Predictive power of home blood pressure in the evening compared with home blood pressure in the morning and office blood pressure before treatment and in the on-treatment follow-up period: A post hoc analysis of the HOMED-BP study

Running title: Home BP in the evening for the prediction of MACEs

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Word counts: Manuscript 4435 words including the abstract but excluding the references

Abstract 255 words

Tables 2; Figures 2; References 34

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Abstract

The predictive power of home blood pressure (BP) in the evening compared with home BP in the morning and office BP has been controversial. The predictive power of evening BP was compared to that of morning BP and office BP. The likelihood ratio test between one model containing a single BP index with traditional risk factors and a similar model further containing another BP index was used to assess whether the additional BP index significantly improved the adequacy of the model. Of 3266 patients with mild-to-moderate hypertension who were on antihypertensive medications (men 50.6%, age 59.5 ± 10.0 years), 58 experienced a major adverse cardiovascular event during a median follow-up of 7.1 years. The hazard ratios for a one standard deviation increment of evening home systolic/diastolic BP were 1.26 (0.98-1.62)/1.43 (1.09-1.88) in the baseline untreated period and 1.46 (1.17-1.81)/1.63 (1.26-2.11) during the on-treatment follow-up period. When evening BP at baseline and that during follow-up were included in the same model, only the latter significantly improved the prediction models (P = 0.006/0.005 for systolic/diastolic BP). Then, evening home BP vs. morning BP during follow-up was tested. The former did not improve the prediction models (P > 0.2), but the latter significantly improved the models (P ≤ 0.048). Similarly, when evening home BP and office BP during follow-up were analyzed, only the former significantly improved the prediction models (P ≤ 0.015). In conclusion, evening BP could be a more potent predictor than office BP, but it was inferior compared to morning BP in the treatment of mild-to-moderate hypertensive patients.

Keywords: antihypertensive drug treatment; blood pressure control; cardiovascular; outcomes, self-measured home blood pressure; prospective study

Introduction

Cardiovascular death is the second leading cause of death in Japan after malignant neoplasms [1], and hypertension is a major risk factor for cardiovascular disease. The estimated number of deaths annually in Japan was reported to be 100,000 [2]. In 2017, there were approximately 43 million hypertensive patients in Japan [3]. Home blood pressure (BP) measurement is widespread; approximately 40% of Japanese people measure their BP at home [4]. The current Japanese hypertension guideline [3] recommends using home BP as a tool for the diagnosis and treatment of hypertension based on an enormous amount of research on its reproducibility, reliability, and better predictive ability than office BP [5].

Evening home BP is essentially different from that in the morning, since the measurement conditions for evening home BP are more lenient than those for morning home BP [3]. For morning home BP, the measurement must be taken within 1 hour after waking up, after micturition, and before taking medications, whereas the only condition for evening home BP is taking the measurement before going to bed. Therefore, evening BP is more easily affected by various activities of daily living [6,7].

Both BP measurements are also different from physiological and pharmacodynamic points of view. Morning BP is related to smoking habits [8], alcohol intake [9], cardiovascular disease [9], sleep apnea [9], and the trough effect of antihypertensive medication [10,11], whereas evening home BP is related to the peak effect of antihypertensive medication [5]. However, whether evening home BP has predictive ability comparable to that of morning BP and whether it has additional predictive ability over and beyond that of morning BP [12-14] has not been established. All of these observational studies relied on only one point in the past.

Therefore, the aim of the present study was to compare evening and morning BPs and examine whether evening home BP has additional prognostic value for the risk of a major

adverse cardiovascular event (MACE); data from the Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) were used in a post hoc analysis, with evening BP measurements taken at baseline before treatment and during the on-treatment follow-up period. The predictive ability of evening BP was also compared with that of office BP, since there is little evidence for evening BP compared with morning BP.

Methods

Design

This study was a post hoc analysis of the HOMED-BP study. The HOMED-BP study was a multicenter, clinical trial that included a prospective, randomized, open-label, blinded endpoint evaluation (PROBE) [15]. With a 2×3 factorial design, BP control (tight vs. usual), as well as the drug classes for starting treatment (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers) were examined [16]. The study began with the first patient randomized on June 6, 2001, with the last patient randomized on October 7, 2009. The primary outcome of the HOMED-BP study was examined as of April 30, 2010 [16], and extended follow-up observations of BP measurements and outcomes continued to the end of 2012.

The study protocol was approved by the institutional review board of the Teikyo University School of Medicine (17-044-2). Written, informed consent was obtained from all study participants. The protocol of the HOMED-BP study conformed with the Helsinki Declaration [17] and was registered with the UMIN Clinical Trial Registry, Number C000000137 (http://www.umin.ac.jp/ctr).

Study patients

The HOMED-BP study [16] involved patients with mild-to-moderate hypertension, aged from 40 to 79 years, who were being treated at 457 general practices throughout Japan. Patients who were eligible for the study included those who were treatment-naïve and those who were previously treated but whose antihypertensive drug treatment could be discontinued for at least two weeks, with the patients maintaining a home systolic BP of 135-179 mmHg or home diastolic BP of 85-119 mmHg when not on treatment. To be eligible, patients could not have any contraindications to antihypertensive agents.

For the present analysis, data from all 3518 patients who were assigned to each intervention arm (tight vs. usual BP control and a comparison of the drug classes for starting treatment) were pooled, based on our previous report that showed that the risks of the cardiovascular outcomes were similar in the intervention arms because there was only a slight BP difference between them [16,18]. However, the doses of antihypertensive medications in the tight vs. usual BP control arms were slightly, but significantly, different (Supplementary Table 1 of the online supplementary materials).

A total of 252 patients were excluded due to the lack of availability of various BP readings, including office BP at follow-up (n=180), evening home BP at baseline (n=60), morning home BP during follow-up (n=5), or evening home BP during follow-up (n=7). Thus, the statistical analysis included a total of 3266 participants.

Blood pressure measurement

The participants in the HOMED-BP study were asked to measure their home BP every morning and evening during the entire study period following the Japanese guidelines for home BP monitoring [19]. Morning BP was measured after resting for ≥2 min in a sitting position, within an hour of waking, before breakfast, and before taking antihypertensive

medications. Evening BP was measured just before going to bed. The subjects were permitted to measure their BP more than twice on each occasion, but the first measurement value from each occasion was used in the analysis to exclude subject selection biases.

