Brief Review

Is the Relation of Systolic Blood Pressure to Risk of Cardiovascular Disease Continuous and Graded, or Are There Critical Values?

William B. Kannel, Ramachandran S. Vasan, Daniel Levy

Because epidemiologic data indicate a continuous incremental risk of cardiovascular disease (CVD) in relation to blood pressure (BP), hypertension treatment guidelines now recommend treating high-normal and mild BP elevations.1 Port and coworkers,2 analyzing Framingham Study data, challenge this assertion. They claim that Framingham data in actuality “contradict the concept that lower pressures imply lower risk and the idea that 140 mm Hg is a useful cut-off value for hypertension for all adults.” They suggest that there is an age- and sex-dependent threshold for “hypertension” and that a substantial proportion of the population currently deemed at increased risk are, in fact, not.

Their conclusion derives from the use of “logistic splines” methodology to examine the relation of systolic blood pressure (SBP) to CVD and all-cause mortality. They contend that previous linear logistic analysis depicting a continuous, graded relation is misleading and that there is actually a threshold at the 70th percentile of SBP for a person at a given age and sex. They also suggest that because BP increases steadily with age, the threshold also increases with age.2 By inference, Port et al seem to suggest that we return to the discarded concept that a “normal” systolic pressure is, roughly, “100+ years of age mm Hg.” They focus on all-cause mortality because “it is most free of misclassifications and, importantly the number of events is sufficiently high to allow accurate estimates of the shape of the relation with systolic blood pressure.” However, the more relevant outcome is CVD mortality and the CVD events promoted by hypertension unconfounded by non-CVD mortality, which could be associated with low BP. Furthermore, even a focus on CVD mortality, excluding the large majority of nonfatal events, needlessly reduces the amount of data on which to determine the shape of the BP–CVD incidence curve.

Normal BP for Age

A review of the evidence for a continuous, graded influence of BP on the incidence and mortality of CVD appears to be in order. The first consideration is the issue of what constitutes a “normal” BP. It is evident that in most developed countries, SBP rises with age.3 Diastolic blood pressure (DBP) rises with age until age 55 years, after which it declines in both sexes.4 However, in some less-developed countries where obesity and high salt intake are uncommon, adults experience little increase in BP with age.5 It is well established that the disproportionate rise in SBP relative to DBP with age is a consequence of a pathologic reduction in arterial compliance: as elastic fibers fragment, the elastic lamellae disrupt, and the collagen-to-elastin ratio in the arterial wall is altered.5

Usual Versus Optimal BP

The current concept of “desirable” BP is based not on what BP level is “usually” but rather on what is “optimal” (ie, associated with a low rate of hypertension-related CVD). It is clear from the Framingham Study and other prospective, epidemiologic data that at all ages, the risk of developing a CVD event increases with SBP and that at any given BP, the absolute vascular risk is substantially greater in the elderly (Table 1). The elderly do not endure their higher average BP well. Although their relative risk of suffering a CVD event might be a bit lower, this is offset by a much higher absolute age-adjusted risk. Examination of the SBPs at which CVD events occurred in Framingham Study male participants not on treatment indicates that 45% occurred at a SBP <140 mm Hg, the value that the logistic splines analysis of Port et al suggests as the threshold of increased risk.6

Incremental BP Risk at Framingham

Framingham Study data, based on 30 years of biennial, prospective surveillance of a cohort for CVD in relation to components of BP, concluded that there is a continuous, graded relation of SBP to the rate of development of CVD at all ages. Without resorting to any type of statistical modeling, no clear indication of a critical BP was discerned in any group from age 35 to 84 years (Table 1). Similar graded relations of BP to coronary heart disease (CHD) and all-cause mortality have been reported in several other cohorts.7–9

A large data set is required to obtain a precise estimate of the trend in CVD incidence at lower BP levels (eg, <140 mm Hg SBP). The Multiple Risk Factor Intervention Trial (MRFIT) provides observations on >350 000 male screenees followed up for CVD mortality.10 Data from MRFIT confirm a continuous and graded influence of SBP on
CHD mortality extending down into the range of SBP <140 mm Hg (Table 2). Perusal of the age-adjusted rates (without statistical modeling) based on 6122 events occurring at SBPs <140 mm Hg shows a stepwise increase in CHD mortality with each 10-mm Hg increment in pressure. The data show no indication of a threshold below which BP is unassociated with a lower CHD death rate. Age-specific data from this MRFIT study indicate a fairly consistent gradient of CHD mortality risk per mm Hg increment in SBP at all ages from 35 to 57 years. Based on the similar size of the regression coefficients for each age decade, there is little to suggest a shifting threshold of risk in relation to BP with advancing age in men (Table 3).

An even more definitive demonstration of the continuous, graded influence of BP on CVD risk comes from a recent meta-analysis of data from 61 prospective studies involving almost 1 million participants and 56 000 vascular deaths. This Prospective Studies Collaboration found that BP is related to vascular mortality, without any indication of a threshold down to 115/75 mm Hg. Persons aged 40 to 69 years had a doubling of risk of stroke or coronary mortality with every 20-mm Hg increment in SBP (or 10-mm Hg higher DBP) throughout the entire range of BP.

