The Relationship Between Visit-to-Visit Variability in Systolic Blood Pressure and All-Cause Mortality in the General Population

Findings From NHANES III, 1988 to 1994

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See Editorial Commentary, pp 141–143

Abstract—Recent data suggest that visit-to-visit variability of blood pressure is associated with stroke incidence. Correlates of increased visit-to-visit variability in blood pressure and the relationship between variability and all-cause mortality were examined using data on US adults ≥20 years of age from the Third National Health and Nutrition Examination Survey (n=956). Three consecutive blood pressure readings were taken during 3 separate study visits from 1988 to 1994. Based on the mean of the second and third measurements from each visit, visit-to-visit blood pressure variability for each participant was defined using the standard deviation and coefficient of variation across visits. Mortality was assessed through December 31, 2006 (median follow-up=14 years; n=240 deaths). The mean of the standard deviation for systolic blood pressure across visits was 7.7 mm Hg. After multivariable adjustment, older age, female gender, history of myocardial infarction, higher mean systolic blood pressure and pulse pressure, and use of angiotensin converting enzyme inhibitors were associated with higher standard deviation in systolic blood pressure. The multivariable adjusted hazard ratios for all-cause mortality associated with a standard deviation of systolic blood pressure of 4.80 to 8.34 mm Hg and ≥8.35 mm Hg, versus <4.80 mm Hg, were 1.57 (95% CI, 1.07 to 2.18) and 1.50 (95% CI, 1.03 to 2.18), respectively. Results were similar when coefficient of variation for systolic blood pressure was evaluated. Visit-to-visit variability for diastolic blood pressure was not associated with mortality. In this population-based study of US adults, higher levels of short-term visit-to-visit variability in systolic blood pressure were associated with increased all-cause mortality. **(*Hypertension*. 2011;57:160-166.) • Online Data Supplement**

Key Words: blood pressure ■ mortality ■ hypertension ■ adults ■ medication use

The prognostic value of blood pressure is based mainly on measurements obtained in a clinic setting, typically averaged over several visits.[1–3] Visit-to-visit variability of blood pressure is often dismissed as random fluctuation around a patient's true basal blood pressure and is thought to be a limitation of measuring blood pressure in the office setting.[4,5] However, recent data suggest that visit-to-visit variability of blood pressure is reproducible and not a random phenomenon.[6]

The concept that variability in blood pressure has a prognostic value for cardiovascular events is not new.[7–10] In 1993, investigators demonstrated that higher diurnal variability of blood pressure assessed by ambulatory monitoring over 24 hours was associated with an increased risk for left ventricular hypertrophy during 7 years of follow-up.[7] In 2010, secondary analyses of several randomized controlled trials demonstrated a strong association between longer-term variability in systolic blood pressure and stroke and coronary heart disease risk.[11] In these studies, blood pressure variability was assessed across multiple visits (ie, visit-to-visit variability) conducted over periods of 12 to 36 months.

Data on visit-to-visit variability in blood pressure have been derived primarily from select populations, mostly secondary analyses of randomized controlled trials including patients with or at high risk for vascular disease. Scarce data are available on the correlates and prognostic significance of higher visit-to-visit variability of blood pressure in the general population. Therefore, we analyzed data from the population-based Third National Health and Nutrition Examination Survey (NHANES III) to determine factors associated with higher visit-to-visit variability of blood pressure. In addition, we examined the association between

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visit-to-visit variability of blood pressure and all-cause mortality.

Methods

NHANES III was a stratified, multistage probability survey designed to select a representative sample of the civilian noninstitutionalized US population.[12] NHANES III consisted of an in-home interview with blood pressure measurements and a visit to a mobile examination center for a medical evaluation including additional blood pressure measurements. Overall, 18 825 adults ≥20 years of age completed the NHANES III interview and examination between 1988 and 1994. A sample of ≈5% (n=2174) of these participants were selected to attend a third visit at the mobile examination center, during which time the complete medical evaluation including blood pressure measurements was repeated. We limited the current analyses to NHANES III participants who were selected for the third study visit and excluded 1040 participants without 3 blood pressure measurements at each of the 3 NHANES III study visits. In addition, 178 participants whose blood pressure was not measured in the same arm at all 3 visits were excluded. After these exclusions, a total of 956 NHANES III participants were included in the current analyses. Among those selected to attend the third visit, participants included (n=956) versus excluded (n=1143) in the current analyses had similar mean systolic blood pressure levels during the in-home visit (127.7 mm Hg and 127.5 mm Hg, respectively; $P=0.804$) and during the first visit to the mobile examination center (125.3 mm Hg and 123.6 mm Hg, respectively; $P=0.061$). The protocol for NHANES III was approved by the National Center for Health Statistics of the Centers for Disease Control and Prevention institutional review board. All participants gave informed consent.

