Impact of Visit-to-Visit Variability in Systolic Blood Pressure on Cardiovascular Outcomes in Korean National Health Insurance Service—National Sample Cohort

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BACKGROUND
Despite an association between visit-to-visit blood pressure (BP) variability (VV-BPV) and cardiovascular (CV) outcomes, many studies performed during the past 4 years have shown conflicting results. This study investigated the impact of VV-BPV on CV outcomes in the Korean National Health Insurance Service (NHIS) database-National Sample Cohort.

METHODS
From the 2002 Korean NHIS database (n = 47,851,928), sample subjects with 3 or more BP measurements (n = 51,811) were divided into 2 groups according to a 10 mm Hg cutoff in the SD of systolic BP (SD-SBP). The CV outcomes of these groups were compared by sensitivity analyses using various sampling methods.

RESULTS
Irrespective of sampling method, subjects with SD-SBPs ≥10 mm Hg had higher rates of CV events or death, nonfatal myocardial infarction (MI) or stroke, and total mortality, but were not associated with CV mortality. The hazard ratios for CV events or death, nonfatal MI or stroke, CV mortality, and total mortality were 1.43 (95% confidence interval [CI], 1.25–1.63, $P < 0.01$), 1.45 (95% CI, 1.27–1.65, $P < 0.01$), 1.32 (95% CI, 0.89–1.94, $P = 0.17$), and 1.18 (95% CI, 1.01–1.38, $P = 0.04$), respectively.

CONCLUSIONS
Increased VV-BPV was an independent risk factor for future CV outcomes, independent of mean BP status, even in normotensive subjects and in all subgroups, except females. Similar VV-BPV values in the sensitivity analyses suggest VV-BPV is a reproducible phenomenon, reflecting the various types of intrinsic physiologic properties.

Keywords: blood pressure; cardiovascular outcome; hypertension; mortality; variability.

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A significant association between the visit-to-visit blood pressure (BP) variability (VV-BPV) and the risk of stroke and coronary heart disease has been documented in numerous epidemiological studies and clinical trials in Western countries.[1,2] However, over the past 4 years, many trials have shown conflicting results.[1,3–8] Likewise, some data obtained in Asian populations showed that the association between VV-BPV and cardiac or stroke mortality differs according to the VV-BPV measurement method used.[9–11]

The mechanisms underlying the association between VV-BPV and cardiovascular (CV) outcomes have not been fully elucidated. Moreover, several practical factors could contribute to VV-BPV.[4,12,13] Consequently, the clinical implications of VV-BPV are both difficult to understand and challenging to apply in practice. Indeed, despite the strong association between VV-BPV and CV outcomes in previous sensitivity analyses,[9,13,14] many clinical situations arise where identifying the appropriate subjects for monitoring or interventions is not feasible. Compared with the evidence obtained from randomized controlled trials or cohort studies,[3–8] studies assessing the actual influence of VV-BPV on future CV outcomes in real practice, particularly in Asian populations, are limited.[11,15] Consequently, the upper limit

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of the level of variability or extent of VV-BPV decrease necessary for a clinical benefit is unknown.[13]

VV-BPV is a type of summary statistic measured throughout the entire duration of the study, and the association between VV-BPV and CV outcomes seems to be cross-sectional rather than prospective. Thus, VV-BPV retrospectively collected at the time of enrollment may be a better indicator of future CV outcomes, with or without, a potential interventional strategy. Sensitivity tests usually include retrospectively measured VV-BPVs at the median time of the study period.

This study aimed to investigate the impact of visit-to-visit systolic BP (SBP) variability (VV-SBPV) on CV outcomes in a representative Korean cohort by comparing various statistical approaches.

METHODS

Study outline

This cohort study is based on the Korean National Health Insurance Service (NHIS) database, comprising 51,811 subjects who participated in the National Health Screening (NHS) program at least 3 times, and consists of BP measurement and follow-up period.[16] BP in NHS participants was annually measured during the early half of the study (usually from 2002 to 2006), and followed up during the remaining late half of the study or after the third visit, until 2010. For the purpose of the robust study outcomes, 2 sensitive analysis models were constructed as a reference of 2006. Model 1 comprised 37,400 subjects who participated in the NHS program at least 3 times until 2006 and had a 4-year follow-up until 2010, whereas model 2 included 48,477 subjects with more than 3 visits until 2006 and were followed up from 2002 to 2010 (Figure 1). The baseline characteristics of the entire study, and models 1 and 2 were defined at 2002, 2006, and 2002, respectively.

Enrollment and data collection of NHS program participants

The Korean NHIS database represents the entire Korean population, regarding all citizens' use of health insurance and all health examinations, which makes it a world leading population-based epidemiology and research-based platform. The NHS program consists of general medical examination for entire population annually and cancer-screening program for all citizens aged 40 or older categorized by age and risk. General medical examination contains history taking, BP measurement, blood sampling, urinalysis, and chest x-ray results. According to the protocol, 2 BP were measured using a mercury sphygmomanometer in a sitting position after a minimum 10-minute rest, after the anthropometric measurement and the average BP was obtained.[17,18] Blood was sampled after a minimum 8-hour overnight fasting. Approximately 70% of all candidates eligible for the NHS were examined in 2010.

