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Postural changes in blood pressure and incidence of ischemic stroke subtypes: the ARIC study

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Abstract

The relation of orthostatic blood pressure decrease, or increase, with occurrence of ischemic stroke subtypes has not been examined. We investigated the association of orthostatic blood pressure change (within 2 minutes after supine to standing) obtained at baseline (1987–89) in the Atherosclerosis Risk in Communities Study with incidence of ischemic stroke subtypes through 2007. Among 12,817 black and white individuals without a history of stroke at baseline, 680 ischemic strokes (153 lacunar, 383 nonlacunar thrombotic, and 144 cardioembolic strokes) occurred during a median follow-up of 18.7 years. There was a U-shaped association between orthostatic systolic blood pressure change and lacunar stroke incidence (quadratic p=0.004). In contrast, orthostatic systolic blood pressure decrease of 20 mmHg or more was associated with increased occurrence of nonlacunar thrombotic and cardioembolic strokes independent of sitting systolic blood pressure, antihypertensive medication use, diabetes, and other lifestyle, physiological, biochemical, and medical conditions at baseline (hazard ratio: 2.02, 95% confidence interval: 1.43–2.84 for nonlacunar thrombotic, hazard ratio: 1.85, 95% confidence interval: 1.01–3.39 for cardioembolic). Orthostatic diastolic blood pressure decrease was associated with increased risk of nonlacunar thrombotic and cardioembolic strokes; the hazard ratios (95% confidence interval) associated with 10 mmHg lower orthostatic diastolic blood pressure (continuous) were 1.26 (1.06–1.50) and 1.41 (1.06–1.88), respectively, in fully-adjusted models. In conclusion, the present study found that nonlacunar ischemic stroke incidence was positively associated with an orthostatic decrease of systolic and diastolic blood pressure whereas greater lacunar stroke incidence was associated with both orthostatic increases and decreases in systolic blood pressure.

Keywords

Stroke; cerebral infarction; lacunar infarction; orthostatic hypotension; blood pressure

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NONE

Introduction

The amount that blood pressure (BP) rises or falls with a change in posture varies considerably among individuals.[1] Large BP changes after orthostatic stress are associated with autonomic and neuro-hormonal abnormalities, altered patterns of nocturnal and diurnal BP variations.[2, 3] and increased risk of hypertension.[4, 5] Both excessive postural BP elevation as well as decline have been associated with an increased prevalence of silent cerebral infarctions in older hypertensives.[2, 6] Orthostatic hypotension (OH) is associated with increased risk of ischemic stroke;[7] but whether orthostatic BP elevation increases the risk of incident ischemic stroke has yet to be determined. Since ischemic stroke consists of subtypes (i.e., lacunar, nonlacunar thrombotic, and cardioembolic), which have some distinct etiologic features,[8] it is of interest to investigate whether the association of orthostatic BP change with ischemic stroke differs by subtype. This could provide clues to their distinct pathophysiologies and have implications for BP control. Indeed, one study reported that lacunar stroke occurs more often than other stroke subtypes during sleep,[9] implying that dysfunction in BP regulation may be an important risk factor for lacunar stroke. We therefore investigated orthostatic BP change in relation to subsequent occurrence of ischemic stroke subtypes in a large population-based cohort study of US adults.

Methods

Study sample

The Atherosclerosis Risk in Communities (ARIC) Study included 15,792 persons between 45 and 64 years of age at the baseline examination (1987–1989). Participants were selected using probability sampling methods from Forsyth County, NC (n=4,035); Jackson, MS (blacks only, n=3,728); the northwest suburbs of Minneapolis, MN (n=4,009); and Washington County, MD (n=4,020). After restricting participants to black (enrolled in Jackson and Forsyth) and white ARIC visit 1 participants (n=15,689), we additionally excluded participants with: (1) missing postural blood pressure (BP) change measurements (n=2,496, most of whom underwent their baseline examination before initiation of the postural change evaluation); (2) missing education attainment (n=18); (3) missing data on resting systolic BP (SBP), antihypertensive medication use, or prevalent diabetes (n=119); or (4) a self-reported history of stroke at visit 1 (n=239). This left 12,817 individuals for the analysis. Institutional review boards at each clinical site approved the study protocol, and written informed consent was obtained from all participants. Procedures followed were in accordance with institutional guidelines to protect human subjects.

Ascertainment of incident stroke

Hospitalized strokes that occurred by December 31, 2007 (median follow-up 18.7 years) were included in the present study. During annual telephone contacts, trained interviewers asked each ARIC participant to list all hospitalizations during the past year. Hospital records for any hospitalizations indentified were then obtained. In addition, all local hospitals annually provided lists of stroke discharges (International Classification of Diseases, Ninth Revision, Clinical Modification codes 430–438), which were scrutinized for ARIC participants' discharges. Details on quality assurance for ascertainment and classification of stroke are described elsewhere.[10] Briefly, the stroke diagnosis was assigned according to criteria adapted from the National Survey of Stroke.[11] Strokes secondary to trauma, neoplasm, hematological abnormality, infection, or vasculitis were excluded, and a focal deficit lasting <24 h was not considered to be a stroke. Out-of-hospital stroke was not ascertained and validated; thus, these potential stroke events were not included. Strokes were classified into hemorrhagic stroke (subarachnoid and intracerebral hemorrhage) and ischemic stroke (thrombotic and embolic brain infarction). A stroke was classified as

