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Abstract—The objective of this study was to elucidate the long-term prognostic significance of ambulatory blood pressure. Ambulatory and casual blood pressure values were obtained from 1332 subjects (872 women and 460 men) aged ≥40 years from the general population of a rural Japanese community. Survival was then followed for 14 370 patient years and analyzed by a Cox hazard model adjusted for possible confounding factors. There were 72 cardiovascular deaths during the 10.8-year follow-up. The relationship between 24-hour systolic blood pressure and the cardiovascular mortality risk was U-shaped in the first 5 years, then changed to J-shaped over the rest of the 10.8-year follow-up. After censoring the first 2 years of data, the risk flattened until it again increased for the fifth quintile of 24-hour systolic blood pressure for the 10.8-year follow-up period. For 24-hour diastolic blood pressure, the J-shaped relationship remained unchanged, regardless of follow-up duration and censoring. Ambulatory systolic blood pressure values consistently showed stronger predictive power for cardiovascular mortality risk than did casual systolic blood pressure in the 10.8-year follow-up data, whereas such relationships became more marked after censoring the first 2 years. When nighttime and daytime systolic blood pressure values were simultaneously included in the same Cox model, only nighttime blood pressure significantly predicted the cardiovascular mortality risk for the 10.8-year follow-up data. We conclude that the relationship between ambulatory systolic blood pressure and cardiovascular mortality is not U-shaped or J-shaped, and that nighttime blood pressure has better prognostic value than daytime blood pressure. **(*Hypertension*. 2005;45:240-245.)**

Key Words: blood pressure monitoring, ambulatory ■ cardiovascular diseases ■ prospective studies

Ambulatory blood pressure (BP) has been used widely to diagnose and evaluate hypertension and to monitor treatment in the clinical setting.[1,2] Moreover, ambulatory BP is known to provide more reproducible information than does casual BP for individual patients with hypertension, [3,4] and is more strongly correlated with target-organ damage than casual BP in hypertensive subjects. Furthermore, the international guidelines for hypertension have emphasized the usefulness of ambulatory BP.[5,6] However, in contrast to the plethora of evidence about casual BP, there is still a lack of data that address the long-term prognostic significance of ambulatory BP. Few longitudinal studies, after ≥10 years, have so far examined the relationship between 24-hour BP and prognosis. Since 1987, we have been conducting a prospective cohort study to investigate the relationship between ambulatory BP and survival in the general population of Ohasama, Japan (the Ohasama Study).[7–9] In a previous report, we presented the results from a 5.1-year follow-up period.[8] The objective of the present study was to determine the prognostic significance of ambulatory BP for cardiovascular mortality risk based on a longer follow-up period, of the same subjects, of >10 years.

Methods

Design

The background rationale, study population, and BP measurement of the Ohasama Study have been presented in detail previously.[7–9] 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, and all participants gave written informed consent.

Study Population

Ambulatory BP data were obtained from 1542 subjects aged ≥40 years from the general population of a rural Japanese community.[8] The 1542 subjects were confirmed previously to be representative of the general Japanese population.[8] Of the 1542 subjects, the 1332

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(86%) who underwent casual BP measurement were the final study population.[8]

Ambulatory BP Monitoring and Casual BP Measurement

Ambulatory BP was monitored every 30 minutes oscillometrically using an automatic device (ABPM-630; Nippon Colin) and was edited according to criteria described previously.[10] Next, 24-hour daytime (waking periods) and nighttime (sleeping periods) BP was calculated for each subject.[8] Casual BP was the mean of 2 consecutive readings measured by nurses or technicians with subjects in a seated position after resting for ≥2 minutes, using a fully automatic device (USM-700F; UEDA Electronic Works Co.), based on the Korotkoff sound technique. Both devices for ambulatory and casual BP have been validated previously[11,12] and meet the criteria of the Association for the Advancement of Medical Instrumentation.[13]

Follow-Up and Outcomes

Primary and secondary outcomes were determined as mortality from cardiovascular disease and noncardiovascular disease, respectively (censor date September 30, 2002). We reviewed death certificates from the national mortality registry and confirmed the results by checking the medical records of Ohasama Hospital, which is the only hospital in the town, and where >90% of subjects undergo regular check-ups. Most cases were admitted to Ohasama Hospital, where stroke was diagnosed by computed tomography or MRI of the brain. According to recommendations of the 10th Revision of the International Classification of Diseases (ICD-10) of the World Health Organization, cardiovascular death was defined as mortality related to disease of the circulatory system (ICD-10 code I). Stroke, heart disease, cancer, and respiratory diseases were ICD code I6, I other than I6, C00-D48, and J, respectively.

