Does the Relation of Blood Pressure to Coronary Heart Disease Risk Change With Aging?

The Framingham Heart Study

Stanley S. Franklin, MD; Martin G. Larson, ScD; Shehzad A. Khan, BS; Nathan D. Wong, PhD; Eric P. Leip, MS; William B. Kannel, MD; Daniel Levy, MD

Background—We examined the relative importance of diastolic (DBP), systolic (SBP) and pulse pressure (PP) as predictors of coronary heart disease (CHD) risk in different age groups of Framingham Heart Study participants.

Methods and Results—We studied 3060 men and 3479 women between 20 and 79 years of age who were free of CHD and were not on antihypertensive drug therapy at baseline. Cox regression adjusted for age, sex, and other risk factors was used to assess the relations of BP indexes to CHD risk over a 20-year follow-up. In the group <50 years of age, DBP was the strongest predictor of CHD risk (hazard ratio [HR] per 10 mm Hg increment, 1.34; 95% CI, 1.18 to 1.51) rather than SBP (HR, 1.14; 95% CI, 1.06 to 1.24) or PP (HR, 1.02; 95% CI, 0.89 to 1.17). In the group 50 to 59 years of age, risks were comparable for all 3 BP indexes. In the older age group, the strongest predictor of CHD risk was PP (HR, 1.24; 95% CI, 1.16 to 1.33). When both SBP and DBP were considered jointly, the former was directly and the latter was inversely related to CHD risk in the oldest age group.

Conclusions—With increasing age, there was a gradual shift from DBP to SBP and then to PP as predictors of CHD risk. In patients <50 years of age, DBP was the strongest predictor. Age 50 to 59 years was a transition period when all 3 BP indexes were comparable predictors, and from 60 years of age on, DBP was negatively related to CHD risk so that PP became superior to SBP. (Circulation. 2001;103:1245-1249.)

Key Words: blood pressure ■ hypertension ■ pulse pressure ■ coronary disease

Despite the acknowledged importance of hypertension as a precursor of cardiovascular complications, considerable uncertainty still exists regarding the relative importance of the various components of blood pressure (BP) in predicting cardiovascular disease risk. Since the introduction of the sphygmomanometer at the beginning of the 20th century, the relative importance of diastolic (DBP), systolic (SBP) and pulse pressure (PP) as indicators of hypertensive cardiovascular disease risk has undergone several changes. Initially, DBP was thought to be the best measure of risk, but in 1971, Kannel et al. using early follow-up from the Framingham Heart Study, concluded, “There was a trend of declining relative importance of DBP with a corresponding increase in the importance of SBP with advancing age” as predictors of coronary heart disease (CHD) risk. This publication, confirmed subsequently by other studies, has been influential in gradually shaping medical opinion that SBP, in addition to DBP, is a more powerful predictor of CHD risk. Subsequent national and international guidelines for the classification of BP and for the diagnosis and management of hypertension have defined cardiovascular disease risk by the elevation of DBP and/or SBP, with the higher of the 2 establishing severity.

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More recently, the relative importance of BP indexes as predictors of CHD risk was reexamined in the original Framingham cohort, with longer follow-up than in the 1971 study and with the use of newer techniques of multivariate Cox regression to eliminate confounding. After adjustment for age, sex, and other risk factors, PP was found to be a robust predictor of CHD events; others have noted similar findings. That recent study was limited to Framingham subjects between 50 and 79 years of age; the question of which BP component or components best predict CHD risk across a wide age range has not been fully evaluated.

In the present study, we extended the age range of study subjects by combining the original Framingham Heart Study cohort with the Framingham Offspring Study cohort; this provided an age distribution of 20 to 79 years. Furthermore, by combining both Framingham cohorts, the study sample was more than tripled and the number of CHD events was...
almost doubled compared with our recent publication. The goal of the present study was to define the roles of SBP, DBP, and PP as predictors of CHD risk in different age groups.

Methods

Overview

The Framingham Heart Study began in 1948 with the enrollment of 5209 men and women, 28 to 62 years of age at entry, with subjects undergoing repeated examinations biennially. In 1971, 5124 men and women were enrolled in the Framingham Offspring Study; these were the children or the spouses of the children of the original Framingham Heart Study participants. They underwent repeated examinations approximately every 4 years. Each examination included an extensive cardiovascular disease history and physical examination, 12-lead ECG, and various blood chemistries. Morbidity and mortality were continuously monitored by clinic examinations, hospital surveillance, and communication with participants who did not attend a clinic examination. A panel of 3 experienced investigators reviewed all new cardiovascular events. Detailed descriptions of study design have been published elsewhere.

