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A Re-Defined Blood Pressure Variability Measure and its Association with Mortality in Elderly Primary Care Patients RR

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Abstract

Visit-to-visit blood pressure variability has received considerable attention recently. The objective of our study is to define a variability measure that is independent of change over time and determine the association between longitudinal summary measures of blood pressure measurements and mortality risk. Data for the study came from a prospective cohort of 2,906 adults, age 60 or older, in an urban primary care system with up to fifteen years follow-up. Dates of death for deceased participants were retrieved from the National Death Index. Systolic and diastolic blood pressure measurements from outpatient clinic visits were extracted from the Regenstrief Medical Record System. For each patient, the intercept, regression slope, and root mean square error for visit-to-visit variability were derived using linear regression models and used as independent variables in Cox's proportional hazards models for both all-cause mortality and mortality due to coronary heart disease or stroke. Rate of change was associated with mortality risk in a U-shaped relationship and that participants with little or no change in blood pressure had the lowest mortality risk. Blood pressure variability was not an independent predictor of mortality risk. By separating change over time from visit-to-visit variability in studies with relatively long follow-up, we demonstrated in this elderly primary care patient population that blood pressure changes over time, not variability, were associated with greater mortality risk. Future research is needed to confirm our findings in other populations.

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Conflicts of Interest:
The authors report no conflict of interest.

Keywords

blood pressure; mortality; cardiovascular disease; cohort studies; elderly population

Introduction

Visit-to-visit blood pressure (BP) variability has received considerable attention recently. Some studies reported that increased visit-to-visit blood pressure was associated with higher risk of cardiovascular diseases (CVD) [1-4] and all-cause mortality. [5-7] There were also suggestions that visit-to-visit BP variability should be used as a potential target for drug development and treatment management.[8] However, results on the relationship between BP variability and health outcomes have not been entirely consistent, as other studies failed to detect significant associations between BP variability and cardiovascular endpoints [9-11] or found a weaker effect of BP variability than mean BP.[12]

Many studies had defined BP variability as the standard deviation of repeated BP measurements from each subject. While such a definition may be a valid measure of variability over a short period when there is little BP change, in studies conducted over longer periods BP standard deviation would reflect both temporal trend in BP and visit-to-visit variability. Thus, individuals with large standard deviation could have increasing or decreasing BP over time but with little deviation from such a trend, or alternatively, they could show little change over time but have large fluctuations in BP across time. A schematic illustration was provided in Figure 1 where two individuals with similar BP mean and standard deviations demonstrated different trends in BP change and variability over time. Using the standard deviation to define visit-to-visit BP variability is therefore incapable of distinguishing change over time from true visit-to-visit variability. A redefined BP variability will be particularly relevant to the elderly population who were known to have decreasing diastolic BP after age 60 and continual rise in systolic BP over time.[13] To the best of our knowledge, only one study thus far has considered a definition of BP variability that is independent of BP temporal trends in postmenopausal women for stroke risk. [4]

In this study, we present results from a longitudinal study of elderly primary care patients enrolled in an urban health care system by capturing three quantitative measures (mean, slope and variability) associated with longitudinal BP measurements and determine their combined association with mortality.

Methods

Study Population

The cohort consisted of elderly primary care patients who were enrolled during regularly scheduled primary care appointments in an urban public health system. From 1991 to 1993, all patients 60 years and older attending the primary care practice in the Wishard Health System were approached for participating in a depression screening study. A total of 4,413 primary care patients were contacted, of whom 115 patients refused; 57 were not able to

complete the testing due to severe cognitive impairment; and 284 patients were not eligible because they did not speak English, were in prison or a nursing home, or had a hearing impairment, leaving 3,957 total enrolled patients. The details of the depression screening program have been previously reported.[14,15] To ensure comparability with previous studies,[1] we restricted the analyses to patients who were followed for at least two years and had at least six BP measurements. Therefore, 2906 patients were included in this analysis. The study was approved by the Institutional Review Boards of Indiana University-Purdue University of Indianapolis.

