Association Between Amplitude of Seasonal Variation in Self-Measured Home Blood Pressure and Cardiovascular Outcomes: HOMED-BP (Hypertension Objective Treatment Based on Measurement By Electrical Devices of Blood Pressure) Study

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Background—The clinical significance of long-term seasonal variations in self-measured home blood pressure (BP) has not been elucidated for the cardiovascular disease prevention.

Methods and Results—Eligible 2787 patients were classified into 4 groups according to the magnitude of their seasonal variation in home BP, defined as an average of all increases in home BP from summer (July–August) to winter (January–February) combined with all decreases from winter to summer throughout the follow-up period, namely inverse- (systolic/diastolic, <0/<0 mm Hg), small- (0–4.8/0–2.4 mm Hg), middle- (4.8–9.1/2.4–4.5 mm Hg), or large- (≥9.1/≥4.5 mm Hg) variation groups. The overall cardiovascular risks illustrated U-shaped relationships across the groups, and hazard ratios for all cardiovascular outcomes compared with the small-variation group were 3.07 (*P*=0.004) and 2.02 (*P*=0.041) in the inverse-variation group and large-variation group, respectively, based on systolic BP, and results were confirmatory for major adverse cardiovascular events. Furthermore, when the summer–winter home BP difference was evaluated among patients who experienced titration and tapering of antihypertensive drugs depending on the season, the difference was significantly smaller in the early (September–November) than in the late (December–February) titration group (3.9/1.2 mm Hg versus 7.3/3.1 mm Hg, *P*<0.001) as well as in the early (March–May) than in the late (June–August) tapering group (4.4/2.1 mm Hg versus 7.1/3.4 mm Hg, *P*<0.001).

Conclusions—The small-to-middle seasonal variation in home BP (0–9.1/0–4.5 mm Hg), which may be partially attributed to earlier adjustment of antihypertensive medication, were associated with better cardiovascular outcomes. (***J Am Heart Assoc***. 2018;7:e008509. DOI: 10.1161/JAHA.117.008509.)

Key Words: cardiovascular outcomes • home blood pressure • hypertension • population studies • seasonal variation

Clinical Perspective

What Is New?

- A part of patients with hypertension shows inverse seasonal variation ie, higher blood pressure (BP) level in summer compared with winter.
- A large amplitude of the seasonal variation and an inverse seasonal variation in self-measured home BP are both associated with high cardiovascular risk.
- Early adjustment of antihypertensive medication by considering the change of seasons reduces summer-winter differences in home BP.

What Are the Clinical Implications?

- Cardiovascular risk can be appropriately managed by evaluating not only the BP itself but also the seasonal variation in BP.

Hypertension is a major risk factor for the mortality and morbidity of cardiovascular diseases that are preventable by reducing blood pressure (BP).[1–3] In addition to BP itself, many studies have recently focused on BP variability which is thought to be related to cardiovascular risk.[4–7]

Seasonal variations in BP have been widely investigated, and BP level is known to be lower in summer and higher in winter on average[8–16]; however, clinical research questions remain despite these studies. Specifically, whether the amplitude of seasonal variation in BP is related to the incidence of cardiovascular diseases is unclear, although cold-induced high BP is likely to be associated with increased cardiovascular mortality.[17–19] Although some patients show inverse seasonal variation such as higher BP in summer and lower BP in winter in clinical practice, we do not have relevant evidence on these patients. It is also unclear whether the summer-winter change in BP can be controlled by adjusting antihypertensive medications, although seasonal variations in BP were reported in patients on stable antihypertensive medications.[10,15] Furthermore, only a few investigators have reported the characteristics of seasonal variation based on self-measured home BP,[9–11,15,16] and none have described the cardiovascular outcomes. Compared with conventional office BP, home BP is a useful tool[20,21] that is highly reproducible[22] and reliable for predicting cardiovascular complications.[23,24] Seasonal BP change can be appropriately assessed based on long-term self-measurement at home.[16]

We investigated the association between seasonal variation in home BP and the onset of cardiovascular diseases and evaluated the effect on seasonal variation induced by the titration or tapering of antihypertensive medications.

Methods

The data, materials, and analytical methods will be made available to other researchers on request by contacting the corresponding author for purposes of reproducing the results or replicating the procedure.

HOMED-BP Trial

This paper is reported as a part of the multicenter HOMED-BP (Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure) trial which aimed to establish the long-term benefits in clinical practice based on self-measured home BP.[1,16,25–27] In the trial, 3518 patients were randomized to normal control (125–134 mm Hg systolic and 80–84 mm Hg diastolic) versus tight control (<125 mm Hg systolic and <80 mm Hg diastolic) of the home BP, and to the initiation of antihypertensive drug treatment with calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, and they were followed up until December 31, 2012 (median of 7.4 years).[27] During the follow-up period, antihypertensive drug medications were titrated or tapered in a step-by-step manner according to their home BP. Based on our previous report indicating that the risks of cardiovascular outcomes were similar in the randomized groups,[1] we integrated all the groups to analyze the whole patients in the present study. The HOMED-BP protocol complies with the Helsinki Declaration for Investigation of Human patients.[28] The institutional review board of the Tohoku University Graduate School of Medicine (2-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan) approved the study protocol, and all study participants provided written informed consent before the treatment designated in the protocol. The trial is registered with the University hospital Medical Information Network (UMIN) Clinical Trial Registry (#C000000137; http:// www.umin.ac. jp/ctr).

All patients were asked to self-measure BP at home every morning once on each occasion throughout the study period in accordance with the Japanese guideline for home BP monitoring[21] as follows: after at least 2 minutes' rest in a sitting position, within an hour of waking, before breakfast, and before taking antihypertensive medications. Validated oscillometric OMRON HEM-747IC-N monitors[29] (Omron Healthcare, Kyoto, Japan) were supplied to patients for the self-measurement of BP at home. At each clinic visit, the recorded home BP values with information on antihypertensive drug use were uploaded by physicians via a local computer to the HOMED-BP data server, and were used for the decision making in the trial on drug treatment.[1] If multiple BP measurement data per one occasion were uploaded, only the first value in each occasion was used. In all processes described in the following parts, systolic and diastolic home BP were separately handled except for the control rates of BP.

Evaluation of Association Between Seasonal Variation in Home BP and Cardiovascular Outcomes

The home BP values collected in the summer and in the winter were averaged in each year. Each season lasted from July to August for summer and from January to February for winter, to enable the sensitive capture of peaks within the 1-year seasonal variation in home BP based on our previous study.[16] A season with less than 5 days of morning home BP measurements was eliminated as a missing value in individuals. We ultimately enrolled 2787 patients who met the following criteria to explore the association between seasonal variation in home BP and the onset of cardiovascular diseases: (1) the patient was followed up for ≥1 year (n=3325); (2) no cardiovascular events developed within 1 year from randomization (n=3299); (3) at least one change in morning home BP, either from summer to winter or from winter to summer, was recorded during the follow-up period (n=2787) (Figure 1).