All patients were given validated [20] oscillometric OMRON HEM-747IC-N monitors (Omron Healthcare, Kyoto, Japan), which store readings in their memory, to measure their home BP. The baseline home BP was defined as the average of the readings from the 5 days (5 readings) immediately prior to randomization, i.e., before antihypertensive drug treatment was started. In patients who had not experienced a cardiovascular event, the follow-up home BP was defined as the average of the last available 5-day home BP readings (5 readings). In patients who had experienced a cardiovascular event, the follow-up home BP was defined as the corresponding home BP values recorded six months before the event; this 6-month interval was specified to minimize bias related to the fall or rise of the follow-up BP as a precursor to an event [21]. Morning home BP and evening home BP were defined and calculated in a similar manner. The 5-day average morning BP was also used to determine eligibility and adjustments to treatment at each visit.

Blood pressure was measured at each office visit by practitioners using a validated [22] oscillometric OMRON HEM-907IT device (Omron Healthcare) after the patients had rested in a sitting position for 2 min; two consecutive BP measurements were obtained, and their average was used as the office BP measurement.

Definitions of events and covariates

The endpoints were coded using the International Classification of Diseases, 10th revision (ICD-10). MACEs were defined as a composite of cardiovascular death (ICD-10 codes I00 to I99), nonfatal stroke (I60, I61, and I63), and nonfatal myocardial infarction (I21) [16,18]. All events were adjudicated by the endpoint committee, which was unaware of the patients'

randomization. Only the first event of an individual was used in the outcome analysis.

The definition of diabetes mellitus was a fasting plasma glucose level ≥ 7.0 mmol/l (126 mg/dl), an HbA_{1c} level ≥ 6.5% [23], or treatment with antidiabetic agents; hypercholesterolemia was defined as a total cholesterol level ≥ 5.69 mmol/l (220 mg/dl), a documented history of hypercholesterolemia, or treatment with cholesterol-lowering drugs.

Statistical analysis

SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA), was used for database management and statistical analysis. All data are expressed as the means ± standard deviations (SDs) unless otherwise stated. A two-sided alpha-level <0.05 was considered significant. Average BP values were compared by the paired *t test*. A Cox proportional hazard model adjusted for the baseline characteristics of sex, age, body mass index, current drinking, current smoking, hypercholesterolemia, diabetes mellitus, history of cardiovascular disease, and randomization group was used to calculate the hazard ratio and 95% confidence interval for MACEs for each 1-SD difference in each BP index [18]. To determine the improvement of the goodness of fit or “informativeness” of adding a BP index to a model, the likelihood ratio statistic for the risk of MACEs was used [16,18,24]. Whether an additional BP index significantly improved the adequacy of a model was determined by the likelihood ratio test between one model with a single BP index with covariables and a similar model containing another BP index.

Results

The patients’ characteristics are shown in Table 1. Of the 3266 patients, 1653 (50.6%) were men. The mean age and body mass index were 59.5 ± 10.0 years and 24.4 ± 3.4 kg/m^2, respectively; 678 (20.8%) patients were current smokers, 1563 (47.9%) drank alcohol, 508

(15.6%) had diabetes mellitus, 1692 (51.8%) had hypercholesterolemia, and 103 (3.2%) had a history of cardiovascular disease. The evening home BPs were lower than the morning home BPs and office BPs at baseline and during follow-up ($P < 0.0001$). The systolic/diastolic BPs during follow-up were 125.0 ± 14.7/71.7 ± 10.2 mmHg for evening home BP, 130.4 ± 13.5/77.0 ± 9.8 mmHg for morning home BP, and 130.9 ± 17.5/75.3 ± 12.1 for office BP. All BPs were lower during follow-up than at baseline ($P < 0.0001$).

Over a median follow-up of 7.1 years (interquartile range 4.6–9.0 years, maximum 11.5 years), MACEs occurred in 58 patients, including cardiovascular death in 6 patients, nonfatal stroke in 42 patients, and nonfatal myocardial infarction in 10 patients. Fig. 1 shows the adjusted hazard ratios and the 95% confidence intervals of BPs for MACEs. Evening home BPs predicted MACEs, except systolic BPs at baseline ($P = 0.067$). Morning home BPs were strongly and consistently associated with MACE risk, both at baseline and during follow-up. Office BP was associated with MACE risk only during follow-up.

Table 2 indicates the formal comparison of predictive power for MACEs between evening home BP at baseline and evening home BP during follow-up by including these variables simultaneously in the same Cox model. Evening home BP during follow-up strongly predicted MACEs, but that at baseline did not. The likelihood ratio statistics were significant when adding evening home BP during follow-up but not when adding evening home BP at baseline, suggesting that the predictive power for MACEs was stronger for evening home BP during follow-up than that at baseline.

The formal comparison of predictive power for MACEs between evening home BP and morning home BP is shown in Fig. 2. For each pair of BP indices, both evening home BP and morning home BP were included in the same model. Evening home BP consistently failed to predict MACEs; however, morning home BP significantly predicted MACEs. The likelihood ratio statistics were not significant when adding evening home BP to the model, but they

were significant when adding morning home BP, suggesting that the predictive power for MACEs was lower for evening home BP than for morning home BP, both at baseline and during follow-up.

The predictive power for MACEs was also compared between evening home BP and office BP (Fig. 2). At baseline, the superiority of evening home BP over office BP was unclear; the hazard ratios and the likelihood ratio statistics for systolic BP at baseline were not significant for either evening home BP or office BP. However, during follow-up, the predictive power for MACEs was stronger for evening home BP than for office BP. A sensitivity analysis by the tight vs. usual BP control arms was also performed because of the slight, but significant, difference in the doses of antihypertensive medications (Supplementary Table 1 of the online supplementary materials). The results were approximately similar to those of the primary analysis, although the difference in predictive power among the BP indices was not significant for systolic BP due to the relatively small number of outcomes (Supplementary Figure 1 and Supplementary Figure 2 of the online supplementary materials).

Discussion

In the present study, the predictive power of evening home BP for MACEs was compared with that of morning home BP and office BP obtained at baseline in the untreated period and during the on-treatment follow-up period in a post hoc analysis of the data of mild-to-moderate hypertensive patients who participated in the randomized, controlled trial of the HOMED-BP study. It was found that (1) evening home BP during follow-up was more closely associated with the risk of MACEs than that at baseline before starting antihypertensive treatment. (2) In addition, evening home BP was more predictive than office BP. However,

evening home BP was significantly inferior to morning home BP, with no additional increase in predictive value during the on-treatment follow-up period.