Data Source during Patient Follow-up

Medical history information from enrollment to December 31, 2006 was extracted from the Regenstrief Medical Record System.[16] At all of the sites of care in the targeted health system, providers electronically recorded BP measurements, height, weight, all diagnoses, laboratory test results, procedures, and prescribed medications. This information was routinely collected and stored in the Regenstrief Medical Record System that had been used extensively for epidemiologic studies of the process and outcomes of care.[17] For this analysis, we retrieved repeated height, weight, systolic BP (SBP) and diastolic BP (DBP) from patients' pre-scheduled outpatient visits. We also retrieved dates for patients' first diagnoses (as indicated by ICD-9 codes) contained in inpatient, outpatient and emergency room records for the following conditions: hypertension, diabetes, atherosclerotic vascular disease, coronary artery disease (CAD), peripheral artery disease (PAD), congestive heart failure (CHF), cerebrovascular disease (CVD), cancer, anemia, chronic obstructive pulmonary disease (COPD), arthritis, liver disease, renal disease, thyroid disease (including both hyperthyroidism and hypothyroidism), hyperlipidemia, dementia, and depression. Demographic information including age, gender, race, years of education, and history of smoking were collected at study enrollment.

Study Endpoint

For deceased patients, date of death from enrollment to December 31, 2006 was retrieved from the National Death Index (NDI) as part of the National Center for Health Statistics. The NDI is a central computerized index of death record information on file in the state vital statistics offices.[18] For surviving patients, date of their last outpatient clinic visit before Dec. 31, 2006 was used as the censoring date. In addition to examining all-cause mortality, we also determined deaths for which ischemic coronary heart disease (CHD) (International Classification of Diseases, Ninth Revision, codes 410–414 and International Classification of Diseases, Tenth Revision, codes I20–I25), or for which stroke (International Classification of Diseases, Ninth Revision, codes 430-434 and International Classification of Diseases, Tenth Revision, codes I60-I69) was listed as the cause of death.

Statistical Analysis

For each patient, three independent BP summary measures were calculated using linear regression models, with BP measurements as dependent variables and the time of BP measurement as the independent variable with baseline time as the time origin: (1) the intercept, which represents BP value at baseline, (2) the regression slope, which estimates the rate of BP change per year during follow-up, and (3) root mean square error, which

estimates BP variability around the fitted linear regression line. The three summary BP measures were calculated separately for SBP and DBP.

Cox's proportional hazards models were used to determine whether the three BP characteristic measures, alone or in combinations, were associated with all-cause or cardiovascular mortality risk. BP intercepts, slopes, and variability were included in the Cox's models first as continuous variables to detect both linear and quadratic effects on mortality risk. For each of the three BP measures, we also used quartile groups in order to detect potential non-linear effects in mortality risk. All medical conditions were used as time-varying covariates in the proportional hazard models and included in the multivariate models for conditions with $p<0.05$. To prevent bias due to reverse causation from decreasing BP prior to death, we also conducted a sensitivity analysis by excluding BP measurements taken within one year of study endpoints.

Comparisons between patients included in this analysis and those excluded were conducted using *t*-tests for continuous outcomes and chi-squared tests for categorical outcomes.

Results

Among 2906 patients included in this analysis, 1711 (59%) died during follow-up, 305 of the deaths had coronary heart disease listed as the cause of death and 123 had stroke as cause of death. Median follow-up time from enrollment to study endpoint was 12.9 years with survival time in the range of 2.0 year to 16.0 years. In Table 1, we included comparisons of baseline demographic information and medical history for patients who died during follow-up and those who survived to Dec. 31, 2006. We also included mean BP intercept, slope, and variability measures for the two groups. BP intercepts did not differ between the deceased and surviving patients, but deceased patients had significantly smaller slopes indicating greater BP decline than patients who survived to Dec. 31, 2006. Mean BP variability was not significantly different on SBP. However, deceased patients had significantly smaller variability than survivors did on DBP ($p=0.002$).

In table 2, we included results from multivariate Cox's models for all-cause mortality using each of the three quantitative BP measures as both continuous or quartile groups adjusting for age, gender, race, smoking status and body mass index (BMI). The models indicated that BP intercepts (baseline BP) were not associated with mortality risk. A U-shaped relationship were seen between BP slopes and all-cause mortality indicating that patients with both large (1^{st} quartile group) and small BP changes (4^{th} quartile group) over the follow-up time had higher mortality risk compared to patients with little changes in BP (3^{rd} quartile group) over time. When both SBP slopes and variability were included in the Cox's model, SBP variability was not associated with mortality ($p=0.32$). Those with *smaller* DBP variability (1^{st} quartile group) was associated with greater mortality risk compared to those in the 4^{th} quartile group (HR=1.355, $p<0.001$). Model results for CHD or stroke mortality were included in Table 3. BP variability was not a predictor of cardiovascular deaths, but higher SBP intercept was significantly associated with higher stroke mortality ($p=0.0297$).