The seasonal variation in an individual was defined as an average of observed seasonal changes in home BP, ie, all increases in home BP from summer to winter combined with all decreases in home BP from winter to summer throughout the follow-up period. In patients who developed any cardiovascular disease during the follow-up period, home BP data after the initial event and the 6 months immediately before the event were excluded from the calculation of seasonal variation; the latter was adopted to minimize bias due to the fall or rise in the on-treatment BP as a forerunner of an event.[30] On the basis of seasonal variation in home BP, patients were classified into 1 of 4 groups: inverse- (BP in summer higher than that in winter, indicating a negative value for the seasonal variation) and small-, middle-, and large-variation groups; all patients except for those in the inverse-variation group were equally divided into small-, middle-, or large-variation groups depending on their seasonal variation in home BP. This classification was based on the hypotheses that: (1) there would be an optimal amplitude of seasonal variation in home BP; and (2) patients
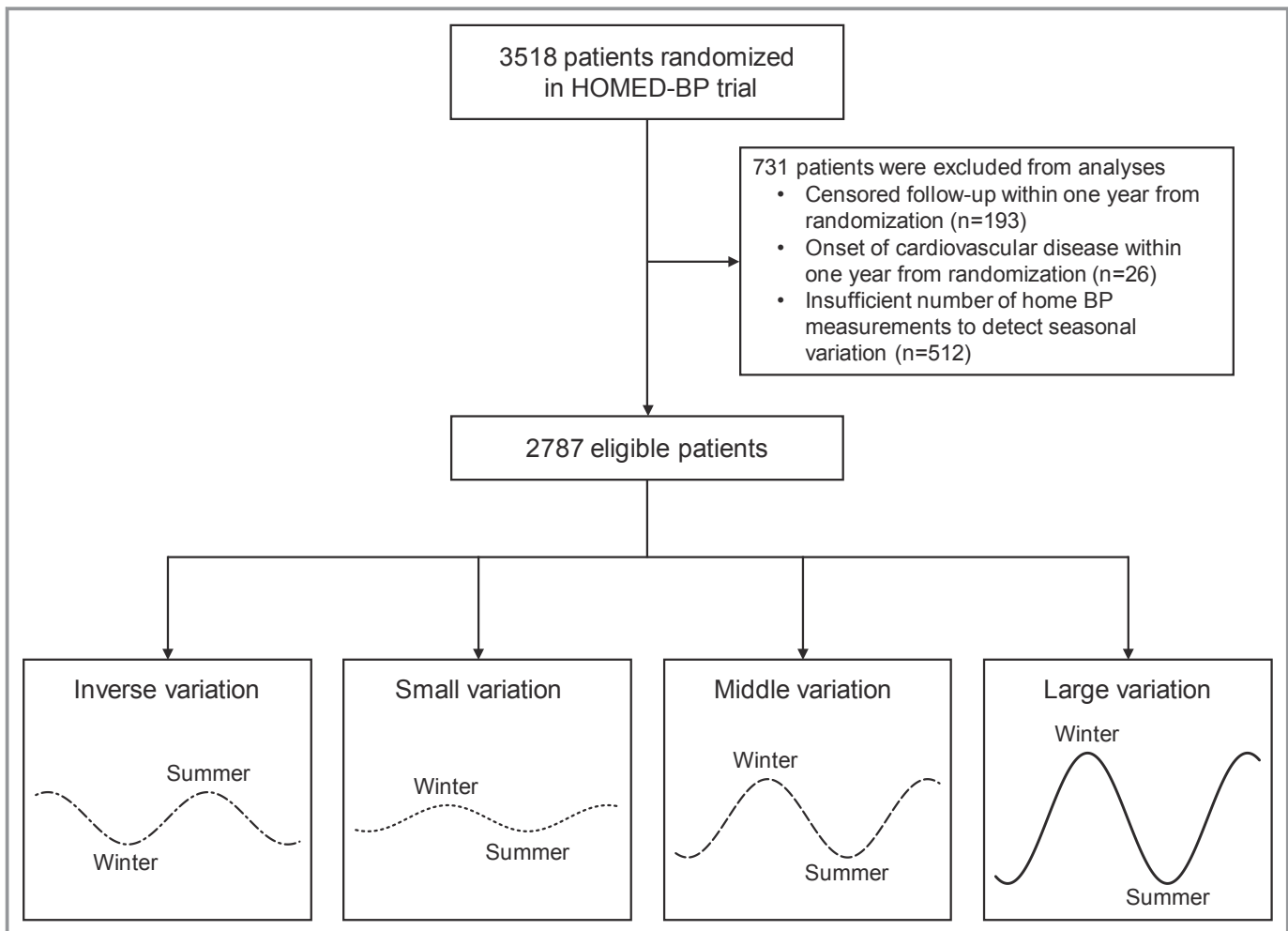

Figure 1. Flow chart of patient selection. The 2787 eligible patients were classified into one of the 4 variation groups, inverse, small, middle, or large, depending on the amplitude of seasonal variation in home systolic and diastolic BP. BP indicates blood pressure; HOMED-BP, Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure.

with larger or smaller, or even inverse ("riser" in summer), BP variations might have a high cardiovascular risk. In a sensitivity analysis, patients were equally divided into 5 20-percentile groups (quintiles) according to their BP difference between summer and winter. Furthermore, the impact of on-treatment office BP level for the predictive power of seasonal variation in home BP was investigated by adding the office BP to the model as a covariate.

Definition of Outcomes

The end points were coded according to the tenth revision of the *International Classification of Diseases, Tenth Revision (ICD-10)*. All cardiovascular outcomes encompassed cardio-vascular death (*ICD-10* codes I00–I99), non-fatal myocardial infarction (I21), non-fatal stroke (I60, I61, and I63), transient ischemic attack (G45), angina pectoris (I20), coronary atherosclerosis (I70), and fatal and non-fatal heart failure (I50). Of these, as in the original report of HOMED-BP trial,[1] major adverse cardiovascular events (MACE) were defined as a composite of cardiovascular death (*ICD-10* codes I00–I99), non-fatal myocardial infarction (I21), and non-fatal stroke (I60, I61, and I63). We examined risks of all cardiovascular outcomes and MACE across the seasonal variation groups. The end-point committee, which was unaware of the patients' randomization, adjudicated all events.

Effect of Antihypertensive Medications On Summer-Winter Difference in Home BP

To attenuate the trend that BP level is lower in summer and higher in winter on average,[8–16] antihypertensive drug prescription can be titrated from summer to winter, and be tapered from winter to summer. Thus, we further examined patients who went through drug titration after summer or tapering after winter to secondarily investigate whether seasonal variations in BP can be controlled by changing drug regimen. Of the 2787 selected patients, the 1135 patients who experienced titration of antihypertensive medications at least once from September to February, ie, between the end of summer and end of winter, during the follow-up period after the first year from randomization were eligible. The data in the first year were excluded to minimize the influence of frequent titrations of the initial antihypertensive treatment. When antihypertensive treatment had been changed ≥2 times during the follow-up period, change in home BP from summer to winter was calculated from the data of the earliest year. To clarify whether or not a proceeding change of antihypertensive treatment was effective in suppressing seasonal variation, patients were classified into early or late titration group (early: September–November or late: December–February; Figure 2). In the same manner, we analyzed the 1118 patients who experienced tapering of antihypertensive medications at least once from March to August, ie, between the end of winter and end of summer, and classified them into 2 tapering groups (early: March–May or late: June–August; Figure 2).

Statistical Analyses

We used SAS software, version 9.4 (SAS Institute, Cary, NC), for database management and statistical analysis. We compared means and proportions using the t test or the analysis of variance and chi-squared test, respectively. Data are expressed as mean and SD or percentages as appropriate unless otherwise stated. All tests were 2-sided and *P* values <0.05 were considered significant.
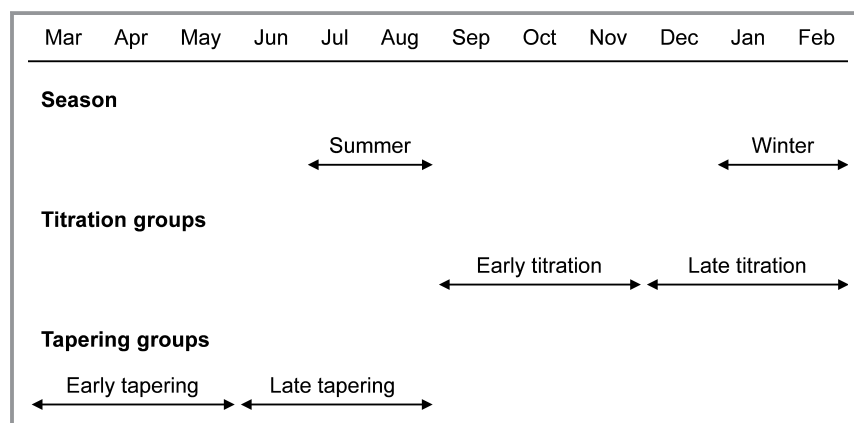
Figure 2. Definition of seasons, titration groups, and tapering groups. Seasons lasted from July to August for summer and January to February for winter. Patients whose medication was titrated from September to November and from December to February were assigned to the early and late titration groups, respectively. Similarly, patients whose drug tapering was done from March to May and June to August were assigned to the early and late tapering groups, respectively.

