Outcome-Driven Thresholds for Increased Home Blood Pressure Variability

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Abstract—Increased blood pressure (BP) variability predicts cardiovascular disease, but lack of operational thresholds limits its use in clinical practice. Our aim was to define outcome-driven thresholds for increased day-to-day home BP variability. We studied a population-based sample of 6238 individuals (mean age 60.0±12.9, 56.4% women) from Japan, Greece, and Finland. All participants self-measured their home BP on ≥3 days. We defined home BP variability as the coefficient of variation of the first morning BPs on 3 to 7 days. We assessed the association between systolic/diastolic BP variability (as a continuous variable and in deciles of coefficient of variation) and cardiovascular outcomes using Cox regression models adjusted for cohort and classical cardiovascular risk factors, including BP. During a follow-up of 9.3±3.6 years, 304 cardiovascular deaths and 715 cardiovascular events occurred. A 1 SD increase in systolic/diastolic home BP variability was associated with increased risk of cardiovascular mortality (hazard ratio, 1.17/1.22; 95% confidence interval, 1.06–1.30/1.11–1.34; P=0.003/<0.0001) and cardiovascular events (hazard ratio, 1.13/1.14; 95% confidence interval, 1.05–1.21/1.07–1.23; P=0.0007/0.0002). Compared with the average risk in the whole population, risk of cardiovascular deaths (hazard ratio, 1.66/1.84; 95% confidence interval, 1.27–2.17/1.42–2.37; P=0.0002/<0.0001) and events (hazard ratio, 1.46/1.42; 95% confidence interval, 1.21–1.76/1.17–1.71; P<0.0001/0.0004) was increased in the highest decile of systolic/diastolic BP variability (coefficient of variation>11.0/12.8). Increased home BP variability predicts cardiovascular outcomes in the general population. Individuals with a systolic/diastolic coefficient of variation of day-to-day home BP >11.0/12.8 may have an increased risk of cardiovascular disease. These findings could help physicians identify individuals who are at an increased cardiovascular disease risk. **(*Hypertension*. 2017;69:599-607. DOI: 10.1161/HYPERTENSIONAHA.116.08603.)** • **Online Data Supplement**

Key Words: blood pressure ■ epidemiology ■ hypertension ■ risk factors

The role of blood pressure (BP) variability as a risk factor for cardiovascular disease has been studied extensively in recent years. Several studies found that increased office,[1–3] ambulatory,[3–7] and self-measured home[8,9] BP variability are associated with adverse cardiovascular outcomes independent of the BP level. However, the clinical use of BP variability in cardiovascular risk stratification has been limited because the current hypertension guidelines do not make any clear recommendations on how to define or manage increased BP variability.[10–12] The report from the panel members appointed to the eighth Joint National Committee does not address BP variability as a risk factor, whereas the European Society of Hypertension guidelines consider increased visit-to-visit office BP variability a possible independent cardiovascular risk factor but do not suggest a threshold for increased BP variability.[10,11] Furthermore, the Japanese Society of Hypertension

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guidelines suggest that a definition and analytic assessing methods should be established for BP variability to enable its use in clinical practice.[12]

Although the first studies that demonstrated the potential dangers of high BP variability used office and ambulatory BP measurement to quantify BP variability,[1,4] home BP measurement could offer a more widely available and feasible option for assessing BP variability. Home BP measurement provides a large number of readings performed in a natural environment that are free from the white-coat effect over a long period of time, and consequently, self-measured home BP has been shown to be a stronger predictor of cardiovascular outcomes than office BP.[13,14] In addition, increased home BP variability has also been recognized as a potential independent predictor of cardiovascular outcomes.[8,9]

The lack of a reference frame for BP variability limits its use in clinical cardiovascular disease risk assessment.[15,16] The purpose of our study was to establish an outcome-driven reference frame for day-to-day variability of self-measured home BP in 4 populations included in the International Database of Home Blood Pressure in Relation to Cardiovascular Outcome. Outcome-driven reference values for increased BP variability could inform guidelines and help clinicians identify individuals at high risk of cardiovascular disease.

Methods

Study Population

The International Database of Home Blood Pressure in Relation to Cardiovascular Outcome consists of studies with a random population sample and longitudinal follow-up of fatal and nonfatal cardiovascular outcomes. The data collection has been previously described in detail, and all studies have been described in peer-reviewed literature.[17] For the present analysis, we considered 6353 participants living in Ohasama, Japan; Tsurugaya, Japan; Didima, Greece; and Finland. The Montevideo cohort was excluded from the current analysis because home BP was measured on only 1 day. After excluding participants with missing covariates (n=28) or with BP measurements that were invalid or performed on <3 days (n=87), the number of participants included in the analyses was 6238 (2775 from Ohasama, 768 from Tsurugaya, 634 from Didima, and 2061 from Finland). All participants gave written informed consent, and all study protocols had received ethical approval.

