Optimal Schedule for Assessing Home BP Variability: The Finn-Home Study

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BACKGROUND
Current guidelines make no recommendations on the optimal timing or number of measurements for assessing home blood pressure variability (HBPV). Our aim was to elucidate the optimal schedule for measuring HBPV in relation to cardiovascular risk.

METHODS
In total, 1,706 Finnish adults (56.5 ± 8.5 years; 54% women) self-measured their home blood pressure (HBP) twice in the morning and evening during 7 consecutive days. The participants were followed up for cardiovascular events. We examined the association between HBPV (coefficient of variation based on 2 through 7 measurement days) and cardiovascular events using Cox regression models adjusted for HBP and other cardiovascular risk factors.

RESULTS
During a follow-up of 11.8 ± 3.1 years, 216 cardiovascular events occurred. Systolic morning HBPV based on three (hazard ratio [HR], 1.039; 95% confidence interval, 1.006–1.074, model c statistic 0.737) through seven (HR, 1.057; 95% confidence interval, 1.012–1.104, model c statistic 0.737) measurement days was significantly associated with cardiovascular events. Agreement in classification to normal vs. increased morning day-to-day HBPV between consecutive measurement days became substantial (κ = 0.69 for systolic and κ = 0.68 for diastolic) after the fourth measurement day. The associations of diastolic HBPV, evening HBPV, all-day HBPV, and variability based on first measurements of each measurement occasion, with cardiovascular outcomes were nonsignificant or remained significant only after the sixth measurement day.

CONCLUSIONS
Our results suggest systolic HBP should be measured twice in the morning for at least 3 days when assessing HBPV. Increasing the number of measurement days from 3 to 7 results in marginal improvement in prognostic accuracy.

Keywords: blood pressure; cardiovascular outcomes; home blood pressure measurement; home blood pressure variability; hypertension; optimal schedule.

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INTRODUCTION

Home blood pressure (HBP) is more closely associated with cardiovascular outcomes than office BP.[1,2] The American hypertension guidelines recently lowered the threshold of hypertension to 130/80 mm Hg and simultaneously recommended out-of-office BP measurements for almost all individuals with suspected hypertension. The importance of HBP measurements is therefore currently increasing.[3] In addition, prior studies have demonstrated that increased BP variability is associated with adverse cardiovascular outcomes, independent of BP.[4–6] Current hypertension guidelines therefore suggest that physicians should also consider assessing BP variability of hypertensive patients.[7,8] Although hypertension guidelines agree that BP variability should be measured systematically,[8,9] these guidelines make no definite recommendation on the exact methods or protocol of BP variability assessment.

Self-measured HBP can be used to assess mid-term BP variability, and the excess cardiovascular risk associated with it.[7,8,10] The clinical use of HBP variability for cardiovascular risk assessment, however, has remained limited. One reason for the lackluster use of HBP variability (HBPV) in clinical practice might be that the optimal schedule for assessing HBPV remains unclear.

Our aim was therefore to determine the optimal timing and number of HBP measurements in the context of cardiovascular risk prediction. We addressed this issue in a random, nationwide, population sample of 1,706 participants with baseline HBP measurements and follow-up for cardiovascular outcomes.

MATERIALS AND METHODS

Study sample

The study sample was drawn from the participants of a multidisciplinary epidemiological survey, the Health 2000 Study, which was carried out in Finland from autumn 2000 to spring 2001. The study sample was a stratified 2-stage cluster sample of 8,028 subjects drawn from the population

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register to represent Finnish adults aged ≥30 years. The stratification and sampling procedures have been reported in detail in previous publications.[11,12] The flow of the participant selection is shown in Figure 1.

Of the 4,388 subjects aged 45 to 74 years, 84% (n = 3,672) participated in a clinical interview and health examination. A total of 2,106 subjects participated also in the HBP measurement substudy (the Finn-Home Study). HBP measurement could not be performed on all of the individuals willing to participate because of the limited number of home monitors (≈800), and study participants were selected on the basis of monitor availability.[11] Individuals who had not performed morning and evening HBP measurements on all the 7 measurement days (n = 372) or who had missing data on alcohol consumption (n = 28) were excluded. The final study population therefore consisted of 1,706 individuals.

The procedures were in accordance with the Helsinki Declaration. The study protocol of the Health 2000 Survey was approved by the epidemiology ethics committee of the Helsinki and Uusimaa hospital region. All participants gave their signed informed consent.

Flow of the study

At an initial health interview at the participant's home, basic background and sociodemographic information, information about health and illnesses, and information about use of medication were gathered by centrally trained interviewers. A physical examination was performed 1 to 6 weeks later at a local health center by centrally trained nurses and doctors. The participant's height and weight were measured. Fasting blood samples for serum lipids and glucose were drawn. At the end of the examination, the participants of the Finn-Home substudy received HBP monitors to measure their HBP during the week after the health interview. A detailed description of the study methodology has been previously published.[11,12]

