Antecedent Blood Pressure and Risk of Cardiovascular Disease
The Framingham Heart Study

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Background—Casual blood pressure (BP) is a powerful predictor of risk of cardiovascular disease (CVD), but a single BP determination may not accurately reflect the residual impact of antecedent BP levels on vascular risk. It is unclear whether time-averaged past BP measures incrementally improve CVD risk assessment.

Methods and Results—We used sex- and age-specific multivariable Cox regression to evaluate the association of current BP (at baseline), recent antecedent BP (average of readings for all available examinations 1 to 10 years before baseline), and remote antecedent BP (average for all available examinations 11 to 20 years before baseline) with the 10-year risk of CVD in 2313 Framingham Study subjects (910 men, 1403 women) free of CVD at baseline. During follow-up, 899 incident initial CVD events were observed (479 in women). In multivariable models incorporating established CVD risk factors, recent and remote antecedent BP predicted CVD risk incrementally over current BP. This effect was consistent in multiple subgroups: men and women, older and younger age groups, and lower and higher BP groups. The relations of antecedent BP to CVD risk were consistent for systolic BP, diastolic BP, and pulse pressure.

Conclusions—Antecedent BP is an important determinant of future risk of CVD events above and beyond current BP. When available, use of long-term average BP may improve the prognostic utility of conventional CVD risk prediction that is based on current BP. Our findings suggest that effective prevention of CVD requires adequate control of BP throughout life. (Circulation. 2002;105:48-53.)

Key Words: blood pressure ■ cardiovascular diseases ■ epidemiology ■ risk factors

Elevated levels of systolic and diastolic blood pressure (BP) are associated with an increased risk of cardiovascular disease (CVD) events.1–3 Consequently, BP is a key component of CVD risk prediction algorithms.4–6 These algorithms typically use BP measured at a single clinic visit (BP at the time of risk assessment, or “current” BP). Individuals are exposed to varying levels of BP during their lifetime, however, and measurement of BP at a single point in time may not accurately reflect an individual’s past BP experience. Therefore, investigators have used time-averaged BP to complement current BP for characterizing long-term BP. In these studies, time-averaged BP was a better predictor of echocardiographic left ventricular hypertrophy7 and the degree of carotid stenosis.8 On the basis of these observations, we hypothesized that time-averaged antecedent BP would predict clinical CVD events incrementally over a single-occasion current BP reading. Accordingly, we examined prospectively the independent association of antecedent BP measures with the incidence of CVD events (coronary, cerebrovascular, and peripheral vascular disease events and heart failure) in a large community-based sample.

Methods

Study Design and Sample
The selection criteria and study design of the Framingham Heart Study have been described previously.9 Subjects who attended routine biennial examinations between 1950 and 1995 were included in the present investigation if they (1) underwent an examination within a year of attaining the age of 60, 70, or 80 years (referred to as baseline examination and baseline ages, respectively) during this time period and were free of CVD at the baseline age (2) attended at least 4 of 5 examinations in each of the 2 previous decades preceding the attainment of the baseline age. Original cohort subjects who were included at a given age remained eligible for the investigation if they reached the next qualifying baseline age free of CVD.

Measurement of BP and Covariates
At each examination, study participants underwent a physical examination (with a medical history), laboratory assessment of CVD risk...
Follow-Up and Outcome Events
All study subjects were under continuous surveillance for the development of CVD events and death. Information about CVD events on follow-up was obtained with the aid of medical histories, physical examination results at the Heart Study, hospitalization records, and communication with personal physicians. All suspected new events were reviewed by a panel of 3 experienced investigators, who evaluated all pertinent medical records.