BP Measurements

Home BP was self-measured with a validated, automated, oscillometric, upper arm cuff device at the participants' homes in all studies. BP was measured in the sitting position, and a cuff of appropriate size was used as previously described.[17] Because home BP was measured in the Tsurugaya cohort only in the morning, we calculated the day-to-day home BP variability based on the individual's first BP reading of every measurement day performed between 5:00 AM and 12:00 AM to minimize the potential impact of between-cohort differences in measurement protocols. BP measurements of the first 3 to 7 days of measurement were included in the analyses. We discarded 76 of 90 432 (0.08%) BP readings with a systolic BP <70 or >250 mm Hg, diastolic BP <40 or >140 mm Hg, or pulse pressure <10 mm Hg to retain physiologically meaningful readings in the analysis and to ensure the reliability of variability indexes. Office BP was the average of 2 consecutive readings measured with a standard mercury sphygmomanometer or an automated device.

BP Variability Indexes

Home BP variability was assessed with 4 different indexes: SD, coefficient of variation (CV), average real variability (ARV), and variation independent of the mean (VIM). SD is the simplest statistical measure for describing variation but is highly dependent on the individual's BP level.

CV is derived from the SD by dividing it by the mean. Consequently, CV is less influenced by BP level and is therefore considered an applicable index in variability studies.[18] In this study, we therefore used CV as our main exposure variable because it can be relatively easily calculated in clinical practice, and a universal reference frame can be defined.

ARV, in turn, takes also into account the order of measurements and is calculated from the mean absolute difference between consecutive BP measurements.[19] The ARV index is calculated using the following formula:

$$\mathrm{ARV}=\frac{1}{n-1}\sum_{k=1}^{n-1}\left|\mathrm{BP}_{k+1}-\mathrm{BP}_{k}\right|$$

where n denotes the number of valid BP measurements in the data corresponding to a given subject, and k ranges from 1 to $n-1$.

Finally, VIM is a transformation of SD that is defined to be uncorrelated with mean BP.[1] VIM is calculated as the SD divided by the mean to the power x and multiplied by the population mean to the power x. The power x is obtained by fitting a curve through a plot of SD against mean using the model $\mathrm{SD}=a\times\mathrm{mean}^{x}$, where x was derived by nonlinear regression analysis. However, no universal reference values can be provided for VIM as it is always population specific.

Definitions

Baseline questionnaires were used to obtain information on the participants' medical history, medication intake, and smoking habits. Smoking was defined as any use of tobacco products. Body mass index was calculated as body weight in kg divided by height in m^2. Serum cholesterol and blood glucose were determined by automated enzymatic methods on venous blood samples. Diabetes mellitus was defined as a self-reported diagnosis of diabetes mellitus, a fasting or nonfasting blood glucose level of at least 7.0 or 11.1 mmol/L, respectively, or the use of antidiabetic drugs. Previous cardiovascular disease included cardiac, cerebrovascular, and peripheral vascular disorders.[20] Information on serum cholesterol level was unavailable for Didima and was extrapolated by sex and 10-year age strata based on data from a large population cohort examined at the same time and in the same geographical area.[21,22]

Outcomes

We ascertained vital status and incidence of fatal and nonfatal cardiovascular events from the appropriate sources in each

country as previously described.[17] The mortality data were based on death certificates acquired from regional (Ohasama and Didima) or national (Finland and Tsurugaya) registers. We used cardiovascular death and a composite end point of all cardiovascular events as the end points. Cardiovascular events included cardiovascular mortality, myocardial infarction, surgical and percutaneous coronary revascularization, pacemaker implantation, heart failure, and stroke (not including transient ischemic attack). Only the first event was considered in the analyses.[17]

Statistical Analysis

The association between home BP variability indexes and cardiovascular risk was examined with Cox regression models. All models were adjusted for cohort, sex, age, body mass index, smoking status, diabetes mellitus status, use of antihypertensive medication, total serum cholesterol, history of cardiovascular disease, and mean systolic/diastolic home BP. We tested for nonlinearity by adding a quadratic term for variability indexes of systolic/diastolic BP into the models.

We examined the improvement in model discrimination and reclassification when CV of home BP was added to a Cox model that included the conventional cardiovascular risk factors with the net reclassification improvement,[23] the integrated discrimination improvement,[23] and Harrell C statistic.[24] The net reclassification improvement was based on 4 risk categories of <5%, 5% to 10%, 10% to 20%, and >20%.