The finding of the inferior predictive ability of evening home BP compared with morning home BP in the present analysis was in line with studies of Japanese residents [13] and Japanese patients with cardiovascular risk factors [12] but were not similar to those of a study with representative Finnish subjects (the Finn-Home study) [14], in which no significant difference in the predictive power of evening BP and morning BP was observed. The results of the present study were also different from those of the Didima outcome study [25], in which evening BP had no prognostic superiority over morning BP. The reason for the inconsistent results between the present study and the European studies [14,25] may be partly explained by differences in the treatment strategies and the degree of 24-hour BP control. The present study's drug adjustment was based solely on morning BP rather than a combination of morning and evening BP. Although the present study did not include 24-hour blood pressure measurements, this treatment strategy may have been disadvantageous for 24-hour BP control. In addition, as shown in Supplementary Table 1 of the online supplementary materials, most patients took antihypertensive medications after breakfast, and fewer took them after dinner or before bedtime. The 24-hour BP control could also be dependent on the duration of action of the medication. Many of the prescribed medications did not have durations of action of more than 24 hours. Since the present study was a post hoc analysis of the HOMED-BP trial, the proportion of patients taking antihypertensive medication was 100%. On the other hand, in the European studies [14,25], the proportion of participants on antihypertensive medication was lower: 15.9% and 23% in the Didima outcome study [25] and the Finn-Home study [14], respectively.

Another possibility for the differences was the less standardized measurement conditions of evening BP in Japanese studies [12,13], including the present study. Evening

home BPs were lower than morning BPs and had a more significant standard deviation (Table 1), indicating less standardized measurement conditions. The less standardized measurement conditions of evening BP lead to interference by different behavioral conditions between morning and evening measurements, such as having a meal, taking a warm bath, drinking alcohol, and resting before measurements [26]. This is also a possible explanation for the agreement of the present findings with the results of previous Japanese studies using the same methodology for the home BP measurement condition. Additionally, this is a possible explanation for the disagreement with the findings of the Finn-Home study [14] (in which no significant difference in predictive power between evening HBP and morning HBP was found) and with those of the Didima outcome study [25] (where evening and morning HBP had similar prognostic values). In the Japanese studies [12,13], evening BP was measured before going to bed. Conversely, evening BP was measured in an earlier time period, from 18:00 to 21:00 in the Finn-Home study [14], and from 17:00 to 23:00 in the Didima outcome study [25]. Blood pressure measurement in this earlier time period may be less affected by daily activities such as drinking alcohol and bathing than measurements taken just before going to bed. Evening BP measurements were insufficiently standardized in the Japanese studies compared with morning BP, which was measured in more strictly specified conditions: within 1 hour after waking up, before taking medication [12,13], after urination, and before breakfast [13]. The difference in the predictive ability of home BP in the evening and the morning may be related to the time period of the measurement and the degree of standardization of the measurement conditions. According to the Japanese guideline [3], evening home BP should be measured before going to bed, but various measurement conditions are allowed. It may be necessary to reconsider the measurement time for the best prediction of cardiovascular events. In addition, since the various measurement conditions are the antithesis of the standardization of BP measurements, there

is a concern that they may decrease the predictive ability of evening BP. Compliance with the guideline also varies from practitioner to practitioner [27]. Further studies will be needed to determine the best measurement time period and measurement conditions of evening BP that have the highest predictive power for cardiovascular diseases.

Unlike previous studies [3,12,13], in which BPs were captured in only one time period, the predictive ability of BPs measured both in the baseline untreated period and during the follow-up on-treatment period was evaluated in the present study. When evening BPs at baseline and during follow-up were included in the same model, only the follow-up values significantly improved the prediction models (Table 2). This might partly depend on the fact that achieved BP is more closely associated with complications of hypertension than initial BP due to the treatment-induced changes over time, as shown in previous studies [28,29]. However, in our previous post hoc analysis of the HOMED-BP study, both the morning home BP at baseline and that during follow-up significantly and independently predicted MACEs when both BPs were adjusted for each other in the same Cox model [18]. Thus, the importance of considering the residual risk of home BP at baseline before treatment initiation to improve the prevention of future cardiovascular diseases remains undeniable. Regardless, we should adhere to the basic policy that has repeatedly stated that achieving lower BP levels is essential for preventing cardiovascular disease with antihypertensive drug treatment [30,31].

The present results showed that evening home BP is superior to office BP for predicting MACEs during follow-up while on treatment. The accumulated past studies show that morning home BP is superior to office BP. However, there are very few studies comparing the predictive power of evening home BP with that of office BP [5,32,33]. Past studies have compared the predictive power of office BP for cardiovascular outcomes, primarily focusing on morning home BP or the average of morning and evening home BPs [5,12,13,32,33]. We

emphasize that the present study is the first to compare the predictive power for MACEs between evening home BP and office BP both at baseline and during follow-up. Although not clear at baseline, evening BP was shown to be superior to office BP during the follow-up period. However, careful interpretation is required because the number of BP measurements was different between evening home BP (5 readings) and office BP (2 readings). Given the previous studies [14,32] showing that the higher the number of measurements, the higher the predictive power, the analysis in the present study may not show the pure predictive power of BP measurements. However, in clinical practice, home BP is measured at least five times, rather than twice, according to the current guidelines. Therefore, it is more clinically relevant to compare the average of the five measurements of home BP in the evening with the average of the two office BP measurements.

The current research findings must be interpreted in the context of potential limitations. First, the results were obtained in patients in clinical trials and cannot be applied to community residents. The results were obtained from Japanese patients and do not apply to subjects in other countries with different lifestyles, such as alcohol drinking and bathing habits. Furthermore, because this was a post hoc analysis of the HOMED-BP study, unmeasured confounding may not have been adequately taken into account. Second, drug adjustments and participant eligibility determinations were based on morning home BP rather than evening home BP in the HOMED-BP study protocol. This treatment strategy may have been disadvantageous in terms of 24-hour BP control and might represent a source of bias when comparing the prognostic values of morning and evening home BPs. Furthermore, unlike other studies [12-14], the standard deviation of the BP measurements was greater in the evening than in the morning (Table 1), suggesting that the measurement conditions for evening BP were less standardized. This may affect the prognostic comparison between evening and morning BP measurements. Third, the results were based on a small number of

events (n=58). Analysis according to the event subtypes could not be performed because of the small number of events, especially for myocardial infarction (n=13). Blood pressure was more closely associated with stroke than with ischemic heart disease [12,34]. The present results, in which MACEs consisted primarily of stroke, may not apply to European or American subjects who are more susceptible to ischemic heart disease than stroke.

