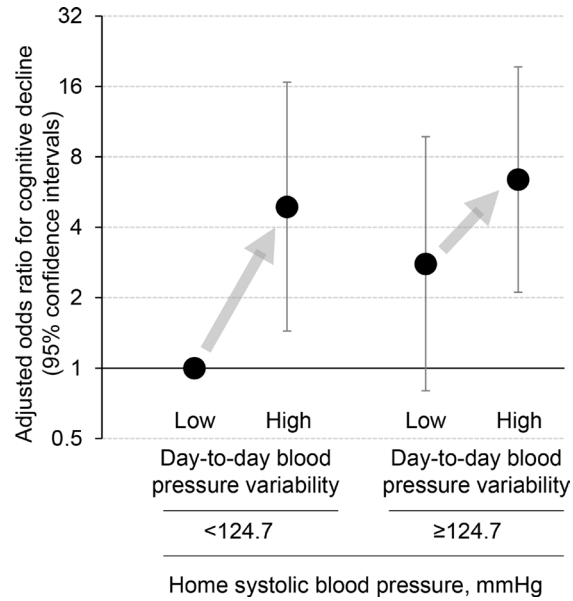

Fig. 4. Adjusted odds ratio for cognitive decline according to home systolic blood pressure and day-to-day systolic blood pressure variability.
The data in the Ohasama report (Matsumoto et al. 2014) was used. The odds ratios were adjusted for sex, age, history of cardiovascular disease, low level of education, baseline Mini-Mental State Examination score < 27, and follow-up duration.

o. Partial white-coat or masked hypertension is associated with a high risk for stroke

Partial white-coat hypertension and masked hypertension identified from measurements of both home blood pressure and 24-hour blood pressure were both associated with a high risk of stroke (Fig. 5) (Satoh et al. 2016). Individuals with partial WCHT or partial MHT can be detected only by both home and ambulatory blood pressure measurements.

Follow-up Study Using 24-Hour Ambulatory Blood Pressure

a. The predictive ability of 24-hour ambulatory blood pressure for cerebrovascular and cardiovascular mortality and stroke is superior to that of office blood pressure

There was a linear "the lower, the better" relationship between 24-hour ambulatory blood pressure and cerebrovascular and cardiovascular mortality risk (Ohkubo et al. 1997). When 24-hour blood pressure and office blood pressure were simultaneously included in a Cox proportional hazards model as continuous variables, only 24-hour blood pressure was significantly related to cerebrovascular and cardiovascular mortality risk. There was also a similar linear relationship between 24-hour ambulatory blood pressure and initial stroke risk, and when 24-hour blood pres-