Baseline Data Collection

Demographic and health-related information was collected using a standardized questionnaire during the in-home interview. The use of antihypertensive medications was ascertained via self-report with classes of antihypertensive medications determined through pill bottle review. Antihypertensive medication classes considered for analysis included angiotensin converting enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, and thiazide-type diuretics. Other classes had too few individuals taking them to provide stable results. During the medical evaluation, height and weight were measured and body mass index was calculated. Blood and spot urine specimens were obtained and processed for analysis. Diabetes mellitus was defined as a fasting plasma glucose ≥126 mg/dL, a nonfasting plasma glucose ≥200 mg/dL, or a self-reported history of diabetes with concurrent use of antidiabetes medication. Serum C-reactive protein (CRP) levels ≥2 mg/L were defined as elevated. Estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney Disease Epidemiology Collaboration equation, and reduced eGFR was defined as levels <60 mL/min/1.73m^2.[13–15] Albuminuria was defined as a urinary albumin to urinary creatinine ratio ≥30 mg/g.[15]

Blood Pressure Measurements

Blood pressure was measured 3 times during the in-home interview and 3 additional times during each of the 2 visits to the mobile examination center. The first visit to the mobile examination center was scheduled within 1 month of the in-home interview, and the second visit was scheduled on completion of the first visit. The median duration between consecutive mobile examination center visits was 17 days (minimum of 1 day and a maximum of 48 days). The same standardized protocol and equipment were used for measuring blood pressure during the in-home and mobile examination clinic visits. Blood pressure was measured by a trained research assistant during the in-home visit and by a trained clinician during the visit to the mobile examination clinic. Additional details regarding blood pressure measurement and quality control procedures are provided in the NHANES III manual of operations. For systolic and diastolic blood pressure, separately, the second and third measurements from each visit were averaged. Using the mean systolic blood pressure from each visit, the standard deviation and coefficient of variation of systolic blood pressure across study visits were calculated. The standard deviation and coefficient of variation of diastolic blood pressure across study visits were also calculated.

Mortality Follow-Up

Adult NHANES III participants were followed for mortality through December 31, 2006. Probabilistic matching was used to link NHANES III participants with the National Death Index to ascertain vital status. Matching was based on 12 identifiers for each participant (eg, Social Security number, sex, and date of birth). Identical matching methodology applied to the NHANES I Epidemiological Follow-Up Study for validation purposes found that 96.1% of deceased participants and 99.4% of living participants were correctly classified.[16]

Statistical Analysis

Two sets of analyses were conducted, one for standard deviation of systolic blood pressure across study visits and the second for coefficient of variation. The analysis for standard deviation of systolic blood pressure is described below with identical methods used for the analysis of coefficient of variation of systolic blood pressure. Baseline participant characteristics were calculated by tertile of standard deviation of systolic blood pressure. Tests for linear trend across tertiles were calculated by including the median of each tertile as a continuous variable in linear or logistic regression models. The association between participant characteristics with standard deviation of systolic blood pressure was assessed using linear regression. Characteristics investigated include age, sex, race–ethnicity, physical inactivity, current smoking, body mass index, total cholesterol, diabetes mellitus, reduced eGFR, albuminuria, elevated CRP, history of myocardial infarction (MI), history of stroke, mean systolic blood pressure and pulse pressure, and antihypertensive medication drug class. Initial regression models included adjustment for age, sex, and race–ethnicity. A subsequent model included all variables associated ($P<0.05$) with the standard deviation of systolic blood pressure in the age-, sex-, and race–ethnicity-adjusted models.