ischemic when a brain CT or MRI revealed acute infarction and showed no evidence of hemorrhage. All definite ischemic strokes were further classified as lacunar, nonlacunar thrombotic, or cardioembolic on the basis of the recorded neuroimaging results. A stroke was classified as "lacunar" when two criteria were met: (1) typical location of the infarct (basal ganglia, brain stem, thalamus, internal capsule, or cerebral white matter) and (2) infarct size of ≤ 2 cm or unstated size.[12] Definite or probable "cardioembolic" stroke required either (1) autopsy evidence of an infarcted area in the brain and a source of possible cerebral emboli in a vessel, or the presence of an embolus in the brain or (2) medical record evidence of a possible non-carotid source of embolus such as moderate or greater valvular heart disease, atrial fibrillation, cardiac or arterial procedure (e.g., cardiac catheterization, open heart surgery, cerebral angiography, and carotid endarterectomy), or intracardiac thrombus. Definite or probable ischemic strokes that were not classified as lacunar or cardioembolic, including atherothrombotic and unclassified thrombotic strokes, were labeled "nonlacunar." For this analysis, the hemorrhagic strokes identified by ARIC were censored at the time of their occurrence.

Measurement of postural BP change

Supine and standing BP measurements were obtained by a Dinamap 1846 SX oscillometric device, which has high within-subject reliability and is comparable to Doppler ultrasound blood pressure measurement.[13] Following 20 minutes of supine rest, the participant was instructed on how to change positions. Automated supine BP measurements were then taken approximately every 30 seconds for two minutes (range of 2–5 measurements, 90% had ≥ 4 measurements). Participants were asked to stand, and as their feet touched the ground, a standing BP measurement was taken. Measurements were repeated during the first two minutes after standing (range of 2–5 measurements, 91% had ≥ four measurements). Because BP restabilization occurs during the first 30 seconds after standing,[14] BP change was defined as the difference between the average of the standing and the supine BP measurements, excluding the 1st standing measurement.

Definition of orthostatic BP change categories

Orthostatic change in SBP was categorized into five categories by the following cut-off points: −63 to −20, −19 to −10, −9 to +10 (reference) +11 to +20 and +21 to +65 mmHg, and orthostatic diastolic BP (DBP) change into four categories by −34 to −10, −9 to 0, +1 to +10 (reference), and +10 to +42 mmHg. The smaller number of categories for orthostatic DBP change was due to its more limited range and less variability (standard deviation: SD for DBP change, 5.7 mmHg) than that for SBP (SD for SBP change: 10.7 mmHg). The reference categories were chosen to include the mean values. The lower cut-off points were chosen to be consistent with established guidelines for defining OH, i.e., a decrease of at least 20 mmHg SBP or a decrease of at least 10 mmHg DBP.[15] There were 547 (4.3%) subjects whose SBP dropped 20 mmHg or more, 203 (1.6%) subjects whose DBP dropped 10 mmHg or more, and 631 (4.9%) subjects who met the consensus criterion for OH.

Covariates

At baseline, standardized interviews were conducted to obtain participants' self-reported socio-demographic and behavioral risk factors. Education was classified as high school diploma or less, or more than high school. Smoking status was categorized as current smoker, former smoker, and never smoked. Alcohol intake was assessed and adjusted for as usual ethanol consumption (grams) per week. A leisure time sports index was derived from questionnaire items on hours per week spent in up to four sports and the months per year each sport was done as in our previous study.[7]

Three seated blood pressure measurements were taken with a random-zero sphygmomanometer; the last two measurements were averaged. The manual for ARIC blood pressure measurement can be accessed online (http://www.cscc.unc.edu/aric/). Prevalent diabetes was defined by a history of, or treatment for, diabetes, a fasting glucose level of 126 mg/dl or greater, or a casual blood glucose level of 200 mg/dl or greater. Resting heart rate was determined from a standard supine 12-lead electrocardiogram (ECG). Waist circumference at the umbilical level was measured with a standardized protocol. High-density lipoprotein cholesterol, albumin, and von Willebrand factor were measured in a central lab using standardized methods.

Pre-existing heart failure at baseline was defined as: (1) an affirmative response to "Were any of the medications you took during the last 2 weeks for heart failure?" or (2) Stage 3 or "manifest heart failure" by Gothenburg criteria.[16] History of coronary heart disease (CHD) at baseline was defined by self-reported prior physician diagnosis of myocardial infarction (MI) or coronary revascularization, or by ECG evidence of a prior MI. Atrial fibrillation (Minnesota code: 8-3-1) and flutter (8-3-2) were also determined from the baseline ECG. Participants were asked to bring current medications to their examination, and use of specific agents was identified. Medications considered in the current analysis include antihypertensive, antiarrhythmic (including all types), anti-Parkinson and selected psychotropic agents (benzodiazepine and tricyclic agents).

Statistical analysis

Crude incidence rates of ischemic stroke subtypes were calculated and expressed as rates per 1,000 person-years. The association between orthostatic BP change categories and incidence of stroke subtypes was evaluated using an age, sex, race-center and education-adjusted Cox proportional hazard regression model (minimum model). A multivariate model included variables in the minimal model plus baseline sitting SBP, antihypertensive medication use, and diabetes (model 1). Antihypertensive medications were also grouped by class of drugs (diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers). An additional model adjusted for baseline covariates including smoking status, usual ethanol intake, leisure time sport index score, resting heart rate, waist circumference, high-density lipoprotein cholesterol, albumin, von Willebrand factor, cardiovascular disease-related comorbidities (histories of CHD or heart failure, atrial fibrillation), and use of selected medications (antiarrhythmic, anti-Parkinson, and psychotropic drugs) (model 2). If the final model still showed a significant association of orthostatic BP change with stroke subtype incidence, further adjustment was attempted for intima-media thickness and ankle-brachial index to evaluate their mediation effects in the available sample. The proportion hazards assumption was assessed by examining the parallelness of the ln (-ln) survival curves for the groups defined by exposure variables.

Tests for linear and quadratic relations of stroke subtype risk with orthostatic BP change were examined using continuous orthostatic BP variables. In addition, restricted cubic spline analyses were performed to qualitatively evaluate any non-linear relationship between orthostatic SBP changes and total stroke, total ischemic stroke, and ischemic stroke subtype incidence adjusted for age, sex, race-center, sitting SBP, antihypertensive medication use, and diabetes. Spline analyses were carried out using a truncated sample at the 1st (−30.3 mmHg) and 99th percentile (24.4 mmHg) of orthostatic SBP change since extreme values could be over-influential. Only results using SBP are presented since spline analyses using orthostatic DBP changes were essentially the same.

Additional analyses excluded those with baseline CHD, heart failure, and those on antihypertensive and other medications associated with orthostatic hypotension. Since orthostatic BP change was associated with incident hypertension incidence in ARIC,[5] we

also included blood pressure or antihypertensive medication use at the three subsequent ARIC examinations as time-varying covariates in an additional analysis. All the statistical analyses were performed with SAS 9.2, and a p value <0.05 was considered as statistically significant.

Results

Baseline characteristics

At baseline, the cohort was 45% men, 74% white, and had a mean age of 54.1 years. On average, SBP decreased −0.4 mmHg (standard deviation: SD, 10.7 mmHg) and DBP increased 3.0 mmHg (SD: 5.7 mmHg) after rising from supine to standing.

Table 1 presents age, sex, and race-center adjusted baseline characteristics by category of orthostatic SBP change. Individuals whose SBP remained stable (within 10 mmHg change) were, on average, four years younger (53.6 y) than those experienced 20 mmHg or more decline (57.6 y). Sitting SBP and DBP were higher in subjects whose SBP declined or increased after rising, compared with those whose SBP remained stable. A similar U-shaped pattern across SBP change categories was observed for the prevalence of diabetes and antihypertensive medication use, although the latter was particularly high (50.0%) among individuals whose orthostatic SBP decline was 20 mmHg or more. Sitting DBP was highest in subjects whose DBP increased after postural change (online supplementary Table S1, please see http://hyper.ahajournals.org). In contrast to the U-shaped pattern observed with orthostatic SBP change categories, an older mean age and an increased prevalence of diabetes were limited to those with orthostatic decreases in DBP.

Spline analyses

During a median follow-up of 18.7 years (max, 20.6 years), 782 strokes occurred. Of 782 total strokes, 680 were ischemic (153 lacunar, 383 nonlacunar thrombotic, and 144 cardioembolic strokes). In multivariable adjusted spline analyses, orthostatic SBP decline was associated with an increased incidence of total, ischemic, nonlacunar thrombotic and cardioembolic strokes (Figure 1a, 1b, 1d, 1e) but not with lacunar strokes (Figure 1c).

Categorical analyses

In minimally-adjusted models, an orthostatic SBP decline of 20 mmHg or more was associated with an increased incidence of lacunar, nonlacunar, and cardioembolic strokes (Table 2). In fully adjusted models, this association persisted and remained significant for nonlacunar thrombotic strokes (hazard ratio: HR, 2.02; 95% confidence interval: CI, 1.43–2.84) and for cardioembolic strokes (HR 1.85, 95% CI: 1.01–3.39). The association remained statistically significant after further adjustment for ankle-brachial index and intima-media thickness (HR: 1.75, 95% CI: 1.21–2.54) for nonlacunar thrombotic stroke but not for cardioembolic stroke (HR: 1.46, 95% CI: 0.74–2.88). In contrast, an orthostatic SBP increase of 20 mmHg or more was only associated with an increased incidence of lacunar stroke (HR in minimally-adjusted model: 2.11, 95% CI: 1.05–4.20). In the fully adjusted model, this association was attenuated and no longer statistically significant (HR 1.82, 95% CI: 0.91–3.63), although the quadratic association between continuous orthostatic SBP change and lacunar stroke incidence remained significant (quadratic p=0.004 in model 2). Similar associations were observed when subtypes of antihypertensive medication were adjusted (data not shown).

The associations between orthostatic DBP change categories and ischemic stroke subtype incidence were generally similar to those for SBP change categories, although a quadratic

association with lacunar stroke incidence was not observed (online supplementary Table S2, please see http://hyper.ahajournals.org).

Consensus OH (SBP decrease of 20 mmHg or more, or DBP decrease of 10 mmHg or more) was also associated positively with incidence of all ischemic stroke subtypes in the minimally-adjusted model (HR ranging from 2.07 to 2.53), and a significant association remained for nonlacunar thrombotic stroke after controlling for potential confounding variables (model 2 HR: 1.97, 95% CI: 1.43–2.72) but not for cardioembolic (model 2 HR: 1.67, 95% CI: 0.94–2.95) or lacunar stroke (model 2 HR: 1.43, 95% CI: 0.78–2.63) (data not shown in table).

Subanalysis

Excluding individuals with baseline CHD, heart failure, and those on antihypertensive and other medications potentially associated with orthostatic blood pressure dysfunction did not change the significant association for nonlacunar thrombotic stroke (model 1 HR for a category with SBP decrease of 20 mmHg or more: 2.28, 95% CI: 1.30–3.99, p=0.004) or the borderline significant association for cardioembolic strokes (HR: 2.42, 95% CI: 0.85–6.90, p=0.099). Analyses using time-varying SBP and antihypertensive medication use did not substantially change the association of orthostatic BP change with each ischemic stroke subtype. Specifically, orthostatic SBP decrease (≤−20mmHg) was statistically significantly and positively associated with all ischemic stroke subtypes (model 1 HR: ranging from 1.91 to 2.36). Orthostatic SBP increase (≥20mmHg) appeared to be associated with increased risk of lacunar stroke only (model 1 HR: 1.88, 95% CI: 0.94–3.75, p=0.075).

Discussion

In this prospective, population-based study, orthostatic SBP and DBP decreases were associated with increased incidence of thrombotic and cardioembolic strokes in a linear fashion. In contrast, both orthostatic SBP decreases and increases were associated with increased incidence of lacunar strokes. Although this is the first prospective study examining these relations, the latter finding is consistent with previous studies that showed U-shaped associations of orthostatic BP change with the prevalence of silent cerebral infarctions[6] or a history of stroke[17] in a population where lacunar stroke is predominant. Although speculative, one possible link between orthostatic BP elevation and lacunar stroke could be endothelial dysfunction. Involvement of endothelial dysfunction has been suggested in the pathogenesis of lacunar stroke already.[18, 19] On the other hand, orthostatic BP elevation could occur as a result of excessive sympathetic activation,[20] which would be manifested in the presence of endothelial dysfunction.[21, 22] Another explanation might be extreme BP dipping during sleep, since nocturnal BP dipping is linked to orthostatic BP elevation[23] and also to lacunar strokes.[24]

There are plausible mechanisms to support the observation that orthostatic decreases in BP were associated with increased incidence of nonlacunar thrombotic and cardioembolic stroke. Standing induces venous pooling and prolonged (30 minutes) standing has been associated with higher coagulability in healthy volunteers due to body fluid shifts.[25] Individuals with enhanced orthostatic BP decline may have impaired control of venous capacitance chronically or on standing, which potentially predisposes them to hypercoagulability. We took account of von Willebrand factor level obtained while the participants were seated in model 2; nevertheless, other factors related to coagulation/fibrinolysis or change in the coagulability upon standing might explain the association. Another possible mechanism is a systemic BP drop directly leading to the occurrence of nonlacunar thrombotic and cardioembolic stroke. Cerebral blood flow and systemic BP are positively associated,[26] and its autoregulation is impaired in patients who have orthostatic

tachycardia during an orthostatic challenge.[27] Moreover, postural change has been identified as the most important trigger of ischemic stroke out of seven predefined emotional, behavioral or environmental stimuli.[28] Alternatively, reduced perfusion related to orthostatic blood pressure decrease might limit the ability of the bloodstream to wash out emboli and microemboli and reduces available blood flow to regions rendered ischemic by emboli that block supply arteries.[29] Another possibility is that autonomic dysfunction—potentially manifested as orthostatic hypotension—might have led to subsequent development of atrial fibrillation, which is a major risk factor for ischemic stroke.[30]

Although residual confounding by the severity of blood pressure is possible, the associations were independent of carefully-assessed resting SBP, and antihypertensive medication use. Incorporating time-varying SBP and medication use, or analyses including a number of other potential confounding or mediating factors did not materially alter the association. Furthermore, the supplementary analysis confirmed an independent association in apparently very healthy individuals with no history of CHD, heart failure, hypertension, or other condition or medication use that may cause orthostatic BP variations.[31] Thus, documented orthostatic BP decrease or increase, per se, preceded occurrences of nonlacunar ischemic or lacunar stroke, respectively.

Strengths of this study include its prospective design, large population-based sample, standardized BP measurement protocols, standardized assessment of stroke and its subtypes, and control for a large number of potential confounders. There are several limitations. First, it is possible that other conditions/medications or residual confounding that could explain the observed associations. Further population-based cohort analyses classifying participants who sustain a stroke according to the time and posture at onset of stroke, or prospective studies of treated hypertensive patients with detailed information on orthostatic BP changes, diurnal BP patterns, and antihypertensive medication and stroke subtypes use, would also be warranted. Second, not all stroke cases had a brain MRI. For such cases, there may be misclassification of the regions and subtypes assigned. Third, although we excluded the first BP reading after standing, the possibility remains that some participants were still hemodynamically unstable when their standing BPs were recorded. Finally, the number of cases for each ischemic stroke subtype was relatively small. In conclusion, the current study confirmed a previously reported association of orthostatic hypotension with total and ischemic stroke incidence. It also found that nonlacunar ischemic stroke incidence was associated with an orthostatic decrease of systolic and diastolic BP, whereas lacunar stroke incidence was possibly associated with both orthostatic increases and decreases in SBP. Clinical trials are needed to examine whether evaluation and control of orthostatic BP changes, especially in hypertensive subjects, may improve stroke prevention.

Perspectives

One clinical implication of the present findings is the potential usefulness of identifying and controlling orthostatic BP increase as well as decrease. However, it is possible that orthostatic BP change is a marker for other known or unknown conditions such as autonomic dysfunction or other underlying comorbidities, and measures for controlling orthostatic BP change are not well established. Further studies regarding the determinants of orthostatic BP change and clinical trials of the efficacy of its treatment with regards to stroke incidence are warranted. One possible measure to be tested is the use of compression garments.[25, 32] A second implication arises from the observation that about half of subjects who experienced a 20 mmHg or more SBP decline were taking antihypertensive medications. However, individuals who used antihypertensive medication and experienced this SBP decline had higher sitting SBP than users who did not experience such decline (133.2 mmHg vs. 126.0 $p<0.001$ after adjustment for age, sex and race-center); the finding

should reinforce recommendations that treated hypertensive patients deserve careful assessment and control of orthostatic BP decrease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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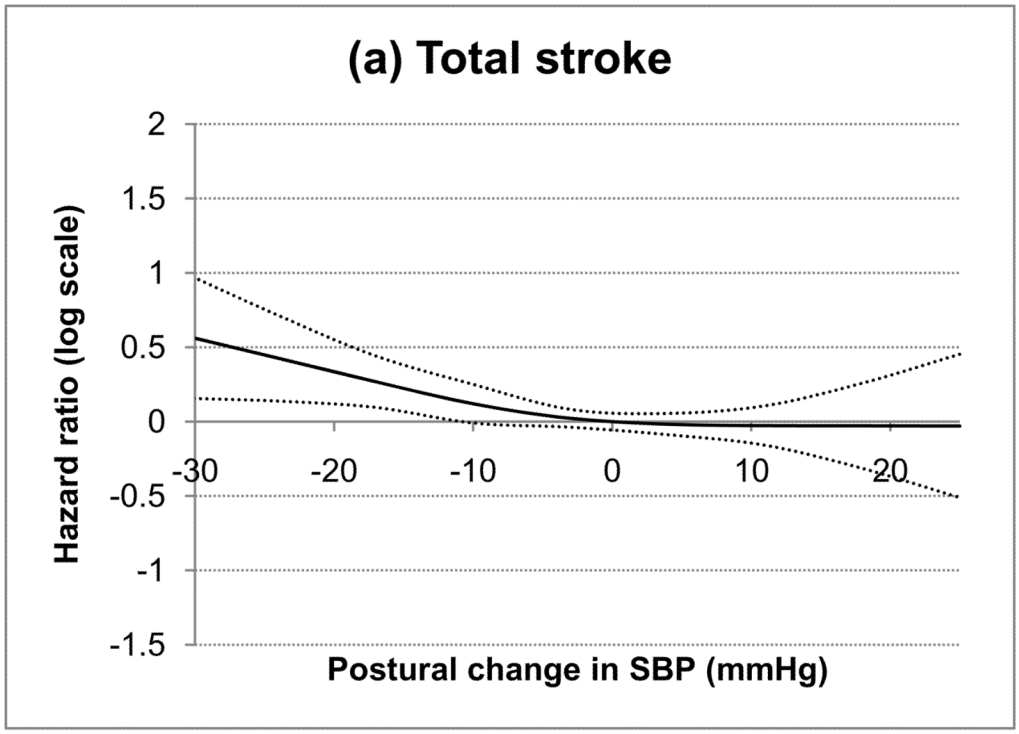

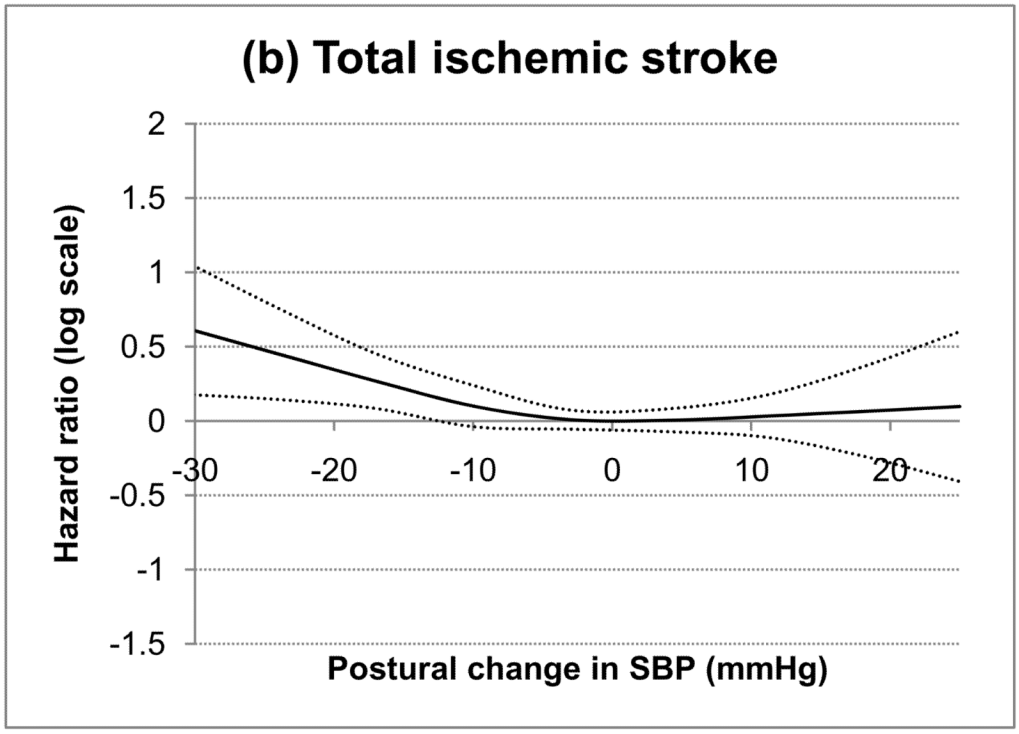

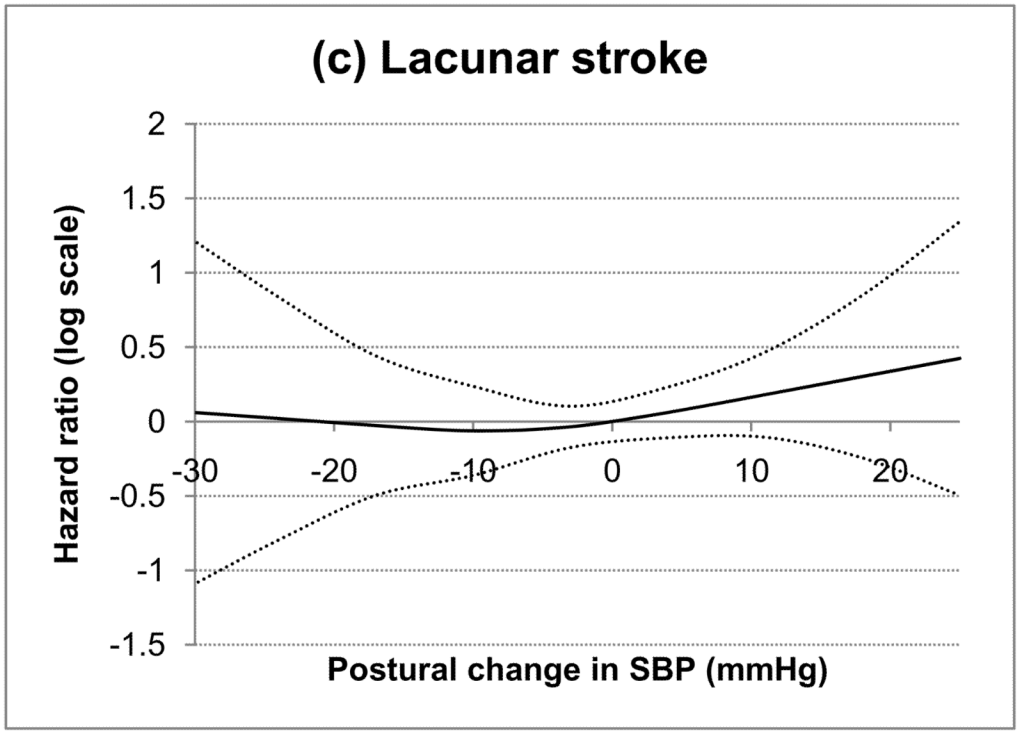

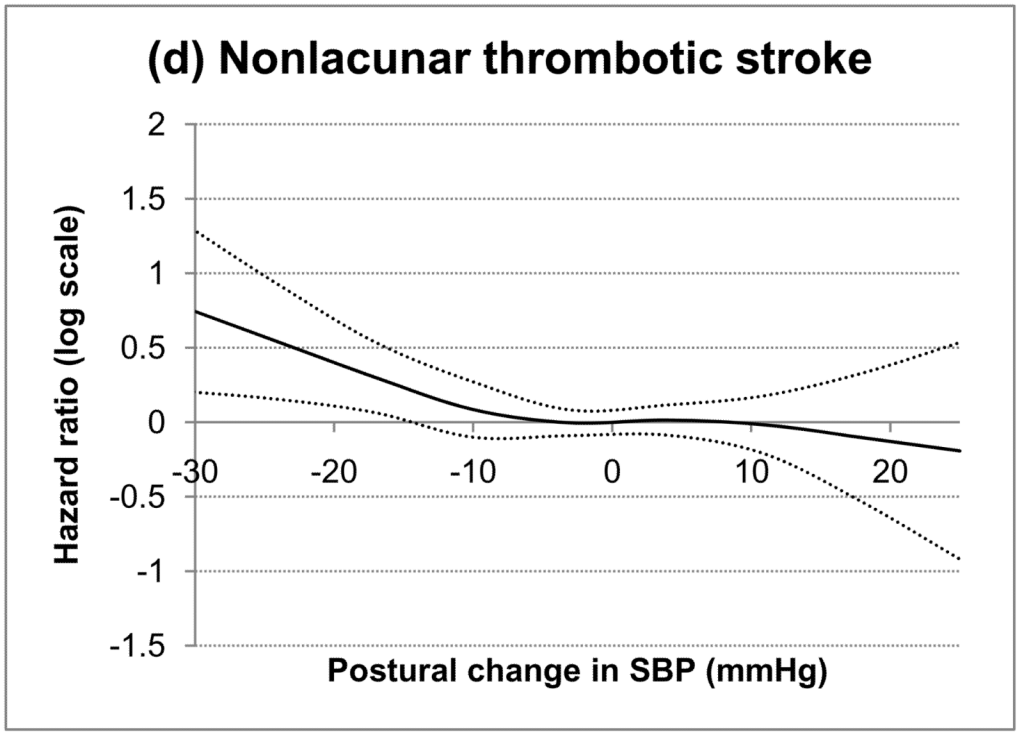

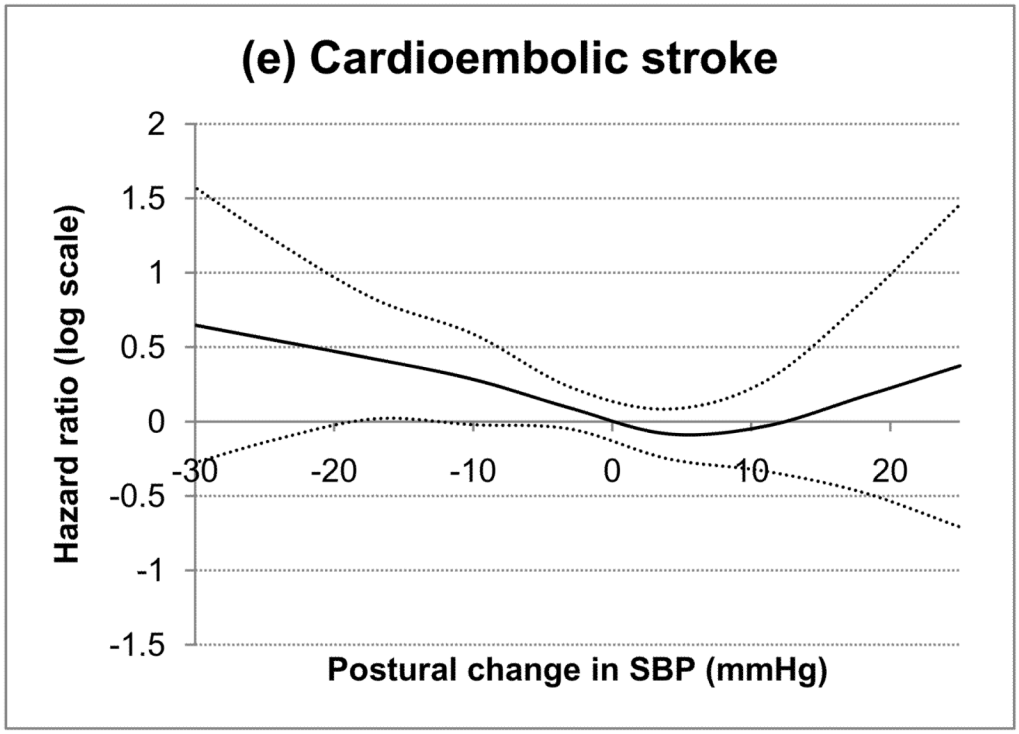

Figure 1.

Hazard ratio of total stroke (panel a), ischemic stroke (b), and lacunar (c), nonlacunar thrombotic (d) and cardioembolic stroke (e) in relation to postural change in systolic blood pressure by cubic spline regression analysis, ARIC, 1987–2007

The solid line represents the hazard ratio; dotted line, 95% confidence intervals. The reference values were set at 0 mmHg. The hazard ratios (HRs) were adjusted for age, sex, race-center, education, sitting systolic blood pressure, antihypertensive medication use, and diabetes. The sample for the spline analysis was truncated at the 1st and 99th percentile of postural SBP change.

Table 1

Age-, sex-, and race-center-adjusted baseline characteristics according to categories of orthostatic SBP changes, ARIC, 1987–89

Characteristics	Orthostatic systolic blood pressure change categories					p†
	Decline		Stable	Increase		
Range (mmHg)	−63≤ ≤−20	−20< ≤−10	−10< ≤10	10< ≤20	20< ≤65	
Number of subjects	547	1,507	8,981	1,479	303	
Age (y)*	57.6	55.5	53.6	53.9	55.1	<.0001
Men (%)*	43.0	45.6	45.3	44.2	32.7	0.0005
Black (%)*	34.0	25.2	23.4	35.3	44.2	<.0001
High school graduate or less (%)	39.8	41.7	45.8	44.1	40.1	0.0009
Systolic blood pressure (mmHg)	128.9	124.1	120.4	124.1	128.1	<.0001
Diastolic blood pressure (mmHg)	75.8	75.0	73.0	74.2	75.8	0.0003
Antihypertensive medication (%)	50.0	36.0	30.0	30.1	35.0	<.0001
Diabetes mellitus (%)	20.2	14.3	11.8	13.2	19.9	<.0001
Resting heart rate (/minute)	69.6	68.4	67.3	67.7	68.1	0.38
Waist circumference (cm)	97.7	97.4	96.7	98.7	104.0	<.0001
High density lipoprotein cholesterol (mg/dl)	51.0	51.4	52.1	51.2	50.6	0.14
von Willebrand Factor (%)	130.5	121.7	118.9	117.6	120.6	<.0001
Albumin (g/dl)	3.80	3.85	3.84	3.84	3.81	<.0001
Heart failure (%)	15.8	12.6	17.2	17.2	21.1	0.62
Coronary heart disease (%)	15.5	18.1	21.0	18.6	20.4	0.78
Anti-Parkinson or psychotropic medication (%)	12.2	7.0	7.0	6.6	5.2	0.0001
Atrial fibrillation (%)	0.3	0.4	0.1	0.2	0.3	0.11
Antiarrhythmic medication (%)	1.7	0.9	0.8	0.5	0.3	0.06
Current smoker (%)	35.4	30.2	28.2	27.7	24.3	0.0006
Usual ethanol intake (g/week)	49.5	42.7	41.2	42.0	44.7	<.0001
Leisure time sports index (>=3) (%)	26.2	27.3	28.7	26.5	23.9	0.11

SBP denotes systolic blood pressure.

*Crude

†Age-, sex-, race-center-adjusted means and proportions, and p-values were calculated by a general linear model.

Table 2

Incidence rate and hazard ratios (95% confidence intervals) of ischemic stroke subtypes in relation to orthostatic systolic blood pressure change categories, ARIC, 1987–2007

Ischemic stroke subtypes	Orthostatic systolic blood pressure change categories					linear p	quadratic p
	Decline		Stable	Increase			
Range (mmHg)	−63≤ ≤−20	−20< ≤−10	−10< ≤10	10< ≤20	20< ≤65		
Person-years	7,512	24,713	154,231	25,432	4,954		
Lacunar							
n of cases/incidence rate*	12/1.6	16/0.6	91/0.6	25/1.0	9/1.8		
Minimal†	2.28 (1.24–4.20)	1.03 (0.61–1.76)	1	1.32 (0.84–2.05)	2.11 (1.05–4.20)	0.63	0.0001
Model 1‡	1.84 (1.00–3.40)	0.96 (0.56–1.64)	1	1.18 (0.75–1.84)	1.82 (0.91–3.63)	0.70	0.003
Model 2§	1.52 (0.79–2.92)	0.94 (0.55–1.61)	1	1.19 (0.76–1.89)	1.73 (0.82–3.65)	0.86	0.004
Non-lacunar thrombotic							
n of cases/incidence rate*	42/5.6	50/2.0	241/1.6	41/1.6	9/1.8		
Minimal†	2.61 (1.87–3.64)	1.12 (0.82–1.52)	1	0.93 (0.67–1.30)	0.97 (0.50–1.89)	0.001	NA
Model 1‡	2.15 (1.53–3.01)	1.03 (0.76–1.40)	1	0.86 (0.62–1.20)	0.83 (0.43–1.63)	0.003	NA
Model 2§	2.02 (1.43–2.84)	1.05 (0.77–1.43)	1	0.84 (0.60–1.19)	0.64 (0.30–1.36)	0.003	NA
Cardioembolic							
n of cases/incidence rate*	13/1.7	22/0.9	87/0.6	17/0.7	5/1.0		
Minimal†	2.27 (1.26–4.11)	1.32 (0.82–2.11)	1	1.01 (0.60–1.70)	1.31 (0.53–3.24)	0.028	0.033
Model 1‡	1.96 (1.08–3.56)	1.26 (0.79–2.02)	1	0.98 (0.58–1.66)	1.22 (0.49–3.02)	0.073	0.15
Model 2§	1.85 (1.01–3.39)	1.23 (0.76–1.97)	1	0.96 (0.56–1.64)	1.10 (0.44–2.77)	0.11	0.24

NA indicates not applicable.

*Per 1,000 person-years.

†Minimal model adjusted for age, sex, race-center and education.

‡Model 1 included variables in minimal model and systolic blood pressure, antihypertensive medication use, and diabetes.

§Model 2 included variables in Model 1 and smoking status (current, past, never), usual ethanol intake, physical activity, resting heart rate, waist circumference, high-density lipoprotein cholesterol, albumin, von Willebrand factor, coronary heart disease, heart failure, atrial fibrillation, and antiarrhythmic, psychotropic and anti-Parkinson medication use (n=12,530).