Blood Pressure Experience and Risk of Cardiovascular Disease in the Elderly

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SUMMARY For the 1254 persons in the Framingham Heart Study who survived to age 65 without prior cardiovascular disease or prior use of antihypertensive medications, significant univariate correlates of the development of cardiovascular disease after age 65 included (1) the systolic blood pressure at age 65, (2) the average systolic blood pressure before age 65, and (3) the slope of blood pressure change up to age 65. After controlling for the systolic blood pressure at age 65, average pre-age 65 blood pressure remained significant (p < 0.05) and the slope of the pre-age 65 blood pressure was marginally significant (p = 0.06). Even after controlling for the mean of up to three blood pressure measurements at age 65, an average systolic blood pressure of 160 mm Hg or greater before age 65 was an independently significant predictor of the post-age 65 development of cardiovascular disease (rate ratio = 1.79; 95% confidence interval = 1.04, 3.07). These data suggest that even after performing multiple measurements at a single examination, knowledge of past systolic blood pressure history, especially if it averages 160 mm Hg or greater, adds a small but statistically significant increment in predicting future cardiovascular disease in the elderly. (Hypertension 7: 118–124, 1985)

KEY WORDS • hypertension • epidemiology • geriatrics

THERE is general agreement that the risk of cardiovascular disease increases in old age. This increase is partly related to increases in blood pressure, especially systolic blood pressure; however, studies that have estimated the risk attributable to systolic blood pressure commonly have been based on models that correlated blood pressure measurement at one point in time to the future risk of developing cardiovascular disease.2

Although the one-point-in-time approach is easy and useful for defining risk in young populations in whom prior blood pressure data are not readily available, it may not be ideal in older populations in whom substantial blood pressure data may be obtainable. A lifetime or cumulative "time-dose product" that summarizes the long-term exposure to a risk factor may be more predictive of the development of cardiovascular disease. To assess the relative importance of blood pressure taken at one point in time versus a patient's exposure over time, we compared the predictive ability of these two factors for the development of cardiovascular disease after the age of 65 in the Framingham Heart Study population.

Materials and Methods

Study Population

In the Framingham Heart Study, a cohort of 5209 men and women aged 28 to 62 years were identified in 1948 and followed biennially for the development of cardiovascular disease. From the Framingham Heart Study population, we selected the subgroup of individuals who survived to age 65 by the twelfth biennial examination, who had no prior evidence of cardiovascular disease (see below), and who were examined within 2 years after reaching age 65. All had been in the Framingham Heart Study for at least 4 years (mean, 13.4 years) before reaching the age of 65 and were potentially eligible for at least 4 years (mean, 12.6 years) of follow-up after age 65.
The focus of the analysis was the evaluation of the contribution of past systolic blood pressure data to the risk of cardiovascular disease. Systolic blood pressure readings at each exam from the time of the patient's entry into the study through the twelfth biennial examination were identified. Systolic blood pressure was measured in the left arm of each subject with a mercury sphygmomanometer and a 14- x 60-cm cuff with the subject seated and the arm supported. The palpatory method was used to check auscultatory systolic readings. Three readings were taken for each subject: an admission blood pressure taken by a nurse, a reading taken by a physician at the start of the examination, and a last reading by a physician at the end of the interview after drawing blood. In this analysis the first pressure recorded by the physician was used unless otherwise noted.

To eliminate the problem of comparing risk in those with treated versus untreated systolic blood pressures, the analysis was restricted to subjects who were documented to be on no antihypertensive drugs from 1948 until they reached age 65. Subjects were not eliminated if they were taking other medications for other purposes, and subjects were included regardless of the levels of any other cardiac risk factors.

The outcome variable was the development of any cardiovascular disease — including coronary heart disease, cerebrovascular accidents, transient ischemic attacks, congestive heart failure, and intermittent claudication — after age 65 and by the time of the fourteenth biennial examination. Criteria for each cardiovascular diagnosis were standardized, and diagnoses were assigned by a panel of Framingham investigators.