Study Sample

This investigation comprised 2033 subjects from the original Framingham Heart cohort, as described in a previous publication, and 4506 subjects from the Framingham Offspring Study. Baseline examinations for subjects from the original Framingham Heart cohort were the earliest examination at which HDL cholesterol was measured; usually this was the 11th biennial examination, but for some it was the 10th or 12th. The baseline examination for subjects from the Framingham Offspring Study was the first examination cycle. Study subjects in the original cohort were between 50 and 79 years of age at baseline to be eligible, and subjects from the offspring cohort were between 20 and 70 years of age at baseline. All subjects had no history or clinical evidence of CHD, and they were undergoing repeated examinations biennially. In 1971, 5124 men and women, 28 to 62 years of age at entry, with subjects who had no history or clinical evidence of CHD, up to the date of the 5th examination cycle in the original cohort; the definition was fasting blood glucose $>$ 126 mg/dL and/or for a 10 mm Hg increase in BP. Models were adjusted for age, sex, body mass index, cigarette smoking (yes/no), diabetes mellitus (yes/no), and ratio of total to HDL cholesterol. SAS statistical software (SAS Institute) was used.

We also assessed whether, across ages, there was constancy of the risk contributed by SBP relative to DBP. Cox models with both SBP and DBP were fitted by age groups (i=1 to 5 for groups <$40$, 40 to 49, 50 to 59, 60 to 69, and 70 to 79 years of age, respectively). The difference between SBP and DBP coefficients, $\Delta = \beta_{SBP} - \beta_{DBP}$, and the corresponding variance, $\text{Var}(\Delta)$, were estimated for each age group. The average age for subjects in each age group, $X_i$, was computed. Weighted regression was used for the model $\Delta = \alpha_i + \alpha_i X_i$, with weights equal to inverse variances, $W_i = 1/\text{Var}(\Delta)$. The test statistic, $t = \alpha_i/\text{se}(\alpha_i)$, was referred to as the t distribution with 3 df. Finally, a simulation procedure was done to validate the probability value. For this, 10,000 replicates of the data were generated under the null hypothesis of no age-related change in $\beta_{SBP} - \beta_{DBP}$. In each replicate, Cox models and weighted regressions were run as outlined above. Across replicates, we counted the number of times the test statistic was obtained as large in absolute value as found in the real data.

In secondary analyses, we introduced a time-dependent antihypertensive treatment variable to incorporate treatment status after the baseline examination. We also tested for a difference in regression coefficients between men and women. Further analyses were performed for hard CHD end points.

Data Analysis

The relations of CHD hazard ratios (HRs) to single (SBP, DBP, or PP) and dual (SBP and DBP) BP components as continuous variables were evaluated by Cox proportional-hazards regression separately for the 3 age groups ($<$50, 50 to 59, and $\geq 60$ years). HRs were estimated, along with 95% CIs, for a 10 mm Hg increase in BP. Models were adjusted for age, sex, body mass index, cigarette smoking (yes/no), diabetes mellitus (yes/no), and ratio of total to HDL cholesterol. SAS statistical software (SAS Institute) was used.

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Results

Demographic and Clinical Characteristics

The sample comprised 3060 men and 3479 women (Table 1). The mean follow-up time was 17 years, during which 807 subjects developed CHD (532 men and 275 women). Of the initial CHD events, 374 were angina pectoris or coronary insufficiency, 336 were myocardial infarction with survival $>1$ day, and 97 were CHD deaths. Older subjects at baseline had higher ratios of total to HDL cholesterol, higher body mass index, higher prevalence of diabetes, but a lower rate of cigarette smoking than did younger subjects. SBP and PP were higher in older subjects. The correlation coefficients