Next, hazard ratios for all-cause mortality associated with tertiles of the standard deviation of systolic blood pressure, with the lowest tertile serving as the referent, were initially calculated unadjusted and after age, sex, and race–ethnicity adjustment. A subsequent model included adjustment for age, sex, race, and variables associated with standard deviation of systolic blood pressure in the age-, sex-, and race–ethnicity-adjusted models as described above. To account for potential differences in blood pressure resulting from measurements taken in the home versus clinic setting, as a sensitivity analysis, a final regression model included adjustment for the difference in mean systolic blood pressure between the in-home visit and the first mobile examination clinic visit. In addition, secondary analyses restricted to participants not taking antihypertensive medication were conducted. Too few participants were taking antihypertensive medications (n=170) to provide valid results among this group.

The association of standard deviation of systolic blood pressure, modeled as a continuous variable, with all-cause mortality was evaluated using Cox proportional hazard models and restricted quadratic splines with knots at the 10th, 50th, and 90th percentiles of the standard deviation (2.2 mm Hg, 6.4 mm Hg, and 15.1 mm Hg) of systolic blood pressure distribution. For spline analysis, the 10th, 50th, and 90th percentiles of the coefficient of variation of systolic blood pressure were 1.9%, 5.1%, and 12.0%, respectively.

Analyses were repeated for tertiles of standard deviation and coefficient of variation of diastolic blood pressure with all-cause mortality. The proportional hazards assumption of the Cox models was confirmed using Schoenfeld residuals. All analyses were conducted without sampling weights as recommended for NHANES III second examination data using SAS version 9.2 (SAS Institute).

Table 1. NHANES III Participant Characteristics by Tertile of the Standard Deviation of Systolic Blood Pressure

	Tertile of Standard Deviation in Systolic Blood Pressure, Range in mm Hg			
Participant Characteristics	1 (n=316) <4.80	2 (n=317) 4.80–8.34	3 (n=323) ≥8.35	*P* Trend
Age, y	41.3 (15.5)	47.4 (17.7)	55.0 (16.3)	<0.001
Women, %	52.9	49.5	52.0	0.837
Race–ethnicity, %				
Non-Hispanic white	41.5	42.0	43.0	Ref
Non-Hispanic black	28.5	28.4	31.3	0.761
Mexican American	25.6	26.5	22.3	0.388
Physically inactive, %	27.9	29.7	35.9	<0.001
Current smoker, %	32.3	26.8	28.8	0.337
Body mass index, kg/m^2	27.4 (5.9)	27.9 (6.3)	27.8 (6.2)	0.484
Total cholesterol, mg/dL	201.4 (39.9)	207.5 (45.6)	212.5 (41.8)	<0.001
Diabetes mellitus, %	5.1	11.4	13.9	<0.001
eGFR <60 mL/min/1.73m^2, %	5.7	9.8	16.4	<0.001
Albuminuria ≥30 mg/g, %	8.9	9.2	15.8	0.006
Elevated CRP, %	32.9	43.9	48.0	<0.001
History of MI, %	1.9	4.1	9.0	<0.001
History of stroke, %	1.9	1.6	4.4	0.036
Mean SBP, mm Hg	118.1 (15.2)	122.9 (17.2)	131.7 (19.0)	<0.001
Mean PP, mm Hg	45.0 (11.8)	50.1 (15.6)	56.5 (17.6)	<0.001
Antihypertensive medication drug class, %				
ACE inhibitor	1.9	3.5	8.1	<0.001
Beta blocker	3.5	6.9	10.2	0.001
Calcium channel blocker	2.9	5.7	12.4	<0.001
Thiazide-type diuretic	5.7	10.1	17.0	<0.001

SBP indicates systolic blood pressure; PP, pulse pressure.

