REVIEW SERIES

Diurnal blood pressure variation and cardiovascular prognosis in a community-based study of Ohasama, Japan
Diurnal variations in blood pressure: clinical implications and pathogenesis

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The introduction of 24-h ambulatory blood pressure (BP) monitoring has enabled BP evaluations at specific times of the day. Associations between diurnal BP variation and cardiovascular prognosis have been investigated in the Ohasama study, which is an epidemiological survey of hypertension using ambulatory and home BP monitoring that has been ongoing since 1985 in the general population of Ohasama, a town located in northern Japan. A diminished nocturnal decline in systolic BP was associated with a greater common carotid intima-media thickness as well as a higher risk of cardiovascular morbidity and mortality, especially the risk for cerebral infarction. The consumption of large amounts of alcohol was associated with a higher morning pressor surge. A large nocturnal decline in BP and a large morning pressor surge were both associated with a risk of cerebral hemorrhage. Ambulatory BP monitoring provides not only static, but also dynamic information about BP that should be considered to ensure effective management of hypertension and cardiovascular diseases.
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INTRODUCTION

High blood pressure (BP) is associated with target-organ damage and a poor cardiovascular prognosis. The introduction of 24-h ambulatory BP monitoring has enabled BP to be evaluated at specific times of day. A single BP value obtained using an ambulatory device on rising in the morning is a better discriminator of future cardiovascular events than the mean of three measurements taken under standardized conditions in a hospital or clinic.[1] Several recently proposed indices of circadian BP variation might be relevant to the diagnosis and management of hypertension with special reference to target-organ damage and prognosis. The present review describes diurnal BP variation and cardiovascular prognosis from the results of the Ohasama study, which is an epidemiological survey of hypertension based on ambulatory BP monitoring that was started in 1985 among the general population of Ohasama, a town located in northern Japan.

STUDY POPULATION

Ohasama had a population of 9400 in 1985. We have obtained ambulatory BP data over the past 20 years by monitoring over 3000 inhabitants aged ⩾20 years, as well as outcomes and information about risk factors and predictors. To prospectively investigate the association between BP levels and subsequent risk of outcomes, we excluded individuals aged <40 years at the time of ambulatory BP monitoring because death or stroke occurrence was less frequent among younger persons. Thus, several indexes of BP obtained by ambulatory monitoring were prospectively analyzed among 1542 inhabitants of Ohasama aged ⩾40 years.

NOCTURNAL DECLINE IN BP

BP generally increases on awakening in the morning and falls while asleep during the nighttime. This circadian variation in BP is regulated by the autonomic nervous and endocrine systems, and modified by several factors such as physical and mental activities as well as environmental stressors. Nocturnal BP usually falls 10–20% from the diurnal value and is referred to as nocturnal dipping. However, nocturnal dipping is attenuated or disappears under several patho-physiological conditions and persons with this phenomenon are referred to as 'non-dippers.' Those with higher nocturnal BP than the diurnal value are referred to as 'inverted dippers' or 'risers.' A person with a large nocturnal decline in BP is defined as an 'extreme

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dipper.' However, nocturnal BP remains normal or high among hypertensive patients. Therefore, 'extreme dippers' among hypertensive patients are equivalent to 'diurnal risers.'[2] Such disordered circadian BP variations are associated with a poor cardiovascular prognosis[3–6] and are regarded as targets for antihypertensive therapy.

The decline in nocturnal BP was calculated in the Ohasama study as follows: nocturnal decline in BP (%)=(daytime BP−nighttime BP)×100/daytime BP. We classified the subtypes of nocturnal decline in BP as follows: extreme dipper (20% nocturnal decline in BP from diurnal value), dipper (10–19% nocturnal decline in BP), non-dipper (0–9% nocturnal decline in BP) and riser (0% nocturnal decline in BP or nocturnal elevation).