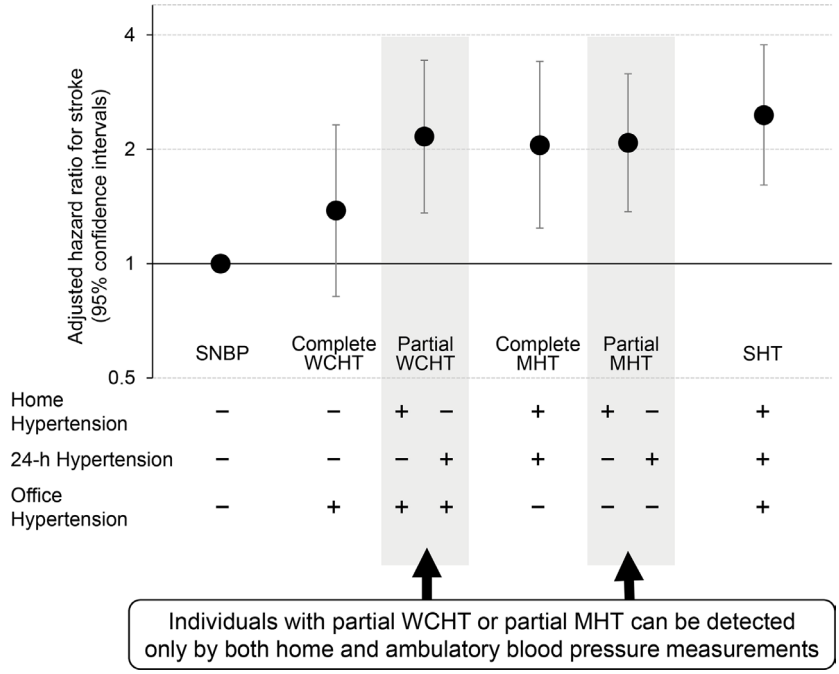

Fig. 5. The stroke risks according to home, 24-h, and office hypertension categories.
The data in the Ohasama report (Satoh et al. 2016) was used. The hazard ratios were for sex, age, body mass index, current smoking, alcohol consumption, diabetes mellitus, total cholesterol, history of cardiovascular disease, and use of antihypertensive drug. Hypertension was defined as systolic/diastolic blood pressure ≥ 135/85 mm Hg for home, ≥ 130/80 mm Hg for 24-h ambulatory, and ≥ 140/90 mm Hg for office. The mark + indicates hypertension. SNBP, sustained normal blood pressure; WCHT, white coat hypertension; MHT, masked hypertension; SHT, sustained hypertension.

sure and office blood pressure were simultaneously included in a Cox proportional hazards model as continuous variables, only 24-hour blood pressure was significantly related to the risk of stroke (Ohkubo et al. 2000).

b. 24-hour ambulatory blood pressure of ≥ 135/80 mmHg is hypertension

In a non-parametric analysis investigating relative risk in which groups were divided by blood pressure level, there was a J-shaped relationship between 24-hour ambulatory blood pressure and all-cause mortality (Ohkubo et al. 1998a). An analysis by cause of death found that there were many cerebrovascular and cardiovascular deaths in people in the high blood pressure range and many non-cerebrocardiovascular deaths in people in a low blood pressure range. These J-shaped relationships were fitted to a second-degree equation, and standard values were obtained from the point where the relative risk increased significantly parametrically. As a result, the value of 135/80 mmHg was thought to be best as a standard value for hypertension, from the perspective of predicting cerebrovascular and cardiovascular mortality risk. This value corresponds to 160/95 mmHg for the case of office blood pressure from the standpoint of the distribution of blood pressure. The risk in the hypertension group with this definition was 2.4 times higher than that in the normotensive group.

c. If blood pressure does not decrease during nighttime sleep, the risk of cerebrovascular and cardiovascular mortality is high

The cerebrovascular and cardiovascular mortality risk was high in non-dipper (attenuated nocturnal decrease in blood pressure) and inverted-dipper (nocturnal elevation in blood pressure) groups, but there was no difference in extreme-dipper (excessive nocturnal decrease) and dipper (nocturnal decline) groups, which showed similar low risks (Ohkubo et al. 2002). Regardless of 24-hour blood pressure level, attenuation of the nocturnal decrease in blood pressure was a significant risk factor for cerebrovascular and cardiovascular mortality risk (Fig. 6).

d. The cerebrovascular and cardiovascular mortality risk is high when daytime blood pressure is susceptible to variability

Shorter-term blood pressure variability expressed by the SD of blood pressure values every 30 minutes day and night can be used as observable blood pressure variability with ambulatory blood pressure. The larger the daytime blood pressure SD, the larger the cerebrovascular and cardiovascular mortality risk (Kikuya et al. 2000).

e. Ambulatory blood pressure is linearly related to cerebrovascular and cardiovascular mortality risk

The linear relationship between ambulatory blood pressure and cerebrovascular and cardiovascular mortality