Results

Correlates of Visit-to-Visit Variability in Systolic Blood Pressure

The mean of the standard deviation and coefficient of variation of systolic blood pressure across study visits was 7.7 mm Hg and 6.1%, respectively. Higher tertiles of the standard deviation of systolic blood pressure across visits were associated with older age, higher total cholesterol levels, mean systolic blood pressure, and mean pulse pressure (Table 1). In addition, individuals in the higher tertiles of standard deviation of systolic blood pressure across study visits were more likely to be physically inactive, have diabetes, reduced eGFR, albuminuria, elevated CRP, a history of MI or stroke, and to use ACE inhibitors, beta blockers, calcium channel blockers, or thiazide-type diuretics. Characteristics of NHANES III participants by tertile of coefficient of variation of systolic blood pressure across study visits are provided in Table I, available in an online supplement at http://hyper.ahajournals.org.

The factors associated with standard deviation of systolic blood pressure across visits after age, sex, and race–ethnicity and multivariable adjustment are shown in Table 2. In a multivariable model, older age, female sex, having a history of MI, taking ACE inhibitors, and mean systolic blood pressure and pulse pressure were associated with higher standard deviation of systolic blood pressure across study visits. Characteristics associated with higher coefficient of variation of systolic blood pressure across study visits after age, sex, and race–ethnicity and multivariable adjustment are provided in Table II, available in an online supplement at http://hyper.ahajournals.org.

Relationship Between Visit-to-Visit Variability in Systolic Blood Pressure and All-Cause Mortality

Over a median of 14 years of follow-up, 240 (25.1%) of the NHANES III sample included in this analysis died. The unadjusted and age-, sex-, and race–ethnicity-adjusted hazard ratios for all-cause mortality increased across tertiles for both standard deviation and coefficient of variation of systolic blood pressure (Table 3). After adjustment for age, sex, race–ethnicity, history of MI, mean systolic blood pressure and pulse pressure, and ACE inhibitor, beta blocker, calcium channel blocker, and thiazide-type diuretic use, the hazard ratio for all-cause mortality was 1.57 (95% CI, 1.07 to 2.18) and 1.50 (95% CI, 1.03 to 2.18) for the middle and highest versus lowest tertile of standard deviation of systolic blood pressure (*P* trend=0.064), respectively, and 1.55 (95% CI,

Table 2. Mean Differences in the Standard Deviation of Systolic Blood Pressure Associated With Participant Characteristics

	Difference Across Visits in Standard Deviation of SBP, mm Hg	
Participant Characteristics	Model 1§	Model 2‖
Age, 10 y	1.19 (0.10)‡	0.47 (0.12)‡
Women	0.53 (0.33)	0.87 (0.33)†
Race–ethnicity		
Non-Hispanic white	0 (ref)	0 (ref)
Non-Hispanic black	1.09 (0.39)†	0.56 (0.38)
Mexican American	0.48 (0.42)	0.31 (0.40)
Physically inactive	0.37 (0.37)	…
Current smoker	0.37 (0.37)	…
Body mass index, 5 kg/m^2	−0.05 (0.13)	…
Total cholesterol, 40 mg/dL	−0.084 (0.16)	…
Diabetes mellitus	0.99 (0.56)	…
eGFR <60 mL/min/1.73m^2	1.05 (0.54)	…
Albuminuria	0.97 (0.52)	…
Elevated CRP	0.34 (0.34)	…
History of MI	2.73 (0.76)‡	1.91 (0.75)*
History of stroke	1.88 (1.00)	…
Mean SBP, 20 mm Hg	1.79 (0.22)‡	1.12 (0.33)‡
Mean PP, 10 mm Hg	0.92 (0.12)‡	0.37 (0.19)*
Antihypertensive medication drug class		
ACE inhibitor	3.61 (0.79)‡	2.42 (0.79)†
Beta blocker	1.70 (0.65)†	0.69 (0.64)
Calcium channel blocker	2.35 (0.66)‡	0.93 (0.65)
Thiazide-type diuretic	1.30 (0.54)*	0.47 (0.54)

*P<0.05; †P<0.01; ‡P<0.001.

Numbers in table are difference (standard deviation).

SBP indicates systolic blood pressure.

§Model 1 includes adjustment for age, sex, and race–ethnicity.

‖Model 2 includes all variables associated with the standard deviation of systolic blood pressure (P<0.05) in Model 1.