Slope and variability measures were significantly correlated for DBP (r=0.107, p<0.001) but not for SBP (r=0.026, p=0.16). To investigate potential interactions among slope and variability measures with a reasonable number of groups, we combined the 2nd and 3rd slope quartile groups into one group and combined the 2nd, 3rd and 4th variability quartile groups into one group since these groups showed similar trends in Table 2. Thus, patients were divided into six groups according to their combined BP slope and variability measures (Supplemental Table). Results from Cox's models for all-cause mortality using the combined six BP slope and variability groups were presented in Table 4. For SBP, patients who had little or no change over time regardless of variability had the smallest mortality risk out of the six groups. In patients with declining BP or little change in BP (the small or medium slope groups), smaller SBP variability was associated with significantly higher all-cause mortality compared to those with medium to large variability. Similar results were also seen for DBP variability. A sensitivity analysis excluding BP measurements obtained within 1 year of study end points was also included in Table 4 and results were similar to those obtained using the entire follow-up data.

Results from multivariate Cox's model on cause specific mortality due to CHD or stroke were presented in Table 5. Similarly to what we had seen for all-cause mortality, patients with little change in SBP over time (groups 3 and 4) were again found to have the lowest mortality risk for both CHD and stroke. Given similar BP change over time, no significant differences in cause-specific mortality risk were found between patients with small variability and those with medium to large variability (p>0.05). However, in contrast to results for all-cause mortality, patients in group 1 generally did not show increased risk for cardiovascular death with the exception of DBP for CHD deaths where those in group still showed an increased risk (HR=1.761, p=0.0130).

Comparisons between participants in the cohort who were excluded from the analysis (n=1051) to those included (n=2906) showed that those included in the analyses were slightly younger (mean age=67.5 vs 69.1, p<0.001), with higher BMI at baseline (mean BMI=29.8 vs 26.9, p<0.001), with higher proportions of female (72.3% vs 59.1%, p<0.001) and African Americans (65.9% vs 56.2%, p<0.001). However, there was no significant difference between years of education or smoking history between those included and those excluded from the analyses.

Discussion

In this elderly primary care patient cohort followed for up to 15 years, we found that participants with little BP change over time had the lowest risk for all-cause mortality or cardiovascular deaths. BP variability was not an independent predictor of mortality risk.

Previous studies, with two exceptions,[4,7] used within-person standard deviation for BP variability that measures BP deviations about the mean. A recent study defined BP variability as the average absolute difference between successive BP measurements that also includes trends of change. [7] Higher within-person standard deviation may be accounted for by BP change over time, not simply visit-to-visit variation. Thus, previous reports of increased CVD and mortality risk with higher BP standard deviation could be due to BP

change over time. In contrast, the BP variability defined in our study measures BP deviations about a fitted regression line. Our results demonstrate that BP change over time was significantly associated with mortality risk while the redefined visit-to-visit variability is not a predictor of mortality. In addition, we note that studies using standard deviation as a variability measure within a short period tend to report non-significant relationship between such measures and cardiovascular diseases, perhaps due to the relatively stable BP change within the short time window. [9,10,19] In studies with BP measured over an extended period, our definition of variability should be preferred, as it separates BP change over time from random variability. It will be interesting to re-evaluate previous studies to determine how much of the reported association between increased variability and disease risks was accounted for by BP changes over time.

There is only one previous study that adopted BP variability similarly defined as in this study.[4] The study population included postmenopausal women aged 50 to 79 years from the Women's Health Initiatives (WHI) for the risk of stroke. However, the WHI study found that larger BP variability was related to higher stroke risk, in contrast to our findings. There is important cohort and methodological differences between our study and the WHI study, however. Our cohort included both men and women who were on average older than WHI participants. Our outcome was mortality, where WHI considered stroke risk. In addition, in our analyses, we considered nonlinear temporal trend to accommodate a U-shaped relationship between BP change and mortality risk, where the WHI study used linear models for BP slopes. These differences and potentially others not postulated here may have contributed to the differences in findings.