Data Analysis

Association between the BP values and mortality was examined using the Cox proportional hazards regression model adjusted for age, gender, smoking status, use of antihypertensive medication at baseline, and history of cardiovascular disease, diabetes, and hypercholesterolemia.[9]

We used 4 durations of follow-up: the first analyses involved the first 5 years of follow-up from the baseline; the second involved 10.8 years of follow-up; the third involved 10.8 years of follow-up but excluded death within the first 2 years; and the fourth involved 10.8 years of follow-up but excluded death within the first 4 years. The rationale for exclusion of the first 2 years of follow-up was based on a previous study on casual BP,[14] which determined that removal of such data adjusted the reverse-causality bias supposedly derived from the poor health conditions of subjects with lower BP.[14–17]

Data represent mean±SD. Differences at $P<0.05$ were considered statistically significant. All statistical analyses were conducted using SAS version 8.2 software (SAS Institute).

Results

Clinical Characteristics at Baseline

The mean age of the 1332 participants was 61.8±9.9 years. Of those, 460 (34.5%) were male, 416 (31.2%) were overweight (body mass index ≥25 kg/m^2), 405 (30.4%) were taking antihypertensive medication, 272 (20.4%) were current or past smokers, 217 (16.3%) had hypercholesterolemia, 232 (17.4%) had diabetes mellitus, and 75 (5.6%) experienced previous cardiovascular disease. The mean duration of ambulatory BP monitoring was 22.3±2.3 hours. The 24-hour daytime and nighttime BP values were 123.3±13.0/72.0±7.7, 128.9±13.9/76.1±8.4, and 112.3±14.4/64.1±8.1 mm Hg, respectively, and were significantly lower than the casual systolic and diastolic BP values (131.2±18.5 and74.1±11.3 mm Hg, respectively; both $P<0.001$).

Follow-Up and Outcomes

The mean duration of follow-up was 10.8±2.9 (maximum 14.3) years. Of the 1332 study subjects, 26 (2.0%) moved away or were lost to follow-up. The total number of patient years was 14 370. Cardiovascular and noncardiovascular death occurred in 72 and 142 subjects (5.0 and 9.9 deaths per 1000 person years), respectively. Among the 72 cardiovascular deaths, 37 were from stroke, and 35 were from heart disease. Among the 142 noncardiovascular deaths, the most common cause was cancer (61 deaths), followed by diseases of the respiratory system (26 deaths).

Of the 72 cardiovascular deaths, the 10 who died in the first 2 years of follow-up tended to have lower baseline 24-hour and casual systolic BP values than the remaining cardiovascular victims; the differences and 95% confidence interval (CI) were on average 9.3 mm Hg (−0.18≈18.8; $P=0.05$) for 24-hour systolic BP and 10.3 mm Hg (−2.28≈22.9; $P=0.10$) for casual systolic BP. The differences and 95% CI between cardiovascular disease victims in the first 4 years (n=18) and the remaining cardiovascular disease victims were 4.7 mm Hg (−2.98≈12.4; $P=0.23$) for 24-hour systolic BP and 6.7 mm Hg (−3.42≈16.8; $P=0.23$) for casual systolic BP. Among the 142 noncardiovascular disease victims, there were rather small differences in mean ambulatory and casual systolic BP between those who died in the first 2 years (n=10) and the remaining noncardiovascular disease victims. The differences were on average −2.2 mm Hg (−11.3≈6.92; $P=0.60$) for 24-hour systolic BP and 0.6 mm Hg (−13.1≈14.3; $P=0.93$) for casual systolic BP. For diastolic 24-hour and casual BP, the differences in BP values between subjects who died in the first 2 years of follow-up and the remaining victims were not statistically significant, regardless of cardiovascular or noncardiovascular death (all $P>0.2$).