Study population

Based on simple random sampling at a 99% confidence interval (CI) for annual medical expenses, the estimated cohort was 905,166 from the 2002 Korean NHIS database (n = 47,851,928; male = 23,993,691; female = 23,858,231), excluding the protected subject identities (n = 1,246,495). Applying proportional allocation, stratified by age (18 categories), gender, and house income (41 categories), 1,025,340 subjects (2.2% of the total population) were designated as the NHIS-National Sample Cohort (NHIS-NSC), which is described in more detail elsewhere.[19] It had practically no nonsampling error. A total 113,641 subjects (11%), within the NHIS-NSC, participated in the NHS program in 2002 and 64,268 subjects were aged 40–75 years. After excluding severely disabled subjects (n = 372), patients suffering from cancer (n = 288), subjects with 3 or more protein-positive by urine dipstick tests (n = 83), and subjects with missing

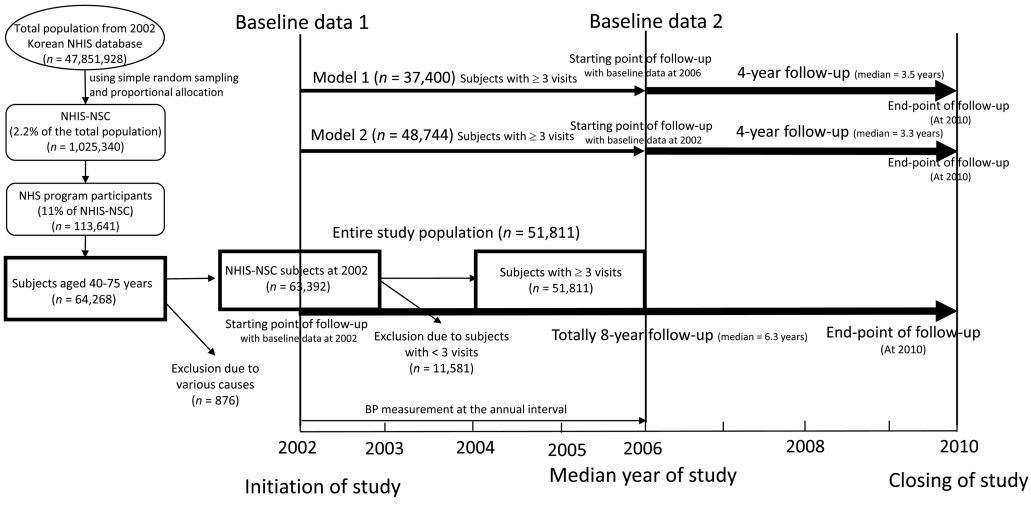

Figure 1. Flow chart of study. This cohort study, comprising blood pressure (BP) measurement and follow-up period, included 51,811 subjects aged 40–75 years who annually participated in the National Health Screening (NHS) program at least 3 times from 2002–2006 and had at least a 4-year follow-up until 2010. BP was typically measured a minimum of 3 times during the early 4-year period and during the last half period of the 4-year follow-up. The robust study results were confirmed, using 2 models for sensitivity analysis that were constructed with the median (i.e., 2006) as the reference year. Abbreviations: NHIS, National Health Insurance Service; NHIS-NSC, National Health Insurance Service–National Sample Cohort; NHS, National Health Screening.

data (n = 133), 63,392 subjects remained. Of them, 51,811 participated in the NHS program at least 3 times until 2006 and were included in the final analysis.

The cutoff value for VV-SBPV was based on the mean SD of SBP (SD-SBP) in the baseline population. Despite some variations in the mean SD value among the 3 cohorts, the rounding of these variations resulted in an SD-SBP of 10 mm Hg. According to the 10 mm Hg cutoff in the mean SD-SBP, the subjects were divided into 2 groups and the CV outcomes of these groups were compared. The study proposal and design were approved by the Institutional Review Board of Hanyang University Seoul Hospital, and the use of data was approved by the Korean NHIS.

Definition of clinical parameters

Hypertension (HT) was defined by a single clinic BP ≥ 140/90 mm Hg or the use of antihypertensive (anti-HT) medication. Diabetes mellitus was defined as a fasting blood glucose ≥ 126 mg/dl or the use of antidiabetic medication. Hypercholesterolemia was defined as a total cholesterol level ≥ 240 mg/dl or the use of statins. Moderate physical exercise was defined as regular, moderate, or heavy physical exercise performed on ≥ 3 days per week. Poor house income was defined as the lowest quintiles of household incomes and moderate alcohol drinking as consuming 5–40 and 5–20 g alcohol per day in males and females, respectively.

Definition of study endpoints

The primary endpoint was defined as CV mortality, myocardial infarction (MI), and stroke. CV events were defined as nonfatal MI and stroke. CV mortality was defined as the death code starting with "I," provided by the Korean National Institute of Statistics.[20] MI was defined as the first "I21 or I22" on the 6th Korean Standard Classification of Diseases code (equivalent to the 10th revision of the International Statistical Classification of Diseases) and stroke as the code I60, I61, I62, I63, I64, or I65.[21,22] The secondary endpoint was total mortality identified as the resident registration number in the Korean National Institute of Statistics.[20]

Statistical analysis

Continuous variables are expressed as means ± SD, and categorical variables are expressed as percentages or frequencies. The 3 groups were compared using the 1-way analysis of variance test for continuous variables and the chi-square (χ^2) test for categorical variables. After adjusting for age, gender, obesity, economic status, physical activity, smoking, alcohol drinking, presence of HT/diabetes mellitus/hypercholesterolemia, past history of stroke, and use of anti-HT medication/aspirin/statins, the estimated relative hazard ratio and the 95% CI were calculated by the Cox proportional hazard model, and survival statistics by the log–rank test for the homogeneity of the group stratified by SD-SBP ≥ 10 mm Hg. The model performance to evaluate the incremental predictive value of SD-SBP ≥ 10 mm Hg for CV risk was assessed by calculating C-statistics and the net reclassification improvement, using a SAS Macros, as described elsewhere.[23–25] Statistical analysis used the Proc Lifetest and Proc Phreg in the Statistical Analysis System software package version 9.4 (SAS Institute, Cary, NC) and $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

Irrespective of the study model, the baseline characteristics and BP parameters, including SD-SBPs, were similar among all 4 study groups (Supplementary materials 1–4). Comparing the SD-SBP tertiles of the entire study model, all parameters were positively associated with SD-SBP values. The highest values and incidence of these parameters were observed in subjects with upper SD-SBP tertiles (T3_SD-SBPs) ($P < 0.01$) (Table 1).