Our primary outcome of interest was the incidence of any of the following first CVD events during a follow-up period of 10 years after attainment of the baseline age: death due to CVD, coronary heart disease (myocardial infarction [recognized or unrecognized], angina, and coronary insufficiency), cerebrovascular disease (stroke or transient ischemic attack), peripheral vascular disease (intermittent claudication), and congestive heart failure. Criteria for these end points have been described previously.10

Statistical Methods
Subjects were categorized into 3 groups based on attaining the baseline ages of 60, 70, or 80 years during the study period. BP was treated as a continuous variable. At each baseline age and for each BP component (SBP, DBP, and pulse pressure [PP]), we defined 3 BP measures for study subjects: (1) current BP, at the baseline age; (2) recent antecedent BP, the average of all available BP readings during the decade preceding the baseline age (ie, BP at ages 50 to 59 years, 60 to 69 years, and 70 to 79 years for the baseline ages of 60, 70, and 80 years, respectively); and (3) remote antecedent BP, the average of all available BP readings obtained 11 to 20 years before the attainment of the baseline age (ie, BP at ages 40 to 49 years, 50 to 59 years, and 60 to 69 years for the baseline ages of 60, 70, and 80 years, respectively).

Sex- and age-specific multivariable Cox proportional hazards regression models11 were fitted to examine the association of BP measures with the incidence of a first CVD event over a follow-up period of 10 years, adjusted for established risk factors defined at the baseline examination (serum total cholesterol, smoking, body mass index, diabetes mellitus, and use of antihypertensive medications). Separate models were examined for current, recent antecedent, and remote antecedent pressures. We estimated hazard ratios for CVD events for a 1-SD increment of the current BP component. Separate analyses were performed for SBP, DBP, and PP. We did not investigate models that incorporated SBP and DBP jointly or evaluate the relative importance of individual BP components at different ages; those findings have been reported previously.12,13

We investigated the incremental prognostic utility of antecedent BP in multivariable Cox models that already adjusted for current BP. We also examined whether current BP entered into multivariable models that incorporated recent antecedent BP measures.

Secondary Analyses
Antecedent BP measures may predict risk of CVD better than current BP simply because the former averaged several measurements, whereas the latter, as a single determination, was more susceptible to regression dilution bias.14 Therefore, we performed supplementary analyses comparing current BP with a single random measure of recent and remote antecedent BP.

For individuals on treatment for hypertension, current on-treatment BP might not reflect vascular risk as well as antecedent BP. Hence, we adjusted for antihypertensive medication use in our primary analyses. We also performed the following secondary analyses: analyses excluding all individuals treated for hypertension at the baseline age, analyses restricted to treated hypertensives, and analyses limited to nonhypertensive individuals. Because the sample sizes for the latter analyses were smaller, we pooled sexes and adjusted for sex in addition to other covariates.

In addition, because not all subjects at a given baseline age reached that age in the same calendar period, the effect of calendar time period on the relations between BP and incidence of CVD events were examined in Cox models incorporating interaction terms (BP–calendar decade; BP–calendar year). All analyses were performed with the SAS system version 8.0 procedures PHREG.15 All probability values reported are 2-sided, with a value of P<0.05 indicating statistical significance.

Results
Study Sample Characteristics
There were 2313 unique subjects (1403 women, 910 men) who contributed data for the present investigation for ≥1 baseline age. Across all baseline ages, 3739 eligible clinic examination attendees (2348 women, 1391 men) attended a biennial examination within 1 year of attaining the baseline ages of 60 (729 women, 522 men), 70 (976 women, 560 men) or 80 (643 women, 309 men) years, were free of CVD at the qualifying examination, and had information on their BP over the previous 2 decades. The baseline characteristics of these subjects are summarized in Table 1.

Incidence of CVD Events on Follow-Up
During a follow-up period of 10 years after attainment of the baseline age, there were 899 first CVD events (479 in women) among study subjects. Of these, 258 events occurred among participants 60 years old at baseline (109 events in women); 399 events were experienced by subjects 70 years old at baseline (211 events in women); and the remaining 242 events occurred in individuals 80 years old at baseline (159 events in women).