Our finding that elderly participants with little or no change in BP had the lowest mortality risk is not surprising. A J- or U-shaped relationship between BP, coronary artery disease and mortality have been reported, where both low and high BP were shown to have increased risk. [20-22] Our results support a nonlinear relationship between BP slopes and all-cause or cardiovascular mortality risk and that participants with both increasing or decreasing BP had higher mortality risk than those with little change in BP over time. Furthermore, the relationship between BP change and mortality was independent of BP variability.

Our finding that given similar diastolic BP change over time, participants with smaller variability had higher all-cause mortality than those with medium to large variability has not been reported before. However, we did not find significant relationship between diastolic BP variability and cause-specific mortality due to CHD or stroke. A plausible mechanism underlying a relationship between smaller BP variability and higher all-cause-mortality is not clear. It is possible that larger BP variability reflects an intact or healthier cardiovascular system to accommodate BP increases when one exercises, for example. Although not directly correlated with BP, reduced heart rate variability had been shown to be a risk factor for cardiac events.[23,24] Additional research is necessary to investigate potential mechanisms linking small BP variability to increased all-cause mortality risk.

Our study has a number of strength. The cohort is relatively large with long follow-up period. The use of electronic medical records (EMR) and National Death Index data eliminates recall and potential attrition bias. A comprehensive list of medical conditions was

available from EMR so that relevant covariates can be included in the analysis. Our study also has important limitations. The first is that BP was obtained as part of clinical practice records, not as a part of research study. Nevertheless, these data were routinely used to support clinical care and in many research projects. The second limitation is that some participants may be experiencing medical events that could adversely affect BP measures taken during that time. However, we have excluded BP taken during emergency room visits or hospital stay by restricting BP measurements to those from pre-scheduled outpatient visits in order to minimize potential contamination bias. We also conducted a sensitivity analysis by excluding BP measured within one year of study endpoints to minimize the potential for reverse causation. Lastly, additional data such as frailty measures on patients in this cohort were not collected in the EMR and they may provide some insight for the higher all-cause mortality risk in patients in group one who experience steep BP decline with small variability.

Perspectives

In this study, we defined visit-to-visit blood pressure variability as a measure independent of blood pressure change over time. In an elderly primary care patient cohort followed over fifteen years, we found that participants with little BP change over time had the lowest all-cause and cardiovascular mortality risk. BP variability was not an independent predictor of mortality risk. Future research is needed to adopt this new measure and confirm our findings in other populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Novelty and Significance

What is New?

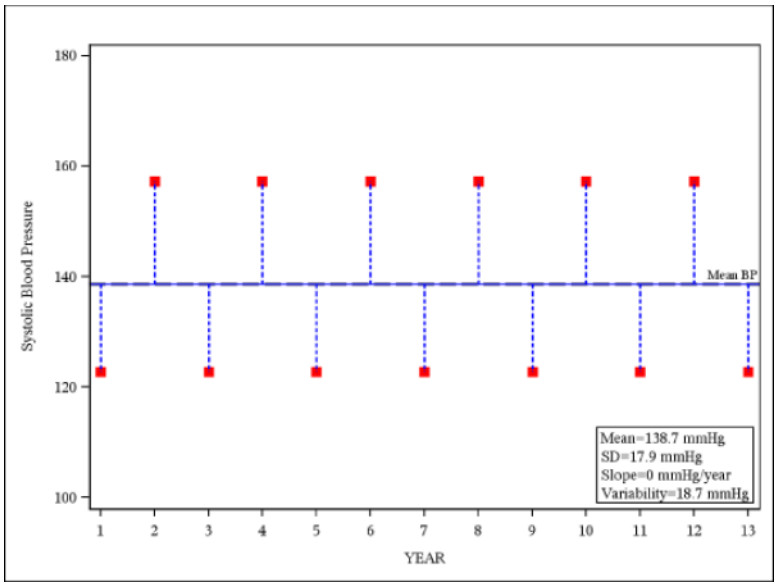
- Visit-to-visit blood pressure variability is defined as a measure independent of change over time;
- The re-defined blood pressure variability is not associated with all-cause mortality or cardiovascular deaths in this elderly primary care patient cohort;
- Rate of blood pressure change is associated with mortality risk in a U-shaped relationship. Participants with little or no change in BP had the lowest risk for all-cause or cardiovascular mortality.

What is Relevant?