NOCTURNAL DECLINE IN BP AND CARDIOVASCULAR MORTALITY

We reported the association between ambulatory BP and cardiovascular prognosis in 1997. That report describes that ambulatory BP predicted mortality more effectively than casual screening of BP during a mean follow-up period of 5.1 years.[7] During the same observation period, the mortality risk was highest among risers, followed by non-dippers. Mortality rates did not differ between extreme dippers and dippers. This relationship in both treated and untreated individuals was more remarkable for cardiovascular, than for non-cardiovascular mortality, and was not changed after adjustment for 24-h, daytime and nighttime BP levels.[8] Follow-up for a mean of 9.2 years showed that a diminished nocturnal decline in BP was associated with a risk for cardiovascular mortality, which was independent of the overall BP load during a 24-h period.[9]

NOCTURNAL DECLINE IN BP AND RISK OF STROKE

Analysis of data over a mean follow-up period of 10.4 years revealed no consistent association between dipping profile and the risk of total stroke. The data did not fit a linear model; the relative hazard per 1 s.d. increase of nocturnal decline in BP was 1.1 (95% CI, 0.8–1.4, $P=0.7$). The risk for cerebral infarction was significantly higher among individuals with a diminished nocturnal decline (risers and non-dippers) than among those with a decline of $\geqslant 10\%$ (dippers and extreme dippers). The relative hazard among individuals with a diminished nocturnal decline was 1.6 (95% CI, 1.0–2.5, $P=0.04$). Extreme dippers had 2.7-fold higher risk (95% CI, 1.1–6.4, $P=0.02$) of cerebral hemorrhage than those with a nocturnal decline of $<20\%$ (dippers, non-dippers and risers).

MORNING BP SURGE

BP that abruptly increases around awakening in the morning is called the 'morning pressor surge.'[10,11] The association between morning BP surge and cardiovascular disease has received focus because cardiovascular events occur more frequently in the morning[12–14] and a mean follow-up of 20 months has revealed that elderly patients with a large morning pressor surge have a threefold higher risk of stroke.[15]

The amplitude of the morning pressor surge in the Ohasama study was defined based on earlier findings[11] as follows: morning pressor surge in systolic blood pressure (SBP)=2-h mean SBP after waking−2-h mean SBP before waking.

The morning pressor surge can also be calculated by a method that generates the 'sleep-trough' morning pressor surge,[15] which is calculated as follows: sleep-trough morning pressor surge in SBP=2-h mean SBP after waking−lowest SBP defined as mean BP of three readings centered on the lowest nighttime reading.

An association between morning pressor surge and the incidence of total stroke ($n=128$) and of cerebral infarction ($n=86$) was not identified during a 10.4-year follow-up. However, the risk for cerebral hemorrhage ($n=27$) was significantly high in the fifth quintile group with a morning pressor surge amplitude of 25 mm Hg (RH, 4.0; 95% CI, 1.1–14.6, $P=0.04$), when the second quintile of the morning pressor surge (amplitude 3–11 mm Hg) was set as the reference category.[16] The predictive value of the sleep-trough morning surge was similar to that of the sleeping-to-waking morning surge in the same population.[16]

The International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome has recently been established.[17,18] A morning surge in BP exceeding the 90th percentile in this database was a significant and independent predictor of mortality and cardiovascular events even after correcting the night-to-day BP ratio, the 24-h BP level and other covariables.[19] Moreover, consistent with our earlier findings,[16] Asians with a morning surge in the top decile were at a significantly higher risk for hemorrhagic stroke ($n=51$; HR [95% CI], 2.28 [1.09–4.26], $P=0.03$), but not for ischemic stroke ($n=127$; HR, 1.41 [0.67–2.98], $P=0.37$), than those with a lower morning surge.

BP AT A SPECIFIC TIME OF DAY

Although the predictive value of BP increases with increasing numbers of measurements,[20,21] BP values obtained at different times of the day (nighttime, morning and daytime) have not been compared with values obtained by the same number of measurements. A simple calculated mean of the BP values recorded every 30 min during the nighttime (8 h) generates 16 values; similarly, a simple mean of the daytime (16 h) BP values recorded every 30 min yields 28 values. Therefore, if the predictive power of BP obtained during the daytime was more powerful than taken during the nighttime, it could reflect the larger number of measurements taken during the daytime.