1.09 to 2.22) and 1.49 (95% CI, 1.05 to 2.10) for the middle and highest versus lowest tertiles of coefficient of variation of systolic blood pressure (P trend=0.040). After additional adjustment for change in systolic blood pressure between the in-home visit and the first clinic visit, the hazard ratios for all-cause mortality were markedly similar (1.57 [95% CI, 1.07 to 2.30] and 1.55 [95% CI, 1.06 to 2.26] for the middle and highest versus lowest tertile for standard deviation, respectively, and 1.55 [95% CI, 1.09 to 2.22] and 1.54 [95% CI, 1.09 to 2.19], respectively, for the middle and highest versus lowest tertile for the coefficient of variation). In addition, among participants not taking antihypertensive medication, the hazard ratios for all-cause mortality associated with the middle and highest tertiles were 1.77 (95% CI, 1.13 to 2.77) and 1.56 (95% CI, 1.00 to 2.44), respectively, for standard deviation, and 1.60 (95% CI, 1.04 to 2.45) and 1.40 (95% CI, 0.91 to 2.14), respectively, for the coefficient of variation.

Modeled as a continuous variable, the multivariable adjusted hazard ratio for all-cause mortality increased progressively from 0 to 10 mm Hg standard deviation of systolic blood pressure and remained elevated, with wide CIs that included the null, at levels >10 mm Hg (Figure, top). The multivariable adjusted hazard ratio for all-cause mortality increased continuously and linearly across the full range of the coefficient of variation of systolic blood pressure (Figure, bottom panel).

Relationship Between Visit-to-Visit Variability in Diastolic Blood Pressure and All-Cause Mortality

The mean of the standard deviation and the coefficient of variation across study visits for diastolic blood pressure were 5.8 mm Hg and 8.1%, respectively. The unadjusted hazard ratios for mortality were 0.93 (95% CI, 0.68 to 1.28) and 1.09 (95% CI, 0.93 to 1.27) for participants in the middle (3.70 to 6.49 mm Hg) and highest (≥6.50 mm Hg) versus the lowest tertile (<3.70 mm Hg) of standard deviation in diastolic blood pressure (Table III, available in an online supplement at http://hyper.ahajournals.org.). In addition, unadjusted hazard ratios for mortality were 1.00 (95% CI, 0.72 to 1.37) and 1.10 (95% CI, 0.94 to 1.28) for participants in the middle (5.1% to 8.7%) and highest (≥8.8%) versus the lowest tertile (<5.1%) of coefficient of variation in diastolic blood pressure. No association between variability in diastolic blood pressure and mortality was present after adjustment for age, sex, race–ethnicity, or other potential confounders.

Discussion

In this population-based study of US adults, older age, female sex, a history of MI, and ACE inhibitor use were associated with higher variability of blood pressure across study visits. In addition, higher visit-to-visit variability in systolic blood pressure was associated with increased mortality risk over 14-year follow-up. A significant association was not present for visit-to-visit variability in diastolic blood pressure.

Several hypotheses have been proposed for mechanisms underlying higher levels of visit-to-visit variability in systolic blood pressure.[6,17,18] It has been suggested that arterial stiffness may be one factor leading to higher blood pressure variability.[19] In the present study, pulse pressure and older age (both directly associated with arterial stiffness) were independently associated with greater visit-to-visit variability in systolic blood pressure.[20,21] Further, it has been suggested that increased blood pressure variability may additionally be a manifestation of baroreflex regulation of blood pressure.[3,22] However, previous evidence indicates that decreased (not increased) heart rate variability is associated with an increased risk of mortality, suggesting that heart rate variability does not play a role in the relationship between blood pressure variability and mortality in the current study.[23] Although some have suggested that higher blood pressure variability might identify people with subclinical inflammation,[24] elevated CRP was not associated with increased visit-to-visit variability in systolic blood pressure in the current analysis. Because CRP was measured using a low-sensitivity assay in NHANES III, this possible mechanism warrants additional study.