In conclusion, evening BP could be a more potent predictor than office BP, but it was an inferior predictor compared to morning BP in treated mild-to-moderate hypertensive patients. Further studies of the predictive ability of evening BP compared with morning BP are needed to determine the best measurement conditions for evening BP that yield the highest predictive power for cardiovascular diseases.

Acknowledgments

The authors are grateful to all the HOMED-BP study collaborators as listed previously [16] for their valuable contributions. The authors would also like to thank the staff of Tohoku University and Teikyo University for their valuable help and Fujitsu Systems East Limited (Tokyo, Japan) and Omron Healthcare Co., Ltd. (Kyoto, Japan), who developed and maintained the internet-based infrastructure for the measurement of blood pressure at home and the management of patients.

Funding

This study was funded by grants from the Japan Cardiovascular Research Foundation, the Japan Arteriosclerosis Prevention Fund, and Tohoku University. This study was also supported by Grants-in-Aid for Scientific Research (16K15359, 17H04126, and 18K06759) from the Ministry of Education, Culture, Sports, Science and Technology, and ACRO Incubation Grants of Teikyo University. No funding agencies had any role in the design or

conduct of the study, in the collection, analysis, or interpretation of the data, or in the preparation, review, or approval of the manuscript.

Conflicts of Interest

Drs. Asayama, Imai, and Ohkubo were concurrent directors of the Tohoku Institute for Management of Blood Pressure, which was supported by Omron Healthcare Co., Ltd. The remaining authors have no disclosures to report.

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Table 1. Patients' characteristics

Characteristic	Baseline
Men, n (%)	1,653 (50.6)
Age, y	59.6 ± 10.0
Body mass index, kg/m^2	24.4 ± 3.4
Current smoker, n (%)	678 (20.8)
Current drinker, n (%)	1,563 (47.9)
Diabetes mellitus, n (%)	508 (15.6)
Hypercholesterolemia, n (%)	1,692 (51.8)
History of CVD, n (%)	103 (3.2)
Evening Home BP, systolic, mmHg	144.3 ± 15.7
Evening Home BP, diastolic, mmHg	82.9 ± 11.1
Morning Home BP, systolic, mmHg	151.6 ± 12.5
Morning Home BP, diastolic, mmHg	89.9 ± 10.1
Office BP, systolic, mmHg	154.3 ± 17.5
Office BP, diastolic, mmHg	90.2 ± 12.2

Values are shown as means ± SD or numbers (percentage). BP, blood pressure; CVD, cardiovascular disease. For missing values of body mass index (n=77), single imputation with regression on sex and age was conducted.

Table 2. Comparison of predictive power for major adverse cardiovascular events between evening home blood pressure (BP) at baseline vs. during follow-up

BP index	HR and 95% CI	LR	*P* for LR
Systolic			
Evening home BP at baseline	1.13 (0.87-1.48)	0.87	0.351
Evening home BP during follow-up	1.41 (1.12-1.77)	7.67	0.006
Diastolic			
Evening home BP at baseline	1.20 (0.89-1.63)	1.44	0.231
Evening home BP during follow-up	1.52 (1.14-2.02)	7.91	0.005

Home blood pressure (BP) in the evening at baseline and during follow-up were simultaneously included in the same model. Hazard ratios (HR) and 95% confidence intervals (CIs) were calculated for a 1-SD increment of BP indices. The likelihood ratio (LR) reflects an increase in the goodness of fit from adding home BP in the evening at baseline to a model with that during follow-up and vice versa. All models were further adjusted for the baseline characteristics of sex, age, body mass index, current smoking, current drinking, diabetes mellitus, hypercholesterolemia, history of cardiovascular disease, and randomization group.

Figure Legend

Fig. 1 Hazard ratios and 95% confidence intervals for major adverse cardiovascular events

Hazard ratios are for a 1-SD increment of blood pressure (BP) indices with an adjustment applied for the baseline characteristics of sex, age, body mass index, current smoking, current drinking, diabetes mellitus, hypercholesterolemia, history of cardiovascular disease, and randomization group.

Fig. 2 Comparison of the predictive power for major adverse cardiovascular events between evening home blood pressure (BP) and morning home BP and between evening home BP and office BP

A pair of BP indices for comparing predictive power, the evening home BP and morning home BP, were included in the same model at the same time. Then, pairs of evening home BP vs. office BP were also analyzed. Hazard ratios and 95% confidence intervals are for a 1-SD increment of the BP indices. The likelihood ratio (LR) reflected an increase in the goodness of fit from adding a BP index to a model with another BP index and vice versa. The greater the LR, the more significant the goodness of fit or “informativeness” with the additional BP index was. All models were further adjusted for the baseline characteristics of sex, age, body mass index, current smoking, current drinking, diabetes mellitus, hypercholesterolemia, history of cardiovascular disease, and randomization group.