Cardiovascular Mortality (Nonparametric Analyses)

In the first 5 years of follow-up, a so-called U-shaped relationship was observed between 24-hour ambulatory systolic BP and the risk of the cardiovascular mortality (Figure 1a). When the follow-up period was extended to 10.8 years (up to 14.3 years), the relationship between 24-hour systolic BP and risk changed from a U-shaped to a J-shaped relationship (Figure 1b). The highest quintiles of 24-hour ambulatory systolic and diastolic BP and casual systolic BP were associated with a significantly increased risk of cardiovascular mortality. After censoring deaths in the first 2 years, the risks for the highest quintiles became more prominent, and the risks for lower quintiles of systolic 24-hour BP were reduced (Figure 1c). Censoring of death in the first 4 years did not change the results (data not shown). The other BP values, except for casual diastolic BP, showed similar results (Figure 1b and 1c).

Cardiovascular Mortality (Parametric Analyses)

In the first 5 years of follow-up, only nighttime BP values were associated with cardiovascular mortality risk (Table). In

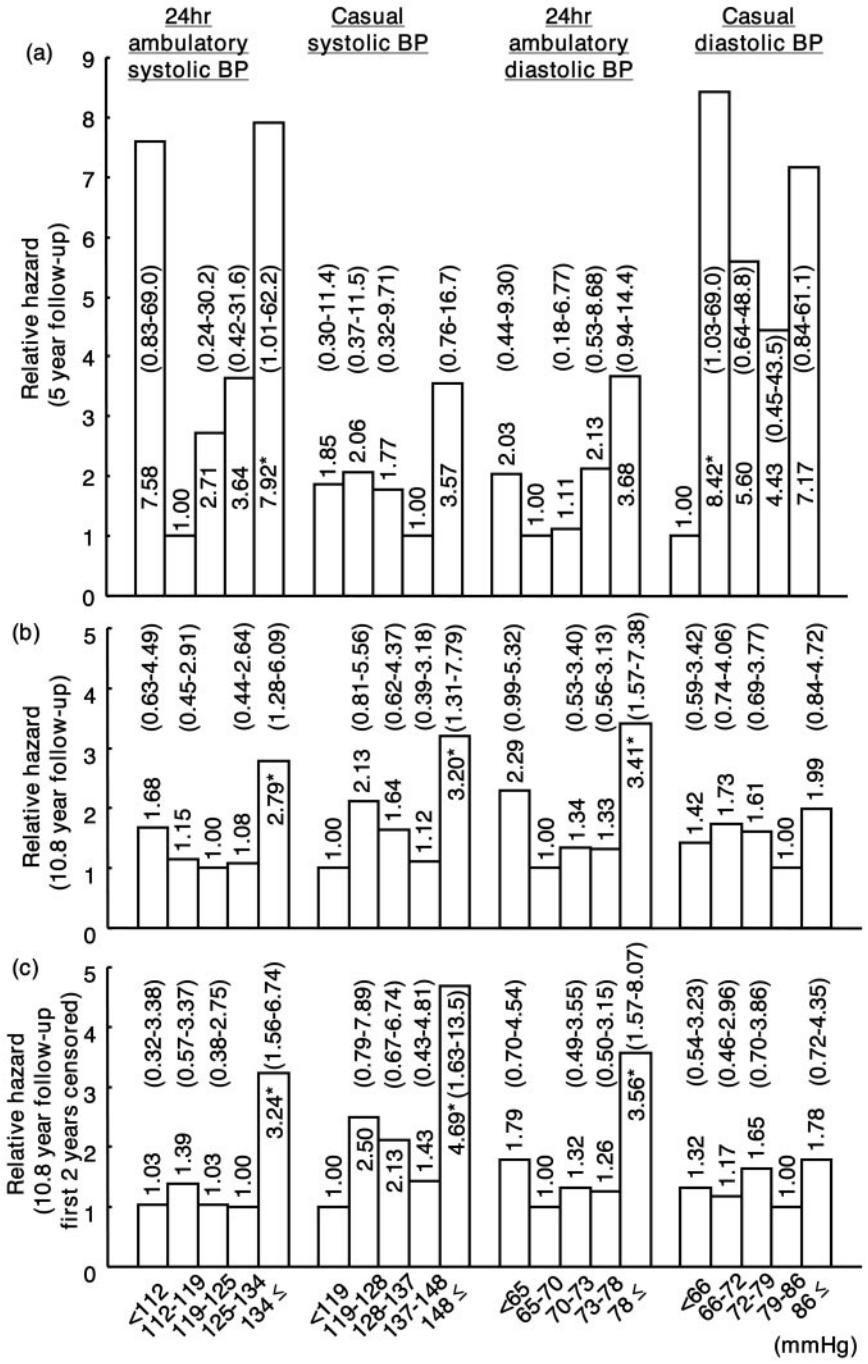

Figure 1. RHs and 95% CIs (in parentheses) for cardiovascular mortality adjusted for gender, age, antihypertensive medication, smoking habit, hypercholesterolemia, diabetes mellitus, and past history of cardiovascular disease during 5-year follow-up (a), 10.8-year follow-up (b), and 10.8-year follow-up (c) after censoring of death in the first 2 years. *$P<0.05$.