Use of antihypertensive medications is a potential determinant of variability in blood pressure. A recent meta-analysis of data from randomized trials comparing antihyperten-

Table 3. Cumulative Mortality and Hazard Ratio for All-Cause Mortality Associated With Tertile of Standard Deviation of Systolic Blood Pressure (Top) and Tertile of Coefficient of Variation of Systolic Blood Pressure (Bottom)

	Tertile of Standard Deviation of SBP			
Outcomes	1 (n=316) <4.80	2 (n=317) 4.80–8.34	3 (n=323) ≥8.35	*P* Trend
Deaths, n (%)	40 (12.7%)	80 (25.2%)	120 (37.2%)	<0.001
		Hazard Ratio (95% CI)		
Unadjusted	1 (ref)	2.19 (1.50–3.20)	3.47 (2.43–4.96)	<0.001
Demographic adjusted*	1 (ref)	1.55 (1.06–2.28)	1.68 (1.17–2.42)	0.008
Multivariable adjusted†	1 (ref)	1.57 (1.07–2.18)	1.50 (1.03–2.18)	0.064
	Tertile of Coefficient of Variation of SBP			
	1 (n=318) <3.9%	2 (n=319) 3.9%–6.7%	3 (n=319) ≥6.8%	
Deaths, n (%)	50 (15.7%)	84 (26.3%)	106 (33.2%)	<0.001
		Hazard Ratio (95% CI)		
Unadjusted	1 (ref)	1.81 (1.28–2.57)	2.38 (1.70–333)	<0.001
Demographic adjusted*	1 (ref)	1.42 (1.00–2.02)	1.53 (1.09–2.14)	0.018
Multivariable adjusted†	1 (ref)	1.55 (1.09–2.22)	1.49 (1.05–2.10)	0.040

SBP indicates systolic blood pressure.

*Demographic adjusted includes age, sex, and race–ethnicity.

†Multivariable adjusted includes age, sex, and race–ethnicity and variables associated ($P<0.05$) with standard deviation or coefficient of variation for systolic blood pressure (history of MI, mean SBP and pulse pressure, and antihypertensive medication drug classes).

sive regimens (with each other and with placebo) suggested that use of calcium channel blockers and thiazide-type diuretics leads to lower variability in blood pressure, whereas use of ACE inhibitors and beta blockers leads to greater variability.[25] In the current study, after age, sex, and race–ethnicity adjustment, taking antihypertensive medications (regardless of class) was associated with higher visit-to-visit variability in systolic blood pressure. Although ACE inhibitors were associated with higher blood pressure variability after multivariable adjustment, no differences in visit-to-visit variability were present for the other antihypertensive medication classes. The limited sample size of participants taking antihypertensive medication precluded a direct head-to-head comparison of drug classes.

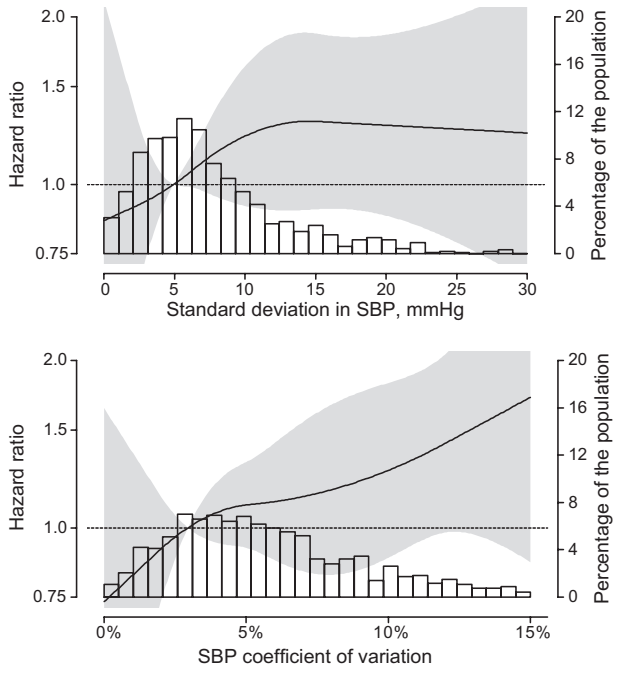

Figure. Association between standard deviation of systolic blood pressure (top panel) and coefficient of variation of systolic blood pressure (bottom panel) with all-cause mortality over a median of 14 years of follow-up.