Incremental Risk Within Normal to High-Normal Range

Furthermore, recent analysis of the relation of nonhypertensive BP to development of CVD in the Framingham Study found a significant, graded influence of BP from optimal (<120/80 mm Hg) to normal (120 to 129/80 to 84 mm Hg) to high-normal (130 to 139/85 to 89 mm Hg) Joint National Committee VI stages among untreated men and women (Table 4). This incremental risk at nonhypertensive BPs was seen in age-adjusted analyses and was also noted after adjustment for coexistent risk factors. Compared with optimal BP, high-normal BP conferred a 1.6- to 2.5-fold risk of a “hard” CVD event.

Impact of Long-Term Antecedent BP on CVD Risk

Assessment of the true CVD risk gradient associated with increased BP must take into account the biologic as well as the analytic coefficient of variation. Recent analysis of Framingham Study data examined the relation of casual BP to subsequent risk of CVD, comparing the impact of a single current BP, the average of all readings over 10 years, and the average for all available values 11 to 20 years before baseline. It was found that antecedent SBP is an important determinant of future CVD events above and beyond current SBP. In particular, it was demonstrated that in nonhypertensive subjects (<140/90 mm Hg and not on treatment) in the 60-, 70-, and 80-year age groups, each standard deviation increase in current, recent, and remote SBP increased the risk of CVD by 12% to 45%, (ie, there was a continuous gradient of CVD risk).

### TABLE 1. Average Annual Incidence of CVD by SBP: Framingham Study 30-Year Follow-Up

<table>
<thead>
<tr>
<th>SBP, mm Hg</th>
<th>Men, Age Range, y</th>
<th>Women, Age Range, y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35–44</td>
<td>45–54</td>
</tr>
<tr>
<td>74–119</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>120–129</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>140–159</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>160–179</td>
<td>13</td>
<td>29</td>
</tr>
<tr>
<td>180–300</td>
<td>10</td>
<td>35</td>
</tr>
</tbody>
</table>

All SBP CVD incidence trends are significant except for ages 35–44 in women.

Source: Cupples and D’Agostino.6

### TABLE 2. Association of SBP and CHD Mortality in 347 978 Men Screened for MRFIT

<table>
<thead>
<tr>
<th>SBP, mm Hg</th>
<th>Men, n</th>
<th>CHD Deaths, n</th>
<th>Age-Adjusted Rate</th>
<th>Age-Adjusted Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>87 459</td>
<td>1412</td>
<td>11.6</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>120–129</td>
<td>98 834</td>
<td>2199</td>
<td>15.5</td>
<td>1.28 (1.19–1.36)</td>
</tr>
<tr>
<td>130–139</td>
<td>79 308</td>
<td>2511</td>
<td>20.8</td>
<td>1.66 (1.56–1.77)</td>
</tr>
<tr>
<td>140–159</td>
<td>65 865</td>
<td>3387</td>
<td>32.1</td>
<td>2.45 (2.30–2.61)</td>
</tr>
<tr>
<td>160–179</td>
<td>13 321</td>
<td>1120</td>
<td>48.4</td>
<td>3.42 (3.16–3.71)</td>
</tr>
<tr>
<td>180–209</td>
<td>2863</td>
<td>376</td>
<td>79.6</td>
<td>5.26 (4.68–5.90)</td>
</tr>
<tr>
<td>&gt;210</td>
<td>328</td>
<td>44</td>
<td>82.6</td>
<td>6.40 (4.74–6.65)</td>
</tr>
</tbody>
</table>

Relative risk was estimated by proportional-hazards regression model stratified by clinic and adjusted for age, race, income, cholesterol, cigarettes, and diabetes.

Source: Neaton et al.10

### TABLE 3. Impact of SBP on CHD Mortality in Men Screened for MRFIT

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Beta Coefficient (SE)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>35–44</td>
<td>0.0232 (0.0022)</td>
</tr>
<tr>
<td>40–44</td>
<td>0.0257 (0.0014)</td>
</tr>
<tr>
<td>45–49</td>
<td>0.0234 (0.0010)</td>
</tr>
<tr>
<td>50–54</td>
<td>0.0208 (0.0008)</td>
</tr>
<tr>
<td>55–57</td>
<td>0.0214 (0.0010)</td>
</tr>
<tr>
<td>All ages</td>
<td>0.0222 (0.0005)</td>
</tr>
</tbody>
</table>

*Increment in log hazard ratio per mm Hg increase in SBP. Risk was estimated by proportional-hazards regression stratified by clinic and adjusted for age, race, income, cholesterol, cigarettes, and diabetes. SE indicates standard error.