the 10.8 years of follow-up, the risk of cardiovascular mortality significantly increased, with an increase in BP values other than casual systolic, casual diastolic, 24-hour diastolic, and daytime diastolic BP (Table). After censoring of death in the first 2 years, the relative hazards (RHs) of cardiovascular mortality with all BP values tended to be higher; however, casual, 24-hour, and daytime diastolic BP were not significantly associated with cardiovascular mortality (Table). The effect of censoring the first 4 years of data on the elevation of RH was similar to that of the 2 years of censoring (Table). No significant interaction was observed between antihypertensive treatment and BP values on the risk of cardiovascular mortality in the first 10.8 years of follow-up (all $P>0.05$).

When 24-hour and casual systolic values were simultaneously included into a Cox model of the 10.8 years of follow-up, only 24-hour systolic BP was significantly related to the cardiovascular mortality risk: the RHs (95% CI) with 10-mm Hg increments in BP values were 1.28 (1.05≈1.55) for 24-hour systolic and 1.06 (0.93≈1.21) for casual systolic. Furthermore, after removal of 24-hour systolic BP from the model, −2log likelihood (ie, "goodness of model fit") was significantly impaired ($P=0.02$), whereas removal of casual systolic BP from the model did not change the goodness of

RHs (95% CIs) for BP Values as a Continuous Variable

Duration of Follow-Up	5-Year Follow-Up	10.8-Year Follow-Up	10.8-Year Follow-Up (First 2 Years Censored)	10.8-Year Follow-Up (First 4 Years Censored)
Cardiovascular death				
Death, No.	23	72	62	54
Systolic BP				
24-hour	1.31 (0.96–1.77)	1.32 (1.10–1.58)†	1.45 (1.19–1.75)‡	1.46 (1.18–1.80)‡
Daytime	1.20 (0.91–1.59)	1.23 (1.05–1.46)*	1.33 (1.12–1.59)†	1.34 (1.10–1.62)†
Nighttime	1.39 (1.05–1.85)*	1.34 (1.14–1.59)‡	1.45 (1.21–1.73)‡	1.48 (1.22–1.80)‡
Casual	1.08 (0.87–1.34)	1.12 (0.99–1.27)	1.18 (1.04–1.34)*	1.19 (1.04–1.36)*
Diastolic BP				
24-hour	1.22 (0.94–1.60)	1.13 (0.97–1.33)	1.20 (1.01–1.41)*	1.18 (0.98–1.42)
Daytime	1.14 (0.89–1.45)	1.10 (0.95–1.26)	1.15 (0.99–1.34)	1.13 (0.96–1.34)
Nighttime	1.31 (1.02–1.68)*	1.19 (1.02–1.38)*	1.24 (1.05–1.46)*	1.24 (1.04–1.48)*
Casual	1.16 (0.97–1.39)	1.02 (0.92–1.13)	1.02 (0.92–1.14)	1.00 (0.89–1.12)
Noncardiovascular death				
Death, No.	35	142	132	113
Systolic BP				
24-hour	0.94 (0.72–1.22)	0.95 (0.83–1.09)	0.94 (0.82–1.08)	0.91 (0.78–1.07)
Daytime	0.89 (0.70–1.15)	0.95 (0.84–1.08)	0.95 (0.84–1.08)	0.94 (0.81–1.08)
Nighttime	1.08 (0.86–1.37)	1.00 (0.88–1.13)	0.98 (0.86–1.11)	0.94 (0.82–1.09)
Casual	1.02 (0.85–1.23)	0.98 (0.90–1.08)	0.98 (0.89–1.08)	0.97 (0.87–1.07)
Diastolic BP				
24-hour	0.83 (0.65–1.06)	0.90 (0.80–1.01)	0.90 (0.79–1.01)	0.88 (0.77–1.01)
Daytime	0.84 (0.67–1.04)	0.92 (0.83–1.02)	0.93 (0.83–1.03)	0.91 (0.81–1.03)
Nighttime	0.94 (0.75–1.17)	0.93 (0.83–1.04)	0.92 (0.82–1.03)	0.90 (0.79–1.03)
Casual	0.98 (0.84–1.14)	0.97 (0.91–1.05)	0.98 (0.91–1.06)	0.97 (0.90–1.06)