To obtain outcome-driven thresholds for home BP variability, we divided the population into 10 groups by deciles of CV. We estimated hazard ratios contrasting the risk for cardiovascular outcomes in each decile versus the average risk in the whole population.[25] We defined the threshold for increased BP variability as the decile above which cardiovascular risk was increased. We performed sensitivity analyses by excluding 1 cohort at a time from the analyses. We investigated the association between BP variability and cardiovascular outcome in subgroups by sex, age, prevalent cardiovascular disease, use of antihypertensive treatment, and ethnicity. We tested for interaction to determine whether the relative effect of BP variability varied significantly among subgroups by introducing an interaction term in the models. For these analyses, CV of BP was dichotomized with the cutoff at the 90th percentile.

P values <0.05 were considered statistically significant. Statistical analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Participant Characteristics

Baseline characteristics in the whole population and by cohort at baseline are shown in Table 1. Our study population consisted of 3543 Asians and 2695 Europeans. The mean number of home BP measurement days was 6.8±0.7 in Ohasama, 6.3±1.3 in Tsurugaya, 3.0±0.0 in Didima, and 6.8±0.6 in Finland.

BP Variability and Cardiovascular Outcomes

During a median follow-up of 8.3 years, 304 cardiovascular deaths and 715 cardiovascular events occurred. In multivariable-adjusted Cox regression models, the variability indexes, SD, CV, VIM, and ARV of systolic and diastolic home BP, were all associated with all-cause mortality, cardiovascular mortality, cardiovascular events, and stroke events (Table 2). No association was found for SD of systolic and diastolic BP, VIM of systolic BP, and ARV of systolic BP in relation to cardiac events. The quadratic terms for the variability indexes, included in the models to test for nonlinearity, did not reach statistical significance ($P \geq 0.06$ for all, data not shown). In addition, in a subset of 5980 participants with office BP available, including systolic/diastolic office BP as a covariate in the models did not materially alter the results (Table S1 in the online-only Data Supplement). The relationship between certain indexes and cardiac events became nonsignificant because of the smaller sample size.

Adding systolic/diastolic CV in Cox regression models that included the conventional cardiovascular risk factors increased the C statistic for cardiovascular events by 0.003/0.002 (*P*=0.02/0.18) and for cardiovascular mortality by 0.003/0.004 (*P*=0.02/0.01). Changes in net reclassification improvement and integrated discrimination improvement were statistically nonsignificant (Table 3).

Cardiovascular Outcomes in Relation to Deciles of CV of Home BP

The relation between home BP variability and cardiovascular outcome in deciles of CV of home BP is shown in Table 4 and Figure. The risk of cardiovascular deaths and events was significantly greater in the highest decile of systolic/diastolic BP variability (CV>11.0/12.8) than the average risk in the whole population. Cardiovascular disease risk was the lowest in the third and fourth deciles of CV of BP. In general, having a CV of BP in the highest decile was associated with adverse cardiovascular outcomes in most subgroups by sex, age, prevalent cardiovascular disease, use of antihypertensive medication, and ethnicity, and no significant interactions were observed (Table 5).

Characteristics of Participants in the Tenth Decile of CV of Home BP

Because the risk of cardiovascular disease was increased only in the tenth decile of CV of home BP, we compared the characteristics of these individuals with those in the other deciles (Table S2). Participants with the greatest systolic/diastolic BP variability were older (*P*<0.0001/0.01) and were more likely to be women (*P*<0.0001/<0.0001) and have a history of cardiovascular disease (*P*=0.001/0.002). In addition, participants with the greatest diastolic BP variability had lower body mass index (*P*<0.0001), systolic BP (*P*=0.0002), diastolic BP (*P*<0.0001), and serum total cholesterol (*P*<0.0001). The Didima cohort was over-represented in the highest decile of systolic BP variability, whereas Ohasama and Didima cohorts were over-represented in the highest decile of diastolic BP variability (Table S2).