HBP measurements

The participants received oral and written instructions on how to measure their BP at home. Prior to the measurement, they were instructed to rest for at least 10 minutes in the sitting position, with the cuff around the nondominant arm for the last 5 minutes. The participants were instructed to measure their BP twice in the morning between 6:00 AM and 9:00 AM and twice in the evening between 6:00 PM and 9:00 PM on 7 consecutive days. BP was measured before breakfast and drug intake. The interval between the first and the second measurements was 2 minutes. HBP was measured using a validated, automatic oscillometric device, Omron HEM-722C (Omron Corp, Tokyo, Japan).[13]

Exposure variable (HBPV)

Home systolic/diastolic BP variability was defined as (i) day-to-day variability of mean daily systolic/diastolic BPs; (ii) morning day-to-day variability of mean morning systolic/diastolic BPs; (iii) evening day-to-day variability of mean evening systolic/diastolic BPs; (iv) variability of individual morning, evening, or all-day systolic/diastolic BPs, instead of daily means; (v) morning day-to-day variability of first morning systolic/diastolic BPs of each day; and (vi) evening day-to-day variability of first evening systolic/diastolic BPs of each day. BP variability indexes based on 2 through 7 measurement days were calculated for each participant. The coefficient of variation was used as the measure of variability because SD is strongly dependent of the BP level itself.[14]

Outcomes

Follow-up data were collected until 31 December 2013. The 10th version of the International Classification of Diseases, Injuries, and Causes of death (ICD-10) was used to classify fatal and nonfatal events. Mortality data were obtained

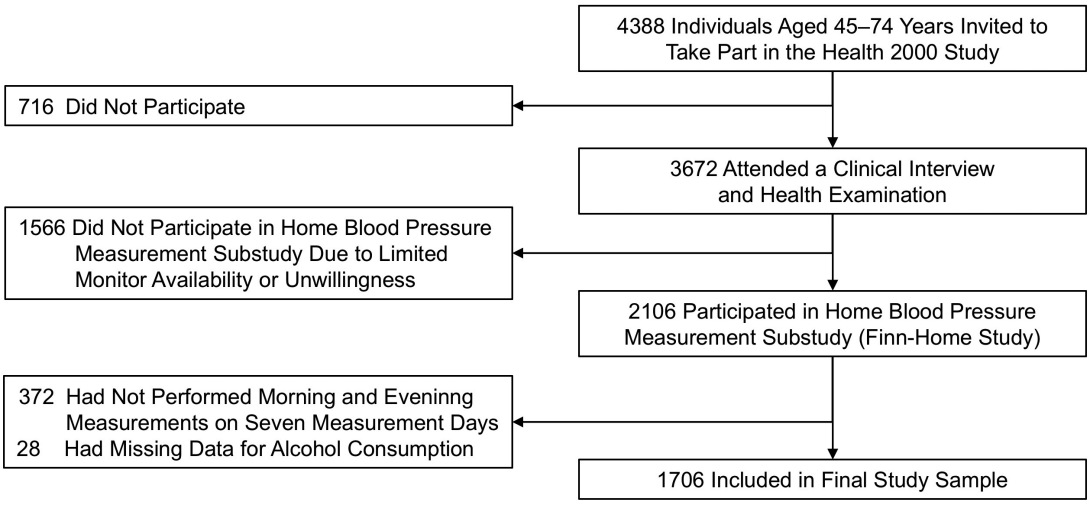

Figure 1. The flow of participant selection.

from the National Causes of Death register based on death certificates. Data on hospitalization due to coronary heart disease, stroke, and heart failure events were obtained from the National Hospital Discharge Register that covers all hospitalizations in Finland. Both registers have been validated for coronary heart disease, stroke, and heart failure diagnoses.[15–17] The ICD codes used for classifying the cardiovascular events have been previously described in more detail.[2]

A composite endpoint of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, and percutaneous or surgical coronary intervention was used as the primary outcome. Only the first event was included in the analysis, if the participant experienced more than one event. Previous cardiovascular disease was defined as having at least one prior hospitalization for angina pectoris, myocardial infarction, or stroke.

Covariates

Diabetes mellitus was defined as a fasting serum glucose level higher or equal to 7.0 mmol/l or the use of hypoglycemic agents. Hypercholesterolemia was defined as a fasting serum total cholesterol level of ≥7.0 mmol/l or use of statins. Smoking was defined as current use of tobacco products.

Alcohol consumption was evaluated with a questionnaire and the alcohol amount consumed was converted to grams of absolute ethanol (g/week). Because 31.0% of the study population reported not drinking alcohol, the participants were divided into 3 groups according to their alcohol consumption: (i) 0 g/week; (ii) 1–280 g/week for men and 1–140 g/week for women; and (iii) >280 g/week for men and >140 g/week for women.[18]

Questions derived from the Basic Nordic Sleep Questionnaire[19] were used to define sleep apnea. The participants were considered to have sleep apnea if they reported having a previous diagnosis of sleep apnea or if they had a finding indicative of sleep apnea in the questionnaire. The finding in the questionnaire was considered positive for sleep apnea if snoring was frequent (at least 3 nights weekly), and, in addition, either of the following was true: (i) the snoring was loud and irregular with occasional respiratory pauses or (ii) respiratory pauses occurred during at least 1 nights every week.