Parameters that affected the CV outcomes

During the entire study period, 1,222 subjects developed CV events or death and 804 subjects died. Nonfatal MI or stroke occurred in 1,138 subjects. As shown in Table 2, age, male, and current smoking were common effectors that significantly increased the occurrence of all 4 components of CV outcomes. Other significant variables that increased the occurrence of nonfatal MI or stroke and CV events or death, were SBP, SD-SBP, diabetes mellitus, hypercholesterolemia, a history of heart disease and stroke, and the use of aspirin. CV mortality had no additional effector, whereas total mortality was significantly associated with obesity, physical exercise, alcohol consumption, diabetes mellitus, hypercholesterolemia, and the use of anti-HT medication.

Survival curve of SBP or SD of SBP on CV outcomes

Mean SBPs were inversely associated with event-free survival rate. Subjects with the highest SBP quartile (Q4_SBP), showed the lowest event-free survival rate ($P < 0.01$) and this trend remained unchanged after adjusting for SD-SBP ($P < 0.01$) (Figure 2). Likewise, in the survival curve of SD-SBP tertiles adjusted by the covariates from a Cox proportional hazard model, subjects with T3_SD-SBPs had the significantly lowest event-free survival rate when compared with the other 2 subgroups, but no significant difference was observed between lower (T1_SD-SBP) and middle (T2_SD-SBP) SD-SBP tertiles. The dominance of T3_SD-SBP on CV outcomes was most evident in the group comparison. Subjects with SD-SBPs ≥ 10 mm Hg showed a significantly lower event-free survival rate than those with SD-SBPs <10 mm Hg ($P < 0.01$) (Figure 3).

Impact of SD of SBP on CV outcomes

In the Cox proportional hazard model adjusted by the multivariables, a significant association existed between SD-SBP ≥10 mm Hg and an increase in the occurrence of CV events (Table 3). Irrespective of sampling methods, subjects with SD-SBPs ≥10 mm Hg had higher rates of CV events or

Table 1. Baseline characteristics of all study subjects, according to the SD tertiles of the visit-to-visit systolic blood pressure

	Low variability (T1)	Middle variability (T2)	High variability (T3)	*P* value
Person (*n*, %)	17,404 (33.6)	17,095 (33.0)	17,312 (33.4)	
Range of SD-SBP (mm Hg)	<8.4	8.4–12.3	≥12.3	
Age (years)	49.9 ± 7.9	50.6 ± 8.1	53.8 ± 9.1	<0.01
Female (*n*, %)	6,631 (38.1)	6,240 (36.5)	7,136 (41.2)	<0.01
Body mass index (kg/m^2)	23.7 ± 2.7	23.9 ± 2.8	24.2 ± 3.0	<0.01
Systolic blood pressure (mm Hg)	122 ± 12.6	124.2 ± 15.1	132.5 ± 21.8	<0.01
Diastolic blood pressure (mm Hg)	77.7 ± 9.7	78.8 ± 10.6	82.8 ± 13.4	<0.01
SD-SBP (mm Hg)	6.1 ± 1.7	10.2 ± 1.1	16.9 ± 4.6	<0.01
Fasting blood glucose (mg/dl)	95.4 ± 24.0	96.5 ± 26.5	99.8 ± 31.4	<0.01
Total cholesterol (mg/dl)	198.3 ± 36.7	200.0 ± 37.2	202.5 ± 38.4	<0.01
Current smoking (*n*, %)	4,368 (25.1)	4,564 (26.7)	4,330 (25.0)	<0.01
Moderate physical exercise (*n*, %)	3,185 (18.3)	3,111 (18.2)	2,996 (17.3)	0.03
Moderate alcohol drinking (*n*, %)	2,384 (13.7)	2393 (14)	2,529 (14.6)	0.04
Hypertension (*n*, %)	4,421 (25.4)	5,607 (32.8)	9,110 (52.6)	<0.01
Antihypertensive medication (*n*, %)	1,044 (6.0)	1,282 (7.5)	2,338 (13.5)	<0.01
RAS blockade (*n*, %)	313 (1.8)	410 (2.4)	762 (4.4)	<0.01
Beta blocker (*n*, %)	461 (2.7)	615 (3.6)	1,195 (6.9)	<0.01
Calcium channel blocker (*n*, %)	104 (0.6)	137 (0.8)	277 (1.6)	<0.01
Diuretics (*n*, %)	696 (4.0)	872 (5.1)	1,628 (9.4)	<0.01
Diabetes mellitus (*n*, %)	1,201 (6.9)	1,453 (8.5)	2,044 (11.8)	<0.01
Antidiabetic medication (*n*, %)	435 (2.5)	530 (3.1)	866 (5.0)	<0.01
Hypercholesterolemia (*n*, %)	2,245 (12.9)	2,376 (13.9)	2,771 (16.0)	<0.01
Statin use (*n*, %)	17 (0.1)	34 (0.2)	69 (0.4)	<0.01
Aspirin use (*n*, %)	331 (1.9)	325 (1.9)	624 (3.6)	<0.01
History of heart disease (*n*, %)	139 (0.8)	154 (0.9)	225 (1.3)	<0.01
History of stroke (*n*, %)	35 (0.2)	51 (0.3)	69 (0.4)	0.02