- In elderly patients with repeated blood pressure measurements, it is important to monitor patients' blood pressure change over time for better health outcomes.

Summary:

Elderly participants with stable blood pressure over time had the lowest mortality risk. Blood pressure variability was not an independent predictor of mortality risk. Participants with little or no change in blood pressure had the lowest all-cause or cardiovascular mortality risk. Future research is needed to adopt this new measure and confirm our findings in other populations.



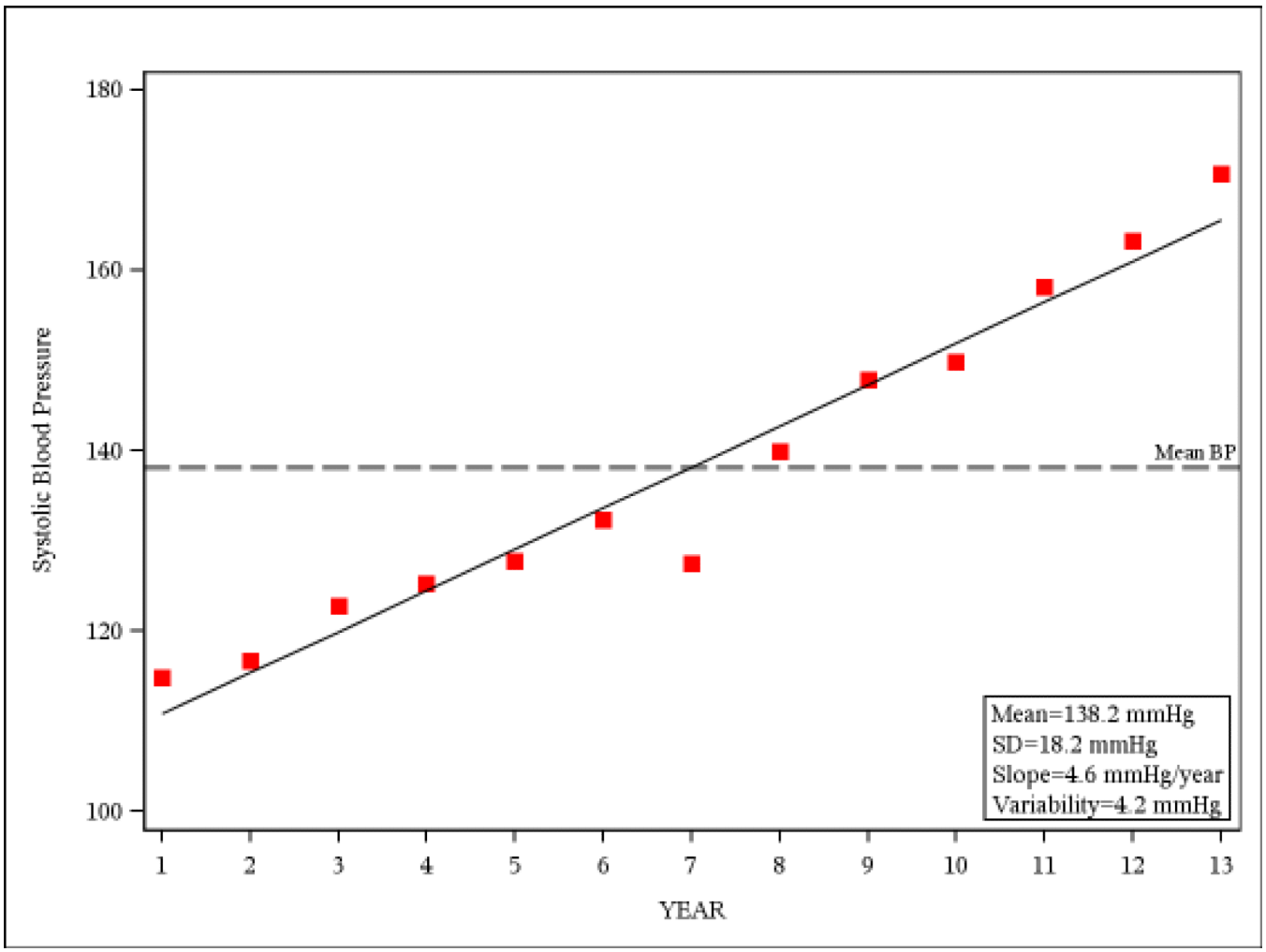


Figure 1.