Statistical analysis

The association between HBPV indexes based on 2 through 7 measurement days and cardiovascular events was examined using Cox proportional hazards regression models. All models were adjusted for age, sex, smoking status, diabetes status, use of antihypertensive medication, hypercholesterolemia, history of cardiovascular disease, body mass index, sleep apnea, alcohol consumption, and mean systolic/diastolic HBP. Mean BP for each model was based on the same number of measurement days as the variability index. Harrell's c statistic was used to assess changes in model discrimination when the number of days used for defining BP and BP variability were increased from 2 to 7. Three measurement days were used as reference, because 3 is the smallest number to assess variability.[20] The C statistics are for the whole model, reflecting how the model fit changes when the number of measurement days is increased for both mean BP and BP variability.

The effect of an increasing number of HBP measurement days on reclassification of participants into normal vs. increased BP variability was also investigated. The participants were categorized as having normal or increased morning systolic/diastolic BP variability using a previously defined outcome-based coefficient of variation threshold of 11.0/12.8.[10] Increased morning systolic BP variability was defined as a coefficient of variation of systolic/diastolic BP >11.0/12.8. Kappa coefficients are reported for the intraindividual agreement in classification to high vs. low BP variability on consecutive measurement days (e.g., classification based on measurements on days 1 through 3 vs. 1 through 4). The kappa coefficients were interpreted as follows: poor ($\kappa \leq 0$), slight ($\kappa = 0.01–0.20$), fair ($\kappa = 0.21–0.40$), moderate ($\kappa = 0.41–0.60$), substantial ($\kappa = 0.61–0.80$), and excellent ($\kappa = 0.81–1.00$).[21] Two-tailed P values <0.05 were considered statistically significant. Statistical analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

The baseline characteristics of the participants are shown in Table 1.

Association of daily mean BP variability with cardiovascular outcomes

During a mean follow-up of 11.8 ± 3.1 years, 216 adverse cardiovascular events occurred. As shown in Table 2, systolic morning day-to-day HBPV based on the measurements

Table 1. Baseline characteristics of the participants

Characteristic	
n	1,706
Age, year	56.5 ± 8.5
Women, %	54.3
Smokers, %	18.4
Diabetes mellitus, %	6.3
Antihypertensive treatment, %	22.8
Hypercholesterolemia, %	29.6
History of cardiovascular disease, %	7.7
Body mass index, kg/m^2	27.3 ± 4.4
Probable sleep apnea, %	10.7
Alcohol consumption, g/week	74.6 ± 142.0
Alcohol consumption	
Nonusers, %	31.0
Moderate users, %	60.7
Excessive users, %	8.3

Data are shown as mean ± SD or percentage.

Table 2. Association of daily mean BP variability with cardiovascular outcomes

	Number of measurement days					
BP parameter	**2**	**3**	**4**	**5**	**6**	**7**
Morning BP						
Systolic BP						
Mean ± SD	129.8 ± 20.5	129.0 ± 20.0	128.3 ± 19.7	127.9 ± 19.5	127.6 ± 19.3	127.4 ± 19.1
CV ± SD	5.0 ± 4.4	5.6 ± 3.6	5.9 ± 3.3	6.0 ± 3.1	6.1 ± 2.9	6.1 ± 2.8
HR (95% CI) for mean	1.018 (1.011–1.025)***	1.019 (1.011–1.026)***	1.019 (1.012–1.027)***	1.020 (1.012–1.028)***	1.020 (1.012–1.028)***	1.021 (1.013–1.029)***
HR (95% CI) for CV	1.020 (0.991–1.050)	1.039 (1.006–1.074)*	1.057 (1.019–1.096)**	1.051 (1.009–1.095)*	1.063 (1.019–1.109)**	1.057 (1.012–1.104)*
C statistic	0.732†	0.737 (ref)	0.738	0.737	0.737	0.737
Diastolic BP						
Mean ± SD	81.0 ± 10.3	80.7 ± 10.0	80.3 ± 9.9	80.2 ± 9.8	80.0 ± 9.7	79.9 ± 9.6
CV ± SD	4.5 ± 4.1	5.0 ± 3.5	5.3 ± 3.1	5.3 ± 2.9	5.5 ± 2.8	5.5 ± 2.7
HR (95% CI) for mean	1.035 (1.021–1.050)***	1.038 (1.023–1.053)***	1.039 (1.024–1.055)***	1.042 (1.026–1.058)***	1.043 (1.027–1.059)***	1.045 (1.029–1.061)***
HR (95% CI) for CV	1.011 (0.977–1.046)	1.033 (0.997–1.071)	1.037 (0.996–1.080)	1.031 (0.986–1.079)	1.042 (0.994–1.093)	1.058 (1.011–1.108)*
C statistic	0.735	0.738 (ref)	0.738	0.739	0.739	0.742
All-day BP						
Systolic BP						
Mean ± SD	131.1 ± 19.5	130.4 ± 19.0	129.9 ± 18.8	129.6 ± 18.6	129.3 ± 18.4	129.1 ± 18.3
CV ± SD	3.6 ± 3.1	4.2 ± 2.6	4.4 ± 2.4	4.6 ± 2.3	4.7 ± 2.2	4.7 ± 2.1
HR (95% CI) for mean	1.019 (1.011–1.027)***	1.020 (1.012 –1.028)***	1.020 (1.012–1.028)***	1.020 (1.012–1.028)***	1.021 (1.012–1.029)***	1.021 (1.013–1.029)***
HR (95% CI) for CV	1.000 (0.957–1.044)	1.040 (0.994–1.089)	1.044 (0.993–1.097)	1.046 (0.992–1.103)	1.056 (1.000–1.115)	1.057 (0.999–1.119)
C statistic	0.733	0.736 (ref)	0.735	0.735	0.735	0.736
Diastolic BP						
Mean ± SD	80.8 ± 9.6	80.5 ± 9.3	80.3 ± 9.2	80.1 ± 9.1	80.0 ± 9.1	79.8 ± 9.0
CV ± SD	3.5 ± 2.9	4.0 ± 2.5	4.2 ± 2.4	4.3 ± 2.2	4.4 ± 2.1	4.4 ± 2.0
HR (95% CI) for mean	1.040 (1.024–1.056)***	1.042 (1.026–1.059)***	1.043 (1.027–1.060)***	1.045 (1.028–1.062)***	1.046 (1.029–1.063)***	1.047 (1.030–1.064)***
HR (95% CI) for CV	1.017 (0.974–1.063)	1.046 (0.996–1.098)	1.043 (0.989–1.100)	1.046 (0.987–1.109)	1.060 (0.999–1.126)	1.081 (1.018–1.147)*
C statistic	0.737	0.741 (ref)	0.740	0.740	0.740	0.742