The baseline home BP was defined as an average of the 5-day morning home BP measured just before randomization, and on-treatment home BP was defined as the mean value of summer and winter BPs in the final year during the follow-up period. Diabetes mellitus was defined as a fasting plasma glucose of ≥126 mg/dL (7.0 mmol/L), an HbA1c of ≥6.5%, or treatment with oral anti-diabetic drugs or insulin. Hypercholesterolemia was defined as total cholesterol of ≥240 mg/dL (6.21 mmol/L), a documented history of hypercholesterolemia, or taking lipid-lowering drugs.

We used the Kaplan–Meier method to obtain survival curves for cardiovascular events (*P* values by Log-rank test with Sidak correction). To evaluate the cardiovascular risk associated with seasonal variation in home BP, hazard ratios with 95% confidence intervals (CI) were estimated using Cox proportional hazard models adjusted for sex, age, body mass index (BMI), current smoking, current habitual drinking, diabetes mellitus, hypercholesterolemia, history of cardiovascular disease, and corresponding baseline, on-treatment home BP (either systolic or diastolic BP according to the seasonal BP information), and the randomized groups in the HOMED-BP study. For missing values of BMI (n=42), single imputation with regression on age and sex was conducted. To compare the 4 seasonal variation groups, the lowest risk group was treated as the reference. Day 0 in the hazard model was set at 365 days after randomization since patients who developed any cardiovascular diseases within 1 year from randomization were excluded to calculate the seasonal variation.

Summer-winter differences in morning home BP were compared between the early and late titration groups or early and late tapering groups based on an analysis of covariance with adjustment for sex, age, BMI, current smoking, current habitual drinking, diabetes mellitus, hypercholesterolemia, history of cardiovascular disease, the pre-change BP (either systolic or diastolic BP according to the seasonal BP information), and the randomized groups in the HOMED-BP study. The pre-change BP was defined as the averaged summer BP or winter BP when assessing the change in BP from summer to winter or from winter to summer, respectively. Values were presented as least square means with 95% CI. Finally, change in the weighted-mean defined daily dose (DDD), an average of the standardized antihypertensive drug effect[31] weighted by treatment duration, from summer to winter and *vice versa*, and the control rates in winter home BP were assessed.

Results

Association Between Seasonal Variation in Home BP and Cardiovascular End Points

Eligible patients provided morning home BP data during 4.5-year, in which 43.8 measurements per season were included on average. Among the 2787 patients evaluated for the relationship between seasonal variation in BP and the onset of cardiovascular diseases, 371 (13.3%) and 539 (19.3%) patients were classified into the inverse-variation group based on their systolic and diastolic BP, respectively (Table 1). The thresholds of seasonal variation in systolic and diastolic home BP were 4.8/2.4 mm Hg between the small- and middle-variation groups and 9.1/4.5 mm Hg between the middle- and large-variation groups. Compared with the inverse-variation group based on systolic BP, patients in the middle- and large-variation groups were 1.6 (*P*=0.041) and 3.9 (*P*<0.001) years older, respectively, and the corresponding differences were 2.4 (*P*<0.001) and 2.3 (*P*<0.001) years based on the diastolic BP. However, sex differences among the 4 groups were not significant, regardless of systolic or diastolic blood pressure (*P*≥0.35). Each variation group showed repeated seasonal variation in systolic and diastolic home BP as a population throughout the follow-up period (Figure 3).

All cardiovascular outcomes and MACE occurred in 79 and 45 patients, respectively (Table 2). The rates of cardiovascular events were lower than 5.0% in all groups but numerically higher in the inverse- and large-variation groups, regardless of classifications based on systolic or diastolic BP. There was no specific tendency on the timing of incidence (Table 3). Figure 4 shows the Kaplan–Meier curves for all cardiovascular outcomes and MACE. Different from the statistical test on differences among all seasonal variation groups (Log-rank *P*≤0.052), each comparison test showed no difference between the 2 central groups (small- versus middle-variation groups: Log-rank *P*≥0.92) or between the endmost groups (inverse- versus large-variation groups: *P*≥0.47), except for a comparison between the inverse- and large-variation groups in systolic for MACE (*P*=0.018).

Overall, when applying the multivariable-adjusted Cox model, cardiovascular risks illustrated a U-shaped relationship (Figure 5; the full results for all covariates are shown in Table S1). The hazard ratios for all cardiovascular outcomes compared with the lowest risk group (small-variation group) were 3.07 (95% CI, 1.44–6.54; *P*=0.004) and 2.02 (95% CI, 1.03–3.97; *P*=0.041) in the inverse- and large-variation groups, respectively, based on the classification by systolic BP. Those by diastolic BP were 2.81 (95% CI, 1.41–5.61; *P*=0.003) in the inverse-variation group and 1.95 (95% CI, 1.00–3.79; *P*=0.050, not statistically significant) in the large-variation group. The cardiovascular risk in the inverse-variation group was also significantly higher than that in the middle-variation group (systolic BP: hazard ratio, 2.75; 95% CI, 1.36–5.57; *P*=0.005, diastolic BP: hazard ratio, 2.64; 95% CI, 1.36–5.13; *P*=0.004). The hazard ratios for MACE compared with the middle-variation group was 2.30 (95% CI 1.02–5.19; *P*=0.046) in the large-variation group based on the classification by systolic BP. Furthermore, when the patients were divided into quintiles, the hazard ratios tended to show U-shaped relationships with the

Table 1. Baseline Characteristics of Eligible Patients in 4 Seasonal Variation Groups Based on Systolic and Diastolic Home BP

Variables	Systolic BP					Diastolic BP				
	Inverse (n=371)	Small (n=805)	Middle (n=806)	Large (n=805)	P value	Inverse (n=539)	Small (n=749)	Middle (n=750)	Large (n=749)	P Value
Seasonal variation in BP										
Mean, mm Hg	−3.6 (3.6)	2.7 (1.3)	6.9 (1.2)	13.7 (4.3)	NA	−2.3 (2.2)	1.3 (0.7)	3.5 (0.6)	7.0 (2.4)	NA
Range, mm Hg	≤0.0	0.0 to 4.8	4.8 to 9.1	≥9.1	NA	≤0.0	0.0 to 2.4	2.4 to 4.5	≥4.5	NA
Demographics										
Women, n	187 (50.4)	411 (51.1)	392 (48.6)	410 (50.9)	0.75	272 (50.5)	396 (52.9)	365 (48.7)	367 (49.0)	0.35
Age, y	58.2 (10.7)	58.4 (9.5)	59.9 (10.0)	62.1 (9.6)	<0.001	58.4 (10.0)	59.2 (9.9)	60.8 (9.9)	60.6 (9.9)	<0.001
Body mass index, kg/m^2	24.8 (3.7)	24.5 (3.4)	24.5 (3.2)	24.1 (3.3)	0.011	24.6 (3.6)	24.5 (3.4)	24.3 (3.2)	24.3 (3.4)	0.54
Current smoking, n	86 (23.2)	155 (19.3)	149 (18.5)	170 (21.1)	0.22	115 (21.3)	150 (20.0)	145 (19.3)	150 (20.0)	0.85
Current habitual drinking, n	177 (47.7)	409 (50.8)	385 (47.8)	369 (45.8)	0.25	269 (49.9)	359 (47.9)	358 (47.7)	354 (47.3)	0.81
Diabetes mellitus, n	47 (12.7)	108 (13.4)	130 (16.1)	142 (17.6)	0.046	77 (14.3)	121 (16.2)	102 (13.6)	127 (17.0)	0.25
Hypercholesterolemia, n	160 (43.1)	336 (41.7)	370 (45.9)	342 (42.5)	0.36	222 (41.2)	333 (44.5)	322 (42.9)	331 (44.2)	0.64
History of cardiovascular disease, n	9 (2.4)	25 (3.1)	27 (3.3)	25 (3.1)	0.87	16 (3.0)	22 (2.9)	22 (2.9)	26 (3.5)	0.92
Baseline home BP										
Morning systolic BP, mm Hg	150.7 (12.6)	150.1 (12.7)	151.0 (12.1)	154.0 (12.3)	<0.001	150.5 (12.6)	151.1 (12.4)	151.7 (12.4)	152.6 (12.5)	0.016
Morning diastolic BP, mm Hg	90.4 (10.0)	90.5 (9.7)	89.6 (10.5)	89.1 (10.0)	0.036	89.9 (10.2)	89.5 (9.7)	89.5 (10.4)	90.3 (9.9)	0.33
Morning heart rate, bpm	68.1 (10.1)	68.4 (9.1)	69.1 (9.3)	68.7 (9.2)	0.28	68.6 (10.1)	68.0 (9.0)	69.1 (9.0)	69.0 (9.4)	0.095
On-treatment home BP										
Morning systolic BP, mm Hg	129.7 (10.4)	127.8 (9.2)	128.6 (9.1)	131.8 (11.1)	<0.001	129.9 (10.6)	128.2 (9.4)	129.2 (9.5)	130.6 (10.5)	<0.001
Morning diastolic BP, mm Hg	77.3 (8.4)	76.3 (7.7)	75.6 (8.3)	75.8 (8.6)	0.010	76.2 (8.7)	75.3 (7.8)	75.7 (8.2)	77.2 (8.3)	<0.001
Morning heart rate, bpm	65.9 (9.3)	66.6 (8.7)	67.0 (8.8)	67.6 (9.2)	0.019	66.0 (9.4)	66.0 (8.4)	67.3 (8.7)	68.0 (9.4)	<0.001