Schematic illustration of two groups of individuals with similar mean and standard deviation of blood pressure measurements over 13 years, but showing different change over time.

Table 1

Participants' demographic characteristics at baseline and within-subject blood pressure summary measures by mortality status.

Patients' Characteristic	Mortality Status		
	Survivors (n =1195)	Deceased (n =1711)	p value
Mean age, (SD)	66 (6.2)	69.4 (7.9)	**<.0001**
Female, n (%)	1166 (78.7)	1555 (62.9)	**<.0001**
Black, n (%)	991 (66.9)	1515 (61.2)	**0.0004**
Smoking, n (%)	350 (23.6)	838 (33.9)	**<.0001**
Mean years of education, (SD)	9.3 (3.1)	8.7 (3.2)	**<.0001**
Body mass index, kg/m^2 (SD)	30.3 (7.2)	28.3 (7.4)	**<.0001**
Body mass index groups, n (%):			
Underweight	46 (3.1)	176 (7.1)	**<.0001**
Normal weight	305 (20.6)	718 (29.0)	
Overweight	435 (29.4)	733 (29.6)	
Obese	696 (47.0)	848 (34.3)	
Anemia, n (%)	215 (14.5)	519 (21.0)	**<.0001**
Arthritis, n (%)	454 (30.6)	710 (28.7)	0.1932
Atherosclerotic vascular disease, n (%)	12 (0.8)	58 (2.3)	**0.0004**
Coronary artery disease, n (%)	252 (17.0)	602 (24.3)	**<.0001**
Cancer, n (%)	148 (10.0)	376 (15.2)	**<.0001**
Cerebrovascular disease, n (%)	98 (6.6)	331 (13.4)	**<.0001**
Congestive heart failure, n (%)	144 (9.7)	521 (21.1)	**<.0001**
COPD, n (%)	119 (8.0)	532 (21.5)	**<.0001**
Dementia, n (%)	36 (2.4)	76 (3.1)	0.2389
Depression, n (%)	137 (11.5)	219 (12.8)	0.2801
Diabetes, n (%)	287 (19.4)	725 (29.3)	**<.0001**
Hyperlipidemia, n (%)	294 (24.6)	405 (23.7)	0.5629
Hypertension, n (%)	1046 (70.6)	1760 (71.1)	0.7220
Liver disease, n (%)	50 (3.4)	109 (4.4)	0.1102
Renal disease, n (%)	5 (0.3)	17 (0.7)	0.1524
Taking antihypertensive medications, n (%)	1111 (93.0)	1496 (87.8)	**<0.001**
Systolic blood pressure			
Mean intercept, mmHg (SD)	142.1 (15.4)	142.5 (16.6)	0.5159
Mean slope, mmHg/year (SD)	0.5 (2.8)	−0.0 (4.7)	**0.0007**
Mean variability, mmHg (SD)	17.6 (4.7)	17.5 (4.8)	0.7071
Diastolic blood pressure			
Mean intercept, mmHg (SD)	80.1 (8.5)	80.1 (9.1)	0.9292
Mean slope, mmHg/year (SD)	−0.9 (1.6)	−1.6 (2.6)	**<.0001**
Mean variability, mmHg (SD)	10.9 (2.7)	10.6 (3.0)	**0.0017**

Table 2

Results from multivariate Cox's proportional hazard models for all-cause mortality using baseline blood pressure, changes in blood pressure over time (slope estimates) or blood pressure variability.*