Association of Antecedent BP Measures and Incidence of CVD Events
Table 2 displays the results of sex-specific multivariable analyses examining the association of BP measures with the 10-year incidence of CVD events in each age group. Generally, risk factor–adjusted hazard ratios for CVD events were higher for antecedent BP measures than corresponding hazard ratios for current BP. For instance, among 80-year-old men, the adjusted hazard ratio for a CVD event associated with a 1-SD increment of current SBP were 1.35 (95% CI 1.08 to 1.68) for current SBP, 1.83 (95% CI 1.31 to 2.54) for averaged recent antecedent SBP, and 1.97 (95% CI 1.45 to 2.67) for averaged remote antecedent SBP. In addition, averaged recent and remote antecedent BP remained associated with an increased risk of CVD events even after adjustment for current BP (Table 2). These observations were broadly consistent for men and women, for each of the 3 age groups examined, and for SBP, DBP, and PP (data for PP not shown). The relative importance of individual BP components varied with age, as reported previously.15

When we examined multivariable models that incorporated recent antecedent BP measures, current BP did not incrementally predict risk of CVD events in any age group or sex (data not shown).
Secondary Analyses

Although the risk factor–adjusted hazard ratios for antecedent BP measures decreased when we selected a single-occasion random reading instead of time-averaged values, several antecedent BP measures remained significantly associated with increased risk of CVD events even after adjustment for current BP (data not presented).

In analyses restricted to individuals not using antihypertensive medications and nonhypertensive participants (Table 3 A and B), hazard ratios for antecedent SBP and PP declined considerably in younger subjects; the statistical significance of antecedent pressures was still retained in several instances. The association of antecedent BP with CVD risk was also evident in treated hypertensives (data not presented). None of the various calendar period–BP interaction terms was statistically significant.

Discussion

Atherosclerotic vascular disease evolves slowly and is undoubtedly related to cumulative exposure of individuals to CVD risk factors over a lifetime.16,17 BP is a prime example of such a lifelong exposure. Consequently, previous analyses1 investigating the relations of casual BP to various analyses1 investigating the relations of casual BP to antecedent BP with CVD risk was also evident in treated hypertensives (data not presented). None of the various calendar period–BP interaction terms was statistically significant.

Comparison With Previous Studies

Several investigators19–22 have reported that single BP measurements predicted risk of CVD outcomes over a follow-up period of 15 to 50 years, although the impact of BP diminished with increasing duration of follow-up. These studies were limited by their failure to consider the influences of antecedent and current BP on the incidence of CVD, they were limited by their failure to consider the narrow age distribution of their samples,23–26 a lack of multivariable analyses,23,24,26 and a restricted focus on SBP in 2 studies.25,26

We used multivariable analyses to examine the impact of recent and remote antecedent BP on CVD risk in a large
Potential Mechanisms
There are several reasons why antecedent BP may predict CVD risk better than current BP. First, antecedent BP provides a more stable characterization of the true BP of an individual because it is less influenced by intradividual physiological fluctuations and measurement error. Second, BP may change over time, in part in relation to aging, comorbidity, antihypertensive treatment, or behavioral modification. Antecedent BP better captures past BP experiences. Last, antecedent BP has been associated with the presence of cardiovascular target organ damage, which serves as an intermediate for subsequent clinical CVD events.

Strengths and Limitations
The large community-based sample and availability of information on remote and recent antecedent BP levels strengthen the present investigation. The predominantly white race of our sample, however, limits the generalizability of our findings to other ethnic groups. An unavoidable limitation is the selection bias due to the investigation of subjects ≥60 years old and the requirement that subjects attain the baseline ages free of CVD. In addition, we defined all CVD risk factors other than BP at a single examination, and levels of these other risk factors may also change over time. We did not incorporate HDL cholesterol as a covariate because it was not routinely estimated at every biennial examination. Last, we did not examine the impact of change in BP levels over time on the risk of CVD.