Values are expressed as the mean (SD) or number (%). *P* values were calculated by an analysis of variance or the chi-squared test among the 4 variation groups. For missing values of body mass index (n=42), single imputation with regression on age and sex was conducted. BP indicates blood pressure; NA, not applicable.
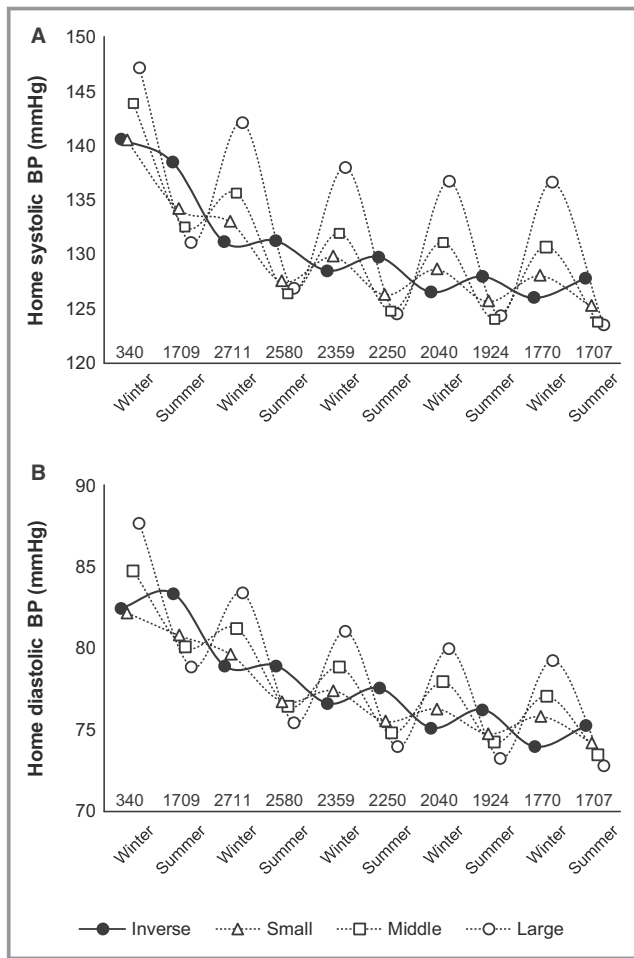
Figure 3. Seasonal variation in home blood pressure (BP) over several years in inverse-, small-, middle-, and large-variation groups. Seasonal variations in home BP were repeated every year in each variation group as a population regardless of (A) systolic or (B) diastolic BP. The first and second points in each variation group are the home BP values in winter (January–February) and summer (July–August) of the year when the patient was randomized, respectively. Therefore, the BP data collection started from the first, second, or third point, varying among patients according to the randomization timing. For example, the BP data of patients randomized in summer season were not included in the first point of winter, instead of starting from the second point.

Table 2. The Number of Cardiovascular Events in Each Group

Group	Inverse	Small	Middle	Large
Systolic home blood pressure-based				
Number of patients	371	805	806	805
All cardiovascular outcomes	16 (4.3)	12 (1.5)	16 (2.0)	35 (4.3)
MACE	5 (1.3)	9 (1.1)	8 (1.0)	23 (2.9)
Non-fatal stroke	3 (0.8)	8 (1.0)	4 (0.5)	15 (1.9)
Non-fatal myocardial infarction	1 (0.3)	1 (0.1)	2 (0.2)	5 (0.6)
Cardiovascular death	1 (0.3)	0	2 (0.2)	3 (0.4)
Diastolic home blood pressure-based				
Number of patients	539	749	750	749
All cardiovascular outcomes	22 (4.1)	13 (1.7)	15 (2.0)	29 (3.9)
MACE	11 (2.0)	7 (0.9)	9 (1.2)	18 (2.4)
Non-fatal stroke	9 (1.7)	7 (0.9)	3 (0.4)	11 (1.5)
Non-fatal myocardial infarction	1 (0.2)	0	4 (0.5)	4 (0.5)
Cardiovascular death	1 (0.2)	0	2 (0.3)	3 (0.4)

Values are expressed as the number (percentage) in each group. MACE indicates major adverse cardiovascular events.

respectively, according to their medication change from summer to winter. The summer-winter differences in home systolic/diastolic BP were significantly smaller ($P<0.001$) in the early titration group, 3.9 (CI: 3.3–4.5)/1.2 (0.8–1.5) mm Hg, than in the late titration group, 7.3 (6.7–8.0)/3.1 (2.7–3.5) mm Hg, as shown in Figure 7. The increase in the weighted-mean DDD from summer to winter was significantly larger in the early titration group than in the late titration group (0.50 versus 0.31; $P<0.001$). Titration was done primarily by the addition of another medication (48.3% and 47.7% in the early and late titration groups, respectively), following an increase in the dosage (37.2% and 34.8%). The home BP in 65.2% and 54.3% patients was controlled below 135/85 mm Hg in the early titration and late titration groups, respectively ($P<0.001$).

amplitude of seasonal variation in systolic and diastolic home BP (Figure 6). Finally, hazard ratios were essentially similar regardless of all cardiovascular outcomes or MACE (numerical value changes of the hazard ratio were ≤0.06) when office BP level was further included in the models.

Effect of Titration of Antihypertensive Medications on Change in Home BP From Summer to Winter

Of the 1135 eligible patients, 632 and 503 patients were classified into the early titration and late titration groups,

Effect of Tapering of Antihypertensive Medications on Change in Home BP From Winter to Summer

Of the 1118 eligible patients, 477 and 641 patients were classified into the early tapering and late tapering groups, respectively, according to their medication change from winter to summer. The summer-winter differences in home systolic/diastolic BP were significantly smaller ($P<0.001$) in the early tapering group, 4.4 (3.7–5.0)/2.1 (1.7–2.5) mm Hg, than in the late tapering group, 7.1 (6.6–7.7)/3.4 (3.0–3.7)

Table 3. Number of All Cardiovascular Outcomes and MACE By 3 Months in Each Seasonal Variation Group