In the comparison among the SD tertiles (T) of systolic blood pressure (T_SD-SBP), age, female, body mass index, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, current smoking, physical exercise, alcohol drinking, hypertension, diabetes mellitus, hypercholesterolemia, antihypertensive medication, antidiabetic medication, aspirin use, statin use, history of heart disease, and history of stroke were positively associated with SD-SBP values, and the highest values and incidence of these parameters were observed in subjects with upper SD-SBP tertiles (T3_SD-SBPs). Continuous variable is expressed as mean ± SD, and categorical variable is expressed as percentage or frequency. Moderate physical exercise is defined as moderate or heavier regular physical exercise performed on 3 or more days per week. Poor house incomes was defined as the lowest quintiles of household incomes and moderate alcohol drinking as drinking 5 to 40 g per day in men and 5 to 20 g per day in women. Abbreviations: RAS, renin angiotensin system; SD-SBP, SD of systolic blood pressure; T1, lower tertile of SD-SBP; T2, middle tertile of SD-SBP; T3, upper tertile of SD-SBP.

death, nonfatal MI or stroke, and total mortality but were not associated with CV mortality. In the sensitivity analysis, the occurrence rates of endpoints were, overall and individually, markedly similar within and between the 2 subsample groups, irrespective of the 2002 or 2006 baseline data (Table 3). Moreover, the association between SD-SBP ≥10 mm Hg and increased CV outcomes was consistently significant.

Impact of SD of SBP on CV outcomes in subgroups

In all subgroups, except females, strong associations were observed between SD-SBP ≥ 10 mm Hg and increased the occurrence of nonfatal MI or stroke, and there were no significant interactions (Table 4). These associations remained consistent, irrespective of age, the presence of HT or use of anti-HT medication. The hazard ratio of the male subgroup for nonfatal MI or stroke was 1.59, which was higher than that of all the patients. Similar findings with no significant interactions were observed in the subgroup analysis, regarding the effect of SD-SBP on CV events or death (despite the heterogeneity trends in gender, all *P* values for interaction were above 0.05). In contrast, no significant association between SD-SBP ≥10mm Hg and CV mortality was observed in all patients, and this trend occurred in all subgroups. Meanwhile, the association between SD-SBP ≥10 mm Hg and total mortality depended on the study population. In all patients, SD-SBP ≥10 mm Hg was associated with an increased occurrence of total mortality, while in all subgroups, SD-SBP ≥10 mm Hg

Table 2. Parameters that affected the CV outcomes during the entire study period

Nonfatal MI or stroke			CV event or death		
Parameter	**Hazard ratio (95% confidence interval)**	***P* value**	**Parameter**	**Hazard ratio (95% confidence interval)**	***P* value**
Q2_SBP (mm Hg)	1.23 (1.00–1.52)	0.05	Q2_SBP (mm Hg)	1.24 (1.00–1.55)	0.05
Q3_SBP (mm Hg)	1.39 (1.14–1.70)	<0.01	Q3_SBP (mm Hg)	1.41 (1.15–1.74)	<0.01
Q4_SBP (mm Hg)	1.67 (1.38–2.02)	<0.01	Q4_SBP (mm Hg)	1.69 (1.39–2.07)	<0.01
Age (years)	1.07 (1.06–1.07)	<0.01	Age (years)	1.07 (1.06–1.07)	<0.01
T2_SD-SBP (mm Hg)	1.09 (0.92–1.30)	0.31	T2_SD-SBP (mm Hg)	1.11 (0.93–1.33)	0.24
T3_SD-SBP (mm Hg)	1.58 (1.35–1.85)	<0.01	T3_SD-SBP (mm Hg)	1.57 (1.34–1.85)	<0.01
Obesity	1.09 (0.96–1.23)	0.18	Obesity	1.09 (0.96–1.24)	0.2
Male	1.56 (1.35–1.80)	<0.01	Male	1.44 (1.24–1.68)	<0.01
Moderate physical exercise	1.03 (0.89–1.20)	0.69	Moderate physical exercise	1.03 (0.88–1.21)	0.71
Moderate alcohol drinking	0.97 (0.81–1.16)	0.73	Moderate alcohol drinking	0.98 (0.77–1.11)	0.42
Current smoking	1.33 (1.16–1.54)	<0.01	Current smoking	1.32 (1.13–1.53)	<0.01
Hyperlipidemia	1.22 (1.04–1.42)	0.01	Hyperlipidemia	1.24 (1.06–1.46)	0.01
Diabetes mellitus	1.56 (1.39–1.82)	<0.01	Diabetes mellitus	1.58 (1.34–1.85)	<0.01
History of heart disease	1.60 (1.14–2.26)	<0.01	History of heart disease	1.58 (1.11–2.26)	<0.01
History of stroke	2.75 (1.71–4.41)	<0.01	History of stroke	3.00 (1.87–4.83)	<0.01
Anti-HT medication	1.18 (0.98–1.41)	0.08	Anti-HT medication	1.15 (0.95–1.39)	0.15
Aspirin use	1.88 (1.48–2.40)	<0.01	Aspirin use	1.93 (1.50–2.48)	<0.01
Statin use	0.98 (0.50–1.94)	0.96	Statin use	0.94 (0.46–1.92)	0.86
CV mortality			**Total mortality**		
Parameter	**Hazard ratio (95% confidence interval)**	***P* value**	**Parameter**	**Hazard ratio (95% confidence interval)**	***P* value**
Q2_SBP (mm Hg)	1.27 (0.67–2.41)	0.47	Q2_SBP (mm Hg)	0.95 (0.75–1.21)	0.67
Q3_SBP (mm Hg)	1.26 (0.68–2.34)	0.47	Q3_SBP (mm Hg)	1.01 (0.81–1.27)	0.91
Q4_SBP (mm Hg)	1.60 (0.89–2.86)	0.11	Q4_SBP (mm Hg)	1.14 (0.91–1.41)	0.25
Age (years)	1.09 (1.07–1.12)	<0.01	Age (years)	1.10 (1.09–1.11)	<0.01
T2_SD-SBP (mm Hg)	0.76 (0.45–1.30)	0.31	T2_SD-SBP (mm Hg)	0.92 (0.76–1.13)	0.43
T3_SD-SBP (mm Hg)	1.33 (0.85–2.10)	0.21	T3_SD-SBP (mm Hg)	1.12 (0.93–1.35)	0.23
Obesity	1.04 (0.71–1.52)	0.85	Obesity	0.77 (0.65–0.91)	<0.01
Male	3.00 (1.84–4.91)	<0.01	Male	2.72 (2.23–3.38)	<0.01
Moderate physical exercise	1.21 (0.75–1.94)	0.44	Moderate physical exercise	1.28 (1.05–1.56)	0.02
Moderate alcohol drinking	1.21 (0.70–2.08)	0.5	Moderate alcohol drinking	0.82 (0.67–0.99)	0.04
Current smoking	1.61 (1.08–2.41)	0.02	Current smoking	1.53 (1.30–1.80)	<0.01
Hyperlipidemia	0.74 (0.42–1.30)	0.3	Hyperlipidemia	0.76 (0.60–0.96)	0.02
Diabetes mellitus	1.36 (0.846–2.19)	0.2	Diabetes mellitus	1.56 (1.28–1.89)	<0.01
History of heart disease	1.93 (0.75–4.95)	0.17	History of heart disease	0.77 (0.42–1.41)	0.39
History of stroke	1.00 (1.0–1.01)	0.97	History of stroke	1.00 (1.0–1.02)	0.94
Anti-HT medication	1.20 (0.69–2.08)	0.52	Anti-HT medication	1.42 (1.13–1.78)	<0.01
Aspirin use	1.80 (0.87–3.72)	0.11	Aspirin use	0.94 (0.65–1.35)	0.72
Statin use	1.36 (0.17–10.71)	0.77	Statin use	1.35 (0.49–3.73)	0.56