Hazard ratios indicate increase in risk of cardiovascular events per 1-unit increase in blood pressure variability (coefficient of variation) or blood pressure (mm Hg). All models were adjusted for age, sex, smoking status, diabetes status, use of antihypertensive medication, hypercholesterolemia, history of cardiovascular disease, body mass index, sleep apnea, alcohol consumption, and mean systolic or diastolic home blood pressure. Two hundred and sixteen adverse cardiovascular events occurred during follow-up. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. †$P < 0.05$ for difference in C statistic compared to reference. The C statistics are for the whole model, reflecting how the model fit changes when the number of measurement days is increased for both mean BP and BP variability. Abbreviations: BP, blood pressure; CI, confidence interval; CV, coefficient of variation; HR, hazard ratio.

performed on the first 3 through first 7 measurement days was significantly associated with incident cardiovascular events. Diastolic morning day-to-day variability was associated with cardiovascular events only when all 7 measurement days were included. Increasing the number of measurement days from 3 did not significantly improve model C statistic (Table 2). The association between morning systolic day-to-day HBPV based on a varying number of measurement days, and cardiovascular outcomes is shown in Figure 2. Systolic day-to-day HBPV of mean daily BPs was not related to cardiovascular events (Table 2), whereas only the 7-day diastolic day-to-day variability was predictive of cardiovascular events. Evening BP variability based on evening BP means was not associated with the risk of cardiovascular events (Table 3).

Association of individual BP reading variability with cardiovascular outcomes

When BP variability was calculated from individual measurements, instead of daily means, the results remained relatively similar (Table 4). Systolic morning BP variability of 3 through 7 days was predictive of cardiovascular events, whereas diastolic morning BP variability reached significance only when based on 7 days of measurement. Increasing the number of measurement days from 3 did not significantly improve the model C statistic (Table 4). Systolic BP variability based on all individual measurements (both morning and evening) was significantly associated with cardiovascular outcomes only when variability was based on readings from 3, 4, and 6 days (Table 4). A significant association between evening BP variability and cardiovascular outcomes was only observed when 7-day diastolic BP variability based on individual measurements was used as the exposure variable (Table 3).

Association of BP variability of the first measurements at each measurement occasion with cardiovascular outcomes

We also related BP variability of the first morning or first evening measurements on 2 through 7 days to cardiovascular outcomes (Table 5). Although the variability in first morning BP readings at each measurement occasion of 4 or more days was related to cardiovascular outcomes, the hazard ratios (HRs) were in general lower than those observed in Table 2.

Classification into normal vs. increased HBPV

Using morning day-to-day BP variability (mean of both morning measurements) as the variability index, we examined the effects of an increasing number of measurement days on participant reclassification into normal vs. increased BP variability (Table 6). Overall, 9–12% of the participants had increased systolic BP variability and 4–6% had increased diastolic BP variability, depending on the number of measurement days. Agreement in classification between consecutive measurement days improved with the number of measurement days, reaching substantial agreement after the fourth measurement day ($\kappa = 0.69$ for systolic and $\kappa = 0.68$ for diastolic), and excellent agreement ($\kappa = 0.85$ for systolic and $\kappa = 0.84$ for diastolic) after the sixth measurement day.