Group	Inverse	Small	Middle	Large
Classification based on systolic blood pressure				
Number of patients	371	805	806	805
All cardiovascular outcomes				
Mar to May	5 (1.3)	2 (0.2)	7 (0.9)	12 (1.5)
Jun to Aug	5 (1.3)	3 (0.4)	2 (0.2)	6 (0.7)
Sep to Nov	3 (0.8)	2 (0.2)	3 (0.4)	10 (1.2)
Dec to Feb	3 (0.8)	5 (0.6)	4 (0.5)	7 (0.9)
Total	16 (4.3)	12 (1.5)	16 (2.0)	35 (4.3)
MACE				
Mar to May	0	2 (0.2)	4 (0.5)	8 (1.0)
Jun to Aug	1 (0.3)	2 (0.2)	1 (0.1)	3 (0.4)
Sep to Nov	3 (0.8)	1 (0.1)	3 (0.4)	8 (1.0)
Dec to Feb	1 (0.3)	4 (0.5)	0	4 (0.5)
Total	5 (1.3)	9 (1.1)	8 (1.0)	23 (2.9)
Classification based on diastolic blood pressure				
Number of patients	539	749	750	749
All cardiovascular outcomes				
Mar to May	5 (0.9)	5 (0.7)	5 (0.7)	11 (1.5)
Jun to Aug	6 (1.1)	2 (0.3)	3 (0.4)	5 (0.7)
Sep to Nov	4 (0.7)	3 (0.4)	5 (0.7)	6 (0.8)
Dec to Feb	7 (1.3)	3 (0.4)	2 (0.3)	7 (0.9)
Total	22 (4.1)	13 (1.7)	15 (2.0)	29 (3.9)
MACE				
Mar to May	1 (0.2)	3 (0.4)	4 (0.5)	6 (0.8)
Jun to Aug	2 (0.4)	1 (0.1)	1 (0.1)	3 (0.4)
Sep to Nov	4 (0.7)	3 (0.4)	4 (0.5)	4 (0.5)
Dec to Feb	4 (0.7)	0	0	5 (0.7)
Total	11 (2.0)	7 (0.9)	9 (1.2)	18 (2.4)

Values are expressed as the number and percentage. There was no particular trend in the timing of the incidence of events throughout all cardiovascular outcomes and MACE (major adverse cardiovascular events).

mm Hg as shown in Figure 7. The decrease in the weighted-mean DDD from winter summer was significantly larger in the early tapering group than in the late tapering group (−0.51 versus −0.33, *P*<0.001). Tapering was done primarily by the withdrawal of medication (44.4% and 47.1% in the early and late tapering groups, respectively), following a decrease in the dosage (32.9% and 35.7%).

Discussion

To our knowledge, this is the first report to demonstrate the clinical significance of long-term day-to-day home BP on seasonal variations to prevent cardiovascular complications in patients treated with antihypertensive medications. We found that: (1) 13% and 19% of the study participants showed inverse seasonal variation in systolic and diastolic home BP, respectively; (2) the cardiovascular risk was significantly higher in patients with inverse and, contrarily, large seasonal variation in home BP than in those with the other 2, small- and middle-sized seasonal variation; and (3) earlier adjustments of antihypertensive medications according to the coming season reduced the summer-winter difference in home BP, which may help improve the BP control during winter.

The present study showed that 13% and 19% patients with hypertension demonstrated inverse seasonal variation in systolic and diastolic home BP, respectively, with the cardiovascular risk in these patients being significantly higher than that in patients with ordinal seasonal BP variation. The SD and SE values for the summer-winter difference in BP in previous reports have implied that some patients with hypertension receiving antihypertensive treatment experience inverse seasonal variation in BP by assuming a normal distribution. Minami et al[10] reported that the summer-winter difference in home BP was 4.7/3.3 (SE: 1.3/0.9) mm Hg in 50 patients with hypertension, which indicates that ≈30% of patients showed an inverse seasonal variation in BP. Furthermore, Nakajima et al[12] examined the 24-hour ambulatory BP and reported that the summer-winter difference in daytime BP was 8/4 (SD: 9/5) mm Hg in treated men (n=38) and 5/2 (11/6) mm Hg in treated women (n=57), which indicates that 19% to 37% of patients in that population showed an inverse seasonal variation. However, conversely, among 16 volunteers with normal BP, the full amplitude of seasonal variation in home BP was 5.2/4.0 (SD: 2.0/1.6) mm Hg.[9] Based on these narrow SD ranges, few people were expected to show inverse phenomenon in a normotensive population. Inverse seasonal variation in BP can therefore be observed mainly in patients under antihypertensive drug treatment, possibly reflecting an abnormal response of biological pathways to the outside temperature. Cold-induced high BP is considered to be connected to the activation of pathways including the sympathetic nervous system and the renin-angiotensin-aldosterone system.[32] Such normal reaction may be altered in part of patients with hypertension, and it may be related to the vulnerability of patients in the inverse-variation group. Otherwise, inverse seasonal variation in BP may partially be attributable to a lack of medication adherence, as some patients may have adjusted their antihypertensive medications on their own, without being instructed to do so by their healthcare providers, after noting a lower home BP during summer, which might have led to their summer BP increasing.[33] Because stress caused by working is known to increase BP,[34] inverse seasonal variation in BP may also be observed in patients engaged in hard labor only during the summer, eg,
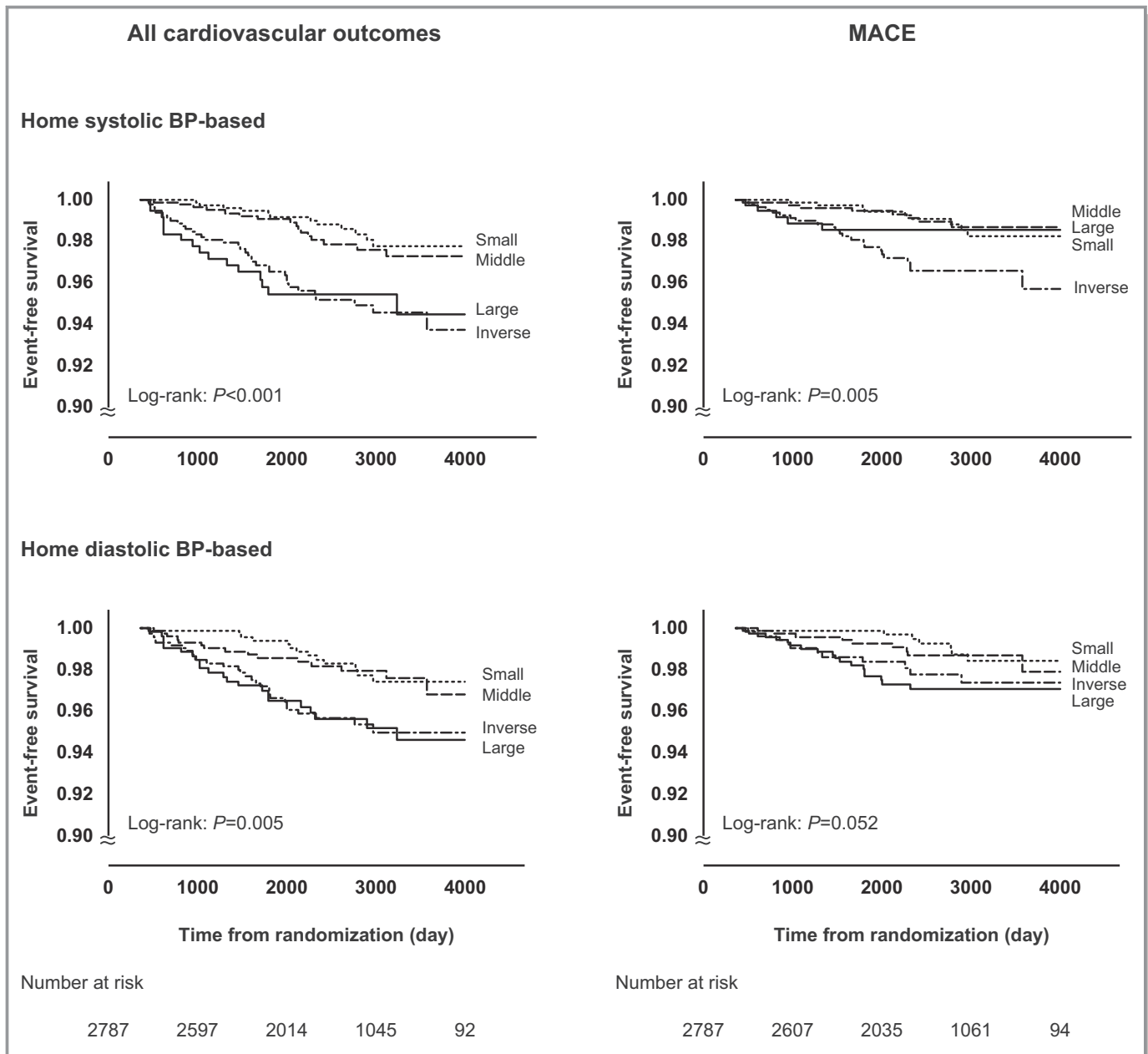
Figure 4. Kaplan–Meier curves of all cardiovascular outcomes and MACE. Follow-up was initiated at 1 year (day 365) after randomization when seasonal variation was fully captured. BP indicates blood pressure; MACE, major adverse cardiovascular events.

agriculture workers. We did not collect such information about occupation and medication compliance that might be related to inverse seasonal variation in BP. As such, what contributes to inverse seasonal variation should be further investigated.

