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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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.

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 documenta-
tion of a focal neurological deficit of abrupt onset, either
maximal from the onset or progressive, lasting for more than
24 hours. Individual stroke subtype classifications were
categorized according to an algorithm based on preestablished diagno-
sis criteria that included 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 docu-
menced on medical history or physical examination but a
contemporaneous brain image showed no hemorrhage or
if an ischemic brain infarct was found on autopsy. Com-
puted tomographic or magnetic resonance imaging con-
firmation was available in 85% of all strokes included in
this study.

The ischemic brain infarct was classified as an ath-
 erosclerotic brain infarct (ABI) if no cardiac sources of
emboli could be found. The category of ABI included
large-artery infarcts, lacunar infarcts, and infarcts of un-
known origin. The brain infarct was classified as cardio-
embolic if a source of embolus was found. Such sources
included atrial fibrillation, significant mitral valve dis-
ease, a mechanical prosthetic valve, endocarditis, left ven-
tricular thrombus or left atrial thrombus on an echocar-
diogram, atrial myxoma, dilated cardiomyopathy, recent
heart surgery, and recent myocardial infarction.

STATISTICAL ANALYSES

We used multivariate sex-specific Cox proportional haz-
ards regression models11 to assess the relative risk (RR) of
stroke per 1 SD 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. Simi-
larly, 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 mel-
tus and smoking status at baseline (defined as current
smoker or nonsmoker). We did not include the cardiac risk
factors for ischemic stroke2 (left ventricular hypertrophy,
coronary artery disease, and atrial fibrillation) in the over-
all multivariate analysis because these risk factors are cor-
related 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 examina-
tions during the decade of interest) to reduce the effects of
regression-dilution bias.15-17 We considered the possibil-
ity 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 ran-
don examination within the decade of interest to repres-
sent the antecedent BP during that period.

Additional secondary analyses explored the consist-
cy of the observed association after stratifying the
sample by current BP status (nonhypertensive [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 indepen-
dent 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 1 SD increment in current BP are
presented in Table 2. The RRs of stroke for the ante-
cedent BP measurements, after adjustment for current BP,
are also shown. As expected and shown in earlier stud-
ies,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 ante-
cedent BP but was also noted for the remote antecedent
BP. For instance, in men aged 70 years, the effect of re-
move 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 an-
tecedent BP was most powerful at the age of 60 years,
with the RRs decreasing at the ages of 70 and 80 years. The analy-
ses demonstrated that overall, all 3 components of ante-
cedent BP were good predictors of future stroke risk. In
70-year-old men, the SBP and PP were relatively more in-
formative than the DBP. In 70-year-old men, while cur-
rent or recent DBP was not a statistically significant risk
predictor, remote DBP remained predictive (Table 2).
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 ($P>0.30$; 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 1. Characteristics of the Study Sample