Coronary heart disease was defined as: (1) a myocardial infarction, based on electrocardiographic (ECG) changes, chest pain with enzyme changes, or autopsy findings; (2) coronary insufficiency, based on transient ECG changes accompanying chest pain; (3) angina pectoris, based on a typical history of chest pain, or (4) coronary death. Cerebrovascular accidents and transient ischemic attacks required evaluation by a neurologist. Congestive heart failure was based on the presence of concurrent major and minor criteria. Intermittent claudication was based on recurrent calf cramping during exercise.

Blood Pressure Variables

For each of these individuals several different variables were computed to express systolic blood pressure. First, systolic blood pressure at age 65 was defined as the measurement obtained at the time of the first examination when or after the subject reached age 65. If this value was missing, the individual was eliminated from the analysis. In addition, to allow for a possible nonlinear effect for this variable, four subranges for systolic blood pressure were created: less than 120 mm Hg, 120 to 139 mm Hg, 140 to 159 mm Hg, and 160 mm Hg or above. Years of systolic blood pressure over 160 mm Hg was a categorical variable that was computed by adding the number of biennial examinations at which an individual's blood pressure was above 160 mm Hg prior to age 65 and then multiplying the number of examinations by 2. The value of 160 mm Hg was chosen because it represents a systolic blood pressure level at which there is a clear increased risk and because it is often selected as the value above which treatment is recommended. Average systolic blood pressure was the mean of all the second of three systolic blood pressure readings taken at each examination in which the individual participated before age 65. Subranges also were constructed for average blood pressure: less than 120 mm Hg, 120 to 139 mm Hg, 140 to 159 mm Hg, and 160 mm Hg or above. The slope of systolic blood pressure from the time of entry into the cohort until the age of 65 was calculated by computing the rate of change of systolic blood pressure by least squares regression of systolic blood pressure on time for each individual. The slope was analyzed as a continuous variable and also as a categorical variable in which the upper 20%, middle 60%, and lower 20% of patients composed the three categories. Person-time analyses were used to compare the incidence of cardiovascular disease after age 65 for various categories of systolic blood pressure at age 65, average systolic blood pressure before age 65, and the pre–age 65 slope of systolic blood pressure.

As the number of pre–age 65 years of systolic blood pressure over 160 mm Hg for a subject in our data was limited by the number of pre–age 65 years of observation, all analyses involving this variable were stratified by the number of pre–age 65 years of observation. A series of contingency tables comparing post–age 65 risk of cardiovascular disease with the number of years of systolic blood pressure over 160 mm Hg was constructed for each stratum. For each stratum the observed number of post–age 65 cardiovascular events was compared with the estimated expected or null number, which was obtained by multiplying the total number of subjects in the stratum by the proportion of subjects without any pre–age 65 years of elevated systolic blood pressure in whom cardiovascular disease after age 65 developed. The overall association between the number of years of systolic blood pressure over 160 mm Hg and post–age 65 cardiovascular disease was examined by a Mantel test of significance for stratified data.

Cox's proportional hazard model analyses were performed to examine the univariate and conditional effect of the four blood pressure variables. These analyses were based on a model that described the hazard rate, which is the instantaneous risk of a cardiovascular event, as a function of the baseline risk and the blood pressure variables. The results of these analyses were expressed in terms of incidence rate ratios and confidence intervals for categories of the blood pressure variables. Continuous variables also were represented by a series of indicator variables for their subranges. The latter approach was preferred when the effect of the blood pressure components was not the same over the entire range. Estimates for the probability of developing post–age 65 cardiovascular disease over time were calculated with a usual life table analysis.
Because of the random error contained in all blood pressure readings, it was expected that all estimates of effect would contain some degree of bias toward their null values. This bias would be expected to be greater for systolic blood pressure at age 65, which was based on a single blood pressure measurement, than for average pre-age 65 systolic blood pressure, which was based on an average of at least 2 and at most 11 blood pressure measurements. In an attempt to compensate for the different amounts of expected misclassifications, a second measure of blood pressure at age 65, namely, the average of the up to three measurements taken at the first examination at which a subject was age 65 or older, was also considered.