The means of four BP readings obtained every 30 min for two consecutive hours in a day (moving averages) during the Ohasama study were defined as '2h-BP' (see Figure 1).[22] When readings were omitted because of missed and/or artifactual measurements, calculations were based on the remaining readings (minimum of one) obtained during the 2-h period. The 2h-BP allows a comparison of
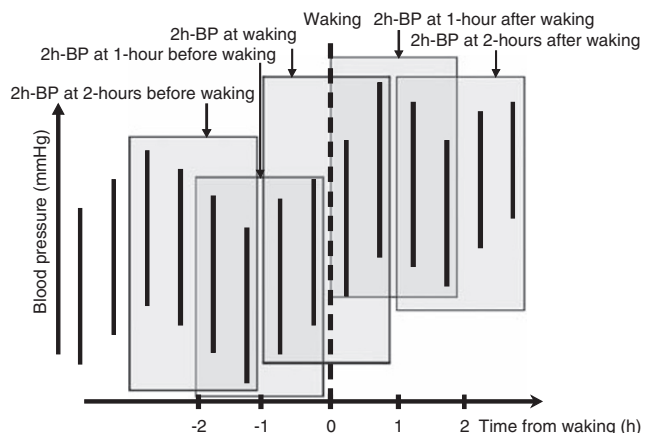
Figure 1 Definition of moving average of 2-h SBP/2-h DBP. Means of four SBP/DBP readings obtained over two consecutive daytime hours (moving averages) are defined as 2h-SBP/2h-DBP. Horizontal line indicates time (hours) from waking. Vertical line shows BP (mm Hg). Reproduced from our earlier article[22] with permission from the Lippincott Williams & Wilkins.

the predictive value of BP taken at different times using the same number of BP measurements.

BP AT A SPECIFIC TIME OF DAY AND CARDIOVASCULAR MORTALITY

When nighttime and daytime SBP values were simultaneously included in the same Cox model, only nighttime BP significantly predicted cardiovascular mortality risk from the 10.8-year follow-up data. We concluded that the relationship between ambulatory SBP and cardiovascular mortality is not U- or J-shaped, and that the prognostic value of BP during the nighttime is better than that during the daytime.[23] We applied 2h-BP to evaluate the relevance of BP at a particular time of day to the risk of stroke mortality. Total cerebrovascular and cardiovascular mortality risk was significantly associated with elevated 2h-BP recorded during the night and early morning. Hemorrhagic stroke mortality was significantly associated with elevated daytime 2h-BP. The mortality of cerebral infarction and heart disease was significantly associated with elevated nighttime 2h-BP.[22]

BP AT A SPECIFIC TIME OF DAY AND RISK OF STROKE

The risk of stroke incidence in the Ohasama study was more closely associated with daytime, than with nighttime BP over a mean follow-up of 6.4 years.[24]

Using 2h-BP to evaluate the relevance of BP taken at a specific time of day to determine the risk of stroke morbidity showed that risk for total stroke incidence was significantly associated with systolic 2h-BP values (2h-SBPs) throughout the day (Figure 2). Risk for incidence of intracerebral hemorrhage was significantly associated with elevated daytime 2h-SBPs, but less so with nighttime 2h-SBPs (Figure 3a). Risk for the incidence of cerebral infarction was significantly associated with nighttime 2h-SBPs, but less so with daytime 2h-SBPs (Figure 3b).

DIURNAL BP VARIATION AND TARGET-ORGAN DAMAGE

Cross-sectional analyses regarding target-organ damage were performed during the Ohasama study. Nighttime BP was most closely associated with carotid artery alterations among values for daytime, nighttime and casual BP. Although a morning pressor surge was not associated with carotid artery alterations, a diminished nocturnal decline in SBP was associated with common carotid intima-media thickness after adjustment for confounding factors.[25] Daytime and nighttime BP values were both associated with silent cerebrovascular lesions, whereas casual BP in the same population was not.[26]

FACTORS ASSOCIATED WITH DIURNAL BP VARIATION

Alcohol consumption and diurnal BP variation

We found, using 2h-BP, that BP rapidly increased before awakening and that morning BP was higher among Ohasama inhabitants who consumed alcohol. The morning pressor surge was significantly higher among those who consumed large amounts of alcohol than in those who consumed none, whereas alcohol consumption status was not significantly associated with the magnitude of the nocturnal decline in BP.[27]