Figure 1

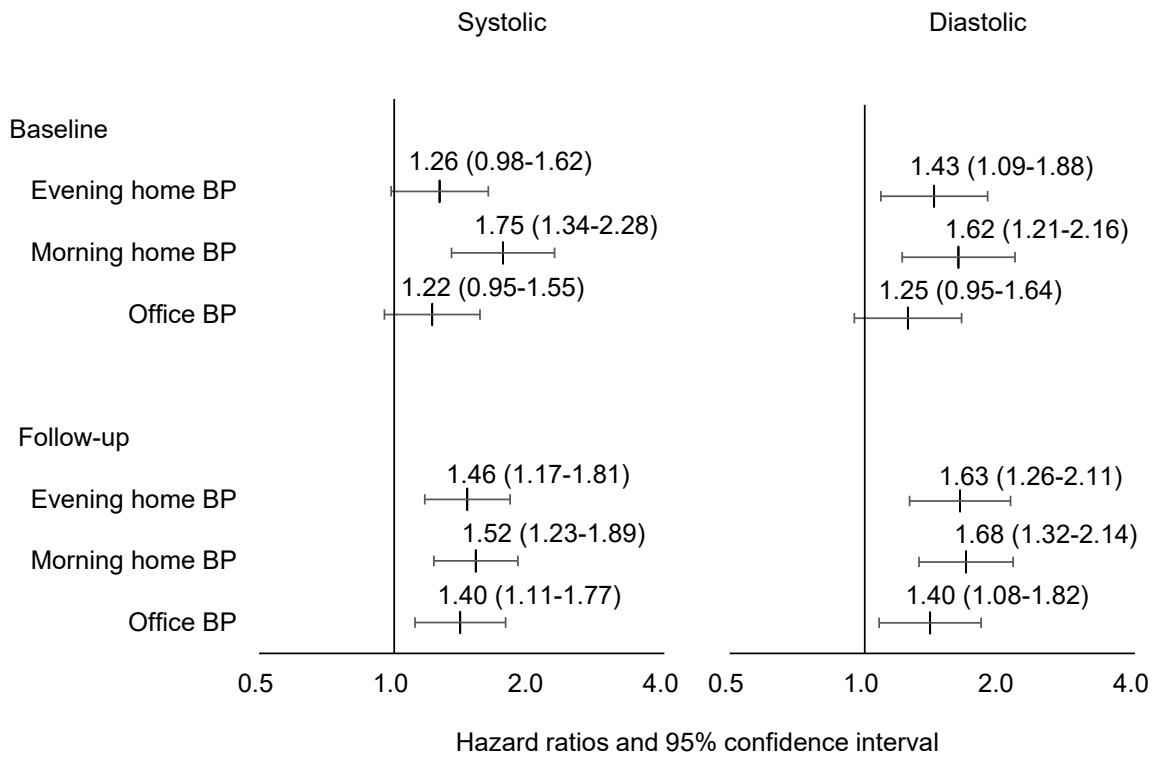
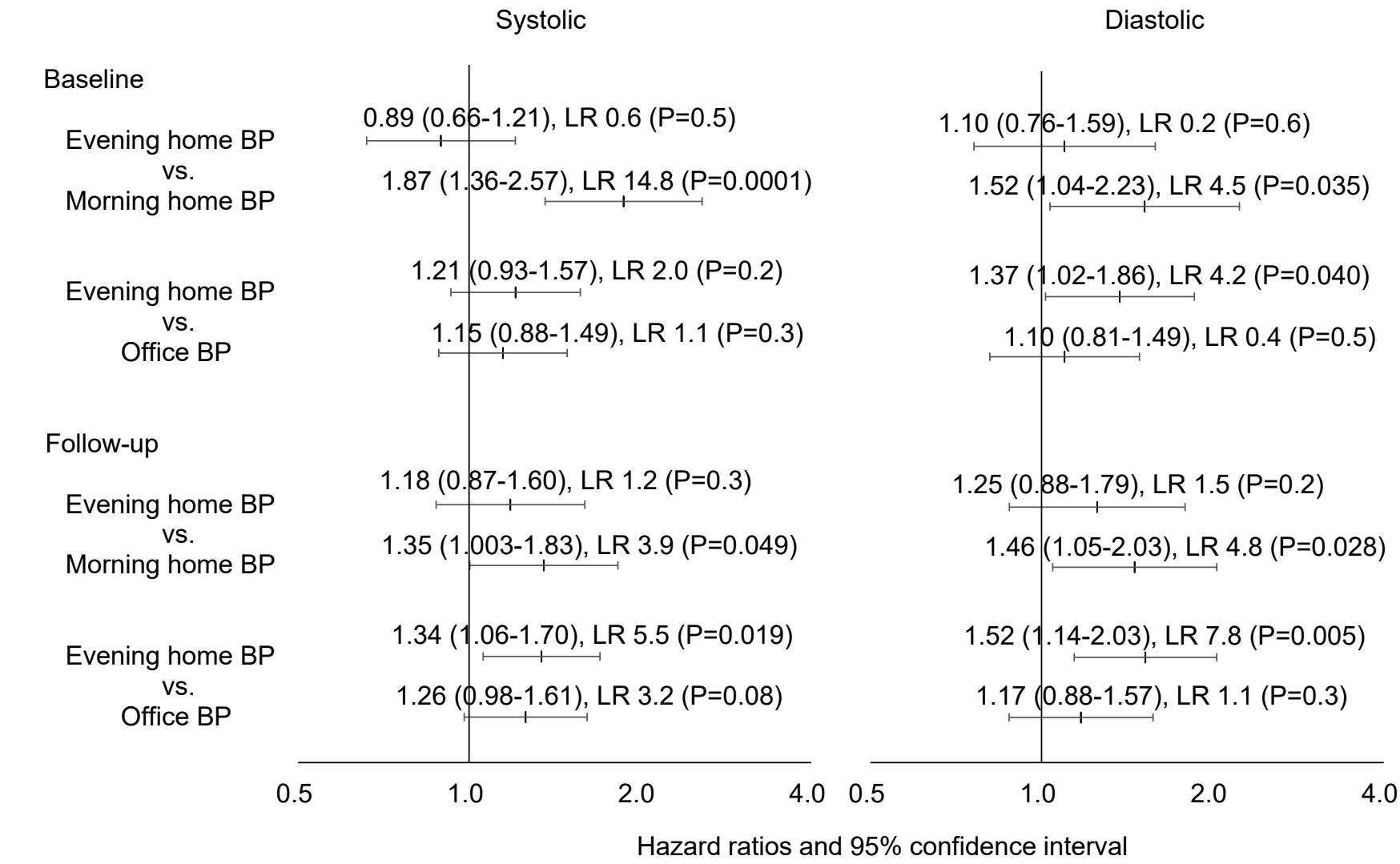

Systolic
Diastolic
Baseline
Evening home BP
Morning home BP
Office BP
Follow-up
Evening home BP
Morning home BP
Office BP
1.26 (0.98-1.62)
1.75 (1.34-2.28)
1.22 (0.95-1.55)
1.43 (1.09-1.88)
1.62 (1.21-2.16)
1.25 (0.95-1.64)
1.46 (1.17-1.81)
1.52 (1.23-1.89)
1.40 (1.11-1.77)
1.63 (1.26-2.11)
1.68 (1.32-2.14)
1.40 (1.08-1.82)
0.5
1.0
2.0
4.0
0.5
1.0
2.0
4.0
Hazard ratios and 95% confidence interval