We also determined whether the lability of pre-age 65 systolic blood pressure was an important correlate of cardiovascular risk after controlling for average systolic blood pressure. Lability was defined as the standard deviation of the measurements that were used to calculate the average systolic blood pressure. Measurement errors may also be the source of possible confounding by the number of years of pre-age 65 observation. If subjects with few pre-age 65 years of observation showed extreme values for average systolic blood pressure or slope of systolic blood pressure because of large error terms and if these same subjects had a higher risk of post-age 65 cardiovascular disease, then the number of pre-age 65 years of observation may confound the effect of these variables. We controlled for this potential problem by also performing proportional hazard model analyses that stratified for the number of pre-age 65 years of observation.

**Results**

Of the original 5209 subjects in the Framingham cohort, 1254 reached the age of 65 by the twelfth biennial examination without any cardiovascular disease and without ever having been on antihypertensive drugs. There were 545 (43%) men and 709 (57%) women. Of these 1254 people, 366 (29%) had at least one cardiovascular event during the 4 to 22 (mean, 12.6 years) potential years of follow-up. The actuarial risk of developing a first cardiovascular endpoint was 10% at 4 years, 20% at 8 years, and 45% at 16 years. The incidence of first cardiovascular events per 1000 person-years was 15.6 for coronary heart disease, 6.6 for a cerebrovascular accident or a transient ischemic attack, 6.1 for congestive heart failure, and 3.8 for intermittent claudication.

**Univariate Analyses**

Table 1 and Figure 1 show the incidence of developing cardiovascular disease after age 65 by level of systolic blood pressure at age 65. The incidence was similar (ns) in subjects with systolic blood pressures less than 120 mm Hg and 120 to 139 mm Hg. Compared with subjects with systolic blood pressures less than 120 mm Hg, however, the incidence was significantly higher in subjects with systolic blood pressures of 140 to 159 mm Hg (p < 0.05) and 160 mm Hg or greater (p < 0.01).

The average systolic blood pressure before age 65 was also strongly related to the development of cardiovascular disease (Table 1; Figure 2). Compared with the incidence in subjects with average systolic blood pressures of 120 mm Hg or less, the incidence was higher in subjects with average systolic blood pressures of 120 to 139 mm Hg (p = 0.06), 140 to 159 mm Hg (p < 0.01), and 160 mm Hg or greater (p < 0.01). Subjects whose average blood pressure was 160 mm Hg or greater were at more than 2.5 times the risk of those with an average systolic blood pressure less than 120 mm Hg. The incidence was similar regardless of whether the systolic blood pressure at age 65 or the average systolic blood pressure before age 65 was used (Figure 3).

**Table 1** Relationship Between Systolic Blood Pressure Measurements and the Development of Cardiovascular Disease After Age 65

<table>
<thead>
<tr>
<th>Blood pressure (mm Hg)</th>
<th>&lt;120</th>
<th>120-139</th>
<th>140-159</th>
<th>≥160</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single measurement of systolic blood pressure at age 65</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>37</td>
<td>93</td>
<td>120</td>
<td>116</td>
</tr>
<tr>
<td>Person-years</td>
<td>1625</td>
<td>4104</td>
<td>3388</td>
<td>2318</td>
</tr>
<tr>
<td>Incidence*</td>
<td>22.77</td>
<td>22.66</td>
<td>35.42</td>
<td>50.04</td>
</tr>
<tr>
<td>Rate ratio, unstratified†</td>
<td>1.00</td>
<td>1.00</td>
<td>1.56</td>
<td>2.20</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>0.68, 1.46</td>
<td>1.08, 2.24</td>
<td>1.53, 3.15</td>
<td></td>
</tr>
</tbody>
</table>

Average systolic blood pressure before age 65

| Cases                  | 37   | 155     | 97      | 77   |
| Person-years           | 1852 | 5494    | 2749    | 1340 |
| Incidence*             | 19.98| 28.21   | 35.29   | 57.46|
| Rate ratio, unstratified† | 1.00 | 1.41    | 1.77    | 2.88 |
| 95% Confidence interval| 0.99, 2.02 | 1.22, 2.57 | 1.98, 4.18 |

*Cases per 1000 person-years
†The reference category is a systolic blood pressure of <120 mm Hg.
By a stratified analysis, the number of years the systolic blood pressure was elevated above 160 mm Hg before age 65 also correlated strongly ($p < 0.001$) with post–age 65 risk of cardiovascular disease (Table 2). With one exception, the number of cardiovascular disease cases exceeded the number that would be expected in each stratum.

