

Elevated Midlife Blood Pressure Increases Stroke Risk in Elderly Persons

The Framingham Study

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Background: Stroke risk predictions are traditionally based on current blood pressure (BP). The potential impact of a subject's past BP experience (antecedent BP) is unknown. We assessed the incremental impact of antecedent BP on the risk of ischemic stroke.

Methods: A total of 5197 stroke-free subjects (2330 men) in the community-based Framingham Study cohort were enrolled from September 29, 1948, to April 25, 1953, and followed up to December 31, 1998. We determined the 10-year risk of completed initial ischemic stroke for 60-, 70-, and 80-year-old subjects as a function of their current BP (at baseline), recent antecedent BP (average of readings at biennial examinations 1-9 years before baseline), and remote antecedent BP (average at biennial examinations 10-19 years earlier), with adjustment for smoking and diabetes mellitus. Models incorporating antecedent BP were also adjusted for baseline BP. The effect of each BP component (systolic BP, diastolic BP, and pulse pressure) was assessed separately.

Results: Four hundred ninety-one ischemic strokes (209 in men) were observed in eligible subjects. The antecedent BP influenced the 10-year stroke risk at the age of 60 years (relative risk per SD increment of recent antecedent systolic BP: women, 1.68 [95% confidence interval, 1.25-2.25]; and men, 1.92 [95% confidence interval, 1.39-2.66]) and at the age of 70 years (relative risk per SD increment of recent antecedent systolic BP: women, 1.66 [95% confidence interval, 1.28-2.14]; and men, 1.30 [95% confidence interval, 0.97-1.75]). This effect was evident for recent and remote antecedent BP, consistent in hypertensive and nonhypertensive subjects, and demonstrable for all BP components.

Conclusions: Antecedent BP contributes to the future risk of ischemic stroke. Optimal prevention of late-life stroke will likely require control of midlife BP.

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STROKE IS the leading neurological cause of mortality and morbidity worldwide. The annual incidence of stroke in the United States has been estimated at more than 600 000.¹ The most important modifiable risk factor for stroke is an elevated blood pressure (BP),² and this fact is recognized in stroke risk prediction models, developed by the Framingham Study researchers and adopted by the American Stroke Association.^{1,3} These risk prediction models, however, consider the BP at the time of risk prediction (current BP) but do not adjust for the potential impact of BP levels experienced by individuals in the past (antecedent or past BP). Some investigators⁴ have suggested that consideration of the current BP provides adequate information for predicting stroke risk, and in clinical trials,⁵ most of the stroke preven-

tion effect of lowering BP is achieved within a few years of starting treatment. On the other hand, some of the known stroke risk factors in observational studies, such as the presence of electrocardiographic left ventricular hypertrophy^{3,6} and increased echocardiographic left ventricular mass,⁷ are related to long-term elevations of BP. In addition, midlife BP has been shown to be predictive of the degree of carotid stenosis (a direct precursor of atherothrombotic stroke) in elderly persons.⁸

The availability of well-standardized, prospectively collected, population-based data on the BP of participants during a 50-year period in the Framingham Study provided us with a unique opportunity to address the importance of past BP measurements in estimating the future risk of stroke. Our objective was to assess the impact of past BP lev-

SUBJECTS AND METHODS

The 5209 subjects enrolled in the Framingham Study between September 29, 1948, and April 25, 1953, are referred to as the original Framingham cohort.⁹ Our study sample was composed of the 5197 subjects (2330 men; age range, 30-62 years) free of prevalent stroke at the index examination. The BP was recorded at every biennial examination that the subject attended, and the mean of 2 BP measurements recorded by a physician was taken as the subject's BP at the examination. All BP measurements were made in the left arm of the seated subject, using a mercury column sphygmomanometer and a cuff of appropriate width. Readings were recorded to the nearest even number. The fifth (disappearance) Korotkoff sound was used as an index of diastolic BP (DBP) unless the sound persisted to zero, in which case the fourth Korotkoff sound was recorded. The pulse pressure (PP) was calculated as the difference between the mean systolic BP (SBP) and DBP values at the examination of interest. Other cardiovascular risk factors were also measured at each biennial examination.

There was active continuous surveillance for incident stroke during the study period. The methods and effectiveness of our stroke surveillance have been previously described.¹⁰

We grouped subjects by age, pooling subjects who reached the age of interest alive and free of stroke (ischemic stroke or intracranial hemorrhage), regardless of the calendar year when they made this transition. We also defined an optimal follow-up period for stroke risk assessment as 10 years, because in this elderly cohort, longer periods of follow-up can result in increased misclassification of subject's exposure status, as BP levels changed during the period of follow-up.¹¹ Thus, a 40-year-old subject enrolled in 1950 would, if he or she reached the age of 60 years alive and free of stroke, provide 10 years of follow-up information from 1970 to 1980. If the same individual reached the age of 70

years alive and free of stroke, he or she then provided an additional 10 years of follow-up information as a 70-year-old individual. We chose to group subjects by age rather than by calendar year or index examination because the risk of stroke is greatly dependent on age.

EXPOSURE VARIABLE

The exposure variable was BP, assessed as a continuous variable. We separately examined each individual component of the BP (SBP, DBP, and PP) to assess if there was a differential effect of any specific component when considering the contribution of past BP measurements to the future risk of stroke.¹² Three aspects of BP were considered: (1) the current BP at the time of risk prediction (baseline age, 60, 70, or 80 years); (2) the recent past BP, in the decade immediately preceding the time of risk prediction (BP at the age of 50-59, 60-69, and 70-79 years, respectively); and (3) the remote past BP (10-20 years before the time of risk prediction, ie, at the age of 40-49 years for a baseline age of 60 years, at the age of 50-59 years for a baseline age of 70 years, and at the age of 60-69 years for a baseline age of 80 years at the time of stroke risk prediction).

OUTCOME

The primary outcome of interest was time to first completed ischemic stroke. Transient ischemic attacks were not included as either an end point or an exclusion criterion. We excluded subjects with intracranial (intracerebral or subarachnoid) hemorrhage from our analysis because many intracerebral hemorrhages in elderly persons are lobar hemorrhages secondary to amyloid angiopathy, a cause known to be independent of the BP level.¹³ Thus, intracranial hemorrhage was not an end point; however, because recognition of an ischemic stroke may be difficult in subjects with a prior intracranial hemorrhage, such subjects were censored from further follow-up at the time of development of the hemorrhagic stroke.

els on the future risk of stroke in older adults (aged ≥ 60 years), after accounting for the influence of current BP.

RESULTS

STUDY SAMPLE CHARACTERISTICS

A total of 3761 subjects reached the age of 60 years alive, were free of stroke, and had information for the variables of interest in our analysis. Similarly, 3049 subjects were able to provide information for the baseline age of 70 years and 1203 for the baseline age of 80 years. The study sample characteristics of the population at the ages of 60, 70, and 80 years are shown in **Table 1**. The mean and SD of each BP component at the ages of 60, 70, and 80 years are also described. As expected, the mean SBP and PP increased with age and the mean DBP declined with age in both sexes. The proportion of subjects taking antihypertensive medication increased with age, reaching nearly 50% in 80-year-old women. The

proportion of current smokers declined with age, reflecting decreased survival in smokers and subjects who had quit smoking. The mean serum cholesterol levels and body mass index in the study cohort are higher than recommended by current guidelines, in part because the study period spans 50 years.

STROKES

Overall, there were 830 completed ischemic strokes during a 50-year period in the 5197 subjects in the original Framingham cohort, and 740 of these were initial strokes in subjects aged 60 to 89 years. Of these strokes, only 521 occurred in the 4275 subjects who attended a biennial examination within 1 year of their baseline age (60, 70, or 80 years) and hence could provide reliable information on current BP at baseline. Four hundred ninety-one of these 521 strokes occurred in the 3761 subjects with adequate information regarding smoking and diabetes mellitus status at the baseline age, and the distribution of these events is

The diagnosis of stroke was based on the documentation of a focal neurological deficit of abrupt onset, either maximal from the onset or progressive, lasting for more than 24 hours.² Individual stroke subtypes were categorized according to an algorithm based on preestablished diagnostic criteria that include clinical features, imaging studies and other laboratory criteria, noninvasive vascular studies, cardiac evaluations for a source of embolus, and, when available, information from autopsy studies. An ischemic brain infarction was diagnosed if a focal deficit was documented on medical history or physical examination but a contemporaneous brain image showed no hemorrhage or if an ischemic brain infarct was found on autopsy. Computed tomographic or magnetic resonance imaging confirmation was available in 85% of all strokes included in this study.

The ischemic brain infarct was classified as an atherothrombotic brain infarction (ABI) if no cardiac sources of emboli could be found. The category of ABI included large-artery infarcts, lacunar infarcts, and infarcts of unknown origin. The brain infarct was classified as cardioembolic if a source of embolus was found. Such sources included atrial fibrillation, significant mitral valve disease, a mechanical prosthetic valve, endocarditis, left ventricular thrombus or left atrial thrombus on an echocardiogram, atrial myxoma, dilated cardiomyopathy, recent cardiac surgery, and recent myocardial infarction.

STATISTICAL ANALYSES

We used multivariate sex-specific Cox proportional hazards regression models¹⁴ to assess the relative risk (RR) of stroke per unit increase in each BP component. An initial analysis assessed the effect of a 1-SD change in current BP (SBP, DBP, or PP) on the 10-year risk of stroke in 60-, 70-, and 80-year-old subjects, without adjusting for past BP. A subsequent analysis assessed the additional effect of a 1-SD change in recent BP after adjusting for current BP. Similarly, we assessed the incremental prognostic utility of

remote BP over current BP alone. Covariates included in these models were the presence or absence of diabetes mellitus and smoking status at baseline (defined as current smoker or nonsmoker). We did not include the cardiac risk factors for ischemic stroke³ (left ventricular hypertrophy, coronary artery disease, and atrial fibrillation) in the overall multivariate analysis because these risk factors are correlated with long-standing BP elevations and, thus, would obscure the effect of past BP elevations.

ADJUSTMENT FOR REGRESSION-DILUTION BIAS

We used multiple measurements for antecedent BP (2-5 BP readings, depending on the number of available examinations during the decade of interest) to reduce the effects of regression-dilution bias.¹⁵⁻¹⁷ We considered the possibility that the incremental utility of the antecedent BP over the current BP may be due to an underestimation of the true association between current BP and 10-year risk of stroke, because current BP was more likely to be affected by a regression-dilution bias. To address this issue, we repeated our analyses using the BP recorded at a single random examination within the decade of interest to represent the antecedent BP during that period.

Additional secondary analyses explored the consistency of the observed association after stratifying the sample by current BP status (nonthypertensive [SBP of <140 mm Hg and DBP of <90 mm Hg] vs hypertensive), by treatment status (whether the subject had ever taken antihypertensive medication), and by the year in which the baseline age (60, 70, or 80 years) was reached (pre-1975 or post-1975). We also evaluated the association of current and antecedent BP measures with the independent risks of ABI alone and cardioembolic stroke alone. Finally, we determined if the impact of BP on stroke risk was modified by the sex of the subject. All analyses were performed using SAS statistical software (SAS Institute Inc, Cary, NC).

as follows. There were 71 strokes in 2197 women and 71 in 1564 men between the ages of 60 and 69 years; the corresponding numbers were 130 strokes in 1875 women and 101 in 1174 men between the ages of 70 and 79 years and 81 strokes in 791 women and 37 in 412 men between the ages of 80 and 89 years.

IMPACT OF CURRENT BP

The RRs of stroke per SD increment in current BP are presented in **Table 2**. The RRs of stroke for the antecedent BP measurements, after adjustment for current BP, are also shown. As expected and shown in earlier studies,^{2,3,12} higher levels of BP at the time of risk prediction were associated with increases in the 10-year risk of stroke by up to 103%, depending on the age at the time of risk assessment and the BP measure used (SBP, DBP, or PP) to predict risk. The effect of current BP was strongest at the age of 60 years and weakest at the age of 80 years, and the RRs were more marked for SBP and PP than for DBP at the age of 80 years.

INCREMENTAL IMPACT OF ANTECEDENT BP

After adjusting for current BP, the antecedent BP further increased the 10-year risk of stroke. The magnitude of the effect ranged from a 68% to 92% increased risk at the age of 60 years to a 14% to 72% increased risk at the age of 70 years and up to a 32% increased risk even at the age of 80 years. This effect was seen not only for the recent antecedent BP but was also noted for the remote antecedent BP. For instance, in men aged 70 years, the effect of remote BP (42%-51% increase in stroke risk) was at least as powerful as the impact of recent antecedent BP (14%-37% increase in stroke risk). The effect of current and antecedent BP was most powerful at the age of 60 years, with the RRs decreasing at the ages of 70 and 80 years. The analyses demonstrated that overall, all 3 components of antecedent BP were good predictors of future stroke risk. In 70-year-old men, the SBP and PP were relatively more informative than the DBP. In 70-year-old men, while current or recent DBP was not a statistically significant risk predictor, remote DBP remained predictive (Table 2).

Table 1. Characteristics of the Study Sample*

Characteristics†	Age at the Start of the Follow-up Period, y					
	60		70		80	
	Women	Men	Women	Men	Women	Men
	All Subjects					
No. of subjects	2197	1564	1875	1174	791	412
Subjects undergoing antihypertensive treatment at baseline‡	17.2	11.9	38.3	28.1	49.2	42.7
Subjects who ever underwent antihypertensive treatment‡	21.8	15.1	45.3	35.9	60.6	52.7
Subjects with diabetes mellitus‡	6.1	4.9	10.4	8.7	14.4	11.7
Current smoker at baseline‡	30.4	45.3	17.8	25.0	16.3	23.5
Serum cholesterol level, mg/dL§	254.5 ± 46.1	229.8 ± 41.1	247.8 ± 44.4	220.1 ± 41.3	226.9 ± 40.9	195.0 ± 36.9
Body mass index, kg/m ²	26.3 ± 4.9	27.0 ± 3.8	26.5 ± 4.8	26.8 ± 3.8	26.0 ± 4.5	25.8 ± 3.3
BP component, mm Hg						
Current						
Systolic BP	141.1 ± 23.7	138.7 ± 21.1	146.4 ± 23.0	142.5 ± 20.9	148.1 ± 23.3	142.5 ± 20.0
Diastolic BP	82.7 ± 12.2	83.2 ± 11.4	79.1 ± 11.2	79.1 ± 10.7	74.2 ± 10.9	74.7 ± 10.0
Pulse pressure	58.4 ± 16.1	55.4 ± 14.6	67.3 ± 18.1	63.4 ± 16.5	73.9 ± 20.2	67.8 ± 17.4
Recent past						
Systolic BP	137.9 ± 21.7	135.4 ± 17.8	142.0 ± 19.0	138.2 ± 16.9	146.0 ± 17.5	140.4 ± 15.6
Diastolic BP	83.9 ± 11.1	84.4 ± 9.8	81.0 ± 9.4	81.1 ± 8.9	77.0 ± 8.3	77.6 ± 7.7
Pulse pressure	53.9 ± 13.3	50.9 ± 11.4	60.9 ± 13.5	57.1 ± 12.3	68.9 ± 14.1	62.8 ± 12.8
Remote past						
Systolic BP	128.7 ± 18.1	129.0 ± 14.2	136.8 ± 20.6	133.3 ± 16.8	140.1 ± 18.7	135.4 ± 15.8
Diastolic BP	81.7 ± 10.1	83.8 ± 9.1	83.4 ± 10.3	83.5 ± 9.4	80.8 ± 9.1	81.3 ± 8.3
Pulse pressure	47.0 ± 10.5	45.2 ± 8.5	53.4 ± 12.9	49.8 ± 10.7	59.3 ± 12.9	54.2 ± 11.0
	Normotensive Subjects Only					
No. of subjects	1157	896	812	574		
BP component, mm Hg						
Current						
Systolic BP	123.8 ± 10.7	124.2 ± 10.2	126.5 ± 10.1	126.1 ± 10.2		
Diastolic BP	75.2 ± 7.3	76.9 ± 7.2	72.6 ± 7.6	73.4 ± 8.1		
Pulse pressure	48.5 ± 8.8	47.3 ± 8.5	53.9 ± 9.9	52.7 ± 9.7		
Recent past						
Systolic BP	125.8 ± 12.9	126.3 ± 12.1	130.8 ± 14.5	129.6 ± 13.8		
Diastolic BP	78.4 ± 7.5	80.1 ± 7.4	76.9 ± 8.0	77.9 ± 7.6		
Pulse pressure	47.4 ± 8.4	46.2 ± 8.1	53.9 ± 10.5	51.7 ± 10.2		
Remote past						
Systolic BP	120.9 ± 12.4	123.5 ± 11.5	127.4 ± 16.0	127.1 ± 15.6		
Diastolic BP	77.9 ± 7.7	80.8 ± 8.0	79.6 ± 9.0	80.4 ± 9.0		
Pulse pressure	43.1 ± 7.4	42.7 ± 7.1	47.8 ± 9.5	46.3 ± 9.8		

*Data are given as mean ± SD unless otherwise indicated. BP indicates blood pressure.

†The 3 aspects of BP (current, recent past, and remote past) are described in the “Exposure Variable” subsection of the “Subjects and Methods” section.

‡Data are given as percentage of subjects.

§To convert serum cholesterol level from milligrams per deciliter to millimoles per liter, multiply milligrams per deciliter by 0.02586.

SECONDARY ANALYSES

Adjustment for Regression-Dilution Bias

We found that the association between antecedent BP and risk of stroke persisted even when we used a single, random BP reading, although the magnitude of the risk ratio diminished. The RRs using single-random SBP recordings (in contrast to time-averaged SBP measures), for recent and remote SBP measurements, in subjects aged 60 and 70 years at baseline are shown in **Table 3**.

Effect in Nonhypertensive Subjects

We repeated the analyses including only those subjects who at the baseline age had an SBP of less than 140

mm Hg and a DBP of less than 90 mm Hg. The RRs of stroke per SD increment in current BP are presented in **Table 4**. Even in subjects who were nonhypertensive, there was an incremental impact of antecedent BP measurements, recent and remote, on the future risk of stroke.

Other Interactions

We looked for a potential differential impact of past BP measures on stroke risk in men vs women, but found no significant effect modification by sex ($P > .30$; results not presented). The effect of antecedent BP was seen in subjects who had taken antihypertensive medication at some time in their life and in subjects who had never taken medication, although the smaller numbers in

Table 2. Regression of Ischemic Stroke Incidence on Current and Antecedent Blood Pressure Measurements, by Blood Pressure Component*

Blood Pressure Measurement	Women			Men		
	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure
Baseline Age of 60 y						
71 Ischemic strokes in 2197 subjects						
Current: age, 60 y	2.03 (1.69-2.44)	1.85 (1.56-2.21)	1.78 (1.48-2.15)	1.39 (1.12-1.72)	1.42 (1.15-1.74)	1.23 (0.98-1.53)
Recent past: mean age, 50-59 y†	1.68 (1.25-2.25)	1.78 (1.33-2.38)	1.80 (1.34-2.42)	1.92 (1.39-2.66)	1.73 (1.26-2.38)	1.82 (1.14-2.58)
Remote past: mean age, 40-49 y†	1.48 (1.07-2.07)	1.57 (1.13-2.17)	1.60 (1.08-2.36)	1.54 (0.96-2.45)	1.30 (0.88-1.91)	1.50 (0.88-2.56)
Baseline Age of 70 y						
130 Ischemic strokes in 1875 subjects						
Current: age, 70 y	1.67 (1.44-1.94)	1.49 (1.27-1.75)	1.53 (1.31-1.78)	1.53 (1.28-1.83)	1.08 (0.89-1.31)	1.66 (1.39-1.99)
Recent past: mean age 60-69 y†	1.66 (1.28-2.14)	1.44 (1.11-1.88)	1.72 (1.31-2.27)	1.30 (0.97-1.75)	1.14 (0.84-1.54)	1.37 (0.99-1.90)
Remote past: mean age, 50-59 y†	1.41 (1.17-1.69)	1.47 (1.23-1.75)	1.52 (1.20-1.93)	1.45 (1.14-1.86)	1.42 (1.13-1.80)	1.51 (1.10-2.08)
Baseline Age of 80 y						
81 Ischemic strokes in 791 subjects						
Current: age, 80 y	1.40 (1.13-1.73)	1.14 (0.91-1.43)	1.37 (1.10-1.69)	1.25 (0.92-1.71)	0.99 (0.71-1.38)	1.30 (0.95-1.77)
Recent past: mean age, 70-79 y†	1.19 (0.84-1.70)	1.21 (0.86-1.70)	1.12 (0.75-1.67)	1.25 (0.76-2.04)	1.32 (0.79-2.21)	1.12 (0.67-1.87)
Remote past: mean age, 60-69 y†	1.05 (0.79-1.42)	1.14 (0.86-1.51)	1.01 (0.69-1.49)	1.25 (0.81-1.93)	1.20 (0.80-1.79)	1.26 (0.74-2.16)

*Data are given as relative risk (95% confidence interval). All relative risks are presented per SD change in blood pressure component at baseline age and are adjusted for diabetes mellitus and smoking status. The mean ± SD values of the baseline, recent past, and remote past blood pressure measurements are given in Table 1.

†Relative risks for antecedent blood pressure measurements are also adjusted for current (baseline) blood pressure measurements.

Table 3. Regression of Ischemic Stroke Incidence on Current and Antecedent Blood Pressure Measurements, Using a Randomly Selected Single Measure Recorded at Baseline or During the Decade of Interest*

Blood Pressure Measurement	Women			Men		
	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure
Baseline Age of 60 y						
71 Ischemic strokes in 2197 subjects						
Current: age, 60 y	2.03 (1.69-2.44)	1.85 (1.56-2.21)	1.78 (1.48-2.15)	1.39 (1.12-1.72)	1.42 (1.15-1.74)	1.23 (0.98-1.53)
Recent past: mean age, 50-59 y†	1.30 (1.01-1.67)	1.32 (1.04-1.69)	1.44 (1.13-1.85)	1.69 (1.29-2.22)	1.46 (1.11-1.92)	1.46 (1.11-1.92)
Remote past: mean age, 40-49 y†	1.52 (1.14-2.02)	1.39 (1.02-1.89)	1.48 (1.05-2.09)	1.04 (0.67-1.61)	1.25 (0.89-1.75)	1.04 (0.68-1.59)
Baseline Age of 70 y						
130 Ischemic strokes in 1875 subjects						
Current: age, 70 y	1.67 (1.44-1.94)	1.49 (1.27-1.75)	1.53 (1.31-1.78)	1.53 (1.28-1.83)	1.08 (0.89-1.31)	1.66 (1.39-1.99)
Recent past: mean age, 60-69 y†	1.38 (1.13-1.69)	1.18 (0.97-1.44)	1.27 (1.03-1.57)	1.12 (0.90-1.41)	1.13 (0.90-1.42)	1.26 (0.99-1.62)
Remote past: mean age, 50-59 y†	1.30 (1.10-1.53)	1.37 (1.17-1.61)	1.41 (0.15-1.72)	1.29 (1.04-1.61)	1.27 (1.02-1.57)	1.17 (0.90-1.53)

*Data are given as relative risk (95% confidence interval). All relative risks are presented per SD change in blood pressure component at baseline age and are adjusted for diabetes mellitus and smoking status. The relative risks for regression of ischemic stroke incidence on current blood pressure measurements are identical to those presented in Table 2. The mean ± SD values of baseline systolic blood pressure measurements are given in Table 1.

†Relative risks for antecedent blood pressure measurements are also adjusted for current (baseline) blood pressure measurements.

each subgroup reduced the statistical power of this secondary analysis (results not presented). In evaluating for a change in the impact of BP on stroke risk over time, we found that in men and women, the effect of recent antecedent SBP on future stroke risk remained statistically significant in the pre-1975 stratum ($P=.03$) and the post-1975 stratum ($P<.001$) (results not presented).

Stroke Subtype Analyses

We found a similar effect of past BP on the risk of each stroke subtype evaluated, ie, ABI and cardioembolic stroke (results not presented). The number of events

was too small to permit separate analysis of large-artery infarcts and lacunar strokes.

COMMENT

Stroke is predominantly a disease of elderly persons. The risk of stroke doubles in each successive decade after the age of 55 years, and 72% of all strokes occur after the age of 65 years.¹ To reduce the population burden of stroke, it is important to address the possible reasons for this increasing risk with age. The cumulative effect of long-term exposure to risk factors such as an elevated BP may partly explain this age-associated increase in risk.

Table 4. Regression of Ischemic Stroke Incidence on Current and Antecedent Blood Pressure Measurements in Nonhypertensive Subjects*

Blood Pressure Measurement	Women			Men		
	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure	Systolic Blood Pressure	Diastolic Blood Pressure	Pulse Pressure
Baseline Age of 60 y						
21 Ischemic strokes in 1157 subjects						
34 Ischemic strokes in 896 subjects						
Current: age, 60 y	1.64 (0.99-2.69)	1.13 (0.73-1.74)	1.50 (0.99-2.25)	1.09 (0.77-1.56)	1.19 (0.84-1.68)	0.95 (0.67-1.33)
Recent past: mean age, 50-59 y†	1.65 (1.18-2.29)	1.46 (0.91-2.34)	1.94 (1.31-2.87)	1.73 (1.42-2.11)	2.09 (1.53-2.86)	1.73 (1.27-2.34)
Remote past: mean age, 40-49 y†	1.17 (0.81-1.68)	1.10 (0.69-1.75)	1.34 (0.84-2.15)	1.65 (1.19-2.28)	1.55 (1.10-2.17)	1.52 (0.94-2.48)
Baseline Age of 70 y						
38 Ischemic strokes in 718 subjects						
37 Ischemic strokes in 574 subjects						
Current: age, 70 y	1.74 (1.17-2.62)	1.01 (0.73-1.41)	1.59 (1.15-2.20)	1.24 (0.87-1.76)	0.96 (0.68-1.35)	1.28 (0.92-1.78)
Recent past: mean age, 60-69 y†	1.36 (1.08-1.71)	1.51 (1.11-2.07)	1.45 (1.04-2.03)	1.24 (0.98-1.57)	1.10 (0.73-1.65)	1.45 (1.05-1.99)
Remote past: mean age, 50-59 y†	1.36 (1.13-1.64)	1.50 (1.20-1.87)	1.56 (1.16-2.10)	1.30 (1.11-1.53)	1.50 (1.15-1.96)	1.46 (1.12-1.91)

*Data are given as relative risk (95% confidence interval). All relative risks are presented per SD change in blood pressure component at baseline age and are adjusted for diabetes mellitus and smoking status. The mean ± SD values of the baseline, recent past, and remote past blood pressure measurements are given in the "Normotensive Subjects Only" section of Table 1.

†Relative risks for antecedent blood pressure measurements are also adjusted for current (baseline) blood pressure measurements.

PRINCIPAL FINDINGS

We found that the antecedent BP increased the future risk of ischemic stroke even after adjusting for current BP levels. This effect was robust, consistent in both sexes, evident at baseline ages 60 and 70 years, demonstrable for all BP components evaluated, and significant in hypertensive and nonhypertensive subjects.

In the Framingham Study,¹⁸ 28% of all ABIs occurred in subjects whose current BP was in the nonhypertensive range. While this is not entirely surprising given the continuum of risk, the importance of a past BP elevation as a potentially modifiable risk factor for the prevention of stroke in this group should not be overlooked. Similarly, earlier observations from the Framingham Study described a higher risk of stroke at comparable levels of BP elevation in subjects taking antihypertensive agents compared with subjects who were not.¹⁹ The higher risk in treated individuals may be explained, in part, by the fact that subjects with more concomitant risk factors and those with target organ damage are more likely to be treated. Our data suggest that an additional explanation may be the residual effect of high antecedent BP.

The present investigation was not designed to address the relative utility of the individual measures of antecedent BP (SBP, DBP, and PP) in predicting the future risk of ischemic stroke. We found that all 3 components were good predictors of future risk in 60-year-old men and women and in 70-year-old women, while the SBP and PP were relatively more useful than the DBP in 70-year-old men. This may be because the DBP peaks earlier in men compared with women.²⁰ Also, we did not address the incremental utility of "remote" over "recent" past BP recordings.

COMPARISON WITH PRIOR STUDIES

A recent review¹¹ of 11 prospective studies exploring the association of hypertension with stroke found that all these

studies defined hypertension based on BP measurements taken at a single visit. Sytkowski et al,²¹ in an earlier study from Framingham, Mass, did examine the risk of cardiovascular disease (CVD) and CVD-related mortality in subjects with long-term sustained hypertension, but did not assess stroke as a separate end point. In their study, long-term sustained hypertension was defined as an SBP of 160 mm Hg or higher and/or a DBP of 95 mm Hg or higher in at least 3 of 5 consecutive biennial examinations. No distinction was made between current and past BP.

Only 3 prior studies have specifically addressed whether "elevated BP levels in the past convey additional risk, given recent BP levels."^{22(p2)} Prentice et al²² studied the relation between the 2-year risk of stroke and BP recorded at 4 preceding biennial examinations in middle-aged Japanese adults enrolled in the Hiroshima and Nagasaki Adult Health Study. They reported that, in addition to current SBP, the SBP 2 to 4 years before baseline did predict the future risk of ischemic stroke. However, they could not demonstrate any additional impact of SBP recorded 4 to 6 years before baseline on the future stroke risk. The age and ethnic differences between the 2 cohorts may account for the differences between our results and those of the Hiroshima and Nagasaki Adult Health Study, in which 90% of the subjects were younger than 65 years. Furthermore, the Japanese study did not assess the effect of remote antecedent BP.

Keli et al²³ studied 630 men (aged 50-69 years) enrolled in the Zutphen Study. They compared a single observation of the SBP in subjects with the SBP averaged over 10 years, and found that the latter measure was a stronger predictor of 15-year stroke incidence. However, they did not study women or assess the effect of remote antecedent BP.

Harris et al²⁴ assessed the future risk of CVD in 1254 persons from the Framingham Study who reached the age of 65 years without a prior CVD. They found a consistent small increase in risk of all cardiovascular

events among those with a higher SBP before the age of 65 years, even after controlling for the average of 3 SBP measurements recorded at the age of 65 years. However, the association between BP and CVD risk was statistically significant only in subjects with an average SBP (before the age of 65 years) of 160 mm Hg or higher. Important differences between the present study and the study by Harris et al deserve emphasis. Harris et al restricted their analysis to untreated subjects, did not examine the end point of stroke, and did not assess the impact of individual BP components (DBP and PP). Furthermore, their analyses did not distinguish between recent and remote antecedent BP and did not examine the effect in subjects older than 65 years.

The present investigation is, therefore, unique in addressing the incremental value of recent and remote antecedent BP in predicting the future risk of ischemic stroke and in examining the effect of DBP and PP as well as SBP. Furthermore, it addresses the issue in elderly subjects, a group at highest risk for incident stroke and a history of hypertension.

POSSIBLE MECHANISMS

The pathophysiological mechanisms whereby hypertension leads to stroke are not entirely clear. An elevated BP is an independent risk factor for carotid atherosclerosis, after adjusting for age, sex, smoking status, and serum cholesterol level.^{8,25} In addition, hypertension may directly cause mechanical damage to blood vessel walls that may persist after the systemic BP has been lowered to nonhypertensive levels by medications. Chronic hypertension has been associated with medial thickening of arterial walls, hyaline degeneration, fibrinoid necrosis, formation of microaneurysms in the intraparenchymal arterioles, and inadequate development of intracranial collaterals in response to carotid occlusive disease.^{26,27} Such changes may be responsible for the long-term adverse effects of an elevated BP seen in our study subjects.

STRENGTHS AND LIMITATIONS

The availability of antecedent BP data, collected by the Framingham Study researchers during a 50-year period, is a unique strength of this study. Almost all participants are white, and this limits the generalizability of the results to other racial and ethnic groups.

CLINICAL AND PUBLIC HEALTH IMPLICATIONS

The results of our study, while based on observational data, strongly suggest that midlife BP levels continue to affect the future risk of stroke not only over a short span, such as 5 years, but over more prolonged periods, up to 30 years. Traditional analyses of the benefits of BP control at a given age use estimates of the 5-year (or 10-year) absolute risk of adverse events for a subject at that age to estimate a "number needed to treat" to prevent a single event during a limited time. Such analyses may underestimate the long-term risk reduction achievable with adequate BP control in midlife.

Recent national data suggest that the awareness, treatment, and control of hypertension may be deteriorating. This insouciance may be greater in middle-aged adults facing fewer short-term risks.²⁸ Our findings reinforce the importance of Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines,²⁹ emphasizing the need to prevent and control an elevated BP at all ages. Emphasizing the long-term adverse effects of midlife BP elevations may serve to motivate middle-aged adults to become aware of and address their elevated BP levels. While the reduction in risk achieved by antihypertensive treatment is impressive at any age and particularly in elderly persons,³⁰⁻³² treatment of hypertension in older subjects who have been exposed to elevated BP levels for many years leaves their risk well above that of nonhypertensive subjects.

Healthy People 2000,³³ the statement of national objectives for promoting health and preventing disease, called for a 34% reduction in the number of deaths caused by stroke from the 1987 stroke mortality rate of 30.4 per 100000. By 1997, less than 50% of this target reduction was achieved.³³ The present study suggests that to achieve optimal reductions in the risk of ischemic stroke in elderly persons, it may be necessary to prevent, diagnose, and manage BP elevations throughout adulthood. The primary prevention of hypertension through nonpharmacological measures throughout adult life, and the early detection and treatment of hypertension in middle-aged and older adults, promises to yield sustained benefits in the form of lower stroke risks later in life.

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