Sensitivity Analyses

To verify the consistency of our results, we performed the Cox regression analyses for cardiovascular death and cardiovascular events after excluding 1 cohort at a time. These exclusions

Table 1. Baseline Characteristics of Participants

Characteristic	Overall	Cohort			
		Ohasama	Tsurugaya	Didima	Finn-Home
n	6238	2775	768	634	2061
Age, y	60.0±12.9	59.2±12.7	75.3±4.6	54.1±17.7	57.1±8.5
Women	3518 (56.4)	1629 (58.7)	410 (53.4)	372 (58.7)	1107 (53.7)
Smokers	1317 (21.1)	586 (21.1)	96 (12.5)	159 (25.1)	476 (23.1)
Antihypertensive treatment	1385 (22.2)	510 (18.4)	319 (41.5)	92 (14.5)	464 (22.5)
Diabetes mellitus	528 (8.5)	252 (9.1)	119 (15.5)	29 (4.6)	128 (6.2)
History of cardiovascular disease	640 (10.3)	211 (7.6)	125 (16.3)	58 (9.2)	246 (11.9)
Body mass index, kg/m^2	25.2±4.1	23.4±2.9	23.9±3.3	27.0±4.3	27.4±4.5
Serum cholesterol, mmol/L	5.4±1.1	5.0±0.9	5.3±0.9	5.1±0.4	6.1±1.1
Systolic home blood pressure					
Mean, mm Hg	128.7±19.0	125.3±15.8	141.1±20.2	125.5±21.0	129.5±19.9
SD	8.8±4.4	8.4±4.0	9.6±4.9	8.8±5.8	9.1±4.3
CV	6.8±3.3	6.7±3.0	6.8±3.3	7.0±4.5	7.0±3.1
VIM	8.8±4.2	8.4±3.8	9.6±4.7	8.8±5.7	9.1±4.0
ARV	9.8±5.4	9.3±4.9	10.4±5.6	10.9±7.7	9.7±4.8
Diastolic home blood pressure					
Mean, mm Hg	77.3±10.4	75.3±10.2	77.5±10.4	74.6±9.9	80.8±10.0
SD	5.7±3.2	6.3±3.0	5.2±2.9	5.5±4.5	5.2±2.8
CV	7.5±4.1	8.4±4.1	6.8±3.6	7.4±5.6	6.4±3.4
VIM	5.7±3.1	6.3±3.0	5.2±2.8	5.5±4.2	5.2±2.8
ARV	6.3±3.9	6.9±3.6	5.7±3.3	7.0±6.3	5.6±3.1

Data are shown as n (%) or mean±SD. ARV indicates average real variability; CV, coefficient of variation; and VIM, variation independent of the mean.

did not markedly change the results (Tables S3 and S4). We also repeated the main analyses of Tables 2 and 4 by including only participants with at least 7 days of BP measurements in the Ohasama, Tsurugaya, and Finnish cohorts (Tables S5 and S6), and by including only the first 3 days of measurement (Tables S7 and S8). Including only those participants with 7 measurement days available did not materially alter our results, but no association was found between 3-day BP variability and stroke (Table S7).

Discussion

Although many of the diagnostic thresholds used to define disease are completely arbitrary, thresholds are still needed in medicine so that clinicians are able to separate abnormal findings from those that are normal. To our knowledge, no operational thresholds have previously been reported for increased BP variability. The current data set with a large, international population-based sample reinforces the role of increased home BP variability as an independent predictor of cardiovascular events and cardiovascular mortality. Our results also suggest that cardiovascular risk increases when systolic/diastolic CV of day-to-day home BP is ≥11.0/12.8. However, the incremental predictive value gained by adding BP variability to a model with established risk factors for cardiovascular events is modest, suggesting that BP level is still more important than BP variability in cardiovascular risk assessment.

Some hypertension guidelines have already noted the need to classify BP variability as normal or increased, but no cutoff points for this categorization have been available to date.[11,12] Our results could help physicians identify with more certainty individuals who could be at an increased risk of cardiovascular disease. However, our proposed thresholds apply only to day-to-day home BP variability, and additional research is also needed on outcome-driven thresholds for ambulatory and office BP variability. In addition, a major obstacle for the widespread use of BP variability in clinical practice is that the optimal way for managing patients with increased BP variability is unknown. BP variability could possibly be reduced through interventions on lifestyle factors such as heavy alcohol use that have been shown to increase BP variability.[26] In addition to lifestyle factors, some antihypertensive drugs and drug combinations could be more beneficial than others in patients with increased BP variability. In the Anglo-Scandinavian Cardiac Outcomes Trial, calcium channel blockers were found to reduce visit-to-visit BP variability, whereas β-blockers had an opposite effect.[27] Furthermore, in the Natrilix SR Versus Candesartan and Amlodipine in the Reduction of Systolic Blood Pressure in Hypertensive Patients study, amlodipine and indapamide reduced ambulatory BP

Table 2. Risk of Cardiovascular Events per 1 SD Increase in Home Blood Pressure Variability