The risk of cardiovascular events in the large-seasonal-variation group was also high in addition to the inverse-variation group, causing the association among the 4 seasonal variation groups on the cardiovascular risk to appear J- or U-shaped. Although the specific mechanism underlying this trend is uncertain, larger seasonal variations may induce long-term vascular damage, resulting in increased arterial stiffness; alternatively, it may reflect vascular conditions based on the

increased arterial stiffness that cannot attenuate the increase in BP caused by the activation of the sympathetic nerves in cold temperatures. This theory is in line with a study by Youn et al[35] demonstrating that the summer–winter difference in systolic BP increased by 0.009 mm Hg per +1 cm/s of brachial-ankle pulse wave velocity ($P=0.045$).

Our findings suggest that seasonal variation in BP should be considered for drug treatment along with BP itself; therefore, early adjustment of antihypertensive medication may contribute to better outcomes because it could markedly affect the seasonal variation in BP for the following potential reasons. First, the antihypertensive medications would be
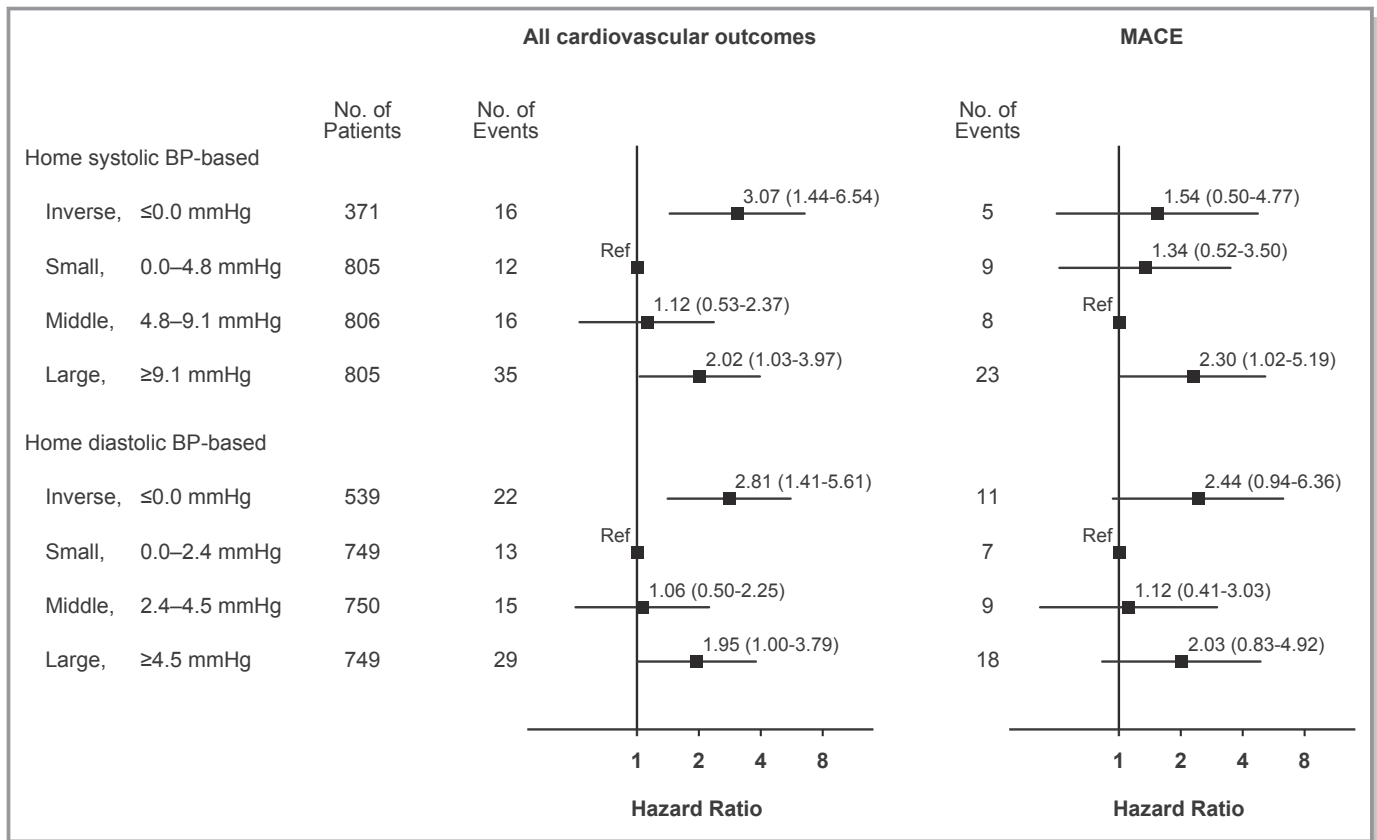
Figure 5. Multivariable-adjusted hazard ratios for all cardiovascular outcomes and MACE. The open box (vertical bar) expresses the hazard ratio (95% confidence interval) in each variation group compared with the group of the lowest cardiovascular risk (shown as Ref). The values were adjusted by sex, age, body mass index, current smoking, current habitual drinking, diabetes mellitus, hypercholesterolemia, history of cardiovascular disease, baseline home BP, on-treatment home BP (either systolic or diastolic BP according to the seasonal BP information), and the randomized groups in the HOMED-BP study. Follow-up was initiated at 1-year (day 365) after randomization in the Cox model. BP indicates blood pressure; HOMED-BP, Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure; MACE, major adverse cardiovascular events.

adjusted after any BP change was observed in the late titration group and late tapering group. BP gradually increases in autumn and peaks during winter in general, but decreases in the spring to reach a trough during summer,[9,11] which would be suppressed by the early adjustment. Second, more frequent clinic visits may enable prescribers to have more opportunities to adjust medications. The difference in the weighted-mean DDD of antihypertensive medications was larger in the early adjustment groups than in the late adjustment groups (0.50 versus 0.31 from summer to winter, and −0.51 versus −0.33 from winter to summer; *P*<0.001). We may reasonably assume that earlier medication adjustment results in better control of seasonal variation with a continual (ideally daily) long-term home BP monitoring. Third, a threshold number of days are required to obtain the maximum effect of antihypertensive treatment after drug treatment;[36,37] this threshold was higher when the same medication was titrated than when another medication was added.[36] Approximately 35% of patients in this study experienced up-titration of the same medication; the stabilization

time of the titration effect might be longer in such patients. The stabilization time should be carefully considered in clinical practice when adjusting antihypertensive medication to control seasonal variation in BP.