<table>
<thead>
<tr>
<th>TABLE 1. Clinical Characteristics by Age Groups</th>
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<tbody>
<tr>
<td>Clinical Characteristics</td>
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<tr>
<td>--------------------------</td>
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<tr>
<td>Sex, M/F</td>
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<tr>
<td>CHD onset, M/F</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Ratio of total to HDL cholesterol</td>
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<tr>
<td>Body mass index, kg/m²</td>
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<tr>
<td>Diabetes, %</td>
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<tr>
<td>Cigarette smoker, %</td>
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<tr>
<td>BP, mm Hg</td>
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<tr>
<td>SBP</td>
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<td>DBP</td>
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<td>PP</td>
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</tbody>
</table>

*Comparison of characteristics across 3 age groupings.
The combination of SBP and DBP in the same model is predictive of CHD risk and SBP was not; HRs were 1.42, 1.14 for DBP, whereas they increased with increasing age for PP. HRs tended to decrease with increasing age for DBP, whereas they increased with increasing age for PP.

### Single BP Component Models by Age

HRs associated with a 10 mm Hg increase in BP in the group <50 years of age were 1.34 for DBP (P < 0.0001), 1.14 for SBP (P = 0.001), and 1.02 for PP (P = 0.79) (Table 2). In the group 50 to 59 years of age, HRs were comparable for all 3 components: SBP, 1.08 (P = 0.01); DBP, 1.14 (P = 0.09); and PP, 1.11 (P = 0.02). In the group ≥60 years, HRs were 1.24 for PP (P < 0.001), 1.17 for SBP (P < 0.001), and 1.12 for DBP (P = 0.08). HRs tended to decrease with increasing age for DBP, whereas they increased with increasing age for PP.

### Dual BP Component Models by Age

The combination of SBP and DBP in the same model is shown in Table 3. In the group <50 years of age, DBP was predictive of CHD risk and SBP was not; HRs were 1.42 (P = 0.001) and 0.95 (P = 0.49), respectively. In the group 50 to 59 years of age, neither SBP (P = 0.07) nor DBP (P = 0.74) predicted CHD risk, possibly because of collinearity. In the group ≥60 years, the combination of SBP (HR, 1.24; P < 0.0001) and DBP (HR, 0.83; P = 0.02) showed a modest improvement over SBP alone.

Plots of β(SBP)−β(DBP) for the 5 age groups, along with their 95% CIs, are shown in the Figure. The estimated slope per decade of age from the weighted regression procedure was 0.29 (SE = 0.046, t = 6.27, P = 0.008). The validation probability value also was 0.008 from 10,000 simulations under the null hypothesis of no age-related slope. The differences in β coefficients for predicting CHD risk favored DBP over SBP in subjects <50 years of age and SBP over DBP in patients ≥60 years of age, with the transition occurring roughly between the ages of 50 and 59 years.

### Secondary Analyses

During follow-up, 1728 subjects (26.4%) began antihypertensive treatment: 17.5% of subjects <50 years of age at baseline, 39.4% of subjects 50 to 59 years of age, and 42.8% of subjects ≥60 years. Analyses were repeated with postbaseline antihypertensive treatment entered as a time-dependent variable. Similar results were obtained with slight attenuation of the coefficients and probability value for the BP variables.

Analysis by sex showed DBP predominance in predicting CHD risk in the group <50 years of age and SBP and PP predominance in the group ≥60 years of age for both sexes. There were no statistically significant sex differences in BP coefficients in any age group for any BP component.

The analyses for Tables 2 and 3 were rerun with hard CHD end points, which reduced the total end points from 807 to 505. The findings remained generally the same: For Table 2, each HR for hard CHD was within 10% of the corresponding estimate for total CHD; for Table 3, a similar pattern of HRs was observed, but with fewer events, only 1 was significant (SBP at ≥60 years of age). Finally, adjustment for heart rate in Tables 2 and 3 had no discernible effect on BP coefficients.

### Table 3. Proportional-Hazard Regression Coefficients Relating Incidence of CHD to Dual BP Indexes of SBP and DBP by Age Groups