BP Characteristic	Systolic Blood Pressure		Diastolic Blood Pressure	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Continuous Models				
BP Intercept	1.002 (0.999, 1.005)	0.2901	1.005 (0.999, 1.010)	0.0855
BP Slope	0.954 (0.944, 0.965)	<.0001	0.933 (0.907, 0.960)	<.0001
BP Slope^2	1.004 (1.003, 1.005)	<.0001	1.012 (1.008, 1.015)	<.0001
BP Variability	0.994 (0.984, 1.004)	0.2563	0.970 (0.953, 0.987)	0.0005
BP Slope	0.954 (0.944, 0.965)	<.0001	0.936 (0.910, 0.963)	<.0001
BP Slope^2	1.004 (1.003, 1.005)	<.0001	1.012 (1.008, 1.015)	<.0001
BP Variability	0.995 (0.985, 1.005)	0.3223	0.979 (0.963, 0.997)	0.0186
Categorical Models				
Baseline quartile groups		0.6395		0.1197
Slope quartile groups		<.0001		<.0001
1st quartile	1.332 (1.177, 1.507)	<.0001	2.047 (1.800, 2.328)	<.0001
2nd quartile	0.607 (0.528, 0.697)	<.0001	0.995 (0.867, 1.141)	0.9372
3rd quartile	0.608 (0.529, 0.699)	<.0001	0.713 (0.615, 0.826)	<.0001
4th quartile	1	Reference	1	Reference
Variability quartile groups		0.3098		<.0001
1st quartile	1.091 (0.953, 1.249)	0.2089	1.355 (1.184, 1.552)	<.0001
2nd quartile	0.963 (0.841, 1.104)	0.5918	1.022 (0.890, 1.174)	0.7541
3rd quartile	0.994 (0.870, 1.136)	0.9291	1.060 (0.923, 1.217)	0.4078
4th quartile	1	Reference	1	Reference

*models adjusted for baseline age, gender, race, smoking status, and body mass index.

Table 3

Results from multivariate Cox's proportional hazard models for mortality due to coronary heart disease or stroke using baseline blood pressure, changes in blood pressure over time (slope estimates) or blood pressure variability.*

BP Characteristic	Systolic Blood Pressure		Diastolic Blood Pressure	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Coronary Heart Disease				
BP Intercept	1.007 (1.000, 1.015)	0.0516	1.013 (0.999, 1.026)	0.0624
BP Slope	0.962 (0.935, 0.991)	0.0098	1.897 (0.829, 0.971)	0.0071
BP Slope^2	1.003 (1.002, 1.005)	<0.0001	1.008 (0.999, 1.017)	0.0939
BP Variability	1.019 (0.995, 1.044)	0.1147	1.009 (0.969, 1.051)	0.6537
BP Slope	0.963 (0.935, 0.992)	0.0114	0.893 (0.824, 0.968)	0.0061
BP Slope^2	1.003 (1.002, 1.005)	<0.0001	1.008 (0.998, 1.017)	0.1051
BP Variability	1.020 (0.995, 1.044)	0.1131	1.021 (0.981, 1.063)	0.3069
Stroke				
BP Intercept	1.011 (1.000, 1.023)	0.0497	1.014 (0.994, 1.036)	0.1774
BP Slope	1.052 (0.988, 1.120)	0.1119	1.063 (0.987, 1.144)	0.1081
BP Slope^2	1.002 (0.999, 1.005)	0.2747	1.017 (1.007, 1.026)	0.0007
BP Variability	1.057 (1.020, 1.096)	0.0022	1.035 (0.972, 1.102)	0.2802
BP Intercept	1.016 (1.002, 1.031)	0.0297	--	
BP Slope	1.106 (1.052, 1.163)	<0.0001	1.060 (0.984, 1.142)	0.1273
BP Slope^2	--		1.017 (1.007, 1.027)	0.0007
BP Variability	1.035 (0.993, 1.079)	0.1081	1.034 (0.972, 1.100)	0.2945

* models adjusted for baseline age, gender, race, smoking status, and body mass index.

Table 4

Multivariate Cox's proportional hazard models assessing the association between longitudinal blood pressure characteristics and risk of all-cause mortality.*

Patient Groups	Systolic BP		Diastolic BP	
	Hazard Ratio (95% Confidence Interval)	P-value	Hazard Ratio (95% Confidence Interval)	P-value
Entire Sample				
Group 1 (small slopes, small variability)	1.672 (1.373, 2.037)	<.0001‡	2.156 (1.788, 2.599)	<.0001
Group 2 (small slopes, medium to large variability)	0.951 (0.824, 1.098)	0.4910	1.952 (1.673, 2.278)	<.0001
Group 3 (medium slopes, small variability)	0.692 (0.578, 0.828)	<.0001‡	1.332 (1.107, 1.601)	0.0024‡
Group 4 (medium slopes, medium to large variability)	0.542 (0.473, 0.621)	<.0001	0.771 (0.669, 0.888)	0.0003
Group 5 (large slopes, small variability)	0.997 (0.799, 1.243)	0.9773	1.573 (1.252, 1.976)	<.0001‡
Group 6 (large slopes, medium to large variability)	1	Reference	1	Reference
Sensitivity Analysis†				
Group 1 (small slopes, small variability)	1.556 (1.283, 1.889)	<.0001‡	2.298 (1.909, 2.766)	<.0001‡
Group 2 (small slopes, medium to large variability)	0.749 (0.648, 0.865)	<.0001	1.725 (1.477, 2.015)	<.0001
Group 3 (medium slopes, small variability)	0.595 (0.496, 0.713)	<.0001‡	1.270 (1.051, 1.534)	0.0132‡
Group 4 (medium slopes, medium to large variability)	0.469 (0.410, 0.537)	<.0001	0.657 (0.570, 0.757)	<.0001
Group 5 (large slopes, small variability)	1.804 (1.465, 2.221)	<.0001‡	2.142 (1.736, 2.644)	<.0001‡
Group 6 (large slopes, medium to large variability)	1	Reference	1	Reference