Genetic polymorphisms and diurnal BP variation

Daytime SBP and diastolic blood pressure (DBP) values were higher in individuals with the C allele in the angiotensin II type 1 receptor gene A/C^{1166} polymorphism ($130.5 \pm 14.0/77.4 \pm 8.3$ mm Hg) than in those with the AA genotype ($127.7 \pm 13.6/75.8 \pm 8.3$ mm Hg, $P=0.03/0.04$), although the difference was not statistically significant after adjusting for age, gender, body mass index and smoking status.[28] Nighttime BP values were significantly lower among individuals with the MM genotype in the angiotensinogen M235T polymorphism than in those with the T allele ($105.2 \pm 13.0/60.1 \pm 6.9$ vs. $110.6 \pm 13.3/63.6 \pm 7.8$ mm Hg, $P=0.04/0.02$). The nocturnal decline in BP was significantly larger among those with the MM genotype than with the T allele ($17.4/19.8$ vs. $13.5/16.2$ mm Hg, $P=0.004/0.01$).[29] The nocturnal decline in BP was significantly greater among individuals with a homozygous CC aldosterone synthase gene (CYP11B2) C-334T polymorphism than in others ($15.4\%/17.7\%$ vs. $13.3\%/16.1\%$, $P=0.007/0.03$), although 24-h ambulatory BP levels did not significantly differ among the genotypes.[30]

We recently focused on the (pro)renin receptor gene. Although casual BP was not associated, 24-h, daytime and nighttime SBP and DBP values were significantly higher among male carriers of the IVS5+169T rather than the C allele of the (pro)renin receptor gene. BP values did not significantly differ among the three genotypes of female IVS5+169C>T carriers.[31]
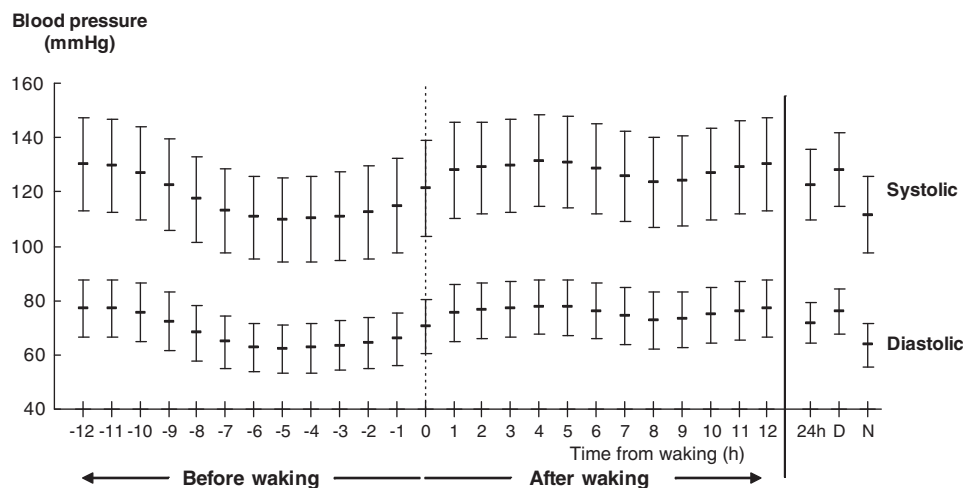