DISCUSSION

Our results show that BP variability of the mean of 2 morning systolic BP measurements on 3 days is related to cardiovascular outcomes. Increasing the number of measurement days from 3 to 7 resulted in only marginally stronger associations between HBPV and cardiovascular outcomes. The association of diastolic HBPV, evening HBPV, all-day BP variability, and variability based on the first measurements

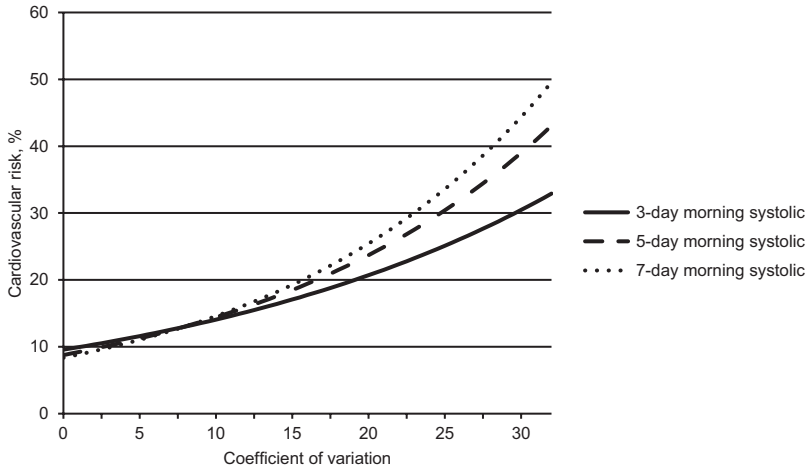

Figure 2. Association of morning systolic day-to-day home blood pressure variability and risk of cardiovascular disease events. Risk of cardiovascular events was adjusted for age, sex, smoking status, diabetes status, use of antihypertensive medication, hypercholesterolemia, history of cardiovascular disease, body mass index, sleep apnea, alcohol consumption, and mean systolic home blood pressure. Abbreviations: CV, coefficient of variation; CVD, cardiovascular disease.

Table 3. Association of evening mean and individual BP reading variability with cardiovascular outcomes

	Number of measurement days					
BP parameter	**2**	**3**	**4**	**5**	**6**	**7**
Evening BP (mean of readings)						
Systolic BP						
Mean ± SD	132.4 ± 19.9	131.8 ± 19.3	131.5 ± 18.9	131.2 ± 18.7	131.0 ± 18.6	130.8 ± 18.4
CV ± SD	4.7 ± 4.1	5.5 ± 3.6	5.8 ± 3.2	4.6 ± 2.3	6.1 ± 2.8	6.1 ± 2.7
HR (95% CI) for mean	1.017 (1.009–1.024)***	1.018 (1.010–1.025)***	1.018 (1.010–1.026)***	1.018 (1.010–1.026)***	1.019 (1.011–1.027)***	1.019 (1.011–1.027)***
HR (95% CI) for CV	0.995 (0.964–1.028)	1.007 (0.971–1.045)	0.993 (0.952–1.036)	1.009 (0.967–1.054)	1.012 (0.967–1.060)	1.015 (0.968–1.066)
Diastolic BP						
Mean ± SD	80.6 ± 9.7	80.3 ± 9.4	80.2 ± 9.4	80.2 ± 9.3	79.9 ± 9.1	79.8 ± 9.0
CV ± SD	4.6 ± 4.1	5.3 ± 3.5	5.6 ± 3.2	5.8 ± 3.0	5.9 ± 2.8	5.9 ± 2.7
HR (95% CI) for mean	1.035 (1.020–1.051)***	1.038 (1.022–1.054)***	1.039 (1.023–1.055)***	1.041 (1.024–1.057)***	1.042 (1.026–1.058)***	1.042 (1.026–1.059)***
HR (95% CI) for CV	1.009 (0.979–1.041)	1.024 (0.988–1.062)	1.017 (0.977–1.058)	1.028 (0.985–1.073)	1.028 (0.981–1.076)	1.046 (0.998–1.097)
Evening BP (individual readings)						
Systolic BP						
Mean ± SD	132.4 ± 19.9	131.8 ± 19.3	131.5 ± 18.9	131.2 ± 18.7	131.0 ± 18.6	130.8 ± 18.4
CV ± SD	5.7 ± 3.4	6.3 ± 3.1	6.6 ± 2.9	6.8 ± 2.8	6.8 ± 2.7	6.9 ± 2.6
HR (95% CI) for mean	1.017 (1.009–1.024)***	1.018 (1.010–1.025)***	1.018 (1.010–1.026)***	1.018 (1.010–1.026)***	1.019 (1.011–1.027)***	1.019 (1.011–1.027)***
HR (95% CI) for CV	1.003 (0.964–1.042)	1.017 (0.977–1.059)	1.007 (0.963–1.053)	1.015 (0.969–1.064)	1.020 (0.971–1.071)	1.022 (0.971–1.075)
Diastolic BP						
Mean ± SD	80.6 ± 9.7	80.3 ± 9.4	80.2 ± 9.4	80.2 ± 9.3	79.9 ± 9.1	79.8 ± 9.0
CV ± SD	5.3 ± 3.6	5.9 ± 3.3	6.2 ± 3.2	6.4 ± 3.0	6.5 ± 2.9	6.6 ± 2.8
HR (95% CI) for mean	1.035 (1.020–1.051)***	1.038 (1.022–1.054)***	1.039 (1.023–1.055)***	1.041 (1.024–1.057)***	1.042 (1.026–1.058)***	1.042 (1.026–1.059)***
HR (95% CI) for CV	1.017 (0.982–1.054)	1.026 (0.987–1.066)	1.017 (0.976–1.059)	1.027 (0.984–1.072)	1.035 (0.990–1.082)	1.050 (1.004–1.098)*

Hazard ratios indicate increase in risk of cardiovascular events per 1-unit increase in blood pressure variability (coefficient of variation) or blood pressure (mm Hg). All models were adjusted for age, sex, smoking status, diabetes status, use of antihypertensive medication, hypercholesterolemia, history of cardiovascular disease, body mass index, sleep apnea, alcohol consumption, and mean systolic or diastolic home blood pressure. Two hundred and sixteen adverse cardiovascular events occurred during follow-up. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Abbreviations: BP, blood pressure; CI, confidence interval; CV, coefficient of variation; HR, hazard ratio.