One possible factor to explain the link between antihypertensive medication use and higher visit-to-visit blood pressure variability is low medication adherence. In the current study, an association between visit-to-visit variability and increased risk for all-cause mortality was present among individuals not taking antihypertensive medication, suggesting adherence is not responsible for this association. Nonetheless, future studies are needed to investigate the mechanisms underlying visit-to-visit variability in systolic blood pressure associated with antihypertensive medication use, different classes of medication, and adherence.

Evidence suggests that visit-to-visit variability in blood pressure is reproducible and not a random phenomenon. In the UK-TIA study, the intraclass correlation coefficient for the standard deviation of systolic blood pressure across the first 4 visits and subsequent 4 visits was 0.25 (95% CI, 0.19 to 0.30).[6] The intraclass correlation coefficient for the coefficient of variation of systolic blood pressure was also found to be reproducible (intraclass correlation coefficient=0.14; 95% CI, 0.08 to 0.20; $P<0.001$). Reproducibility in visit-to-visit variability in systolic blood pressure was also present in the European Carotid Surgery Trial.[6] In these 2 previous studies, blood pressure was based on a single measurement at each visit. Having multiple blood pressure measurements at

each visit, as was available in the current study, should result in a higher degree of reproducibility in the level of visit-to-visit variability in blood pressure.

There is some previous evidence to suggest that visit-to-visit variability in systolic blood pressure has prognostic value, independent of average blood pressure.[11,17,22,26] In a study of 1433 men from the Honolulu Heart Program, visit-to-visit variability in systolic blood pressure was associated with incident coronary heart disease events, even after controlling for potential confounders including average systolic blood pressure across study visits.[27] In a recent publication including the secondary analysis of several randomized controlled trials, higher visit-to-visit variability in systolic blood pressure was associated with an increased incidence of stroke in a cohort of subjects who had previously experienced a transient ischemic attack.[11] Higher visit-to-visit variability in systolic blood pressure also was associated with stroke and coronary events in treated hypertensive patients enrolled in the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm.[25] The results of the current study are consistent with the findings from these previous studies and extend them in several important ways. The current study population included a multiethnic sample of patients taking and not taking antihypertensive medications, and, unlike most previous studies on visit-to-visit variability in blood pressure, participants were not randomized to interventions.

In the current study, no association was present between visit-to-visit variability in diastolic blood pressure and all-cause mortality. This is consistent with previous research.[11,27] For example, in the Honolulu Heart Program, variance of diastolic blood pressure across 4 visits was not associated with subsequent coronary heart disease incidence.[27] In addition, in the UK-TIA study, the visit-to-visit variability in diastolic blood pressure was not associated with stroke, and an association was present only in the highest deciles in the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm.[11]

This study should be interpreted in the context of several possible limitations. Most notably, the first set of blood pressure measurements occurred during an in-home examination, whereas the latter 2 sets of measurements occurred in a medical evaluation conducted in a mobile examination center. In addition, the in-home blood pressure measurements were obtained by a research assistant, whereas the clinic measurements were obtained by a physician. However, the study protocol and equipment used were identical for all blood pressure measurements, and adjustment for the change in blood pressure between measurements taken in the home and clinic setting did not effect the association of visit-to-visit variability with mortality. Another potential limitation is that blood pressure measurements were available at only 3 time points. It would be valuable to calculate variability, with more visits occurring over a longer time period. Finally, only a subsample of participants were asked to attend the second clinic examination. Three blood pressure measurements were available for only 956 of the 2174 participants who were asked to complete the second clinic examination. The small sample size prevented us from conducting subgroup analyses and investigating cause-specific mortality. Given its strong association with age, visit-to-visit variability in systolic blood pressure may prove to have greater prognostic importance among older adults. This should be addressed in future studies.

Perspectives

Visit-to-visit variability in systolic blood pressure can be identified in clinical practice, and the natural assumption may be that it is the result of measurement error. However, the findings from the present study suggest that such variability is associated with increased mortality. Additional research is needed to confirm these results, identify the putative mechanisms involved in this association, and evaluate approaches to reduce visit-to-visit variability in blood pressure and its clinical sequelae.

Disclosures

None.

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