Variability Index	End Point	Systolic BP		Diastolic BP	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
SD	All-cause mortality	1.13 (1.06–1.20)	0.0003	1.14 (1.07–1.22)	<0.0001
	Cardiovascular mortality	1.15 (1.04–1.28)	0.005	1.21 (1.10–1.33)	<0.0001
	Cardiovascular events	1.12 (1.04–1.19)	0.002	1.12 (1.05–1.20)	0.0008
	Cardiac events	1.10 (0.98–1.23)	0.11	1.11 (0.99–1.24)	0.08
	Stroke events	1.14 (1.04–1.25)	0.006	1.13 (1.03–1.24)	0.01
CV	All-cause mortality	1.13 (1.06–1.21)	0.0002	1.15 (1.08–1.22)	<0.0001
	Cardiovascular mortality	1.17 (1.06–1.30)	0.003	1.22 (1.11–1.34)	<0.0001
	Cardiovascular events	1.13 (1.05–1.21)	0.0007	1.14 (1.07–1.23)	0.0002
	Cardiac events	1.12 (1.003–1.26)	0.04	1.13 (1.004–1.27)	0.04
	Stroke events	1.14 (1.04–1.25)	0.008	1.14 (1.04–1.26)	0.006
VIM	All-cause mortality	1.13 (1.06–1.21)	0.0002	1.14 (1.07–1.21)	<0.0001
	Cardiovascular mortality	1.17 (1.05–1.30)	0.003	1.21 (1.10–1.33)	<0.0001
	Cardiovascular events	1.13 (1.05–1.21)	0.0008	1.13 (1.05–1.21)	0.0005
	Cardiac events	1.12 (0.999–1.25)	0.051	1.12 (1.003–1.26)	0.04
	Stroke events	1.14 (1.04–1.26)	0.008	1.12 (1.02–1.23)	0.02
ARV	All-cause mortality	1.13 (1.06–1.20)	0.0002	1.14 (1.07–1.21)	<0.0001
	Cardiovascular mortality	1.13 (1.02–1.25)	0.02	1.20 (1.10–1.31)	<0.0001
	Cardiovascular events	1.10 (1.02–1.17)	0.01	1.12 (1.05–1.20)	0.0009
	Cardiac events	1.09 (0.98–1.23)	0.12	1.12 (1.003–1.25)	0.04
	Stroke events	1.11 (1.01–1.23)	0.03	1.11 (1.01–1.22)	0.03

During the follow-up, 832 deaths of any cause, 304 cardiovascular deaths, 715 cardiovascular events, 243 cardiac events, and 399 stroke events occurred. All models were adjusted for cohort, sex, age, body mass index, smoking status, diabetes mellitus status, use of antihypertensive medication, total serum cholesterol, history of cardiovascular disease, and mean systolic/diastolic home blood pressure. ARV indicates average real variability; CI, confidence interval; CV, coefficient of variation; HR, hazard ratio; and VIM, variation independent of the mean.

variability more than candesartan.[28] In contrast, Asayama et al[29] observed that angiotensin-converting enzyme inhibitors, calcium channel blockers, and angiotensin receptor blockers had similar effects on home BP variability. In any case, clinical trials are still needed to resolve whether reducing BP variability would provide any incremental protection from cardiovascular disease over BP reduction.

Long-term visit-to-visit variability of office BP and short-term variability of 24-hour ambulatory BP have been shown to predict both stroke[1,2,5] and cardiovascular events.[3,6,7] Although the quadratic term for variability indexes of BP did not reach statistical significance in the Cox models ($P \geq 0.06$), our results suggest that the relationship between BP variability and outcomes may not be perfectly linear. In our study,

Table 3. Incremental Predictive Value of Home Blood Pressure Variability for Cardiovascular Outcomes

Model	Cardiovascular Mortality			Cardiovascular Events		
	Improvement in C Statistic	NRI	IDI	Improvement in C Statistic	NRI	IDI
Model 1: Conventional risk factors	0.835			0.765		
Model 2: Model 1+SBP	0.002	2.4	0.1	0.007*	2.7	0.8*
Model 3: Model 2+CV of SBP	0.003†	–1.0	0.2	0.003†	–0.6	0.2
Model 4: Model 1+DBP	0.0002	0.6	–0.03	0.004†	1.3	0.3
Model 5: Model 4+CV of DBP	0.004†	–0.1	0.6	0.002	–0.5	0.4

The conventional risk factors included sex, age, cohort, body mass index, smoking, serum cholesterol, diagnosis of diabetes mellitus, history of cardiovascular disease, and antihypertensive treatment. CV indicates coefficient of variation; DBP, diastolic blood pressure; IDI, integrated discrimination improvement; NRI, net reclassification improvement; and SBP, systolic blood pressure.