BP is affected by various measurement conditions such as room temperature,[38,39] atmospheric pressure,[40] weather changes,[41] and temperature variability,[42] as well as outside temperature. Hours of daylight[43] and the availability of air conditioning or heating[44] are also associated with the amplitude of seasonal variation in BP. It is too complicated to untangle the relationship between these atmospheric aspects and cardiovascular risks directly. However, because BP ultimately demonstrates seasonality, assessment of seasonal variation in BP in relation to such factors is clinically relevant. For instance, in the region where the temperature varies throughout a year such as Japan[45] (Figure 8) as well as other countries in the temperate area, the seasonal variation in BP should be carefully considered, though we could not evaluate the difference in outside temperature for cardiovascular risk because of the small number of events in the present study.
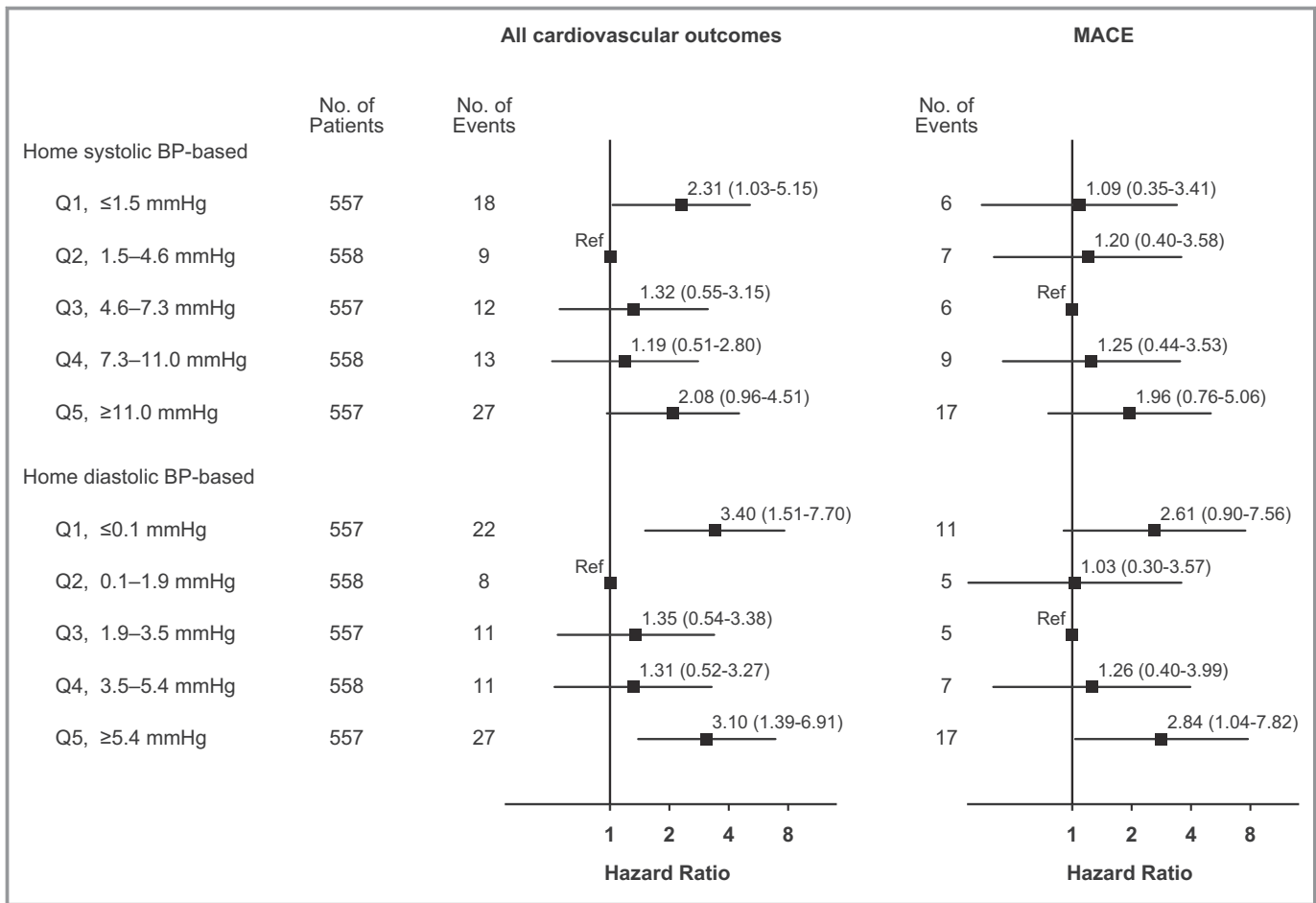
Figure 6. Multivariable-adjusted hazard ratios for all cardiovascular outcomes and MACE in quintile groups (sensitivity analyses). The open box (vertical bar) expresses the hazard ratio (95% confidence interval) in the quintile groups (Q1–Q5) depending on the amplitude of seasonal variation in home BP, compared with the group of the lowest cardiovascular risk (shown as Ref). The values were adjusted by sex, age, body mass index, current smoking, current habitual drinking, diabetes mellitus, hypercholesterolemia, history of cardiovascular disease, baseline home BP, on-treatment home BP (either systolic or diastolic BP according to the seasonal BP information), and the randomized groups in the HOMED-BP study. Follow-up was initiated at 1-year (day 365) after randomization in the Cox model. BP indicates blood pressure; HOMED-BP, Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure; MACE, major adverse cardiovascular events.

Several limitations associated with the present study warrant mention. First, the present study is an observational study based on the randomized controlled trial which has focused on home BP level, and it was not designed specifically to investigate the seasonal variation in BP. Accordingly, as analytical limitations, the number of provided BP measurements included in each summer and winter was unbalanced within or among patients because of missing daily BP measurements; the number of years, ie, summer and winter, during which patients participated in the study also varied depending on the duration of the follow-up period. Second, cardiovascular event subtypes, eg, myocardial infarction and stroke, were not assessed because of the relatively small number of events. In general, Cox models should be used with at least 10 events per variable, and is acceptable with 5 to 9 events per variable;[46] however, we observed only 79 and 45

events for all cardiovascular outcomes and MACE, respectively, which might have reduced the accuracy of the models. The low rate of cardiovascular events, eg, <5% even in the high-risk groups, was attributed to the well-controlled BP in the HOMED-BP study, where 55.8% patients achieved a home systolic BP <130 mm Hg.[1] However, even in this well-controlled patient population, the risk of cardiovascular events was significantly higher in the inverse- and larger-variation groups than in the small- and middle-variation groups. Third, because of the small number of events, we did not compare the predictive power between seasonal variations in morning home BP and other BP-related factors, eg, office BP, evening home BP, morning-evening difference in home BP, visit-to-visit BP variations, and seasonal variations in office BP. We primarily focused on morning home BP in this study based on a previous report that on-treatment office BP
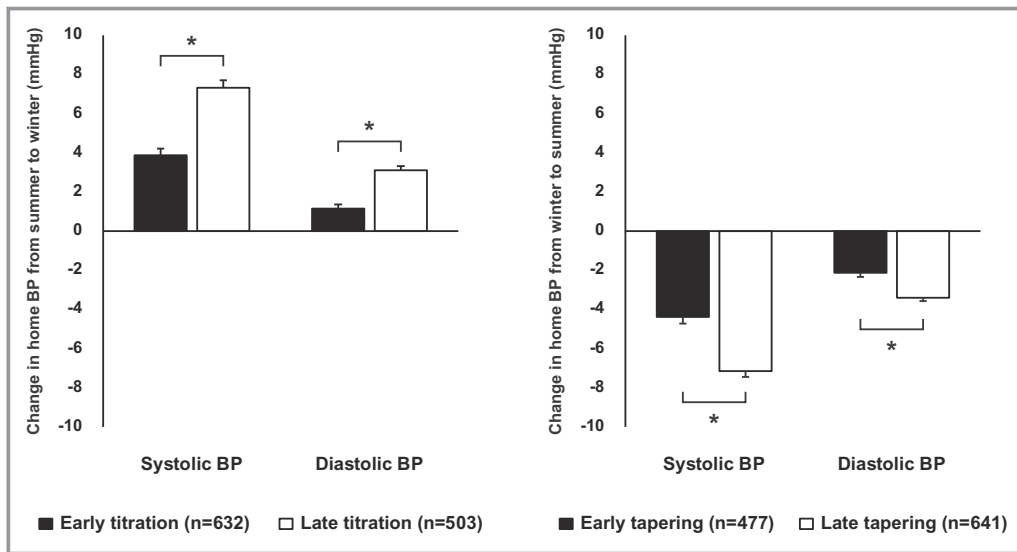
Figure 7. Comparison of seasonal change in home BP between early- and late-adjustment groups. A, The differences in the BP from summer to winter were compared between the early and late titration groups, and (B) those from winter to summer were compared between the early and late tapering groups. Least square means and confidence intervals were estimated by an analysis of covariance model adjusted for sex, age, body mass index, current smoking, current habitual drinking, diabetes mellitus, hypercholesterolemia, history of cardiovascular disease, pre-change home BP (either systolic or diastolic BP according to the seasonal BP information), and the randomized groups in the HOMED-BP study. *$P<0.001$. BP indicates blood pressure; HOMED-BP, Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure.