<table>
<thead>
<tr>
<th>Dual BP Components*</th>
<th>β†</th>
<th>SE†</th>
<th>Wald x²†</th>
<th>HR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;50 y SBP</td>
<td>0.05</td>
<td>0.07</td>
<td>0.5</td>
<td>0.95 (0.83–1.09)</td>
</tr>
<tr>
<td>DBP</td>
<td>0.35</td>
<td>0.11</td>
<td>10.9</td>
<td>1.42 (1.15–1.74)</td>
</tr>
<tr>
<td>Age 50–59 y SBP</td>
<td>0.09</td>
<td>0.05</td>
<td>3.4</td>
<td>1.10 (0.99–1.21)</td>
</tr>
<tr>
<td>DBP</td>
<td>0.03</td>
<td>0.09</td>
<td>0.1</td>
<td>0.97 (0.81–1.16)</td>
</tr>
<tr>
<td>Age ≥60 y SBP</td>
<td>0.21</td>
<td>0.04</td>
<td>33.7</td>
<td>1.24 (1.15–1.33)</td>
</tr>
<tr>
<td>DBP</td>
<td>0.19</td>
<td>0.08</td>
<td>5.2</td>
<td>0.83 (0.71–0.98)</td>
</tr>
</tbody>
</table>

*Both SBP and DBP appear in the same model, adjusted for age, sex, body mass index, cigarette smoking, diabetes mellitus, and ratio of total to HDL cholesterol.
†HR was associated with a 10 mm Hg increase in BP.
‡Wald x² = (β/SE)².
§P < 0.05, |P < 0.001.
Discussion
This study demonstrated that with advancing age there was a gradual shift from DBP to SBP and eventually to PP as predictors of CHD risk. In patients <50 years of age, DBP was a stronger predictor of CHD risk than SBP or PP. Age 50 to 59 was a transition state when all 3 indexes were comparable, and from age 60 years on, when considered together with SBP, DBP was negatively related to CHD risk and PP emerged as the best predictor.

Hemodynamic Mechanisms of Risk
The finding that SBP and DBP both predicted CHD risk in the group <50 years of age is consistent with increased peripheral resistance being dominant in determining CHD risk in young hypertensives.\textsuperscript{10,20–23} Similarly, the finding that PP and SBP dominate as predictors of CHD risk in the group ≥60 years of age is consistent with large artery stiffness contributing to CHD risk in older hypertensives.\textsuperscript{10,20–23}

The finding that DBP was a stronger predictor of CHD risk than SBP in patients <50 years of age is not consistent with increased small vessel resistance alone\textsuperscript{20,21} and therefore suggests the additional effect of pulse wave reflection on the recording of BP in the upper limb.\textsuperscript{23–25} In young normotensive adults, when the body is fully grown but the aorta is still very distensible, peripheral amplification of the arterial pulse wave will result in considerably higher brachial artery peak SBP compared with SBP values in the ascending aorta.\textsuperscript{23–25} In young adult hypertensives, however, there is a functional increase in large artery stiffness secondary to increased vascular resistance with a resulting decrease in brachial artery pulse wave amplification. This may partially offset the peripheral rise in SBP without affecting the rise in DBP; thus, peripheral DBP becomes superior to SBP as a predictor of CHD risk.

Age-related differences favoring DBP over SBP in predicting CHD risk in young adults were noted in some\textsuperscript{3,26–28} but not in all previous studies.\textsuperscript{29} The finding that there was a preference for DBP over SBP for the group <50 years of age in an early Framingham report\textsuperscript{1} and in the present study was confirmed in the Whitehall British male civil servants study\textsuperscript{26} and in a Norwegian study of men.\textsuperscript{27} Follow-up of middle-aged men screened for the Multiple Risk Factor Intervention Trial\textsuperscript{28} revealed a superiority of DBP for subjects 35 to 39 years of age, whereas SBP was a better predictor of CHD mortality for subjects 40 to 57 years of age. In contrast, in the Western Collaborative Study of Californian Male Employees,\textsuperscript{29} SBP was the superior predictor for men 39 to 59 years of age. The observed differences in BP predictors of CHD risk in these studies may be due to differences in population characteristics or differences in BP measurements.