*$P<0.001$ for improvement in NRI, IDI, and Harrell C statistic.

†$P<0.05$ for improvement in NRI, IDI, and Harrell C statistic.

Table 4. Relation Between Deciles of CV of Day-to-Day Home Blood Pressure and Cardiovascular Outcomes

Decile of CV Distribution	CV Range		Cardiovascular Death, HR (95% CI)		Cardiovascular Events, HR (95% CI)	
	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
1	0–3.3	0–3.3	1.04 (0.73–1.50)	0.86 (0.56–1.32)	1.06 (0.84–1.33)	1.06 (0.84–1.34)
2	3.4–4.3	3.4–4.2	1.26 (0.90–1.77)	1.29 (0.88–1.90)	1.11 (0.89–1.39)	1.18 (0.94–1.48)
3	4.4–5.0	4.3–5.0	0.55 (0.33–0.90)*	0.74 (0.47–1.15)	0.79 (0.61–1.03)	0.83 (0.65–1.06)
4	5.1–5.6	5.1–5.8	0.92 (0.62–1.37)	0.54 (0.33–0.87)*	0.88 (0.69–1.13)	0.61 (0.47–0.81)†
5	5.7–6.3	5.9–6.6	0.93 (0.64–1.36)	1.33 (0.96–1.86)	0.95 (0.75–1.21)	1.07 (0.86–1.33)
6	6.4–7.1	6.7–7.5	1.05 (0.75–1.48)	0.76 (0.52–1.09)	0.90 (0.71–1.14)	0.83 (0.66–1.04)
7	7.2–8.0	7.6–8.6	1.03 (0.74–1.44)	1.24 (0.89–1.72)	0.998 (0.81–1.24)	1.15 (0.93–1.43)
8	8.1–9.1	8.7–10.2	1.04 (0.74–1.46)	0.86 (0.60–1.24)	0.99 (0.79–1.23)	0.94 (0.75–1.18)
9	9.2–10.9	10.3–12.7	0.86 (0.62–1.19)	1.15 (0.85–1.56)	0.98 (0.80–1.21)	1.15 (0.94–1.41)
10	11.0–37.7	12.8–43.3	1.66 (1.27–2.17)†	1.84 (1.42–2.37)‡	1.46 (1.21–1.76)‡	1.42 (1.17–1.71)†

The risk of events in each decile of blood pressure variability was assessed with multivariable-adjusted Cox models while using the overall risk in the whole population as reference. All models were adjusted for cohort, sex, age, body mass index, smoking status, diabetes mellitus status, use of antihypertensive medication, total serum cholesterol, history of cardiovascular disease, and mean systolic/diastolic home blood pressure. CI indicates confidence interval; CV, coefficient of variation; and HR, hazard ratio.

*$P<0.05$.

†$P<0.001$.

‡$P<0.0001$.

cardiovascular risk increased only in the tenth decile of BP variability, although it was inconsistently significantly lower in the third and fourth deciles. This finding also highlights the need for operational thresholds for BP variability. Another new finding of our study was that BP variability was consistently associated with different cardiovascular end points. A previous study based on the Ohasama cohort showed that home BP variability is predictive of stroke, but no statistical significance was found for cardiac events,[9] whereas a study based on the Finn-Home cohort provided opposite results.[8] These discrepancies are most likely explained by the differences in the incidence of cardiovascular event subtypes and by the lack of statistical power to detect the risk for event subtypes. In Asia, the incidence of stroke is substantially higher than in Europe and vice versa is true for coronary heart disease.[30,31] In our study with a large sample of Asians and Europeans, increased BP variability was associated with both stroke and cardiac morbidity.

Several factors have previously been shown to correlate with increased home BP variability. Old age, excessive alcohol use, and high home BP level were associated with increased day-to-day BP variability in the Finn-Home and Ohasama populations.[32,33] In addition, the Ohasama investigators have shown that female sex, low heart rate, elevated home heart rate variability, and a lack of antihypertensive treatment are determinants of increased home BP variability.[33] The effects of antihypertensive drug therapy on BP variability are especially relevant in this context because BP-lowering drugs have been suggested to be an important driver of the association between BP variability and cardiovascular outcomes.[34] In our large individual-level meta-analysis, increased BP variability was associated with cardiovascular disease in both