*models adjusted for age, gender, race, smoking status, body mass index, history of anemia, arthritis, atherosclerotic vascular disease, cardiovascular disease, cancer, cerebrovascular disease, congestive heart failure, hyperlipidemia, hypertension, COPD, dementia, diabetes, liver disease, renal disease and use of antihypertensive medications.

†Analysis excludes blood pressure measurements within one year of study end points.

‡$p<0.05$, significant difference in hazard ratios comparing the small variability group to the medium to large variability group within the same slope groups.

Table 5

Multivariate Cox's proportional hazard models assessing the association between longitudinal blood pressure characteristics and mortality due to coronary heart disease or stroke.*

Patient Groups	Systolic BP		Diastolic BP	
	Hazard Ratio (95% Confidence Interval)	P-value	Hazard Ratio (95% Confidence Interval)	P-value
Coronary heart disease				
Group 1 (small slopes, small variability)	1.176 (0.686, 2.017)	0.5554	1.761 (1.127, 2.754)	0.0130
Group 2 (small slopes, medium to large variability)	1.371 (0.991, 1.896)	0.0567	2.307 (1.635, 3.254)	<.0001
Group 3 (medium slopes, small variability)	0.643 (0.420, 0.987)	0.0432	1.044 (0.671, 1.624)	0.8490
Group 4 (medium slopes, medium to large variability)	0.471 (0.339, 0.654)	<.0001	0.708 (0.510, 0.982)	0.0384
Group 5 (large slopes, small variability)	1.116 (0.689, 1.808)	0.6549	1.046 (0.590, 1.855)	0.8765
Group 6 (large slopes, medium to large variability)	1	Reference	1	Reference
Stroke				
Group 1 (small slopes, small variability)	0.797 (0.331, 1.915)	0.6113	0.739 (0.323, 1.686)	0.4718
Group 2 (small slopes, medium to large variability)	0.655 (0.382, 1.124)	0.1244	1.028 (0.580, 1.821)	0.9259
Group 3 (medium slopes, small variability)	0.361 (0.178, 0.735)	0.0050	0.510 (0.233, 1.115)	0.0915
Group 4 (medium slopes, medium to large variability)	0.458 (0.291, 0.719)	0.0007	0.637 (0.406, 0.999)	0.0497
Group 5 (large slopes, small variability)	0.630 (0.276, 1.438)	0.2726	1.149 (0.561, 2.354)	0.7044
Group 6 (large slopes, medium to large variability)	1	Reference	1	Reference
Coronary heart disease or Stroke				
Group 1 (small slopes, small variability)	1.044 (0.660, 1.651)	0.8541	1.391 (0.944, 2.050)	0.0952
Group 2 (small slopes, medium to large variability)	1.120 (0.851, 1.667)	0.4199	1.846 (1.381, 2.468)	<.0001
Group 3 (medium slopes, small variability)	0.545 (0.379, 0.785)	0.0011	0.854 (0.584, 1.249)	0.4148
Group 4 (medium slopes, medium to large variability)	0.466 (0.357, 0.608)	<.0001	0.680 (0.522, 0.886)	0.0043
Group 5 (large slopes, small variability)	0.941 (0.622, 1.424)	0.7748	1.087 (0.695, 1.700)	0.7141
Group 6 (large slopes, medium to large variability)	1	Reference	1	Reference

*Cause specific mortality models adjusted for age, gender, race, smoking status, history of anemia, arthritis, hyperlipidemia, COPD, dementia, diabetes, and renal disease.