Figure 2


Systolic
Diastolic
Baseline
Evening home BP
vs.
Morning home BP
0.89 (0.66-1.21), LR 0.6 (P=0.5)
1.87 (1.36-2.57), LR 14.8 (P=0.0001)
1.10 (0.76-1.59), LR 0.2 (P=0.6)
1.52 (1.04-2.23), LR 4.5 (P=0.035)
Evening home BP
vs.
Office BP
1.21 (0.93-1.57), LR 2.0 (P=0.2)
1.15 (0.88-1.49), LR 1.1 (P=0.3)
1.37 (1.02-1.86), LR 4.2 (P=0.040)
1.10 (0.81-1.49), LR 0.4 (P=0.5)
Follow-up
Evening home BP
vs.
Morning home BP
1.18 (0.87-1.60), LR 1.2 (P=0.3)
1.35 (1.003-1.83), LR 3.9 (P=0.049)
1.25 (0.88-1.79), LR 1.5 (P=0.2)
1.46 (1.05-2.03), LR 4.8 (P=0.028)
Evening home BP
vs.
Office BP
1.34 (1.06-1.70), LR 5.5 (P=0.019)
1.26 (0.98-1.61), LR 3.2 (P=0.08)
1.52 (1.14-2.03), LR 7.8 (P=0.005)
1.17 (0.88-1.57), LR 1.1 (P=0.3)
0.5
1.0
2.0
4.0
0.5
1.0
2.0
4.0
Hazard ratios and 95% confidence interval

ONLINE SUPPLEMENT

Predictive power of home blood pressure in the evening compared with home blood pressure in the morning and office blood pressure before treatment and in the on-treatment follow-up period: A post hoc analysis of the HOMED-BP study

Running title: Home BP in the evening for the prediction of MACEs

Shinya Uchida [1], Masahiro Kikuya [1 2], Kei Asayama [1 3 4], Chiaki Ohata [1], Takahiro Kimura [1 5], Yukako Tatsumi [1], Kyoko Nomura [1 6], Yutaka Imai [4], Takayoshi Ohkubo [1 4], Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) Investigators

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Tables 1; Figures 2

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Supplementary Table 1. Detailed information on quantities of prescribed medications and the timing of their administration according to the defined daily dose by intervention arm

	Usual control arm (N= 1625)					Tight control arm (N= 1639)				
	Daily total	Morning	Evening	Bed	Unknown	Daily total	Morning	Evening	Bed	Unknown
Total	1.64±1.08	1.10±0.90	0.10±0.32	0.24±0.59	0.19±0.59	**1.72*±1.13**	1.14±0.96	0.12±0.34	0.26±0.63	0.20±0.61
CCBs	0.58±0.67	0.38±0.53	0.05±0.20	0.09±0.30	0.06±0.28	**0.63*±0.70**	0.41±0.57	0.06±0.21	0.09±0.30	0.07±0.29
Amlodipine	0.29±0.50	0.21±0.41	0.01±0.11	0.04±0.19	0.04±0.21	0.30±0.50	0.21±0.42	0.01±0.10	0.04±0.18	0.04±0.22
Benidipine	0.09±0.38	0.05±0.26	0.01±0.12	0.01±0.14	0.01±0.13	0.09±0.37	0.05±0.25	0.01±0.10	0.01±0.14	0.01±0.15
Nifedipine CR	0.06±0.28	0.04±0.20	0.01±0.08	0.01±0.08	0.01±0.08	0.07±0.31	0.04±0.18	0.02±0.11	0.01±0.10	0.01±0.09
Cilnidipine	0.05±0.25	0.03±0.16	0.00±0.06	0.01±0.11	0.00±0.07	0.06±0.28	0.03±0.19	0.01±0.10	0.01±0.11	0.00±0.05
Other CCBs	0.08±0.31	0.05±0.25	0.01±0.06	0.02±0.12	0.01±0.09	0.11±0.41	0.08±0.34	0.01±0.08	0.02±0.14	0.01±0.08
ACEs	0.15±0.40	0.11±0.31	0.01±0.10	0.01±0.10	0.02±0.17	0.13±0.35	0.08±0.25	0.01±0.10	0.01±0.11	0.02±0.16
Imidapril	0.05±0.19	0.03±0.14	0.00±0.05	0.01±0.07	0.01±0.07	0.05±0.19	0.03±0.15	0.00±0.03	0.00±0.05	0.01±0.08
Perindopril	0.05±0.28	0.03±0.22	0.00±0.06	0.00±0.07	0.01±0.13	0.04±0.24	**0.02*±0.14**	0.00±0.07	0.00±0.09	0.01±0.12
Enalapril	0.01±0.11	0.01±0.09	0.00±0.02	0.00±0.03	0.00±0.04	0.02±0.11	0.01±0.08	0.00±0.03	0.00±0.01	0.00±0.04
Lisinopril	0.01±0.14	0.01±0.13	0.00±0.03	0.00±0.02	0.00±0.01	0.01±0.11	0.01±0.08	0.00±0.04	0.00±0.01	0.00±0.01
Other ACEs	0.03±0.17	0.02±0.11	0.00±0.05	0.00±0.01	0.00±0.07	0.02±0.13	0.01±0.09	0.00±0.04	0.00±0.04	0.00±0.05
ARBs	0.54±0.60	0.37±0.51	0.03±0.16	0.06±0.26	0.07±0.28	0.57±0.61	0.39±0.51	0.03±0.16	0.07±0.28	0.07±0.27
Valsartan	0.16±0.43	0.10±0.33	0.01±0.10	0.01±0.13	0.02±0.16	0.16±0.41	0.11±0.32	0.01±0.09	0.02±0.15	0.02±0.13
Candesartan	0.15±0.35	0.10±0.30	0.00±0.05	0.01±0.11	0.02±0.15	0.14±0.35	0.10±0.30	0.00±0.04	0.02±0.15	0.02±0.14
Telmisartan	0.09±0.34	0.06±0.25	0.01±0.08	0.02±0.15	0.01±0.09	0.10±0.35	0.07±0.29	0.00±0.06	0.01±0.12	0.01±0.13
Olmesartan	0.09±0.31	0.06±0.24	0.00±0.06	0.01±0.12	0.01±0.09	0.09±0.34	0.07±0.26	0.01±0.10	0.01±0.12	0.00±0.07
Other ARBs	0.06±0.26	0.04±0.20	0.00±0.05	0.00±0.08	0.01±0.12	0.07±0.29	0.04±0.21	0.00±0.06	0.01±0.10	0.01±0.14