RH (95% CIs) indicated the risk associated with a 10-mm Hg and 5-mm Hg increase in systolic and diastolic BP, respectively. RHs were adjusted for sex, age, antihypertensive medication, smoking status, hypercholesterolemia, diabetes mellitus, and past history of cardiovascular disease.

*$P<0.05$; †$P<0.01$; ‡$P<0.001$.

model fit ($P=0.4$). These results were more obvious after censoring of the first 2 or 4 years: all $P<0.005$ when ambulatory BP was removed; all $P>0.2$ when casual BP was removed. In addition, these results were almost identical for the other ambulatory BP values other than 24-hour or daytime diastolic BP values, which were not associated with cardiovascular mortality after adjusting casual BP.

When daytime and nighttime systolic ambulatory BP values were simultaneously included into a Cox model of 10.8 years follow-up, only nighttime systolic BP was significantly related to the cardiovascular mortality risk: the RHs (95% CI) with 10-mm Hg increments in BP values were 1.32 (1.06≈1.64) for nighttime systolic and 1.03 (0.83≈1.29) for daytime systolic BP. Furthermore, removal of nighttime systolic BP from the model of 10.8 years of follow-up significantly impaired the goodness of model fit ($P=0.02$), whereas removal of daytime systolic BP from the model did not change the goodness of model fit ($P=0.8$). After censoring of the first 2 or 4 years, these results were more obvious: all $P<0.01$ when nighttime systolic BP was removed; all $P>0.5$ when daytime systolic BP was removed. For diastolic BP values, these results were similar but not significant.

Noncardiovascular Mortality

In the nonparametric analyses, the lowest quintile of 24-hour and daytime diastolic BP values was associated with a significantly increased risk of noncardiovascular mortality, regardless of follow-up period or censoring of death (Figure 2). This tendency did not change after censoring of the first 4 or 6 years (data not shown). The other BP values showed inconsistent or no association with noncardiovascular mortality. In the parametric analyses, decreases in BP values tended to be related to noncardiovascular death risks but not statistically significantly (Table). Death by cancer, which was the leading cause of noncardiovascular death, was also significantly related to lower levels of 24-hour ambulatory BP (RH, 0.76; 95% CI, 0.63≈0.92; $P=0.005$ for each 5 mm Hg) and casual diastolic BP (RH, 0.86; 95% CI, 0.76≈0.96; $P=0.008$ for each 5 mm Hg) in the 10.8-year follow-up. After censoring of the first 2 or 4 years, the significant relationship was maintained (all $P<0.02$). The other BP values, except for ambulatory and casual systolic BP, produced almost identical results (data not shown).

Discussion

Several meta-analyses of prospective observational cohort studies[18–19] and randomized clinical trials[20] based on casual