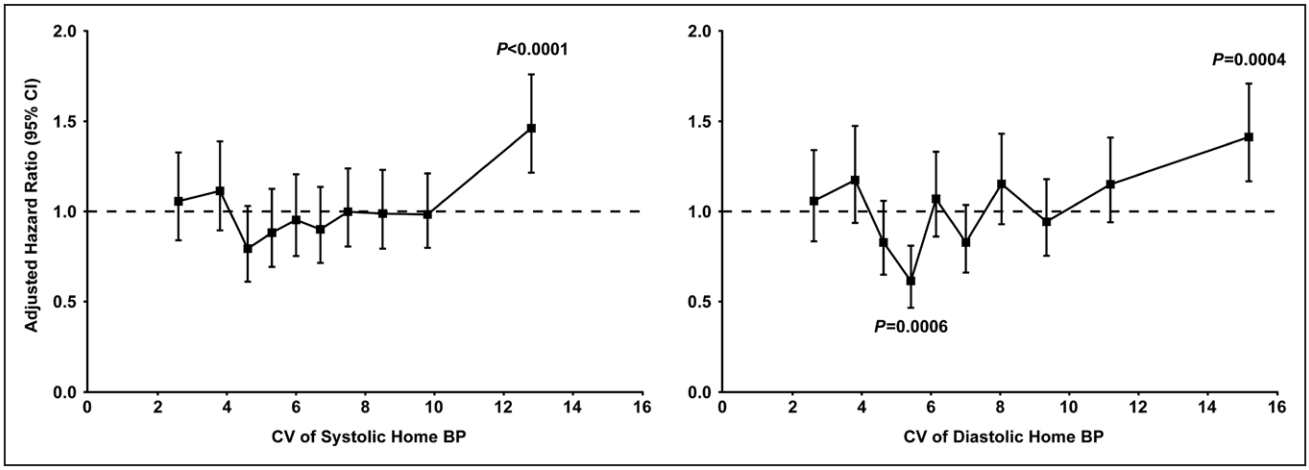

Figure. Risk of cardiovascular events in deciles of coefficient of variation (CV) of day-to-day home blood pressure (BP). The risk of events in each decile of blood pressure variability was assessed with multivariable-adjusted Cox models while using the overall risk in the whole population as reference. Hazard ratios are plotted at the median of each decile. CI indicates confidence interval.

Table 5. Risk of Cardiovascular Outcomes per 1 SD Increase in the Coefficient of Variation of Home Blood Pressure by Subgroup

Subgroup	n	Cardiovascular Deaths					Cardiovascular Events				
		Events	Systolic CV, HR (95% CI)	*P*int	Diastolic CV, HR (95% CI)	*P*int	Events	Systolic CV, HR (95% CI)	*P*int	Diastolic CV, HR (95% CI)	*P*int
Sex											
Women	3518	129	1.70 (1.12–2.57)*	0.89	1.73 (1.14–2.63)†	0.58	302	1.50 (1.12–2.02)†	0.91	1.48 (1.10–2.00)*	0.53
Men	2720	175	1.68 (1.10–2.56)*		2.06 (1.41–3.00)‡		413	1.52 (1.14–2.03)†		1.45 (1.07–1.96)*	
Age											
<60	3095	42	2.26 (0.97–5.25)	0.60	1.99 (0.87–4.53)	0.47	156	1.56 (0.94–2.61)	0.76	1.19 (0.69–2.08)	0.07
≥60	3143	262	1.81 (1.33–2.48)‡		2.33 (1.73–3.12)§		559	1.63 (1.30–2.05)§		1.72 (1.37–2.16)§	
Prevalent CVD											
Yes	640	95	1.72 (1.02–2.90)*	0.65	2.42 (1.52–3.85)‡	0.14	187	1.42 (0.96–2.08)	0.86	1.84 (1.28–2.67)†	0.10
No	5598	209	1.68 (1.17–2.41)†		1.66 (1.16–2.36)†		528	1.53 (1.20–1.96)‡		1.30 (0.998–1.68)	
AH treatment											
Yes	1385	133	1.59 (1.04–2.44)*	0.71	1.81 (1.15–2.86)*	0.71	296	1.53 (1.13–2.07)†	0.93	1.64 (1.18–2.28)†	0.30
No	4853	171	1.84 (1.22–2.77)†		1.96 (1.37–2.80)‡		419	1.53 (1.15–2.02)†		1.34 (1.01–1.76)*	
Ethnicity											
Asian	3543	224	1.84 (1.31–2.60)‡	0.49	1.73 (1.25–2.40)‡	0.49	452	1.55 (1.19–2.02)†	0.56	1.29 (1.00–1.67)	0.20
White	2695	80	1.61 (0.89–2.91)		2.52 (1.45–4.38)†		263	1.49 (1.07–2.07)*		1.83 (1.26–2.66)†	