Table 4. Association of individual BP reading variability with cardiovascular outcomes

	Number of measurement days					
BP parameter	**2**	**3**	**4**	**5**	**6**	**7**
Morning BP						
Systolic BP						
Mean ± SD	129.8 ± 20.5	129.0 ± 20.0	128.3 ± 19.7	127.9 ± 19.5	127.6 ± 19.3	127.4 ± 19.1
CV ± SD	6.0 ± 3.8	6.5 ± 3.3	6.7 ± 3.0	6.9 ± 2.9	7.0 ± 2.8	7.0 ± 2.8
HR (95% CI) for mean	1.018 (1.011–1.025)***	1.019 (1.011–1.027)***	1.019 (1.012–1.027)***	1.020 (1.013–1.028)***	1.021 (1.013–1.028)***	1.021 (1.013–1.029)***
HR (95% CI) for CV	1.032 (0.997–1.067)	1.047 (1.008–1.088)*	1.067 (1.024–1.111)**	1.057 (1.012–1.104)*	1.064 (1.017–1.113)**	1.056 (1.008–1.106)*
C statistic	0.733	0.737 (ref)	0.738	0.737	0.737	0.737
Diastolic BP						
Mean ± SD	81.0 ± 10.3	80.7 ± 10.0	80.3 ± 9.9	80.2 ± 9.8	80.0 ± 9.7	79.9 ± 9.6
CV ± SD	5.4 ± 3.9	5.9 ± 3.6	6.1 ± 3.3	6.2 ± 3.1	6.3 ± 3.0	6.4 ± 3.0
HR (95% CI) for mean	1.035 (1.021–1.050)***	1.038 (1.023–1.053)***	1.039 (1.024–1.055)***	1.042 (1.026–1.057)***	1.043 (1.027–1.059)***	1.045 (1.029–1.062)***
HR (95% CI) for CV	1.014 (0.977–1.052)	1.028 (0.990–1.067)	1.033 (0.992–1.076)	1.028 (0.984–1.074)	1.043 (0.997–1.090)	1.052 (1.006–1.099)*
C statistic	0.735	0.737 (ref)	0.738	0.738	0.739	0.741
All-day BP						
Systolic BP						
Mean ± SD	131.1 ± 19.5	130.4 ± 19.0	129.9 ± 18.8	129.6 ± 18.6	129.3 ± 18.4	129.1 ± 18.3
CV ± SD	7.0 ± 3.0	7.4 ± 2.8	7.5 ± 2.7	7.6 ± 2.6	7.7 ± 2.6	7.7 ± 2.5
HR (95% CI) for mean	1.019 (1.012–1.027)***	1.020 (1.012–1.028)***	1.021 (1.013–1.029)***	1.021 (1.013–1.029)***	1.021 (1.013–1.030)***	1.022 (1.013–1.030)***
HR (95% CI) for CV	1.025 (0.980–1.071)	1.055 (1.009–1.103)*	1.053 (1.005–1.103)*	1.044 (0.994–1.097)	1.052 (1.000–1.105)*	1.047 (0.995–1.103)
C statistic	0.733	0.738 (ref)	0.737	0.736	0.736	0.736
Diastolic BP						
Mean ± SD	80.8 ± 9.6	80.5 ± 9.3	80.3 ± 9.2	80.1 ± 9.1	80.0 ± 9.1	79.8 ± 9.0
CV ± SD	6.4 ± 3.2	6.8 ± 3.0	6.9 ± 2.9	7.0 ± 2.8	7.0 ± 2.7	7.1 ± 2.7
HR (95% CI) for mean	1.040 (1.024–1.056)***	1.043 (1.026–1.059)***	1.044 (1.027–1.060)***	1.045 (1.029–1.062)***	1.047 (1.030–1.064)***	1.048 (1.031–1.066)***
HR (95% CI) for CV	1.010 (0.967–1.055)	1.030 (0.986–1.076)	1.031 (0.985–1.079)	1.040 (0.992–1.090)	1.053 (1.003–1.104)*	1.063 (1.014–1.115)*
C statistic	0.736	0.738 (ref)	0.739	0.740	0.741	0.742

Hazard ratios indicate increase in risk of cardiovascular events per 1-unit increase in blood pressure variability (coefficient of variation) or blood pressure (mm Hg). All models were adjusted for age, sex, smoking status, diabetes status, use of antihypertensive medication, hypercholesterolemia, history of cardiovascular disease, body mass index, sleep apnea, alcohol consumption, and mean systolic or diastolic home blood pressure. Two hundred and sixteen adverse cardiovascular events occurred during follow-up. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. The C statistics are for the whole model, reflecting how the model fit changes when the number of measurement days is increased for both mean BP and BP variability. Abbreviations: BP, blood pressure; CI, confidence interval; CV, coefficient of variation; HR, hazard ratio.