The rate of change of systolic blood pressure before age 65 also was related to the post–age 65 development of cardiovascular disease ($p < 0.01$) in the univariate analysis. For patients in the highest 20%, who had a rate of increase in systolic blood pressure of 3 mm Hg or more per 2 years, the rate ratio compared with patients in the lowest 20% was 1.37, with a 95% confidence interval of 1.03 to 1.82.

**Bivariate Analyses**

Despite a high correlation ($r = 0.72$) between systolic blood pressure at age 65 and average systolic blood pressure before age 65, both average systolic
blood pressure ($p < 0.05$) and systolic blood pressure at age 65 ($p = 0.01$) maintained a significant association with the risk of cardiovascular disease in the bivariate Cox regression analysis. Cumulative years of systolic blood pressure greater than 160 mm Hg ($p = 0.07$) and the slope of systolic blood pressure before age 65 ($p = 0.06$) each were marginally significant when entered into separate bivariate models that already included systolic blood pressure at age 65. In the subrange analysis (Table 3) the risk ratios for the development of cardiovascular disease were higher for increasing levels of systolic blood pressure at age 65 even after controlling for average systolic blood pressure before age 65. Similarly, risk ratios were higher for increasing levels of average systolic blood pressure, even after controlling for level of systolic blood pressure at age 65. Average pre-age 65 systolic blood pressure also remained important after controlling for the mean of the up to three systolic blood pressures at age 65 (Table 3). The risk ratio for the highest level of average pre-age 65 systolic blood pressure was significant, compatible with a small effect in increasing risk of cardiovascular disease ($p < 0.05$) After controlling for average pre-age 65 systolic blood pressure, greater degrees of pre-age 65 lability of systolic blood pressure had a marginal positive correlation with the risk of cardiovascular disease ($p = 0.08$), and lability did not affect risk in subjects with average systolic blood pressures 160 mm Hg or greater.

**Discussion**

These data support the univariate relationship of several measures of systolic blood pressure over time with increased risk of cardiovascular disease. In bivariate analyses the results consistently suggested a small increase in risk among those with higher average pre-age 65 blood pressures even after controlling for either a single measurement or multiple measurements of systolic blood pressure at age 65. This analysis did not address a second-order question, namely, the correlation of various blood pressure measurements with cardiovascular disease after controlling for other potential risk factors.

The finding that systolic blood pressure was an important correlate of cardiovascular mortality in the aged was consistent with data from several epidemiological surveys of the occurrence of cardiovascular disease in aging or aged populations. These surveys were based on measurements of blood pressure at one point in time, however.

Previous approaches to the problem of summarizing exposure over time have ranged from simple additive measures to complex mathematical models. The most common summary measures, used in studies of drug toxicity, smoking, or occupational exposures, have included both time and dose relationships. With a risk factor such as hypertension, analysis is further complicated by treatment regimens, which may alter the risk of developing disease. In addition, there may be variable amounts of data available on each person depending on the duration of the study and enrollment of the cohort. To address these problems only individuals who had never been treated for hypertension during the exposure period were selected, even though this restriction excluded individuals for whom lifetime exposure potentially would be most important. To eliminate potential bias, stratified analyses were used to control for variable pre-age 65 observation periods and life table methods were used to control for variable follow-up periods after age 65.