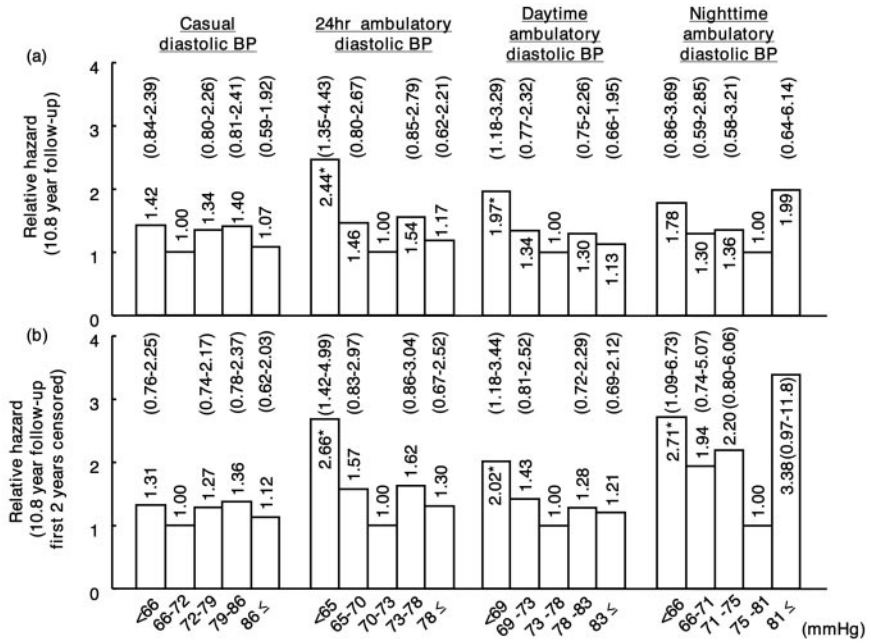

Figure 2. RHs and 95% CIs (in parentheses) for noncardiovascular mortality adjusted for gender, age, antihypertensive medication, smoking, hypercholesterolemia, diabetes mellitus, and past history of cardiovascular disease during 10.8-year follow-up (a), and 10.8-year follow-up (b) after censoring of death in the first 2 years. *$P<0.05$.

BP have concluded that the relationship between casual BP and cardiovascular mortality is essentially linear. Ambulatory BP has also been suggested to have a positively linear or curvilinear relationship with cardiovascular mortality and morbidity.[21–24] This may be partially supported by the observation noted in the present study that the increased risk for cardiovascular mortality at lower BP was reduced after censoring of death in the first several years to adjust the reverse-causality bias supposedly derived from the poor health conditions of subjects with lower BP.[14–17]

In the present study, cardiovascular victims in the first 2 years of follow-up tended to have lower baseline systolic BP values than the remaining cardiovascular victims. However, the magnitude of the BP difference between the cardiovascular victims in the first 4 years of follow-up and those after the 4 years was lower. Furthermore, the effect of the 2-year censoring on the RH of cardiovascular mortality was similar to that of the 4-year censoring (Table). These results suggest that 2-year censoring is an appropriate period with which to exclude reverse-causality bias effectively without losing statistical power.

After adjustment of the reverse-causality by censoring of the first several years of follow-up, we found a stronger RH of cardiovascular mortality with ambulatory BP compared with those of previous studies in which censoring was not conducted.[21–23] For example, the RH (95% CI) of cardiovascular mortality with a 10 mm Hg increase in the 24-hour systolic BP before censoring of the first several years was only 1.32 (1.10≈1.58), which is very similar to that observed in the Syst-Eur Trial,[21] in which censoring of the first several years was not conducted (RH, 1.34 [1.03≈1.75]). In the present study, censoring of death in the first 2 years produced an enhanced RH of 1.45 (1.19≈1.75).

There is a growing body of evidence,[21–24] including our previous reports,[8,9,25] that ambulatory BP provides better prognostic value than casual BP, although the median follow-up of all these reports was <10 years. In the present study, we validated the previous findings using data from long-term follow-up (ie, >10 years). We also found that censoring of the first several years made the superiority of ambulatory BP to casual BP more marked.

Although daytime BP has been reported to be a good predictor of outcomes,[8,21–25] some studies have shown nighttime BP to be a stronger predictor of cardiovascular mortality.[21,26] The Syst-Eur Trial[21] found that only nighttime BP was a significant predictor of cardiovascular mortality the among placebo and total groups when daytime and nighttime BP were included in the same Cox model. This previous finding was confirmed with the longer follow-up period and censoring of the first several years in the present study.

For noncardiovascular mortality, we observed an increased risk in lower BP values regardless of follow-up period and censoring. A deterioration in general health is a possible mechanism.[17] Another possibility is that low BP is mediated by less activity. In fact, in the present study, the association between low BP and noncardiovascular mortality was observed only for 24-hour and daytime ambulatory diastolic BP values, which were measured under unrestricted physical activity, and was not observed for casual and nighttime ambulatory BP values, which were measured under fixed conditions and during sleep, respectively. In the present study, we also observed an inverse association between cancer death risk and diastolic BP values, regardless of censoring of the first several years, supporting a previous study[27] but not all.[28,29] Further studies are required to clarify this controversy.

Perspectives

We conclude that in the general Japanese population, ambulatory systolic BP predicts cardiovascular mortality risk after correcting for reverse-causality bias. In addition, nighttime BP is a stronger predictor of cardiovascular mortality than

daytime BP. The present study further demonstrated the better prognostic value of ambulatory BP than casual BP, using long-term follow-up data from >10 years and censoring of the first several years.

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