Middle-Aged and Elderly Hypertensive Subjects
With aging and the development of structural arterial stiffening, there is a gradual reduction in peripheral amplification.\textsuperscript{23,25} In addition, there is an increase in amplitude and velocity of incident waves, so left ventricular ejection becomes affected by early wave reflection during systole rather than diastole, further increasing aortic SBP and adding to afterload.\textsuperscript{30} Given the same stroke volume and ejection rate, increased central arterial stiffness and early wave reflection will produce a higher brachial artery SBP, a lower DBP, and a wider PP (ie, isolated systolic hypertension). The increased CHD risk of isolated systolic hypertension may be due not only to elevated peak SBP in the aorta (ie, increased afterload) but also to low DBP (ie, decreased coronary blood flow).\textsuperscript{23}

Predictive Role of BP Indexes Across the Age Spectrum
The changing contribution of SBP relative to DBP in the diagnosis of CHD risk is continuous and graded over an extended adult age range (the Figure). Because peak SBP at the ascending aorta largely determines cardiac afterload, distortion of the peripheral SBP by wave reflection most likely accounts for the age-related change in BP indexes that predict CHD risk. In young hypertensive individuals, diminished peripheral amplification of SBP by altered wave reflection results in a greater peripheral increase in DBP than in SBP despite a parallel rise in central SBP and DBP. Consequently, elevated peripheral DBP is superior to SBP in predicting CHD risks. However, with age-dependent increases in large artery stiffness, there is a narrowing of differences between central and peripheral SBP as a result of both diminished peripheral amplification and early wave reflection, thereby gradually improving the utility of peripheral SBP while diminishing that of DBP in the prediction of CHD risk. From age 60 years on, with central and peripheral PPs approximating each other, PP becomes the dominant predictor of CHD risk by incorporating both the positive predictive role of SBP and the negative predictive role of DBP.

Clinical Implications
The finding in the present study that BP measured in young and middle-aged adults is positively related to CHD risk in later life implies that the risk of cardiovascular disease starts early in adult life. These findings are confirmatory of the University of Glasgow Student Study, which showed that BP in men at a mean age of 20.5 years—a time when most youths were not yet hypertensive—predicted future cardiovascular disease.\textsuperscript{31} Thus, the onset of CHD risk begins long before middle age, and primary preventive measures may be more effective if applied earlier in the course of the disease.

The finding that DBP is stronger than SBP as a predictor of CHD risk in young adults, whereas the opposite is true in older persons, emphasizes the importance of the roles of both DBP and SBP in the staging of hypertension.\textsuperscript{7,9} The favoring of diastolic over systolic hypertension by earlier generations of physicians may have been due to the emphasis of hypertension as a young person’s disease.\textsuperscript{32} We must also recognize, however, that hypertension has become largely a disease of older people and that inadequate control of systolic rather than diastolic hypertension is by far the more pressing public health problem.\textsuperscript{8} Furthermore, the greatest burden of hypertension-related cardiovascular disease at present occurs in the middle-aged and elderly, in whom systolic hypertension predominates.\textsuperscript{8}
Study Strengths and Limitations
This study confirms earlier findings from Framingham and extends them to a larger, younger cohort free of clinical CHD and not on antihypertensive therapy at baseline. There are potential limitations regarding the interpretation of these data. Because few women in the youngest age group subsequently developed CHD, our findings in this group require confirmation.

Although a postbaseline treatment bias is possible, we found little evidence to support this conclusion. When a time-dependent covariate term for antihypertensive therapy was used in the model, the magnitude of coefficients for BP components was reduced slightly but did not affect the pattern of age-related indexes for predicting CHD risk.

Because the study sample consisted almost exclusively of whites, most of whom were middle class, results may not apply to other ethnic or socioeconomic groups. Indeed, there is evidence of an even greater BP-dependent increase in aortic stiffness in blacks than in whites.33 Finally, the inferences to underlying hemodynamic mechanisms in this study are not based on direct physiological measurements. Studies now underway in Framingham and elsewhere that include pulse-wave velocity measurements and applanation tonometry for recording high-fidelity central pulse-wave forms may eventually clarify these issues.

In conclusion, aging plays an important role in influencing the relation of BP indexes to CHD risk. In patients <50 years of age, DBP is a stronger predictor of CHD risk than SBP or PP, suggesting that increased peripheral resistance and altered peripheral pulse-wave amplification are dominant in determining CHD risk. Between the ages of 50 and 59 years, all 3 BP indexes are similarly predictive of CHD risk, suggesting a balance between small vessel resistance and large artery stiffness. From age 60 years on, there is a shift in favor of PP and SBP as predictors of CHD risk, suggesting that large artery stiffness with early wave reflection are the dominant hemodynamic determinants of risk. Although DBP predominates over SBP in young adults, the greatest burden of cardiovascular disease occurs in older subjects with isolated systolic hypertension and a wide PP.

Acknowledgments
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References
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