Figure 2 Circadian BP variation of SBP and DBP using 2-h SBP/2-h DBP. Left panel: 2-h moving averages of SBP and DBP over 24-h period based on time (hours) from waking. Right panel: 24-h, daytime and nighttime mean BP values are shown as 24 h, D and N, respectively.
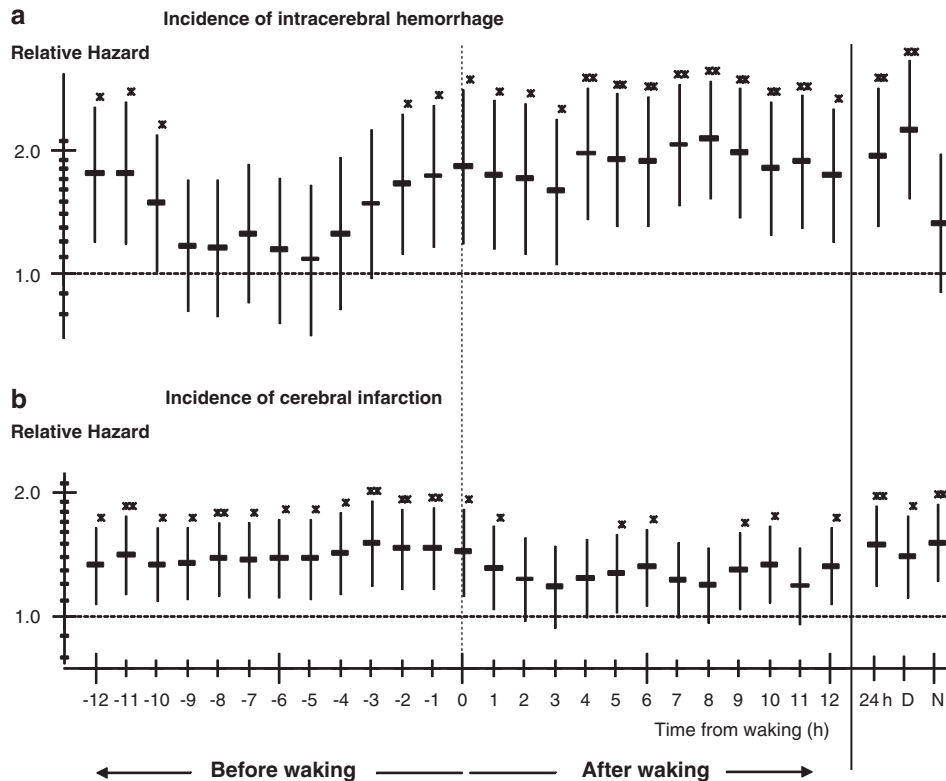
Figure 3 Relative hazard for incidence of stroke subtypes per 1-s.d. elevation of SBP values. Relative hazards and 95% confidence intervals for incidence of (**a**) hemorrhage stroke and (**b**) cerebral infarction per 1-s.d. elevation of SBPs over a mean follow-up of 10.2 years in Ohasama, Japan. Left panel: Numbers indicate 2-h moving averages of SBP over 24-h period. Right panel: 24 h, D and N on the right slide panel indicate 24-h, daytime, and nighttime mean SBP values, respectively. Each analysis was adjusted for age, gender, smoking status, antihypertensive medication, history of heart disease, hypercholesterolemia and diabetes mellitus. $*P < 0.05$; $**P < 0.002$ (Bonferroni's adjustment).

CONCLUSION

The results of the Ohasama study show that ambulatory BP values are uniquely associated with cardiovascular diseases and their prognosis. Ambulatory BP values provide not only static, but also dynamic information about BP that is applicable to the effective management of hypertension and cardiovascular diseases.