is not a constant predictor of cardiovascular complications in the HOMED-BP population.[25] Such insensitiveness of office BP for cardiovascular risk was also observed in epidemiological studies on treated patients.[47,48] Finally, though DDD was used to standardize the antihypertensive drug effect for comparing the BP changes between summer
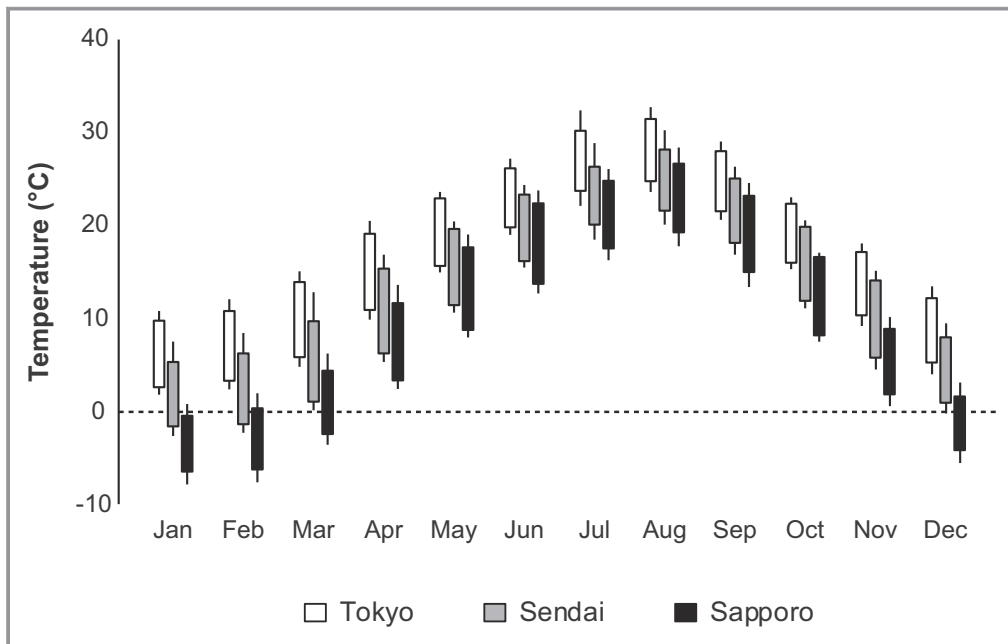

Figure 8. The temperature in Tokyo (capital city), Sendai (the city where the study center is located), and Sapporo (the central city in a subarctic climate), Japan, throughout a year represented as a monthly average during 2001 to 2012. Each column represents a monthly average during 2001 to 2012. The upper and lower part of each column (with error bar) shows the maximum and minimum temperatures (with their SD) of a day in the corresponding month.

and winter, medication information could not be included in the Cox model since antihypertensive drug treatment was constantly adjusted throughout the follow-up period. The patterns of titration and tapering vary widely among different patients as a result of multiple changes in drug regimen. Thus, we could not directly evaluate the relationship between the adjustment timing of antihypertensive drugs and cardiovascular risks. However, the adjustment of antihypertensive medications at an early timing might reduce the summer-winter difference in BP, suggesting that the cardiovascular risk can be mitigated by the adjustment of medications based on seasonal variation in BP.

The present study showed a higher cardiovascular risk in patients with a larger seasonal variation in home BP and with inverse seasonal variation in home BP even after adjustment for the on-treatment home BP level. Regarding cardiovascular risks, the optimum seasonal variation in BP was likely to be an amplitude shift from 0 to 9.1/4.5 mm Hg (small- and middle-variation groups). Furthermore, seasonal variation may be controlled by the early adjustment of antihypertensive medication based on the long-term self-measurement of home BP. These results have further enhanced the clinical benefit of long-term continuous self-measured home BP. Although the importance of BP level as a dominant predictor for cardiovascular events should be again emphasized,[49] cardiovascular risk can be more appropriately managed by considering the seasonal variation in home BP in addition to the BP level. In the clinical setting, continuous self-measurement of home BP over several years is therefore recommended for capturing the long-term condition, such as seasonal variation.

Acknowledgments

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Disclosures

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Supplemental Material

Appendix

Hypertension Objective Treatment Based on Measurement by Electrical Devices of Blood Pressure (HOMED-BP) investigators:

Coordination and management

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Table S1. Multivariable-adjusted hazard ratios for all covariates in Cox proportional hazard models.

	Hazard Ratio per Unit			
	All cardiovascular outcomes		MACE	
	Systolic BP-based	Diastolic BP-based	Systolic BP-based	Diastolic BP-based
Patient Characteristics				
Body mass index (kg/m²)	0.94 (0.88–1.02)	0.96 (0.89–1.03)	0.99 (0.90–1.10)	1.01 (0.91–1.11)
Age (years)	1.05 (1.02–1.08)	1.08 (1.05–1.11)	1.07 (1.03–1.11)	1.11 (1.07–1.15)
Women (vs. men)	0.74 (0.42–1.29)	0.79 (0.45–1.39)	0.88 (0.42–1.83)	1.00 (0.48–2.10)
Diabetes mellitus	2.01 (1.22–3.33)	2.28 (1.38–3.78)	1.48 (0.74–2.95)	1.87 (0.94–3.74)
Hypercholesterolemia	1.00 (0.63–1.59)	0.97 (0.61–1.54)	0.96 (0.52–1.77)	0.91 (0.49–1.69)
Previous cardiovascular disease	5.57 (2.91–10.63)	5.11 (2.69–9.71)	3.68 (1.40–9.65)	3.13 (1.20–8.17)
Current smoking	1.57 (0.91–2.70)	1.82 (1.06–3.11)	1.46 (0.70–3.06)	1.64 (0.79–3.40)
Current habitual drinking	1.12 (0.66–1.92)	1.11 (0.65–1.92)	1.44 (0.70–2.95)	1.41 (0.68–2.92)
Home BP				
Baseline home BP (mmHg)	1.03 (1.01–1.05)	1.02 (0.99–1.05)	1.04 (1.02–1.07)	1.03 (0.99–1.07)
On-treatment home BP (mmHg)	1.01 (0.99–1.03)	1.02 (0.98–1.05)	1.01 (0.99–1.04)	1.04 (1.00–1.09)
Randomization group				
ACEIs vs. ARBs	1.33 (0.78–2.27)	1.35 (0.79–2.29)	1.66 (0.80–3.46)	1.70 (0.82–3.53)
ACEIs vs. CCBs	1.32 (0.77–2.27)	1.36 (0.79–2.34)	1.38 (0.69–2.77)	1.33 (0.66–2.65)
ARBs vs. CCBs	0.99 (0.56–1.75)	1.01 (0.57–1.78)	0.83 (0.38–1.81)	0.78 (0.36–1.70)
Usual control vs. tight control	0.79 (0.50–1.24)	0.82 (0.52–1.29)	0.85 (0.47–1.53)	0.85 (0.47–1.53)
Seasonal variation group				
Inverse vs. small	3.07 (1.44–6.54)	2.81 (1.41–5.61)	1.15 (0.38–3.47)	2.44 (0.94–6.36)
Middle vs. small	1.12 (0.53–2.37)	1.06 (0.50–2.25)	0.75 (0.29–1.94)	1.12 (0.41–3.03)
Large vs. small	2.02 (1.03–3.97)	1.95 (1.00–3.79)	1.71 (0.77–3.79)	2.03 (0.83–4.92)
Inverse vs. middle	2.75 (1.36–5.57)	2.64 (1.36–5.13)	1.54 (0.50–4.77)	2.18 (0.90–5.30)
Large vs. middle	1.81 (0.99–3.31)	1.83 (0.97–3.44)	2.30 (1.02–5.19)	1.81 (0.81–4.08)
Inverse vs. large	1.52 (0.82–2.80)	1.44 (0.82–2.55)	0.67 (0.25–1.79)	1.20 (0.56–2.59)

Values are expressed as the hazard ratio and 95% confidence interval. The definitions of the inverse, small, middle, and large seasonal variation group are shown in Table 1. The hazard ratios for seasonal variation groups are also illustrated in Figure 5. BP indicates blood pressure; MACE, major adverse cardiovascular events; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers.