Orthostatic Hypotension as a Risk Factor for Stroke
The Atherosclerosis Risk in Communities (ARIC) Study, 1987–1996

Marsha L. Eigenbrodt, MD; Kathryn M. Rose, PhD; David J. Couper, PhD; Donna K. Arnett, PhD; Robert Smith, MD; Daniel Jones, MD

Background and Purpose—The association between orthostatic hypotension (OH) and stroke has rarely been investigated in longitudinal studies. The purpose of the present study was to determine whether OH predicts ischemic stroke in a middle-aged, biethnic population after adjustment for known stroke risk factors. Diastolic, systolic, and consensus OH were evaluated for baseline associations and for the ability to predict stroke.

Methods—In 11 707 persons from the Atherosclerosis Risk in Communities (ARIC) cohort who were free of stroke and overt heart disease at baseline, Cox proportional hazards analyses modeled the association between OH at baseline and incident ischemic stroke over 7.9 years of follow-up. OH was defined as a systolic blood pressure drop ≥20 mm Hg (systolic OH), a diastolic blood pressure drop ≥10 mm Hg (diastolic OH), or a drop in either (consensus OH) when a person changed from a supine to standing position.

Results—OH was predictive of ischemic stroke, even after adjustment for numerous stroke risk factors (consensus OH: hazard ratio, 2.0; 95% CI, 1.2 to 3.2). While the baseline characteristics associated with OH varied depending on the type of OH, all types of OH had a similar risk of stroke.

Conclusions—OH is an easily obtained measurement that may help to identify middle-aged persons at risk for stroke. **(*Stroke*. 2000;31:2307-2313.)**

Key Words: cerebral infarction ■ epidemiology ■ hypotension, orthostatic ■ prospective studies

Stroke contributes significantly to morbidity and mortality in industrialized countries.[1–4] The decline in stroke mortality in several countries in the mid 1900s, attributed by many to the better control of blood pressure (BP) or other risk factors,[4,5] suggests that stroke is largely a preventable disease.[5,6] Identifying modifiable risk factors is therefore important, and clinical studies have suggested that orthostatic hypotension (OH) could be such a risk factor.[7–11]

However, while numerous studies have documented the effects of BP and hypertension[12–16] and use of antihypertensive medication[17–20] on stroke, few epidemiological studies have evaluated OH as a risk factor for stroke.[11] In cross-sectional studies, postural hypotension was associated with cerebrovascular disease, neurological symptoms, and/or transient ischemic attacks.[9,21,22] One cross-sectional study that evaluated 3 definitions of OH suggested that each type of OH identifies a population subgroup characterized by different sets of risk factors.[23] Longitudinal studies evaluating OH and cardiovascular disease[24,25] or mortality[26–29] include the Honolulu Heart Study, in which both systolic and diastolic OH were predictive of all-cause mortality,[28] and a Finnish study in which only diastolic OH was associated with increased vascular mortality.[29] OH is not even listed as a potential risk factor for stroke in several reviews,[3,4,6] and most prospective investigations of stroke have not evaluated OH as a risk factor.[15,16,30–32] Only 1 large longitudinal study, the Cardiovascular Health Study (CHS), was identified that included OH as a potential risk factor for stroke. In that study of persons aged 65 years and older, neurological symptoms, but not OH, were significantly associated with an increase in stroke incidence.[14] Thus, whether OH is a significant predictor of stroke is unclear from the literature.

To our knowledge, the present study is the first prospective, population-based study of a middle-aged population to evaluate the association of OH and ischemic stroke. The study evaluates characteristics associated with types of OH and whether OH is a risk factor for incident ischemic stroke in a population without overt heart disease. While the main focus is on consensus OH, this study also evaluates whether a fall in systolic or diastolic BP conveys greater risk of stroke.

Subjects and Methods

The Atherosclerosis Risk in Communities (ARIC) Study is a prospective investigation of atherosclerosis in a population-based cohort of 15 792 participants from 4 communities: Jackson, Missi-

Received May 23, 2000; final revision received July 5, 2000; accepted July 5, 2000.

From the Departments of Epidemiology (M.L.E., K.M.R.) and Biostatistics (D.J.C.), School of Public Health, University of North Carolina, Chapel Hill; Division of Epidemiology, School of Public Health, University of Minnesota, Minneapolis (D.K.A.); Mississippi Family Health Center, Jackson (R.S.); and Division of Hypertension, University of Mississippi Medical Center, Jackson (D.J.).

Reprint requests to Marsha L. Eigenbrodt, MD, Department of Epidemiology, Cardiovascular Disease Program, 137 E Franklin St, Bank of America Center, Suite 306, University of North Carolina at Chapel Hill, Chapel Hill, NC 27514. E-mail meigenbr@sph.unc.edu

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sippi; Forsyth County, North Carolina; suburban Minneapolis, Minnesota; and Washington County, Maryland.[33] All Jackson participants were black; 14% of Forsyth County participants were black; and Washington County and Minneapolis participants were almost exclusively white. Institutional review committees at the ARIC Study centers approved the study, and informed consent was obtained from all participants. The study includes annual telephone interviews, triennial clinical examinations, and ongoing community surveillance.

Main Exposure

At the first clinical examination, BP measurements for calculating postural change were taken with a Dinamap 1846 SX oscillometric device. BP was measured at 30-second intervals for 2 minutes in both the supine (after 20 minutes of rest in the supine position) and standing (beginning as the participant's feet touched the floor) positions. Postural change in BP was calculated as the difference between the average supine and standing BPs (excluding the first standing measurement to make the ARIC postural change measurement similar to measurements used in other studies).[34] Three types of OH were evaluated: systolic OH (a systolic postural drop ≥20 mm Hg irrespective of the diastolic change), diastolic OH (a diastolic postural drop ≥10 mm Hg irrespective of the systolic change), and consensus OH (≥20 mm Hg systolic or ≥10 mm Hg diastolic postural BP drop).[35]

Other Variables

Pulse pressure, mean arterial pressure, and ankle brachial index (ABI) were determined and evaluated as covariates. Brachial and ankle BP measurement procedures have been previously described.[36] The average brachial BP was used to define pulse pressure (the difference between the systolic and diastolic BPs) and mean arterial pressure (the average diastolic BP plus one third of the pulse pressure). ABI was calculated as the average systolic ankle pressure divided by the average of the first 2 brachial systolic BPs.

Baseline history of physician-diagnosed stroke, highest level of education (<high school, high school graduate, >high school), current smoking status (yes/no), current drinking status (yes/no), and level of alcohol consumption in grams per week (calculated from the usual number of drinks/glasses of beer, wine, and hard liquor consumed per week) were based on self-report. Prevalent myocardial infarction or coronary heart disease was defined as a history at baseline of physician diagnosis of a myocardial infarction, evidence of myocardial infarction from the examination ECG, or history of heart or arterial surgery, coronary artery bypass surgery, or balloon angioplasty. Use of medication for hypertension, congestive heart failure, arrhythmias, or diabetes was based on the self-report of medication use in the past 2 weeks for "high BP," "heart failure," "control of heart rhythm," or "diabetes or high blood sugar," respectively. Additionally, medications that were brought to the clinic were recorded and later categorized. For this study, specific antihypertensive medication types (diuretics, β-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, and other antihypertensive medications) were included in some models.

Eight-hour fasting blood was drawn from the vein in the antecubital fossa and processed by a standardized protocol.[33] White blood cell counts (WBCs) were determined by Coulter counters. Diabetes was defined as a nonfasting glucose ≥200 mg/dL (hexokinase method), fasting glucose ≥126 mg/dL, self-report of a history of diabetes, or use of diabetes medication in the prior 2 weeks.[37] Fibrinogen was measured by the thrombin-time titration method, and von Willebrand factor antigen was assayed by ELISA.[38] Total cholesterol and HDL cholesterol were measured by an enzymatic method. HDL was measured after precipitation of non-HDL lipoproteins, and LDL cholesterol was calculated.[39] Body mass index (BMI) was calculated as the measured weight/height^2 (kg/m^2). Carotid artery intima-media thickness (IMT) was the average of 6 far-wall B-mode ultrasound measurements with imputed estimates used for missing values.[40,41] A sport index, ranging from 1 (low) to 5 (high), characterized physical activity.[42] Left ventricular hypertrophy (LVH) was determined by Cornell voltage criteria for the resting ECG.[43]

Ascertainment of Incident Ischemic Stroke Events

This report is based on validated clinical events that were identified through annual self-report or through ongoing community surveillance. Hospital and autopsy records were used to classify and validate strokes on the basis of the occurrence and duration of neurological signs and symptoms, neuroimaging results, and other diagnostic procedures and treatments, as previously described.[2] In this study, only events classified as definite or probable ischemic (thrombotic and cardioembolic) strokes were included. Events lasting <24 hours and events secondary to trauma, neoplasm, hematologic abnormality, infection, or vasculitis were not considered strokes. Among hospitalized persons with neurological symptoms lasting ≥24 hours, 61% of the events were validated as definite or probable strokes in a recent ARIC study.[2] Follow-up time was the time between baseline and the first of the following events: ischemic stroke, death, last contact, or December 31, 1996.

Statistical Methods

Exclusions from the present study included ethnicity other than white or black, blacks from Minneapolis and Washington County (n=103), age younger than 45 or older than 64 years at baseline (n=158), missing brachial BP (n=14), positive or unknown history of physician-diagnosed stroke at baseline (n=319), missing follow-up time (n=1), positive or unknown history of myocardial infarction or coronary heart disease at baseline (n=1007), atrial fibrillation/flutter on ECG at baseline (n=22), use of medication for congestive heart failure or arrhythmias at baseline (n=400), and missing BP measurements that precluded the calculation of postural BP change (n=2061, of whom 1502 underwent their baseline examination before initiation of the postural change evaluation). Thus, 11 707 participants were included in the study.

Characteristics were determined for participants with and without OH at baseline. Distributions of antihypertensive medication and antidiabetic medication use by OH status were determined for those with hypertension and diabetes, respectively. We used t tests, adjusted for unequal variances, and χ^2 tests to test for significant differences in baseline characteristics by OH status. To assess the association between OH and incident ischemic strokes, Cox proportional hazard models were evaluated after assessment of the proportional hazard assumption for OH and each covariate. The ln (−ln) survivor curves were assessed for categorical variables and quartiles of continuous variables. When curves were not roughly parallel, further evaluation was performed by including an interaction term of the covariate with time, which was evaluated for significance ($P<0.05$) and for whether inclusion resulted in a change of ≥20% of the hazard ratio for the main effect. When these criteria were used, no significant departure from the proportional hazard assumption was found. Consensus OH was tested for an association with stroke in several models. Unadjusted analysis was followed by a model including sociodemographic factors (age, sex, ethnicity, education, and center). An intermediate model added potential risk factors for OH and stroke (mean arterial pressure, diabetes, hypertension medication use [yes/no]). Other potential risk factors for stroke (current smoking, current drinking, level of alcohol consumption, fibrinogen, HDL, LDL, IMT, sport index, ABI, pulse pressure, LVH, von Willebrand factor, and WBC) were added to the final model. Interaction terms between covariates and the main exposure were tested in nested models and retained at an α of ≤0.05. All sociodemographic covariates were kept in the final model. Other covariates were retained if removing them resulted in a change in the OH hazard ratio of ≥20% or if they reached an α of ≤0.05. Diastolic and systolic OH were evaluated in the unadjusted and final model. The final model evaluating consensus OH was repeated after (1) substitution of specific BP medications for general antihypertensive medication use; (2) addition of diabetic medication use; and (3) stratification by use of medications (antihypertensive and diabetic).

TABLE 1. Distribution and Means of Baseline Characteristics by Systolic and Diastolic OH*

	Systolic OH*		Diastolic OH*	
Characteristic	No (n=11 245)	Yes (n=462)	No (n=11 538)	Yes (n=169)
Age, mean, y	53.7	57.0‖	53.8	56.5‖
Men, %	43.6	42.0	43.4	54.4‖
Black, %	26.5	36.4‖	26.9	29.0
Center, %				
Forsyth County	25.9	27.7‖	25.9	30.2
Jackson	23.6	29.7	23.8	23.7
Minneapolis	26.7	15.6	26.4	18.3
Washington County	23.8	27.1	23.9	27.8
Diabetes, %	10.3	19.0‖	10.4	27.4‖
Hypertension, %	31.1	60.1‖	31.8	58.0‖
Systolic BP, mean, mm Hg	120.4	131.7‖	120.8	127.6‖
Diastolic BP, mean, mm Hg	73.5	76.5‖	73.6	74.9
Mean arterial pressure, mean, mm Hg	89.2	94.9‖	89.3	92.5‖
Pulse pressure, mean, mm Hg	46.9	55.2‖	47.2	52.6‖
Current smoker, %	25.4	33.4‖	25.7	30.2
Current drinker, %	57.9	43.9‖	57.5	48.8
Alcohol, mean, g/wk†	74.2	102.2	74.7	103.3
IMT, mean, mm	0.73	0.83‖	0.73	0.87‖
ABI, mean	1.15	1.09‖	1.14	1.13
Educational level, %				
<High school	21.1	39.6‖	21.6	34.3‖
High school	41.2	35.4	41.1	32.5
>High school	37.3	25.0	37.3	33.1
Antihypertensive medication, %‡	70.2	76.5	70.6	72.5
Diabetic medication, %§	41.7	64.4‖	42.4	67.4‖
Physical activity index, mean	2.45	2.38	2.45	2.37
Fibrinogen, mean, mg/dL	299.3	327.1‖	300.0	326.0‖
von Willebrand factor, % of standard	115.3	133.3‖	115.6	139.4‖
HDL, mean, mmol/L	1.35	1.34	1.35	1.23‖
LDL, mean, mmol/L	3.52	3.77‖	3.52	3.73‖
WBC, mean, leukocyte count 1000/mm^3	6.1	6.4‖	6.1	6.5‖
BMI, mean, kg/m^2	27.6	27.6	27.6	29.1‖
LVH, %	1.6	6.1‖	1.8	1.8

*For systolic OH, Yes=systolic pressure drop ≥20 mm Hg; No=systolic pressure drop <20 mm Hg. For diastolic OH, Yes=diastolic pressure drop ≥10 mm Hg; No=diastolic pressure drop <10 mm Hg.

†Mean consumption among current drinkers.

‡Medication use among hypertensives.

§Medication use among diabetics.

‖$P \leq 0.01$.

Results

Baseline Associations

At baseline, 462 participants (3.9%) had systolic OH, 169 (1.4%) had diastolic OH (Table 1), 533 (4.6%) had consensus OH, and 98 had both systolic and diastolic OH. The baseline characteristics are presented only for systolic and diastolic OH since the associations for consensus OH were essentially identical to the associations for systolic OH. For many cardiovascular risk factors, the prevalence or means were significantly higher in participants with systolic or diastolic OH than in those without OH (Table 1). Participants with OH were significantly ($P<0.01$) older, were less educated, were more likely to have diabetes and hypertension, and reported drinking less frequently, and diabetics with OH were on medication more often than diabetics without OH. Measures

TABLE 2. Unadjusted Incidence of Ischemic Stroke and Mean Follow-Up Time Until Stroke Occurrence by OH Status for 3 Types of OH*

	n	Incident Ischemic Stroke, No. (%)	Follow-Up Time to Stroke, Mean, y	P†
Consensus OH				
Absent	11 174	151 (1.4)	5.12	
Present	533	27 (5.1)‡	4.77	0.46
Systolic OH				
Absent	11 245	152 (1.4)	5.12	
Present	462	26 (5.6)‡	4.75	0.44
Diastolic OH				
Absent	11 538	169 (1.5)	5.09	
Present	169	9 (5.3)‡	4.61	0.54

*Systolic pressure drop ≥20 mm Hg (systolic OH), diastolic pressure drop ≥10 mm Hg (diastolic OH), or either (consensus OH).

†*P* value for *t* test for difference by OH status.

‡$P \leq 0.001$ for difference in incidence by OH status.

of mean arterial pressure, pulse pressure, systolic pressure, IMT, fibrinogen, von Willebrand factor, LDL, and WBC were higher for persons with than for persons without OH. In comparison to participants without OH, participants with diastolic OH had a significantly higher BMI and lower HDL and were more likely to be male, while these same characteristics did not vary significantly by systolic OH status. In contrast, there were significantly more blacks, more current smokers, and more persons with LVH, higher diastolic BP, and lower ABI among those with systolic OH compared with persons without OH, but these characteristics did not vary significantly by diastolic OH status.

Longitudinal Results

Within the study population, there were 178 incident ischemic strokes (1.5%) over 7.9 years of follow-up. The incidence of ischemic strokes was significantly higher among those with OH relative to those without OH regardless of the type of OH (Table 2). Among persons with stroke, follow-up time was slightly less for those with OH than for those without OH, but the values did not vary significantly. In the unadjusted model, the hazard of stroke for participants with OH was 4 times that of participants who did not have OH (Table 3). The hazard ratio was attenuated after we adjusted for sociodemographic factors (age, sex, ethnicity, center, and education) and further attenuated after we controlled for mean arterial pressure, diabetes, and antihypertensive medication use. In the final model, which included additional covariates for current smoking, ABI, IMT, and WBC, OH remained a significant predictor of stroke, with an associated hazard ratio of 2. Systolic and diastolic OH had similar adjusted risks of stroke, with hazard ratios of 2.1 (95% CI,1.3 to 3.4) and 2.2 (95% CI, 1.1 to 4.6), respectively. Specific classes of antihypertensive medications were substituted (and

TABLE 3. Cox Proportional Hazards Regression Models of Association Between Consensus OH and Incident Ischemic Stroke for Participants Free of Prevalent Coronary Heart Disease and Stroke* at Baseline

	Total Population		At Age 45 y	At Age 55 y	At Age 64 y
Consensus OH/Stroke Model	n	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Unadjusted model	11 707	4.2 (2.8–6.3)			
SES model†	11 691	3.1 (2.0–4.7)	7.0 (2.5–20.0)	3.7 (2.4–5.8)	2.1 (1.1–4.1)
Intermediate model‡	11 593	2.5 (1.6–3.8)	4.8 (1.6–14.2)	2.9 (1.8–4.6)	1.8 (0.9–3.6)
Final model					
General hypertensive medication§	10 799	2.0 (1.2–3.2)	6.1 (2.1–18.4)	2.5 (1.5–4.1)	1.1 (0.5–2.4)
Specific BP medication‖	10 726	2.2 (1.3–3.5)	6.4 (2.2–19.0)	2.7 (1.7–4.4)	1.2 (0.6–2.7)
Specific BP and diabetic medication¶	10 675	2.0 (1.2–3.2)	6.2 (2.1–18.5)	2.5 (1.5–4.0)	1.1 (0.5–2.3)
Stratified models#					
By antihypertensive medication					
Yes	2697	2.3 (1.3–4.3)	5.5 (1.4–22.2)	2.7 (1.5–5.1)	1.5 (0.6–3.9)
No	8102	1.4 (0.6–3.3)	5.4 (0.8–37.5)	1.9 (0.8–4.4)	0.7 (0.2–3.1)
By diabetic medication					
Yes	441	2.6 (1.1–6.1)	2.8 (0.3–25.6)	2.6 (1.0–6.7)	2.4 (0.6–10.0)
No	10 322	1.6 (0.9–2.8)	7.6 (2.1–27.4)	2.1 (1.2–3.8)	0.7 (0.2–1.8)

*Participants without baseline history of stroke, prevalent myocardial infarction or coronary heart disease, with no atrial fibrillation or flutter, and no reported use of medication for either congestive heart failure or arrhythmias at baseline.

†Covariates include age at exam 1, ethnicity, sex, center, and educational level.

‡Additional covariates include mean arterial pressure, general antihypertensive medication use (yes/no), and diabetes status.

§Additional covariates include ABI, IMT, current smoking status, and WBC. $P < 0.05$ for interaction term between consensus OH and continuous age.

‖Specific medication use (yes/no) of β-blockers, diuretics, angiotensin-converting enzyme inhibitor, calcium channel blocker, or other.

¶Adds use of diabetic medication (yes/no).

#Stratified for medication use and adjusted for covariates in the final general model (excluding stratifying variable).

retained regardless of significance) for the covariate "use of any antihypertensive medication" in the final model for consensus OH. The hazard ratio changed little. Addition of a covariate for use of diabetic medication had little effect on the hazard ratio. Age significantly modified the relationship between OH and stroke ($P<0.05$). Therefore, the hazard ratios for 3 ages were estimated by using interaction terms between OH and age as a continuous variable centered at 45, 55, and 64. Age-specific hazard ratios were found to be lower at older ages (Table 3). After stratification for antihypertensive and diabetic medication use, the risk of stroke for persons with OH compared with persons without OH was increased in all medication use strata (hazard ratio >1) but was somewhat stronger overall for those on medication (Table 3).

Discussion

The present study provides evidence that OH is a risk factor for incident stroke in a subset of the middle-aged ARIC population who were free of overt heart disease even after controlling for numerous established stroke risk factors. The risk of stroke was similar for systolic, diastolic, and consensus OH.

Potential Mechanisms or Risk Factors for OH

Normally, the immediate rapid fluctuations in BP that occur within seconds after standing are followed within 30 seconds to 20 minutes by a stabilized BP.[44,45] Fluid shifts and the effects of gravity on standing cause low carotid baroreceptor pressure, resulting in catecholamine release with peripheral vasoconstriction and increased heart rate that normally produces pressure stabilization. Malfunction in one or more of these normal processes has been implicated in OH.[46–49] Since primary dysfunction of the heart, such as heart failure or arrhythmias, may cause OH[46,47,50] and since significant heart disease is strongly associated with stroke,[14,15,31] the present study has eliminated participants with evidence of overt heart disease. A number of other mechanisms have been proposed for OH, and 1 study suggested that different types of OH would identify different sets of risk.[23] Mechanisms for OH other than cardiac dysfunction include autonomic nervous system dysfunction,[46,47,49,51,52] reduced effective intravascular volume, and impaired baroreceptor function.[46,47,49,52] Aging, diabetes, medication, alcoholism, and other neurological diseases have been implicated in autonomic dysfunction and with OH.[47] In the total ARIC population, the decile of largest systolic pressure drop was previously shown to be associated with older age and concomitant disease.[36] The present study also found that both systolic and diastolic OH were associated with increased age, prevalence of diabetes, and medication use among diabetics. Drinkers with systolic or diastolic OH had higher alcohol consumption than those without OH (approximately 3 more drinks per week), but the difference was not statistically significant. Decreased arterial wall compliance in hypertension and arteriosclerosis is thought to contribute to OH by diminishing baroreceptor responsiveness or by allowing pooling of blood in the peripheral vascular system.[29,53] In the present study the presence of higher IMT (a marker of subclinical atherosclerosis) and the presence of hypertension were associated with both systolic and diastolic OH, while low ABI (a marker of lower extremity arterial stenosis) was associated with systolic but not diastolic OH. Other cardiovascular risk factors significantly associated with 1 but not both types of OH included ethnicity, sex, diastolic BP, LVH, smoking status, HDL, and BMI. Many more participants had systolic than diastolic OH. Therefore, the study indicates that the type of OH studied can potentially identify different populations with somewhat different risk factor associations, as suggested previously.[23]

OH as a Risk Factor for Ischemic Stroke

Few prospective studies have evaluated the association of OH with stroke, although several have evaluated the association between OH and various vascular outcomes[24,25,29] or all-cause mortality.[26–28] In 2 studies, OH was related to coronary heart disease[24] and all-cause mortality[28] independently of other risk factors. The CHS, which examined the association of OH with stroke, found that several neurological symptoms were associated with incident stroke but that OH was not.[14] The most likely reason for the apparent discrepancy between the present study and CHS is age differences in the population. CHS participants were aged 65 years and older. In the present study the hazard associated with OH was lower with older age, and therefore there was no increased risk of stroke associated with OH at age 64 years in the overall population. Several other risk factors for stroke, such as smoking, transient ischemic attacks, hypertension, and elevated cholesterol, are reported to be stronger in younger persons.[15] As an outcome becomes more frequent with age, it is not surprising to find a negative interaction on a multiplicative scale.

OH might predict stroke for a number of reasons. First, the pressure fall itself may contribute to decreased cerebral perfusion, directly or indirectly. There is evidence that OH may be associated directly with decreased cerebral perfusion,[10] and other studies indicate that very low BP in general may have negative effects.[14,20,54] One study found significantly lower cerebral blood flow in patients with low diastolic BP.[54] At least 2 studies have suggested that there is an increase in mortality or stroke risk for persons on antihypertensive medication in the lowest stratum of BP compared with persons with more moderate BP.[14,20] The present study suggests that OH is associated with a higher risk of stroke among those with lower BP, but the difference across pressures was not statistically significant (data not shown). OH could act indirectly as well. Investigators have suggested that the autoregulation of the cerebrovascular blood flow that occurs in response to peripheral pressures could exacerbate the decrease in cerebral blood flow associated with hypotension if hemodynamic instability develops.[55] Given that OH has been associated with myocardial injury,[24] postural hypotension may contribute to cerebral hypoperfusion through myocardial ischemia and concomitant hemodynamic instability.

There are other potential reasons for the OH/stroke association. In the present study, adjustment for sociodemographic and numerous stroke risk factors removed approximately one half of the stroke risk associated with OH. Thus, at least part of the unadjusted stroke risk is because OH is a

marker for, or is in the causal pathway of, these other risk factors. However, adjustment for risk factors did not remove all of the association between OH and incident stroke. Reasons for the continued association between OH and stroke (other than causality) may be that OH is a marker of severity for measured stroke risk factors or is a marker for unmeasured risk factors, such as cardiac dysfunction, general frailty, or subclinical cerebrovascular disease. Persons with overt heart disease were removed from the study, but OH may be an indicator for other cardiac impairment such as left ventricular dysfunction or arterial stiffness, which were not directly measured. The association could remain because OH is a marker of general frailty. The Honolulu Heart Program identified an association between OH and several markers of frailty but found that OH continued to be associated with all-cause mortality even after controlling for those measures.[28] Finally, the association could remain because of other residual confounding. Thus, the fact that OH is an independent risk factor for stroke in the present study does not exclude the possibility that OH acts as a measure of disease severity, frailty, or cardiac dysfunction or is in the causal pathway of these other risk factors.

In cross-sectional studies, medications for treating hypertension and diabetes have been associated with OH,[21,56,57] and therefore the present findings might be attributed to medication. However, since OH remained predictive of stroke after stratification for use of medication to treat hypertension and diabetes, it is unlikely that the association between OH and stroke occurred because of medication use alone. Overall results suggested a nonsignificantly higher risk among persons treated for either diabetes or hypertension compared with those not on medication. Whether the differences in risk were because the medications interacted in some way with OH to contribute to stroke, because treatment indicated more severe disease, or merely because of chance cannot be determined from the present data.

Study Strengths and Limitations

Study strengths include its prospective design, the standardized procedures used, and the population basis for the original sample. Additionally, the use of average supine and standing BPs rather than the first supine BP and a single standing pressure avoids 2 potential problems. One is the overestimation of the prevalence of OH that may occur when the first supine pressure is used.[58] Another is the potential for missing OH if a single standing pressure is used since measuring standing pressure at 1 versus 3 minutes may identify different individuals.[59] Using an average standing pressure should identify all persons with significant pressure drop of more than fleeting duration. However, the fact that we did not specifically time postural pressure change prevents us from evaluating whether there were differences in persons who had postural pressure changes at 1 and 3 minutes. More than 2000 participants had missing postural change data. Since induction and clinic date assignment were random, participants missing data because their examinations were before institution of the postural change protocol should not have contributed to bias in the study. Another limitation was that persons with nonfatal events who were not hospitalized and persons who died but were not autopsied could not be included as stroke cases because they could not be validated. Nonhospitalized stroke may range from 3% to 28%.[1]

Our study indicates that, as previously suggested, different types of OH may identify different populations with somewhat different characteristics.[23] However, over a mean follow-up of 7.9 years, each type of OH was predictive of ischemic stroke even after adjustment for numerous accepted stroke risk factors. The ease and minimal expense of postural change measurement may make OH a useful tool in detecting a population at increased risk of stroke. Additional clinical and epidemiological studies are needed to further our understanding of the risk posed by OH and the potential benefit of treating it.

Acknowledgments

This study was supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022. Support was also provided to the lead author, Dr Eigenbrodt, by a National Institutes of Health, National Heart, Lung, and Blood Institute National Research Service Award grant (5T32HL07055), Cardiovascular Disease Epidemiology Training Program. The authors thank the staff and participants in the ARIC Study for their important contributions.

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