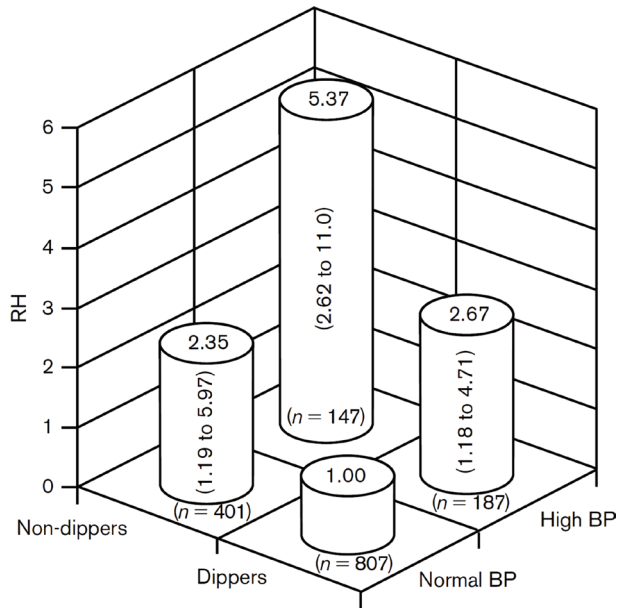

Fig. 6. Relative hazards (RH) and confidence intervals (inside the bars) for cardiovascular mortality associated with combinations of groups with and without a sizeable decline in nocturnal blood pressure (BP), and high and normal 24-h BP values, adjusted for age, sex, smoking status, use of antihypertensive, and a history of cardiovascular disease, hypercholesterolaemia or diabetes mellitus.
n = number in group.

risk became more explicit with the exclusion of deaths in the first two years in the extended follow-up study (Kikuya et al. 2005).

f. With masked hypertension, the prognosis is poor

The cerebrovascular and cardiovascular mortality risk and risk of stroke with masked hypertension, in which there is hypertension in daytime ambulatory blood pressure and normotension in office blood pressure, was found to be about two times higher than in people who are normotensive for both daytime ambulatory blood pressure and office blood pressure (Ohkubo et al. 2005) (Fig. 7).

g. Attenuation of nocturnal decrease in blood pressure is a risk for cerebral infarction, and a morning surge is a risk for cerebral hemorrhage

The risk of cerebral infarction is high in non-dipper (attenuated nocturnal decrease in blood pressure) and inverted-dipper (nocturnal elevation in blood pressure) groups, but a group with a large elevation in blood pressure upon rising (morning surge) and their mirror image, extreme dipper (excessive nocturnal decrease), showed a high risk of cerebral hemorrhage (Metoki et al. 2006b).

h. Nighttime blood pressure is related to a risk for cerebral infarction mortality and heart disease mortality, and daytime blood pressure is related to a risk for cerebral hemorrhage mortality

The relationship between blood pressure at different times of the day and mortality risk was investigated using two-hour moving blood pressure averages. It was found that high blood pressure during nighttime sleep was related to the risk of cerebral infarction mortality and heart disease

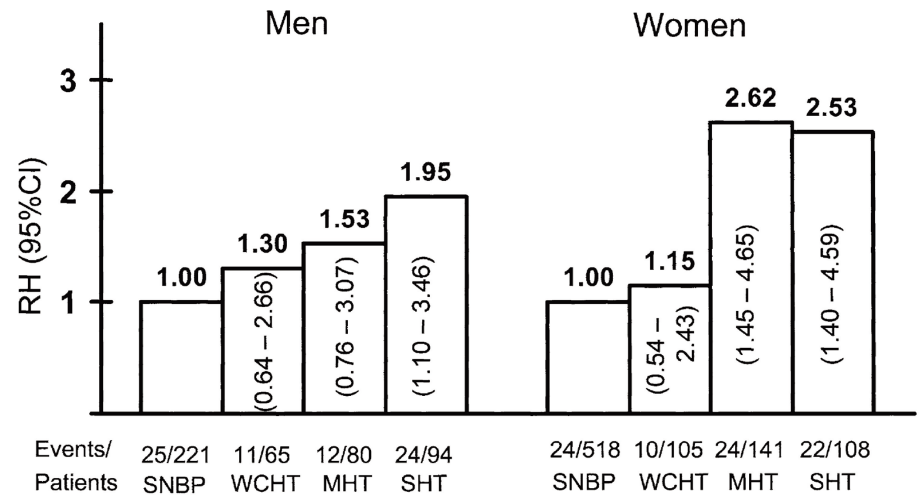

Fig. 7. Relative hazards (RH) and 95% confidence intervals (CI) of sustained normal blood pressure (SNBP), white-coat hypertension (WCHT), masked hypertension (MHT), and sustained hypertension (SHT) for cardiovascular disease (CVD) mortality, stroke morbidity, and the composite of CVD mortality/stroke morbidity.
Numbers inside bars indicate 95% CI. The SNBP group was treated as the reference category.