<table>
<thead>
<tr>
<th>Characteristics†</th>
<th>60</th>
<th>70</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of subjects</td>
<td>2197</td>
<td>1564</td>
<td>1875</td>
</tr>
<tr>
<td>Subjects undergo-</td>
<td>17.2</td>
<td>11.9</td>
<td>38.3</td>
</tr>
<tr>
<td>ing antihyperten-</td>
<td></td>
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</tr>
<tr>
<td>tive treatment at</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline‡</td>
<td>21.8</td>
<td>15.1</td>
<td>45.3</td>
</tr>
<tr>
<td>Subjects who ever</td>
<td>6.1</td>
<td>4.9</td>
<td>10.4</td>
</tr>
<tr>
<td>underwent antihyp-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tensive treatment‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum cholesterol</td>
<td>254.5 ± 46.1</td>
<td>229.8 ± 41.1</td>
<td>247.8 ± 44.4</td>
</tr>
<tr>
<td>Body mass index,</td>
<td>26.3 ± 4.9</td>
<td>27.0 ± 3.8</td>
<td>26.5 ± 4.8</td>
</tr>
<tr>
<td>BP component, mm</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Current Systolic</td>
<td>141.1 ± 23.7</td>
<td>138.7 ± 21.1</td>
<td>146.4 ± 23.0</td>
</tr>
<tr>
<td>Current Diastolic</td>
<td>82.7 ± 12.2</td>
<td>83.2 ± 11.4</td>
<td>79.1 ± 11.2</td>
</tr>
<tr>
<td>Current Pulse</td>
<td>58.4 ± 16.1</td>
<td>55.4 ± 14.6</td>
<td>67.3 ± 18.1</td>
</tr>
<tr>
<td>Recent past Systolic</td>
<td>137.9 ± 21.7</td>
<td>135.4 ± 17.8</td>
<td>142.0 ± 19.0</td>
</tr>
<tr>
<td>Recent past Dista-</td>
<td>83.9 ± 11.1</td>
<td>84.4 ± 9.8</td>
<td>81.0 ± 9.4</td>
</tr>
<tr>
<td>Recent past Pulse</td>
<td>53.9 ± 13.3</td>
<td>50.9 ± 11.4</td>
<td>60.9 ± 13.5</td>
</tr>
<tr>
<td>Remote past Systolic</td>
<td>128.7 ± 18.1</td>
<td>129.0 ± 14.2</td>
<td>136.8 ± 20.6</td>
</tr>
<tr>
<td>Remote past Dista-</td>
<td>81.7 ± 10.1</td>
<td>83.8 ± 9.1</td>
<td>83.4 ± 10.3</td>
</tr>
<tr>
<td>Remote past Pulse</td>
<td>47.0 ± 10.5</td>
<td>45.2 ± 8.3</td>
<td>53.4 ± 12.9</td>
</tr>
<tr>
<td>BP component, mm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current Systolic</td>
<td>123.8 ± 10.7</td>
<td>124.2 ± 10.2</td>
<td>126.5 ± 10.1</td>
</tr>
<tr>
<td>Current Diastolic</td>
<td>75.2 ± 7.3</td>
<td>76.9 ± 7.2</td>
<td>72.6 ± 7.6</td>
</tr>
<tr>
<td>Current Pulse</td>
<td>48.5 ± 8.8</td>
<td>47.3 ± 8.5</td>
<td>53.9 ± 9.9</td>
</tr>
<tr>
<td>Recent past Systolic</td>
<td>125.8 ± 12.9</td>
<td>126.3 ± 12.1</td>
<td>130.8 ± 14.5</td>
</tr>
<tr>
<td>Recent past Dista-</td>
<td>78.4 ± 7.5</td>
<td>80.1 ± 7.4</td>
<td>76.9 ± 8.0</td>
</tr>
<tr>
<td>Recent past Pulse</td>
<td>47.4 ± 8.4</td>
<td>46.2 ± 8.1</td>
<td>53.9 ± 10.5</td>
</tr>
<tr>
<td>Remote past Systolic</td>
<td>120.9 ± 12.4</td>
<td>123.5 ± 11.5</td>
<td>127.4 ± 16.0</td>
</tr>
<tr>
<td>Remote past Dista-</td>
<td>77.9 ± 7.7</td>
<td>80.8 ± 8.0</td>
<td>79.6 ± 9.0</td>
</tr>
<tr>
<td>Remote past Pulse</td>
<td>43.1 ± 7.4</td>
<td>42.7 ± 7.1</td>
<td>47.8 ± 9.5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Blood Pressure Measurement</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic Blood Pressure</td>
<td>Diastolic Blood Pressure</td>
</tr>
<tr>
<td>Baseline Age of 60 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current: age, 60 y</td>
<td>2.03 (1.69–2.44)</td>
<td>1.85 (1.56–2.21)</td>
</tr>
<tr>
<td>Recent past: mean age, 50-59 y†</td>
<td>1.68 (1.25–2.25)</td>
<td>1.78 (1.33–2.38)</td>
</tr>
<tr>
<td>Remote past: mean age, 40-49 y†</td>
<td>1.48 (1.07–2.07)</td>
<td>1.57 (1.32–2.17)</td>
</tr>
<tr>
<td>Baseline Age of 70 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current: age, 70 y</td>
<td>1.67 (1.44–1.94)</td>
<td>1.49 (1.27–1.75)</td>
</tr>
<tr>
<td>Recent past: mean age, 60-69 y†</td>
<td>1.66 (1.28–2.14)</td>
<td>1.44 (1.11–1.88)</td>
</tr>
<tr>
<td>Remote past: mean age, 50-59 y†</td>
<td>1.41 (1.17–1.69)</td>
<td>1.47 (1.23–1.75)</td>
</tr>
<tr>
<td>Baseline Age of 80 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current: age, 80 y</td>
<td>1.40 (1.13–1.73)</td>
<td>1.14 (0.91–1.43)</td>
</tr>
<tr>
<td>Recent past: mean age, 70-79 y†</td>
<td>1.19 (0.84–1.70)</td>
<td>1.21 (0.86–1.70)</td>
</tr>
<tr>
<td>Remote past: mean age, 60-69 y†</td>
<td>1.05 (0.79–1.42)</td>
<td>1.14 (0.88–1.51)</td>
</tr>
</tbody>
</table>

*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.

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. 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.
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, 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 over 10 years, and found that the latter measure was a potential risk factor. 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. 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 did not study women or assess the effect of remote 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. Also, we did not address the incremental utility of “remote” over “recent” past BP recordings.

**COMPARISON WITH PRIOR STUDIES**

A recent review 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 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.” Prentice et al 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 al 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 al 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.6,16 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 100 000. 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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