Several investigators have used past blood pressure experience to predict the future risk of developing hypertension. The methods employed have included the calculation of mean blood pressure, the calcula-

**Table 3**

<table>
<thead>
<tr>
<th>Blood pressure (mm Hg)</th>
<th>120–139</th>
<th>140–159</th>
<th>≥160</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single measurement of SBP at age 65, controlling for average SBP before age 65</td>
<td>Incidence rate ratios*</td>
<td>0.95</td>
<td>0.93</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>0.63, 1.42</td>
<td>0.93, 2.15</td>
<td>1.05, 2.80</td>
</tr>
<tr>
<td>Average SBP before age 65, controlling for a single measurement of SBP at age 65</td>
<td>Incidence rate ratios*</td>
<td>1.22</td>
<td>1.21</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>0.82, 1.81</td>
<td>0.77, 1.92</td>
<td>1.05, 2.92</td>
</tr>
<tr>
<td>Average SBP before age 65, controlling for average SBP at age 65</td>
<td>Incidence rate ratios*</td>
<td>1.18</td>
<td>1.22</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>0.79, 1.75</td>
<td>0.76, 1.95</td>
<td>1.04, 3.07</td>
</tr>
</tbody>
</table>

*The reference category is a systolic blood pressure of < 120 mm Hg
†Based on up to three separate measurements at first examination at age 65 or older
SBP = systolic blood pressure
tion of the rate of change or slope of the blood pressure by the least squares method or by the maximum likelihood model. The use of tracking correlations between two blood pressure measurements in the same person at two different times, and the use of growth curves or other modeling techniques. Such studies have shown that among adults, subjects who initially have higher blood pressures tend to remain high relative to other subjects in their cohort.

Fewer studies have used repeated measurement data to predict the risk of cardiovascular disease. Prentice and colleagues demonstrated that coronary heart disease was more closely associated with systolic blood pressure levels taken several years in the past than with the most recent readings. Other authors using age cohort analysis and a single blood pressure measurement, found that systolic blood pressure was more strongly associated with risk in the older age groups than was diastolic blood pressure.

Two prior analyses from Framingham used summary variables. Serum cholesterol was analyzed with several measures, including the slope, baseline, and most recent measures as well as the mean cholesterol level. The rate of change in serum cholesterol was a better predictor of outcome than was mean cholesterol, baseline cholesterol, or most recent cholesterol in a population aged 55 to 64 years. Gordon, Sorlie, and Kannel compared the predictive ability of a single casual blood pressure measurement versus the average of two measurements for four separate examinations. They found that the averages of both systolic and diastolic blood pressures were more predictive of cardiovascular disease than was one casual reading, but this effect was thought to be small and to be secondary to a more stable characterization of blood pressure from the inclusion of more numbers in the calculation. Shepard suggested that random error was decreased by averaging readings and that the reliability of blood pressure readings was markedly strengthened by measurements over time. To control for this measurement effect, we compared the predictive ability of the average of three measures at one point in time to the predictive ability of the average of measurements taken during the pre-age 65 experience. There was a persistent small effect even after controlling for the level of mean blood pressure at age 65. Furthermore, the ratios and confidence intervals for categories of average pre-age 65 systolic blood pressure were essentially identical when controlling for a single systolic blood pressure reading at age 65 as when controlling for the mean of all three readings at age 65.

Another approach to summarizing blood pressure is to calculate the rate of change and to correlate this rate with the occurrence of cardiovascular disease. Hofman and co-workers, using the entire Framingham cohort, found that blood pressure change during the first 12 years of the study, as calculated by the least squares method, was related to the risk of cardiovascular disease over 14 years of follow-up. This relationship persisted after controlling for entry blood pressure but not after controlling for the blood pressure measured at the twelfth year. We noted similar univariate results in the elderly population in Framingham, and we found that the slope of pre-age 65 systolic blood pressure was only of borderline statistical significance after controlling for systolic blood pressure at age 65.

Conclusion
Our data support the clinical teaching that one or several systolic blood pressure readings at a single examination are remarkably predictive of the future development of cardiovascular disease, even in old age. If additional readings are available from previous examinations, this additional information should increase predictive ability, especially if the past readings averaged 160 mm Hg or more.

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