Age, male, and current smoking significantly increased the occurrence of all 4 components of CV outcomes. Abbreviations: Anti-HT, antihypertensive; CV, cardiovascular; MI, myocardial infarction; SBP, systolic blood pressure; Q2_SBP, 2nd quartile of SBP; Q3_SBP, 3rd quartile of SBP; Q4_SBP, 4th (highest) quartile of SBP; SD-SBP, SD of systolic blood pressure; T2_SD-SBP, middle tertile of SD-SBP;T3_SD-SBP, upper tertile of SD-SBP.

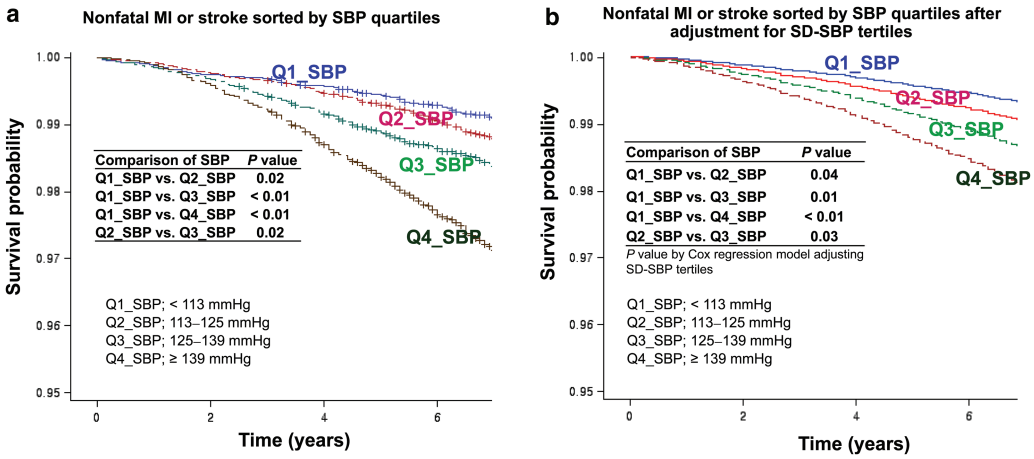

Figure 2. Survival curves of systolic blood pressure on cardiovascular outcomes. (**a**) In the Kaplan–Meier survival curve, subjects with the highest quartile of systolic blood pressures (SBP) showed the lowest event-free survival rate. The blue, red, green, and dark green lines represent the group of subjects with the lowest (Q1_SBP), 2nd (Q2_SBP), 3rd (Q3_SBP), and highest quartiles (Q4_SBP) in SBP, respectively. (**b**) Likewise, in the survival curve for the SBP quartiles adjusted by the covariates from a Cox proportional hazard model, subjects with the Q4_SBP also showed the lowest event-free survival rate. The blue, red, green, and dark green lines represent the group of subjects with the lowest (Q1_SBP), 2nd (Q2_SBP), 3rd (Q3_SBP), and highest quartiles (Q4_SBP) in SBP, respectively. Q1_SBP, lowest quartile of SBP; Q2_SBP, 2nd quartile of SBP; Q3_SBP, 3rd quartile of SBP; and Q4_SBP, highest quartile of SBP.