Source: Neaton et al.10
Likewise, the stroke risk in relation to increments in antecedent, current, recent, and remote long-term BP was recently examined in the Framingham Study. Models for antecedent long-term BP influence were adjusted for smoking, diabetes, and baseline BP, thereby reflecting the additional, independent, long-term BP impact. It was determined that in nonhypertensive persons (<140/90 mm Hg), the stroke risk increased substantially with each standard deviation increase in SBP in men and women at the current ages of 60 and 70 years.\textsuperscript{14} It thus appears from Framingham Study data that there is a significant and lingering gradient of risk in relation to SBPs below the alleged 140-mm Hg threshold suggested by the analysis of Port et al.

### Antecedent BP and Hypertension

Antecedent BP within the normal range has also been shown to be a determinant of future hypertension. Recent data from the Framingham Study indicate that development of hypertension over 4 years of observation in subjects aged <65 years occurred 7 times more often in subjects with high-normal than optimal BPs and over that age, at 3 times the rate.\textsuperscript{15} This is another reason for concern about even minimally elevated (nonhypertensive) BP.

### Role of Pulse Pressure

The influence of SBP on CVD should be evaluated, taking the accompanying DBP into account. Data from the Framingham Study indicate that at SBPs of 120 to 139 mm Hg in the elderly, the relative risk of CHD increases the lower accompanying DBP.\textsuperscript{16} Hence, pulse pressure appears to emerge as an important BP determinant of CVD incidence in the elderly.\textsuperscript{17} Perusal of Framingham Study data indicates a continuous, graded influence of pulse pressure on CVD incidence (Table 5).\textsuperscript{18} Thus, rather than the threshold for BP risk changing with advancing age, as alleged by the spline analysis of Port et al, it appears that it is the influence of the different components of BP that changes.

### Perspectives

There is overwhelming evidence of a continuous, graded influence of SBP on CVD morbidity and mortality at all ages in both sexes. An optimal BP for avoiding CVD is <140/90 mm Hg, and there is no clearly defined critical BP that distinguishes normal from abnormal. It is the level of BP that kills, not arbitrarily defined hypertension. Because the hazard of CVD increases in a continuous, graded fashion in relation to BP, a population approach as advocated by Rose\textsuperscript{19} must accompany efforts to detect and treat elevated values. For cost-effective treatment of persons with prehypertension and stage 1 hypertensive BPs, multivariable risk stratification is required, and the goal of therapy should be to improve the global risk.\textsuperscript{1,20} The hazard of any level of BP elevation is increased when there is concomitant dyslipidemia, proteinuria, diabetes, or already existing overt renal disease, coronary disease, or peripheral artery disease.\textsuperscript{1} The importance of what appear to be trivial differences in BP, even within the high-normal BP range, should not be underestimated. The extra effort needed to lower the BP down to the recommended goals for avoiding CVD is worthwhile. Further clinical trials are needed to address the unanswered question about the efficacy of individualized treatment of patients whose BPs are <160 mm Hg systolic and 90 mm Hg diastolic by using global risk assessment to set goals for BP lowering.

### Acknowledgments

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### Table 4: Relation of Nonhypertensive BP Categories to Development of Hard CVD in Framingham Study Subjects, Ages 35–90 Years

<table>
<thead>
<tr>
<th>BP Category (mm Hg)</th>
<th>Women</th>
<th></th>
<th></th>
<th>Men</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age-Adjusted Rate</td>
<td>HR*</td>
<td></td>
<td>Age-Adjusted Rate</td>
<td>HR*</td>
<td></td>
</tr>
<tr>
<td>Optimal (&lt;120/80)</td>
<td>1.9%</td>
<td>1.0</td>
<td></td>
<td>5.8%</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Normal (120–129/80–84)</td>
<td>2.8%</td>
<td>1.5 (0.9–2.5)</td>
<td></td>
<td>7.6%</td>
<td>1.3 (1.0–1.9)</td>
<td></td>
</tr>
<tr>
<td>High-normal (130–139/85–89)</td>
<td>4.4%</td>
<td>2.5 (1.6–4.1)</td>
<td></td>
<td>10.1%</td>
<td>1.6 (1.1–2.2)</td>
<td></td>
</tr>
<tr>
<td>P for trend across categories</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Kannel.\textsuperscript{18}

### Table 5: Risk of CV Events by Pulse Pressure: 30-Year Follow-Up of the Framingham Study

<table>
<thead>
<tr>
<th>Pulse pressure, mm Hg</th>
<th>Age-Adjusted Rate per 1000</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age 35–64 Years</td>
<td>Age 65–94 Years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>9</td>
<td>4</td>
<td>2</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>13</td>
<td>6</td>
<td>16</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>16</td>
<td>7</td>
<td>32</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>22</td>
<td>10</td>
<td>39</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>33</td>
<td>16</td>
<td>58</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Increment per 10 mm Hg</td>
<td>19.7%</td>
<td>20.9%</td>
<td>23.4%</td>
<td>10.5%</td>
<td></td>
</tr>
</tbody>
</table>

Source: Kannel.\textsuperscript{18}
References


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