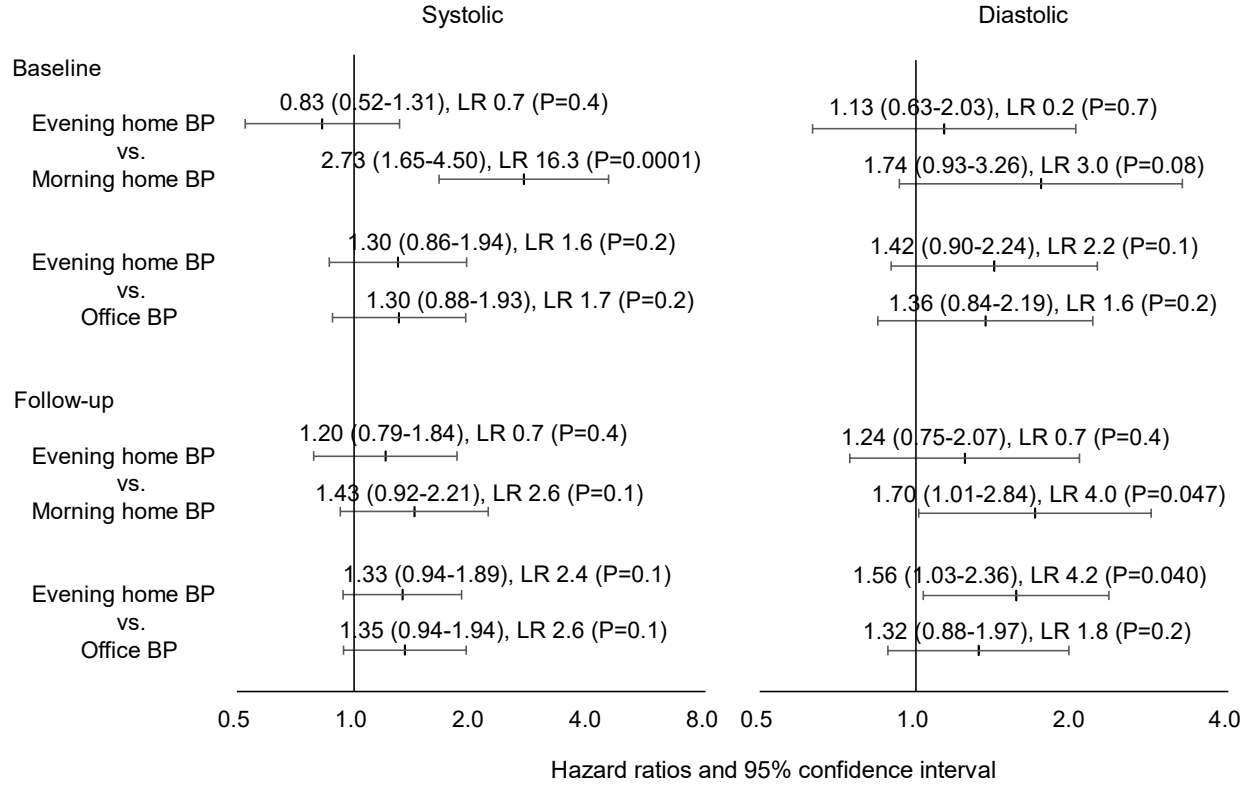
Supplementary Table 1. Continued

	Usual control arm (N= 1625)					Tight control arm (N= 1639)				
	Total	Morning	Evening	Bed	Unknown	Total	Morning	Evening	Bed	Unknown
Diuretics	0.15±0.23	0.13±0.22	0.00±0.02	0.01±0.06	0.02±0.10	0.17±0.25	0.14±0.22	0.00±0.04	**0.01*±0.06**	0.02±0.10
Indapamide	0.05±0.14	0.04±0.13	0.00±0.00	0.00±0.02	0.01±0.06	0.06±0.15	0.05±0.14	0.00±0.00	**0.00*±0.03**	0.01±0.07
Trichlormethiazide	0.04±0.12	0.03±0.11	0.00±0.00	0.00±0.01	0.01±0.05	0.05±0.12	**0.04*±0.11**	0.00±0.01	0.00±0.01	0.01±0.05
Eplerenone	0.01±0.10	0.01±0.07	0.00±0.02	0.00±0.05	0.00±0.00	0.02±0.11	0.01±0.09	0.00±0.03	0.00±0.05	0.00±0.00
Hydrochlorothiazide	0.01±0.07	0.01±0.07	0.00±0.00	0.00±0.00	0.00±0.00	0.01±0.09	**0.01*±0.09**	0.00±0.00	**0.00*±0.01**	0.00±0.00
Other Diuretics	0.03±0.14	0.03±0.13	0.00±0.00	0.00±0.01	0.00±0.06	0.03±0.14	0.03±0.12	0.00±0.03	0.00±0.01	0.00±0.05
Alpha-blockers	0.06±0.18	0.02±0.12	0.00±0.03	0.03±0.12	0.01±0.06	0.07±0.19	0.03±0.11	0.00±0.03	0.03±0.13	0.01±0.07
Doxazosin	0.06±0.18	0.02±0.11	0.00±0.03	0.03±0.12	0.01±0.06	0.07±0.19	0.03±0.11	0.00±0.03	0.03±0.13	0.01±0.07
Other Alpha	0.00±0.03	0.00±0.02	0.00±0.01	0.00±0.02	0.00±0.02	0.00±0.03	0.00±0.02	0.00±0.01	0.00±0.01	0.00±0.00
Beta-blockers	0.09±0.21	0.06±0.17	0.00±0.04	0.02±0.08	0.01±0.07	0.09±0.19	0.06±0.16	0.00±0.04	0.01±0.08	0.01±0.06
Atenolol	0.03±0.14	0.02±0.11	0.00±0.02	0.01±0.06	0.00±0.04	0.03±0.12	0.02±0.11	0.00±0.02	0.00±0.04	0.00±0.04
Bisoprolol	0.02±0.10	0.01±0.08	0.00±0.01	0.00±0.04	0.00±0.01	0.02±0.10	0.01±0.08	0.00±0.02	0.00±0.05	**0.00*±0.03**
Carvedilol	0.01±0.06	0.01±0.05	0.00±0.01	0.00±0.02	0.00±0.03	0.02±0.08	0.01±0.06	0.00±0.02	0.00±0.02	0.00±0.03
Other Beta	0.02±0.12	0.01±0.09	0.00±0.04	0.00±0.04	0.00±0.04	0.02±0.10	0.01±0.08	0.00±0.02	0.00±0.04	0.00±0.02
Others	0.07±0.25	0.03±0.16	0.01±0.07	0.03±0.14	0.00±0.04	0.07±0.25	0.03±0.15	0.01±0.06	0.03±0.13	0.01±0.06