Table 5. Association of BP variability of the first measurements at each measurement occasion with cardiovascular outcomes

	Number of measurement days					
BP parameter	**2**	**3**	**4**	**5**	**6**	**7**
Morning BP						
Systolic BP						
Mean ± SD	131.2 ± 21.1	130.4 ± 20.6	129.7 ± 20.3	129.3 ± 20.0	129.0 ± 19.8	128.7 ± 19.6
CV ± SD	5.8 ± 5.1	6.4 ± 4.1	6.7 ± 3.6	6.9 ± 3.4	7.0 ± 3.2	7.1 ± 3.1
HR (95% CI) for mean	1.018 (1.011–1.025)***	1.019 (1.012–1.026)***	1.020 (1.012–1.027)***	1.020 (1.013–1.028)***	1.020 (1.013–1.028)***	1.021 (1.013–1.029)***
HR (95% CI) for CV	1.005 (0.978–1.033)	1.027 (0.996–1.059)	1.046 (1.010–1.082)*	1.041 (1.001–1.082)*	1.054 (1.012–1.097)*	1.045 (1.003–1.090)*
C statistic	0.733	0.734 (ref)	0.737	0.737	0.738	0.736
Diastolic BP						
Mean ± SD	81.7 ± 10.7	81.3 ± 10.3	80.9 ± 10.2	80.7 ± 10.0	80.6 ± 9.9	80.4 ± 9.8
CV ± SD	5.2 ± 4.8	5.8 ± 4.2	6.1 ± 3.7	6.2 ± 3.6	6.3 ± 3.4	6.4 ± 3.4
HR (95% CI) for mean	1.031 (1.017–1.045)***	1.035 (1.020–1.050)***	1.036 (1.021–1.052)***	1.039 (1.024–1.054)***	1.041 (1.025–1.057)***	1.043 (1.028–1.059)***
HR (95% CI) for CV	1.010 (0.982–1.039)	1.012 (0.981–1.045)	1.014 (0.978–1.052)	1.014 (0.976–1.055)	1.025 (0.985–1.066)	1.033 (0.994–1.075)
C statistic	0.733	0.735 (ref)	0.736	0.738	0.738	0.740
Evening BP						
Systolic BP						
Mean ± SD	134.2 ± 20.5	133.5 ± 19.7	133.2 ± 19.3	132.8 ± 19.1	132.6 ± 19.0	132.4 ± 18.9
CV ± SD	5.4 ± 4.6	6.3 ± 4.0	6.6 ± 3.5	6.8 ± 3.3	6.9 ± 3.0	6.9 ± 2.9
HR (95% CI) for mean	1.016 (1.009–1.023)***	1.017 (1.010–1.025)***	1.018 (1.010–1.026)***	1.018 (1.010–1.026)***	1.018 (1.011–1.026)***	1.019 (1.011–1.027)***
HR (95% CI) for CV	1.002 (0.974–1.031)	1.008 (0.976–1.041)	0.996 (0.960–1.034)	1.011 (0.972–1.051)	1.010 (0.969–1.054)	1.015 (0.971–1.062)
C statistic	0.730	0.732 (ref)	0.733	0.730	0.731	0.731
Diastolic BP						
Mean ± SD	81.3 ± 10.0	81.0 ± 9.5	80.8 ± 9.4	80.6 ± 9.2	80.5 ± 9.1	80.4 ± 9.1
CV ± SD	5.1 ± 4.6	5.9 ± 4.0	6.2 ± 3.7	6.4 ± 3.4	6.5 ± 3.2	6.6 ± 3.1
HR (95% CI) for mean	1.031 (1.016–1.046)***	1.034 (1.018–1.049)***	1.035 (1.020–1.051)***	1.037 (1.021–1.054)***	1.039 (1.023–1.056)***	1.041 (1.024–1.057)***
HR (95% CI) for CV	1.006 (0.978–1.035)	1.017 (0.985–1.051)	1.011 (0.975–1.049)	1.018 (0.978–1.059)	1.017 (0.975–1.061)	1.033 (0.990–1.078)
C statistic	0.730	0.732 (ref)	0.733	0.735	0.735	0.736

Hazard ratios indicate increase in risk of cardiovascular events per 1-unit increase in blood pressure variability (coefficient of variation) or blood pressure (mm Hg). All models were adjusted for age, sex, body mass index, diabetes mellitus status, hypercholesterolemia, history of cardiovascular disease, use of antihypertensive medication, smoking status, alcohol consumption, diagnosis of probable sleep apnea, and mean systolic/diastolic home blood pressure. Two hundred and sixteen adverse cardiovascular events occurred during follow-up. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. The C statistics are for the whole model, reflecting how the model fit changes when the number of measurement days is increased for both mean BP and BP variability. Abbreviations: BP, blood pressure; CI, confidence interval; CV, coefficient of variation; HR, hazard ratio.