1 Gosse P, Cipriano C, Bemurat L, Mas D, Lemetayer P, N'Tela G, Clementy J. Prognostic significance of blood pressure measured on rising. *J Hum Hypertens* 2001; **15**: 413–417.
2 Nishiyama A, Imai Y, Ohkubo T, Tsuji I, Nagai K, Kikuchi N, Kato J, Sekino M, Aihara A, Kikuya M, Satoh H, Hisamichi S. Determinants of circadian blood pressure variation: a community-based study in Ohasama. *Tohoku J Exp Med* 1997; **183**: 1–20.
3 Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, Mancia G, Nachev C, Palatini P, Parati G, Tuomilehto J, Webster J. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. systolic hypertension in Europe trial investigators. *JAMA* 1999; **282**: 539–546.
4 Shimada K, Kawamoto A, Matsubayashi K, Ozawa T. Silent cerebrovascular disease in the elderly. Correlation with ambulatory pressure. *Hypertension* 1990; **16**: 692–699.
5 Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Guerrieri M, Gatteschi C, Zampi I, Santucci A, Santucci C, Reboldi G. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* 1994; **24**: 793–801.
6 Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. *Hypertension* 2001; **38**: 852–857.
7 Ohkubo T, Imai Y, Tsuji I, Nagai K, Watanabe N, Minami N, Itoh O, Bando T, Sakuma M, Fukao A, Satoh H, Hisamichi S, Abe K. Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. *J Hypertens* 1997; **15**: 357–364.
8 Ohkubo T, Imai Y, Tsuji I, Nagai K, Watanabe N, Minami N, Kato J, Kikuchi N, Nishiyama A, Aihara A, Sekino M, Satoh H, Hisamichi S. Relation between nocturnal decline in blood pressure and mortality. The Ohasama study. *Am J Hypertens* 1997; **10**: 1201–1207.
9 Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, Matsubara M, Hashimoto J, Hoshi H, Araki T, Tsuji I, Satoh H, Hisamichi S, Imai Y. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. *J Hypertens* 2002; **20**: 2183–2189.
10 DeQuattro V, Lee DD, Allen J, Sirgo M, Plachetka J. Labetalol blunts morning pressor surge in systolic hypertension. *Hypertension* 1988; **11**: I198–I201.
11 Gosse P, Lasserre R, Minifie C, Lemetayer P, Clementy J. Blood pressure surge on rising. *J Hypertens* 2004; **22**: 1113–1118.
12 Muller JE, Stone PH, Turi ZG, Rutherford JD, Czeisler CA, Parker C, Poole WK, Passamani E, Roberts R, Robertson T, Sobel BE, Willerson JT, Braunwald E. Circadian variation in the frequency of onset of acute myocardial infarction. *N Engl J Med* 1985; **313**: 1315–1322.
13 Muller JE, Ludmer PL, Willich SN, Tofler GH, Aylmer G, Klangos I, Stone PH. Circadian variation in the frequency of sudden cardiac death. *Circulation* 1987; **75**: 131–138.
14 Tsementzis SA, Gill JS, Hitchcock ER, Gill SK, Beevers DG. Diurnal variation of and activity during the onset of stroke. *Neurosurgery* 1985; **17**: 901–904.
15 Kario K, Pickering TG, Umeda Y, Hoshide S, Hoshide Y, Morinari M, Murata M, Kuroda T, Schwartz JE, Shimada K. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. *Circulation* 2003; **107**: 1401–1406.
16 Metoki H, Ohkubo T, Kikuya M, Asayama K, Obara T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognostic significance for stroke of a morning pressor surge and a nocturnal blood pressure decline: the Ohasama study. *Hypertension* 2006; **47**: 149–154.

17 Kikuya M, Hansen TW, Thijs L, Bjorklund-Bodegard K, Kuznetsova T, Ohkubo T, Richart T, Torp-Pedersen C, Lind L, Ibsen H, Imai Y, Staessen JA. Diagnostic thresholds for ambulatory blood pressure monitoring based on 10-year cardiovascular risk. *Circulation* 2007; **115**: 2145–2152.

18 Boggia J, Li Y, Thijs L, Hansen TW, Kikuya M, Bjorklund-Bodegard K, Richart T, Ohkubo T, Kuznetsova T, Torp-Pedersen C, Lind L, Ibsen H, Imai Y, Wang J, Sandoya E, O'Brien E, Staessen JA. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. *Lancet* 2007; **370**: 1219–1229.

19 Li Y, Thijs L, Hansen TW, Kikuya M, Boggia J, Richart T, Metoki H, Ohkubo T, Trop-Pedersen C, Kuznetsova T, Stolarz-Skizypek K, Tikhonoff V, Malyutina S, Casiglia E, Nikitin Y, Sandoya E, Kawecka-Jaszcz K, Ibsen H, Imai Y, Wang J, Staessen J. Prognostic value of the morning blood pressure surge in 5645 subjects from 8 populations. *Hypertension* 2010; **55**: 1040–1048.

20 Fagard RH, Staessen JA, Thijs L. Prediction of cardiac structure and function by repeated clinic and ambulatory blood pressure. *Hypertension* 1997; **29**: 22–29.

21 Ohkubo T, Asayama K, Kikuya M, Metoki H, Hoshi H, Hashimoto J, Totsune K, Satoh H, Imai Y. How many times should blood pressure be measured at home for better prediction of stroke risk? Ten-year follow-up results from the Ohasama study. *J Hypertens* 2004; **22**: 1099–1104.

22 Metoki H, Ohkubo T, Kikuya M, Asayama K, Obara T, Hara A, Hirose T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Prognostic significance of night-time, early morning, and daytime blood pressures on the risk of cerebrovascular and cardiovascular mortality: the Ohasama Study. *J Hypertens* 2006; **24**: 1841–1848.

23 Kikuya M, Ohkubo T, Asayama K, Metoki H, Obara T, Saito S, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Ambulatory blood pressure and 10-year risk of cardiovascular and noncardiovascular mortality: the Ohasama study. *Hypertension* 2005; **45**: 240–245.

24 Ohkubo T, Hozawa A, Nagai K, Kikuya M, Tsuji I, Ito S, Satoh H, Hisamichi S, Imai Y. Prediction of stroke by ambulatory blood pressure monitoring versus screening blood pressure measurements in a general population: the Ohasama study. *J Hypertens* 2000; **18**: 847–854.

25 Shintani Y, Kikuya M, Hara A, Ohkubo T, Metoki H, Asayama K, Inoue R, Obara T, Aono Y, Hashimoto T, Hashimoto J, Totsune K, Hoshi H, Satoh H, Imai Y. Ambulatory blood pressure, blood pressure variability and the prevalence of carotid artery alteration: the Ohasama study. *J Hypertens* 2007; **25**: 1704–1710.

26 Aono Y, Ohkubo T, Kikuya M, Hara A, Kondo T, Obara T, Metoki H, Inoue R, Asayama K, Shintani Y, Hashimoto J, Totsune K, Hoshi H, Satoh H, Izumi S, Imai Y. Plasma fibrinogen, ambulatory blood pressure, and silent cerebrovascular lesions: the Ohasama study. *Arterioscler Throm Vasc Biol* 2007; **27**: 963–968.

27 Nakashita M, Ohkubo T, Hara A, Metoki H, Kikuya M, Hirose T, Tsubota-Utsugi M, Asayama K, Inoue R, Kanno A, Obara T, Hoshi H, Totsune K, Satoh H, Imai Y. Influence of alcohol intake on circadian blood pressure variation in Japanese men: the Ohasama study. *Am J Hypertens* 2009; **22**: 1171–1176.

28 Kikuya M, Sugimoto K, Katsuya T, Suzuki M, Sato T, Funahashi J, Katoh R, Kazama I, Michimata M, Araki T, Hozawa A, Tsuji I, Ogihara T, Yanagisawa T, Imai Y, Matsubara M. A/C1166 gene polymorphism of the angiotensin II type 1 receptor (AT1) and ambulatory blood pressure: the Ohasama Study. *Hypertens Res* 2003; **26**: 141–145.

29 Fujiwara T, Katsuya T, Matsubara M, Mikami T, Ishikawa K, Kikuya M, Ohkubo T, Hozawa A, Michimata M, Suzuki M, Metoki H, Asayama K, Araki T, Tsuji I, Higaki J, Satoh H, Hisamichi S, Ogihara T, Imai Y. T+31C polymorphism of angiotensinogen gene and nocturnal blood pressure decline: the Ohasama study. *Am J Hypertens* 2002; **15**: 628–632.

30 Matsubara M, Kikuya M, Ohkubo T, Metoki H, Omori F, Fujiwara T, Suzuki M, Michimata M, Hozawa A, Katsuya T, Higaki J, Tsuji I, Araki T, Ogihara T, Satoh H, Hisamichi S, Nagai K, Kitaoka H, Imai Y. Aldosterone synthase gene (CYP11B2) C-334 T polymorphism, ambulatory blood pressure and nocturnal decline in blood pressure in the general Japanese population: the Ohasama Study. *J Hypertens* 2001; **19**: 2179–2184.

31 Hirose T, Hashimoto M, Totsune K, Metoki H, Asayama K, Kikuya M, Sugimoto K, Katsuya T, Ohkubo T, Hashimoto J, Rakugi H, Takahashi K, Imai Y. Association of (pro)renin receptor gene polymorphism with blood pressure in Japanese men: the Ohasama study. *Am J Hypertens* 2009; **22**: 294–299.