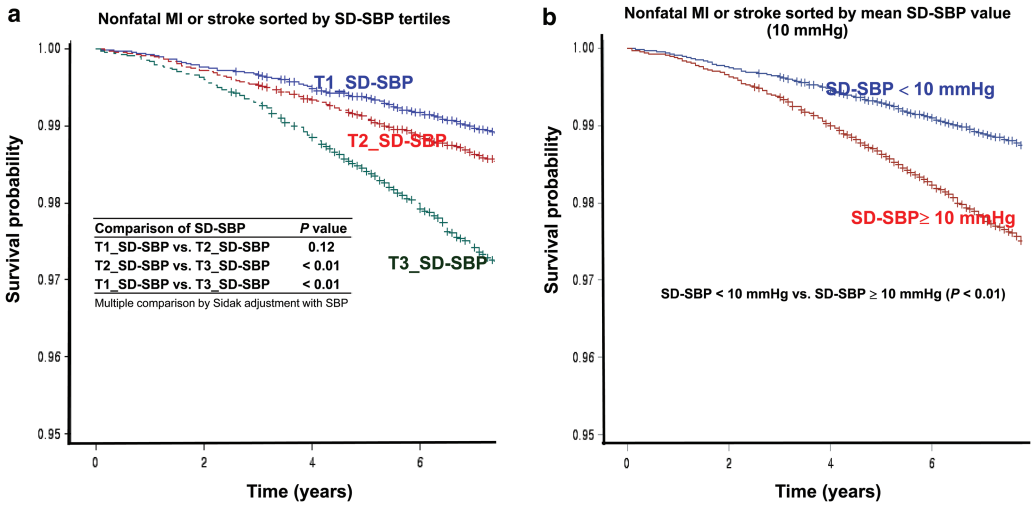

Figure 3. Survival curves of SD of visit-to-visit systolic blood pressure on cardiovascular outcomes. (**a**) In the survival curve adjusted by the covariates from a Cox proportional hazard model, subjects with upper tertiles in the SD of systolic blood pressures (T3_SD-SBPs) showed significantly the lowest event-free survival rate compared to the other 2 subgroups but no significant difference was observed between lower (T1) and middle tertiles (T2). The blue, red, and green lines represent the group of subjects with lower, middle, and upper tertiles in SD-SBPs, respectively. (**b**) In the Kaplan–Meier survival curve adjusted by multivariables, subjects with the SD of systolic blood pressures (SD-SBPs) ≥10 mm Hg showed a lower event-free survival rate than those with SD-SBPs <10 mm Hg. The red line represents the group of subjects with SD-SBP ≥10 mm Hg, and the blue line represents those with SD-SBPs <10 mm Hg.

was not associated with total mortality. In the female subgroup, there was no association between SD-SBP ≥10 mm Hg and CV outcome parameters.

DISCUSSION

This study investigated the effects of VV-SBPV, represented as SD-SBP, on CV outcomes. SD-SBP ≥10 mm Hg was significantly associated with increased occurrence of CV events or death, nonfatal stroke or MI, and total mortality. After adjusting for various risk factors, the strong associations between SD-SBP ≥10 mm Hg and CV outcomes remained significant, independent of mean BP control status and this trend existed consistently in all 3 subsamples. This suggests that SD-SBP, representing VV-SBPV, can be a useful prognostic marker to predict future CV outcomes, irrespective of sampling methods. Moreover, in the net reclassification improvement analysis, the adding of SD-SBP ≥10 mm Hg to an original model significantly improved the prediction ability for occurrence of CV events or deaths (Supplementary material 5).

The strength of this research is that the study population was a large-scale sample, consisting of relatively healthy individuals who participated in the Korean NHS program and comprised representative data from clinical settings in

Table 3. Impact of SD of visit-to-visit systolic blood pressure on the CV outcome

During the entire study period (median follow-up = 6.3 years)				
End points	**SD-SBP < 10 (*n* = 25,443)**	**SD-SBP ≥ 10 (*n* = 26,368)**	**Hazard ratio (95% confidence interval)**	***P* value**
Nonfatal MI or stroke	381	757	1.45 (1.27~1.65)	<0.01
CV events or death	404	818	1.43 (1.25~1.63)	<0.01
CV mortality	42	90	1.32 (0.89~1.94)	0.17
Total mortality	299	505	1.18 (1.01~1.38)	0.04
Model 1 (median follow-up = 3.5 years)				
End points	**SD-SBP < 10 (*n* = 20,725)**	**SD-SBP ≥ 10 (*n* = 16,675)**	**Hazard ratio (95% confidence interval)**	***P* value**
Nonfatal MI or stroke	209	311	1.41 (1.16~1.70)	<0.01
CV events or death	234	356	1.43 (1.20~1.72)	<0.01
CV mortality	40	64	1.42 (0.93~2.17)	0.11
Total mortality	265	385	1.35 (1.13~1.60)	<0.01
Model 2 (median follow-up = 3.3 years)				
End points	**SD-SBP < 10 (*n* = 28,160)**	**SD-SBP ≥ 10 (*n* = 20,584)**	**Hazard ratio (95% confidence interval)**	***P* value**
Nonfatal MI or stroke	217	297	1.30 (1.07~1.58)	0.01
CV events or death	243	346	1.30 (1.09~1.56)	<0.01
CV mortality	42	62	1.13 (0.74~1.74)	0.57
Total mortality	256	345	1.24 (1.04~1.49)	0.02

Irrespective of sampling methods, subjects with SD-SBPs ≥ 10 mm Hg had higher rates of CV events or death, nonfatal MI or stroke, and total mortality, but not associated with CV mortality. All *P* values are adjusted by age, sex, obesity, economic status, physical activity, smoking, alcohol drinking, the presence of hypertension, diabetes mellitus, hypercholesterolemia, the past history of CV disease, and the use of antihypertensive medication, aspirin and statin. Abbreviations: CV, cardiovascular; MI, myocardial infarction; SD-SBP, SD of systolic blood pressure.