When testing the interactions, the coefficient of variation of home blood pressure was used as a dichotomized categorical variable (deciles 1–9 vs the 10th decile). All models were adjusted for cohort, sex, age, body mass index, smoking status, diabetes mellitus status, use of antihypertensive medication, total serum cholesterol, history of cardiovascular disease, and mean systolic/diastolic home blood pressure. For systolic variability, 605 cardiovascular events and 248 cardiovascular deaths occurred in deciles 1–9, and 110 and 56 in the 10th decile. For diastolic variability, 609 cardiovascular events and 235 cardiovascular deaths occurred in deciles 1–9, and 106 and 69 in the 10th decile. AH indicates antihypertensive; CI, confidence interval; CV, coefficient of variation; CVD, cardiovascular disease; HR, hazard ratio; and *P*int, *P* for interaction.

*$P<0.05$.

†$P<0.01$.

‡$P<0.001$.

§$P<0.0001$.

treated and untreated participants with no between-group interaction. Furthermore, we found an association between increased BP variability and increased cardiovascular risk in both sexes, in younger and older participants, in those with and without prevalent cardiovascular disease, and in Asians and Europeans. These results suggest that home BP variability is a risk factor for cardiovascular disease in nearly all populations.

Self-measurement of BP at home can be considered a reliable method for assessing BP variability because it provides a large number of BP readings that are free from the white-coat effect. There are, however, a few factors that should be taken into account when interpreting an individual's home BP variability. For example, home BP may be slightly higher during working days than during weekends in employed individuals.[35] This within-week oscillation in BP may be caused by differences between weekdays and weekends in stress level, sleep quality,[36] and intake of alcohol[37] and salt.[38] Furthermore, diurnal BP patterns seem to differ between various cultures. In Japanese studies, morning home BP has been shown to be higher than evening BP,[39–42] whereas opposite findings have been made in Europe.[43–46] However, in certain circumstances such as with sleep apnea, prevalent cardiovascular disease, or excessive use of alcohol, this relationship between morning and evening BP may be reversed.[47]

Some potential limitations must be considered when interpreting the results of this study. First, the impact of alcohol consumption, which has been shown to affect BP variability, could not be evaluated.[26,48] However, alcohol intake is not considered a classical, established cardiovascular risk factor. Second, the home measurement protocols differed between studies, and we therefore strived to minimize the impact of these differences by using only the first measurements of each measurement day. Third, data on serum cholesterol were missing in the Didima cohort and were extrapolated from the results of another similar Greek population study.[21] Fourth, the validation of cardiovascular events was nonconsistent across the populations because some relied on register data whereas others relied on contact with the participants, their relatives, and the treating physicians. Fifth, because our study population consists solely of individuals of Asian and European origin, our results may not be generalizable to other populations. Sixth, split sample validation could have improved the reliability of the results. However, because our study sample is already split into deciles, repeating the analyses in split samples would have resulted in too small decile sizes and number of events per decile. On the other hand, we performed sensitivity analyses by excluding 1 cohort at a time and by testing a different number of measurement days to increase the validity of our results.

Perspectives

Home BP variability is associated with an increased risk of cardiovascular death and events in the general population. A CV of >11.0 for systolic and >12.8 for diastolic day-to-day home BP seems to be independently associated with an increased risk of cardiovascular events. Treating physicians should consider looking for underlying factors, such as obstructive sleep apnea or excessive alcohol use, if a patient's home BP variability exceeds this threshold. Although more research is needed into elucidating the generalizability of these cutoff points and the optimal way to manage individuals with increased BP variability, our findings might help physicians identify individuals with high BP variability who are at an increased risk of cardiovascular disease. For example, in patients with labile and elevated office BP, diagnostic confidence might be improved by determining also home BP. If home BP variability would exceed the thresholds presented in this study, the management could be targeted toward maximal reduction of BP variability with, for example, calcium channel blockers.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This study is the first that aims to establish reference values for increased home blood pressure (BP) variability.
- The prognostic significance of home BP variability was studied in a large international population-based sample.

What Is Relevant?

- This study reinforces the role of increased home BP variability as an independent cardiovascular risk factor.
- Individuals with a systolic/diastolic coefficient of variation of day-to-day home BP >11.0/12.8 may have an increased risk of cardiovascular disease.

Summary

Although more research is needed into elucidating the generalizability of these cutoff points and the optimal way to manage individuals with increased BP variability, our findings might help physicians identify individuals with high BP variability who are at an increased risk of cardiovascular disease.