Abbreviations: CCBs, calcium channel blockers; Nifedipine CR, nifedipine controlled release; ACEs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers. Among the 3266 patients, the information of prescribed medication was unclear in two patients. The antihypertensive medications were quantified in each participant at the last visit according to the defined daily dose version 2021 (World Health Organization Collaborating Centre for drug statistics methodology system of defined daily doses, https://www.whocc.no/atc_ddd_index/ Accessed 25 November 2021). Timing of administration was categorized as the morning, evening, before going to bed (bed), and unknown timing.

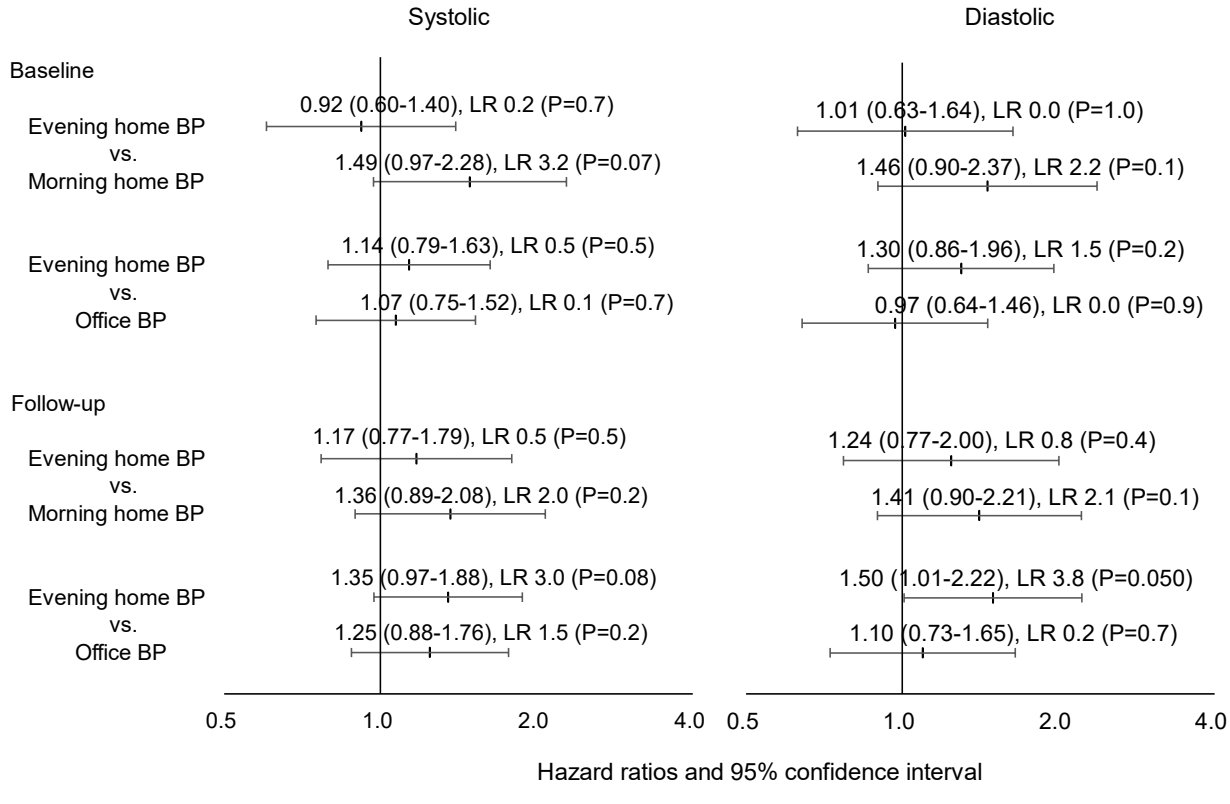
* Wilcoxon rank-sum test, P <0.05 vs. usual control arm.

Supplementary Figure 1. Comparison of predictive powers for major adverse cardiovascular events between evening home BP and morning home BP, and between evening home BP and office BP in patients in the usual control arm (N= 1627)



The number of events was 26. A pair of BP indices for comparing predictive power, the evening home BP and the morning home BP, are included in the same model at the same time. Then, evening home BP vs. office BP pairs are also analyzed. Hazard ratios and 95% confidence intervals are for a 1-SD increment of BP indices. The likelihood ratio (LR) reflects an increase in the goodness of fit from adding a BP index to a model with another BP index and vice versa. The greater the LR, the more significant the goodness of fit or “informativeness” with the additional BP index. All models were further adjusted for the baseline characteristics of sex, age, body mass index, current smoking, current drinking, diabetes mellitus, hypercholesterolemia, and history of cardiovascular disease.

Supplementary Figure 2. Comparison of predictive power for major adverse cardiovascular events between evening home BP and morning home BP and between evening home BP and office BP in patients in the tight control arm (N= 1639)



The number of events was 32. A pair of BP indices for comparing predictive power, the evening home BP and the morning home BP, are included in the same model at the same time. Then, evening home BP vs. office BP pairs are also analyzed. Hazard ratios and 95% confidence intervals are for a 1-SD increment of BP indices. The likelihood ratio (LR) reflects an increase in the goodness of fit from adding a BP index to a model with another BP index and vice versa. The greater the LR, the more significant the goodness of fit or “informativeness” with the additional BP index. All models were further adjusted for the baseline characteristics of sex, age, body mass index, current smoking, and current drinking, diabetes mellitus, hypercholesterolemia, history of cardiovascular disease.