Korea. This allowed generalization of such evidence to real practice. Despite the study population being comprised of subjects with a well-controlled BP status and low CV event risk, significant differences in CV outcomes were determined based solely on an SD-SBP ≥10 mm Hg. Evidently, the BP-lowering effect in HT subjects plays a key role in decreasing the risk of mortality and CV events. Despite the controlled BP status, HT subjects with high VV-BPV may continue to be at increased risk.[1,26,27] Therefore, novel therapies should focus on decreasing VV-BPV to lower this excess risk in HT subjects with controlled BP levels.[1]

Furthermore, 60–70% of the study population consisted of non-HT subjects. Previously, most VV-BPV results were obtained from randomized controlled trials and cohort studies composed primarily of HT or high-risk patients.[1,2,15,28] In contrast, our data were extracted from HT as well as normotensive and healthy subjects. In the subgroup analysis, irrespective of HT presence or use of anti-HT medication, SD-SBP ≥10 mm Hg was significantly associated with increased CV events in all subgroups, except females. The hazard ratio values were higher in patients not taking medication than in those taking anti-HT drugs, which concurs with previous results.[1,13,14,28] In contrast, the hazard ratio values of the HT subgroup were higher than those of the non-HT subgroup, which contrasts with previous results, whereby a stronger association between higher VV-SBPV and increased risk of stroke was observed in those with mean SBPs in the lowest range.[3,12,29] Consequently, previous studies found that a high VV-BPV could affect CV outcomes in HT subjects with a well-controlled BP status,[1,2,14] whereas our study of mainly non-HT subjects showed that an SD-SBP ≥10 mm Hg was associated with an increased occurrence of future CV outcomes. This suggests that VV-BPV in non-HT subjects may also play a role as a prognostic surrogate marker to predict CV outcomes. Altogether, our study confirms that VV-BPV can be a strong predictor of CV outcomes, regardless of the presence of HT, a controlled BP status and the use of anti-HT drugs.

A third notable finding is that an SD-SBP ≥10 mm Hg was not associated with CV mortality. Moreover, in the subgroup analysis, total mortality showed no significant association with SD-SBP and only an increasing trend with increase in SD-SBP. This may have been due to the low statistical power. Another possibility is that VV-SBPV is less likely to be a major determinant of patient survival after CV events. Indeed, published epidemiological data[30–34] showed that an improved BP control was the main determinant of the decline in stroke deaths.[30] Furthermore, the decrease in the long-term mortality of post-MI patients was ascribed to improved practices associated with the use of CV medications after MI and to increased use of revascularization procedures.[34,35] Consequently, although VV-BPV has an impact on the occurrence of CV events, evidence-based therapy is the main contributors that leads to improved patient outcomes and the decline in patient mortality after CV events.[30,33,36]

As shown in Figure 4, MI or stroke is a direct effector of VV-BPV, through artery remodeling and autonomic/

Table 4. Impact of SD of visit-to-visit systolic blood pressure during the entire study period on the CV outcome in subgroups sorted by age, gender, the presence of hypertension, or the use of antihypertensive medication

Nonfatal MI or stroke				CV events or death			
Parameter	Hazard ratio (95% confidence interval)	*P* value	*P* value for interaction	Parameter	Hazard ratio (95% confidence interval)	*P* value	*P* value for interaction
All	1.45 (1.27~1.65)	<0.01		All	1.43 (1.25~1.63)	<0.01	
Age < 50 (years)	1.52 (1.19~1.96)	<0.01	0.41	Age < 50 (years)	1.53 (1.19~1.98)	<0.01	0.50
Age ≥ 50 (years)	1.40 (1.20~1.63)	<0.01		Age ≥ 50 (years)	1.37 (1.17~1.60)	<0.01	
Hypertension	1.47 (1.23~1.76)	<0.01	0.95	Hypertension	1.46 (1.22~1.76)	<0.01	0.97
Normotension	1.37 (1.13~1.66)	<0.01		Normotension	1.35 (1.11~1.64)	<0.01	
Male	1.59 (1.35~1.86)	<0.01	0.08	Male	1.58 (1.34~1.87)	<0.01	0.08
Female	1.20 (0.95~1.50)	0.12		Female	1.17 (0.93~1.47)	0.18	
Anti-HT medication (−)	1.44 (1.24–1.66)	<0.01	0.48	Anti-HT medication (−)	1.43 (1.23–1.66)	<0.01	0.62
Anti-HT medication (+)	1.38 (1.03–1.85)	0.03		Anti-HT medication (+)	1.32 (0.98–1.80)	0.07	
CV mortality				**Total mortality**			
Parameter	Hazard ratio (95% confidence interval)	*P* value	*P* value for interaction	Parameter	Hazard ratio (95% confidence interval)	*P* value	*P* value for interaction
All	1.32 (0.89~1.94)	0.17		All	1.18 (1.01~1.38)	0.04	
Age < 50 (years)	1.06 (0.49~2.46)	0.89	0.55	Age < 50 (years)	1.20 (0.86~1.66)	0.28	0.92
Age ≥ 50 (years)	1.37 (0.88~2.14)	0.17		Age ≥ 50 (years)	1.16 (0.97~1.39)	0.09	
Hypertension	1.16 (0.71~1.89)	0.56	0.36	Hypertension	1.21 (0.97~1.51)	0.09	0.85
Normotension	1.61 (0.86~3.01)	0.14		Normotension	1.15 (0.92~1.43)	0.22	
Male	1.38 (0.89~2.13)	0.15	0.70	Male	1.16 (0.98~1.38)	0.09	0.80
Female	1.08 (0.45~2.56)	0.87		Female	1.26 (0.89~1.79)	0.19	
Anti-HT medication (−)	1.18 (0.77–1.81)	0.45	0.40	Anti-HT medication (−)	1.17 (0.99–1.39)	0.06	0.87
Anti-HT medication (+)	2.05 (0.77–5.50)	0.15		Anti-HT medication (+)	1.21 (0.82–1.80)	0.34	

In the subgroup analysis, irrespective of the presence of hypertension or use of antihypertensive (anti-HT) medication, a SD of systolic blood pressure (SD-SBP) ≥ 10 mmHg was significantly associated with increased nonfatal MI or stroke in all subgroups except for females. All *P* values are adjusted by age, sex, obesity, economic status, physical activity, smoking, drinking, the presence of hypertension, diabetes mellitus, hypercholesterolemia, the past history of CV disease, and the use of antihypertensive medication, aspirin and statin. Abbreviations: Anti-HT medication (-), subjects not taking the antihypertensive mediation; Anti-HT medication (+), subjects taking the antihypertensive medication; CV, cardiovascular; MI, myocardial infarction.

baroreflex dysfunction,[28] whereas cardiac mortality and total mortality are indirectly influenced by VV-BPV, through the high-risk group for future MI or stroke. Compared to the powerful impact of treatment modality and prevention on the association between VV-BPV and cardiac mortality,[33,36,37] VV-BPV plays a key role as an indirect, physiological marker to detect the association between total mortality and VV-BPV. Although the mechanisms underlying the association between total mortality and VV-BPV are primarily associated with CV events,[1,29] total mortality consists of CV mortality mediated by CV events and non-CV mortality by underlying comorbidities, which are associated with VV-BPV through the baroreflex regulation pathway and autonomic factors. Consequently, a significant association between total mortality and VV-BPV depends on the proportion of CV mortality and the presence of a successful treatment modality.