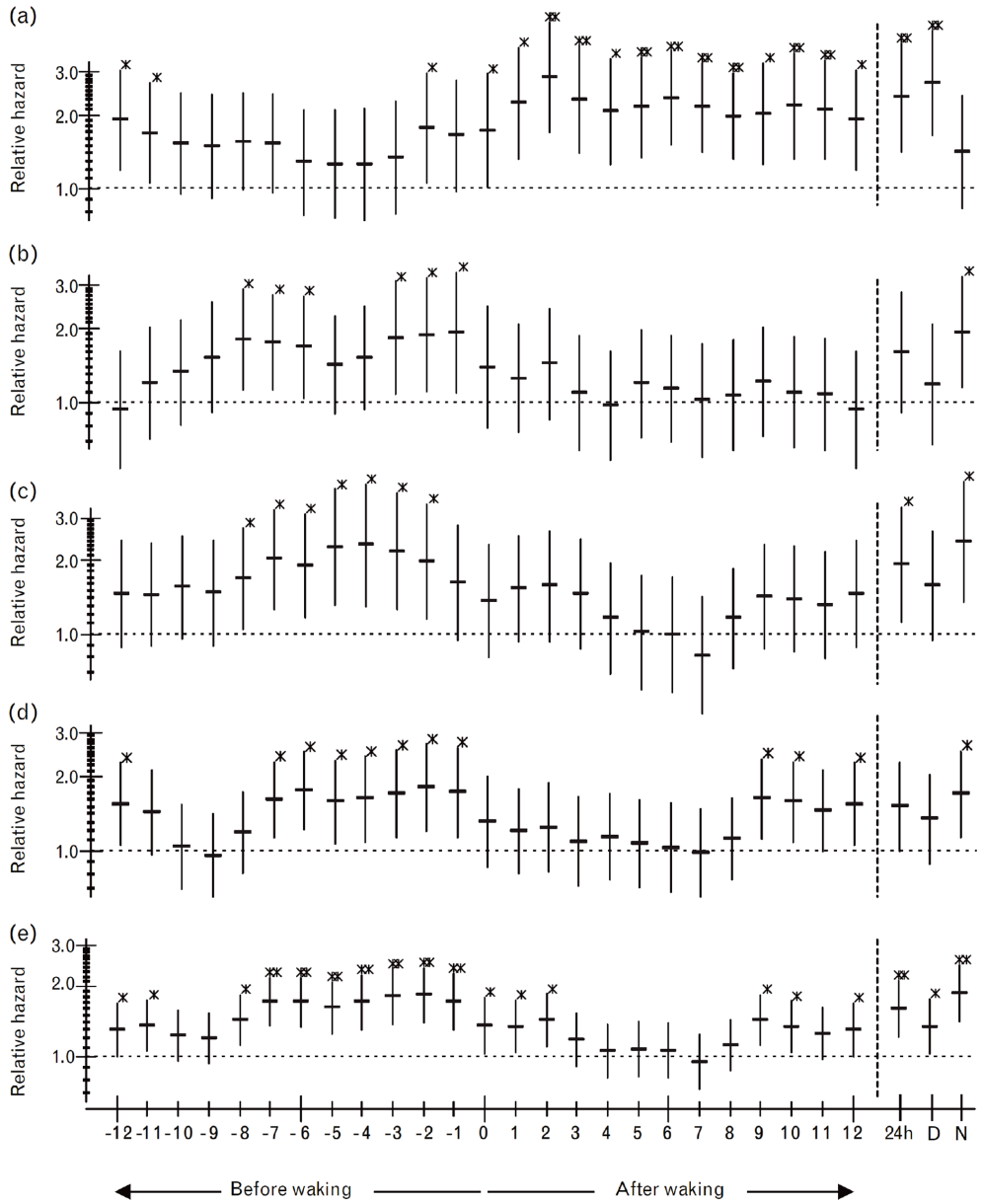

Fig. 8. Relative hazard of the mortality risk per 1-SD elevation of systolic blood pressures.
Relative hazards and 95% confidence intervals for the mortality risk of (a) haemorrhagic stroke, (b) cerebral infarction, (c) ischaemic heart disease, (d) non-ischaemic heart disease, and (e) composite of cerebral infarction and heart diseases per 1-SD elevation of systolic blood pressures. Each analysis was adjusted for age, sex, smoking status, and the use of antihypertensive medication, as well as for a history of cerebrovascular and cardiovascular diseases, hypercholesterolemia, and diabetes mellitus. Numbers on the lefthand side panel of the figure indicate the 2-h moving averages of systolic blood pressure over a 24-h period. 24 h, D, and N on the right-hand side panel indicate conventional 24-h, daytime, and night-time mean systolic blood pressures, respectively. $*P < 0.05$, $**P < 0.002$ (Bonferroni adjustment).