Table 6. Classification of participants into normal and increased morning home blood pressure variability with an increasing number of measurement days

	Home measurement days used for calculating the variability index					
Classification	**1–2**	**1–3**	**1–4**	**1–5**	**1–6**	**1–7**
Systolic blood pressure						
Normal variability	1,488	1,504	1,526	1,523	1,545	1,539
Increased variability	213	197	175	178	156	162
Kappa coefficient		0.55 (0.49–0.61)	0.69 (0.64–0.75)	0.69 (0.64–0.75)	0.74 (0.69–0.80)	0.85 (0.81–0.90)
Diastolic blood pressure						
Normal variability	1,594	1,614	1,612	1,613	1,625	1,622
Increased variability	107	87	89	88	76	79
Kappa coefficient		0.55 (0.47–0.64)	0.68 (0.60–0.76)	0.79 (0.72–0.86)	0.77 (0.70–0.84)	0.84 (0.78–0.91)

Kappa coefficients (95% confidence intervals) are reported for comparing intraindividual agreement in classification to high vs. low BP variability on consecutive measurement days (e.g., classification based on measurements on days 1 through 3 vs. 1 through 4). Increased blood pressure variability was defined as a coefficient of variation >11.0 for systolic and >12.8 for diastolic blood pressure.

of each measurement occasion with cardiovascular disease was nonsignificant or remained significant only after the sixth measurement day.

To our knowledge, studies on the optimal schedule of HBP measurement for assessing BP variability are scarce to nonexistent. In a study with a sample of 153 participants, Kikuya *et al.* briefly mention that 10 home measurements could be sufficient for estimating BP variability.[5] This suggestion was, however, based solely on the observations of a 10-day SD of HBP being similar to a 30-day HBP SD. Although HBP measurement is well accepted by the patients, making it feasible to obtain a relatively large number of readings, the patient compliance tends to decrease with an increasing number of measurements.[22] A requirement of 10 HBP measurement days to assess BP variability could therefore be challenging in a real-life clinical setting. In our study, for example, we excluded nearly 20% of the sample because HBP measurements were not performed on all 7 days.

Systolic morning day-to-day HBPV based on 3 measurement days, with 2 readings on each measurement occasion was significantly related to cardiovascular outcomes. The HRs for cardiovascular disease were relatively similar irrespective of whether the 2 measurements on each measurement occasion were averaged (Table 2) or not (Table 4). As further demonstrated by the HRs and the model C statistics, the association between BP variability and cardiovascular outcomes became only slightly stronger when the number of measurement days was increased from 3 to 7. However, 7 measurement days were needed to achieve excellent agreement in a diagnosis of increased BP variability between consecutive days of measurement (Table 6). Although 2 morning measurements on 3 days might provide an acceptable estimate of HBPV, our findings also suggest that 7 measurement days might be needed for a more reliable estimate. These findings are mainly in line with those from previous studies that have examined the optimal number of home measurement days for assessing HBP, instead of HBPV. In the Finn-Home[22] and Didima[23] studies, the predictive value of HBP was demonstrated to increase with the number of measurements. However, most of this increase occurred during the first 3 days of measurement. On the other hand, the Ohasama investigators recommended that as many home measurements as possible should be obtained because they did not observe any definite threshold effects between the number of home measurements used to define HBP and stroke risk.[24] Overall, however, prognostic data from this and previous studies[22,23,25] suggest that HBP should be measured preferably for a period of 7 days, or for at least 3 days, to obtain a thorough image of an individual's HBP and HBPV.

In the current study, morning day-to-day HBPV was more robustly associated with cardiovascular morbidity than evening or all-day (average of morning and evening measurements) day-to-day BP variability. One explanation for this finding could be that morning BP variability is a better surrogate marker than evening BP for several traits that are simultaneously associated with increased BP variability and increased cardiovascular risk, such as sleep loss, obstructive sleep apnea, or excessive alcohol use.[26–28] In any case, our findings suggest that morning BP variability is more strongly associated with cardiovascular risk than is evening BP variability.

Our current study has several limitations which should be taken into account when interpreting its results. First, people may adhere to a BP measurement schedule more stringently in a research setting than in a clinical setting.[29] Our results are therefore only applicable to individuals who have received proper training on how to properly measure BP and who are expected to follow these instructions. Second, the study population only consisted of Finnish, Caucasian, participants which may limit the generalizability of the results to other races or ethnicities. Third, the BP monitors used in our study were not equipped with a memory function and all BP readings were self-reported. Fourth, HBP was measured in the nondominant arm instead of the arm with highest BP values, as recommended by the current HBP measurement guidelines.[25]

In conclusion, our study reinforces the role of BP variability, and especially morning day-to-day systolic BP variability, as an independent cardiovascular risk factor. Prior results from our group have demonstrated that HBPV predicts cardiovascular events, irrespective of an individual's sex, age, history of cardiovascular disease, antihypertensive treatment status, and ethnicity.[10] Two systolic BP readings in the morning on a minimum of 3 days appear to be sufficient for measuring HBPV in the general population. Increasing the number of measurement days from 3 results in only marginal improvement in prognostic accuracy. Our results could inform future guidelines on the optimal schedule for assessing HBPV.

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DISCLOSURE

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