Study limitations

First, as the treatment modalities, causes of total mortality, and patient conditions that affect the treatment outcome were not investigated, the effect of those parameters on VV-SBPV or CV outcomes could not be assessed. Second, the mechanism responsible for the association between VV-BPV and CV outcomes was based on previous studies and our study was unable to identify a causal association between these parameters. Third, our clinical follow-up data inevitably had VV-BPV measurement method limitations. Indeed, the SD-SBP values were higher than those of previous studies. However, our data were obtained by well-trained investigators, according to the standard protocol, and the SD-SBP values were similar among all 3 cohorts. Moreover, a consistently strong association between SD-SBP values and CV outcomes was obtained, irrespective of the cohort types. Meanwhile, no standard guideline to measure VV-BPV has been established and the parameter considered most reflective of VV-BPV is controversial.[38] Fourth, anti-HT agents are a determinant of VV-BPV,[1,4] and changes in the BP-lowering treatment regimen during follow-up may affect the associations.

In conclusion, based on a large, representative Korean NHIS database, our study showed that high VV-SBPV was associated with increased occurrence of CV events and total

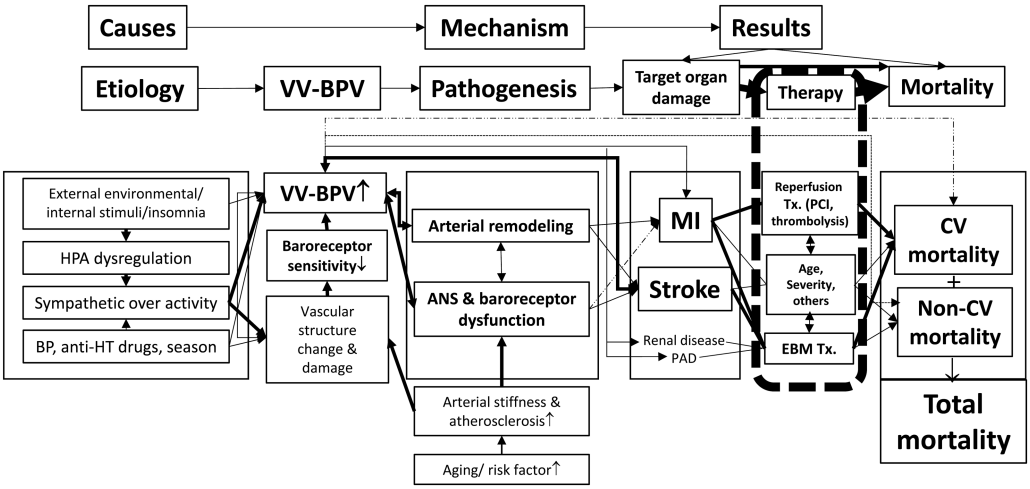

Figure 4. Schematic flowchart showing the association between visit-to-visit blood pressure variability and CV outcomes. An increased visit-to-visit blood pressure variability (VV-BPV) directly aggravates the arterial remodeling and indirectly affects the dysfunction of autonomic factors and arterial baroreceptors. Using these two mechanisms, a high VV-BPV can directly increase the occurrence of myocardial infarction (MI) and stroke. However, the main determinant of mortality after CV events is not an increased VV-BPV but evidence-based therapy. Although age is the most powerful predictor of prognosis in both MI and stroke, clinical profiles and treatment modalities affect the prognosis in patients with stroke and MI differently. The lowering of blood pressure (BP) and improvement of BP control are main determinants of the significant decline in stroke deaths. Conversely, the observed decrease in long-term mortality of post-MI is attributable to improved practice associated with effective acute treatment, long-term secondary prevention after MI, and widespread use of revascularization procedures, including percutaneous coronary intervention during MI hospitalizations. Hence, MI or stroke is a direct effector of increased VV-BPV, whereas cardiac mortality and total mortality may be affected indirectly, particularly in terms of high-risk groups for future CV events. However, the evidence-based therapy is the main determinant of long-term mortality in patients with CV events. Dashed line, unproven and inconclusive; dotted line, unproven and hypothetically reasonable; solid line, proven; one-headed arrow, effector; two-headed arrow, interacting association; thin line, weak association; thick line, strong association. Abbreviations: anti-HT, antihypertensive; BP, blood pressure; CV, cardiovascular; EBM Tx., evidence-based medical therapy; HPA, hypothalamic-pituitary-adrenal axis; HT, hypertension; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; Tx., therapy; VV-BPV, visit-to-visit blood pressure variability.

mortality but not CV mortality. These significant associations were evident after multivariable adjustment and were consistent across several subgroups, showing the clinical importance of consistent BP control, independent of mean BP control status, and the necessity of the stabilization of VV-SBPV as a therapeutic target to prevent both CV diseases and events. In particular, our study showed that NHS program records may be a useful tool to address an epidemiological question and a daily practice of recording BP measurement can assist with the prediction and prevention of future CV events.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* online.

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DISCLOSURE

The authors declared no conflict of interest.

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