mortality, and, conversely, that high blood pressure during daytime waking hours was related to cerebral hemorrhage mortality risk (Metoki et al. 2006a) (Fig. 8).

i. Ambulatory systolic blood pressure has a superior predictive ability to pulse pressure for stroke

Systolic blood pressure in ambulatory blood pressure monitoring was shown to have a higher predictive ability than pulse pressure for stroke (Inoue et al. 2006). The risk of stroke from isolated systolic hypertension was similar to that in people with systolic and diastolic hypertension, and about two times higher than in people with normotension (Inoue et al. 2007). This suggested that antihypertensive treatment targeting ambulatory systolic blood pressure

would be effective in preventing stroke.

j. High nighttime heart rate is related to mortality risk

High nighttime heart rate was related to all-cause mortality and risk of death from non-cerebrocardiovascular disease, but it was not significantly related to risk of death from cerebrovascular and cardiovascular disease (Hozawa et al. 2008). High daytime heart rate did not show a constant relationship with any cause of death.

k. Ambulatory arterial stiffness index is a predictor of cerebrovascular and cardiovascular mortality risk

The ambulatory arterial stiffness index (AASI), a parameter calculated from 24-hour systolic and diastolic blood pressure, was a predictor of death from cerebrovascular and cardiovascular disease independent of pulse pressure (Kikuya et al. 2007b).

l. Nighttime blood pressure predicts chronic kidney disease

Nighttime ambulatory blood pressure was a better predictor than daytime ambulatory blood pressure of chronic kidney disease (Kanno et al. 2013).

m. Blood pressure surge power is related to cerebrovascular and cardiovascular mortality and stroke in women

Blood pressure surge power (an indicator obtained by multiplying the blood pressure elevation rate by the difference between sleeping and waking blood pressure) showed a U-shaped relationship with death from cerebrovascular and cardiovascular disease and the percentage of stroke occurrence in women only (Head et al. 2019).

n. The 24-hour pulse pressure elastic component (elPP) is a predictor of mortality

The hazard ratios for all-cause mortality, cardiovascular mortality, and stroke of the 24-hour pulse pressure elastic component (elPP) and stiffening component (stPP), separated from a model based on the arterial pressure-volume curve, were estimated with a Cox regression model. In a subgroup with a pulse rate at or below the median, elPP significantly predicted all-cause mortality and cardiovascular mortality, but no significant relationships were seen in other groups or indices (Bursztyn et al. 2020).

Conclusion

The JSH 2014 and 2019 guidelines recommend home blood pressure measurements based on evidence and specify for the first time in the world that, when there is a difference in the diagnosis between office blood pressure and home blood pressure, the diagnosis based on home blood pressure should be given precedence. Home blood pressure data collected in the Ohasama Study and other studies are thought to have made a significant background contribution to this. Investigations related to home blood pressure will continue as the Ohasama Study. The results will be returned to community residents and are expected to convey the importance of home blood pressure to Japan and the world.

The significance of the Ohasama Study has been established as core data in the International Database on Home Blood Pressure in Relation to Cardiovascular Outcome (IDHOCO) (Asayama et al. 2014a), the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes (IDACO) (Kikuya et al. 2007a; Asayama et al. 2014b), and other international meta-analyses. These international reports have significantly expanded the evidence on blood pressure and has an aspect of support for the validity of the findings of the Ohasama Study. The Ohasama Study will continue to produce a great deal of evidence in the future.

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Conflict of Interest

T.O. concurrently held the position of director of the Tohoku Institute for Management of Blood Pressure, supported by Omron Healthcare Co., Ltd. T.O. received a joint research grant from Omron Healthcare Co., Ltd. M.S. received the Academic support from Bayer Yakuhin Co., Ltd.

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