Clinical Implications
Our results support the notion that BP levels in middle-aged subjects may have a “carry-over” effect in later life. Our results call into question the approach in which the decision to treat elevated BP is based solely on the presence of an increased short-term absolute risk of CVD.
TABLE 3. Association of Current and Antecedent BP With Incidence of CVD Events: Results in Subjects Not on Antihypertensive Medications and in Nonhypertensive Subjects: Hazards Ratios for CVD Events (95% CI) per 1-SD Increment in Current BP Component*

<table>
<thead>
<tr>
<th></th>
<th>A. Subjects Not Using Antihypertensive Medications</th>
<th></th>
<th>B. Nonhypertensive Subjects†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic BP</td>
<td>Diastolic BP</td>
<td>Systolic BP</td>
</tr>
<tr>
<td>Baseline age 60 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current BP at age 60 y</td>
<td>1.39 (1.21–1.59)†</td>
<td>1.22 (1.06–1.41)†</td>
<td>1.37 (1.11–1.69)‡</td>
</tr>
<tr>
<td>Recent BP (50–59 y)</td>
<td>1.35 (0.96–1.90)‡</td>
<td>1.56 (1.15–2.13)‡</td>
<td>1.27 (0.95–1.70)</td>
</tr>
<tr>
<td>Remote BP (40–59 y)</td>
<td>1.17 (0.90–1.52)§</td>
<td>1.29 (1.02–1.64)§</td>
<td>1.12 (0.89–1.42)</td>
</tr>
<tr>
<td>Baseline age 70 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current BP at age 70 y</td>
<td>1.34 (1.19–1.52)‡</td>
<td>1.09 (0.96–1.24)‡</td>
<td>1.45 (1.17–1.80)‡</td>
</tr>
<tr>
<td>Recent BP (60–59 y)</td>
<td>1.25 (0.93–1.67)</td>
<td>1.23 (0.92–1.64)</td>
<td>1.34 (1.04–1.73)</td>
</tr>
<tr>
<td>Remote BP (50–59 y)</td>
<td>1.18 (0.94–1.47)</td>
<td>1.33 (1.09–1.64)§</td>
<td>1.25 (1.04–1.50)‡</td>
</tr>
<tr>
<td>Baseline age 80 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current BP at age 80 y</td>
<td>1.28 (1.08–1.53)‡</td>
<td>1.13 (0.93–1.38)</td>
<td>1.42 (0.99–2.02)‡</td>
</tr>
<tr>
<td>Recent BP (70–79 y)</td>
<td>2.53 (1.61–3.96)§</td>
<td>1.60 (1.02–2.49)†</td>
<td>1.78 (1.18–2.68)§</td>
</tr>
<tr>
<td>Remote BP (60–69 y)</td>
<td>1.78 (1.30–2.43)‡</td>
<td>1.58 (1.14–2.17)‡</td>
<td>1.31 (0.99–1.74)§</td>
</tr>
</tbody>
</table>

‡1 SD of current SBP and DBP for subjects not using antihypertensive agents—18 and 10, respectively, for 60-year-old subjects; 20 and 10, respectively, for 70-year-old subjects; and 22 and 11, respectively, for 80-year-old subjects. 1 SD of current SBP and DBP for nonhypertensive subjects—11 and 7, respectively, for 60-year-old subjects; 10 and 8, respectively, for 70-year-old subjects; and 10 and 9, respectively, for 80-year-old subjects.

*All models adjust for sex, smoking, BMI, diabetes, cholesterol, and antihypertensive treatment. Models with recent and remote BP also adjust for current BP.
†Nonhypertensive subjects are those with BP<140/90 and not on antihypertensive medication.
‡P<0.05.
§Borderline statistical significance (0.05<P<0.10).

Postponement of treatment of elevated BP with a view to intervene later in life if and when absolute risk crosses a threshold may not adequately reduce the risk of CVD events, possibly because target organ damage may have occurred already. Overall, our findings underscore the importance of preventing hypertension and of detecting and optimally controlling elevated BP throughout the course of a lifetime to reduce the risk of CVD maximally.

Acknowledgments
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