Altered Blood Pressure Progression in the Community and Its Relation to Clinical Events

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Background: Long-term blood pressure (BP) progression and its importance as a predictor of clinical outcome have not been well characterized across different periods.

Methods: We evaluated period trends for 3 BP variables (long-term slope and mean BP during a baseline period of 16 years, and last baseline value) in an earlier period (1953-1971; n=1644, mean participant age, 61 years) and in a later period (1971-1990; n=1040, mean participant age, 58 years) in participants in the Framingham Heart Study who initially did not have hypertension. In addition, we explored the relation of BP to cardiovascular disease incidence and all-cause mortality in the 2 periods, each with up to 16 years of follow-up.

Results: Long-term slope, mean, and last baseline BP measurements were significantly lower in the later period (P < .001). Rates of hypertension control (BP <140/90 mm Hg) were higher in the later vs the earlier period (32% vs 23%; P < .001). Multivariate hazard ratios for the relation of BP to outcomes were generally lower in the later period; this was statistically significant for the relation of last baseline BP to all-cause mortality (hazard ratio for 1-SD increase in systolic BP, 1.02 vs 1.25, P = .03; hazard ratio for diastolic BP, 1.00 vs 1.23, P = .04).

Conclusions: We found evidence that BP levels in the community have changed over time, coinciding with improved rates of hypertension control and attenuation of BP-mortality relations. These findings are consistent with the hypothesis that hypertension treatment in the community has altered the natural history of BP progression and its relation to clinical outcome.

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Elevated blood pressure (BP) is a major risk factor for cardiovascular disease (CVD), with doubled risk for each 20-mm Hg increment of systolic BP or 10-mm Hg increment of diastolic BP above 115/75 mm Hg.1 Rates of hypertension awareness, treatment, and control have increased steadily over the last few decades,2 leading to reduced prevalence of high BP and target organ damage3 and lower mortality from hypertension.4 Some recent studies, however, have reported increasing prevalence and inadequate control of hypertension, especially in certain population groups.5-7

Most causative studies have focused on a single BP reading without accounting for previous or subsequent readings. Some previous investigations, however, have highlighted the importance of BP levels over time vis-à-vis CVD risk,8-10 often considering the contribution of antecedent BP readings compared with a single baseline measurement, without assessing the effect of within-individual BP progression (ie, long-term slope). Further, studies that assessed BP progression were conducted before widespread introduction of effective antihypertensive therapy. To our knowledge, no contemporary investigations exist tracking the effect of BP progression on CVD incidence. The Framingham Heart Study, with more than 50 years of repeated BP measurements and follow-up data, provides a unique opportunity to examine BP progression in relation to CVD incidence and all-cause mortality in 2 periods.

The objective of the present study was to determine whether there have been changes in BP progression and the relation of BP to risk of clinical events in the community. We examined several BP measures and their relation to CVD incidence and all-cause mortality, comparing periods before and after widespread introduction of antihypertensive therapy.

Methods

Study Samples

We used long-term follow-up data for the Framingham Heart Study original cohort for the earlier period and for the offspring cohort for the later period. The selection of examinations, follow-up periods, and exclusion criteria for the 2 periods was done a priori to make them comparable, and all analyses were conducted separately in these 2 study samples. All
study protocols were approved by the Boston University Medical Center Institutional Review Board.

EARLIER PERIOD

The design of the Framingham Heart Study has been described previously. Original cohort participants have been examined approximately every 2 years. Only participants who attended the 3rd (1953-1956), 7th (1960-1964), 9th (1964-1968), and 11th (1968-1971) examination cycles (1953-1971; used for slope and mean BP calculations) were eligible for the present study (n=2605). Participants were excluded for the following reasons: age younger than 50 years at the last baseline examination (n=10), major CVD at or before the last baseline examination (n=162), systolic BP 140 mm Hg or higher or diastolic BP 90 mm Hg or higher at the first baseline examination (n=600), and antihypertensive therapy at any of the baseline examinations (n=189). After these exclusions, 1644 individuals (mean age, 61 years; 57% women) remained eligible for this investigation.

LATER PERIOD

The Framingham Heart Study Offspring Study has been described previously. There were 8 years between the first and second examinations; thereafter, examinations have been conducted approximately every 4 years. Only participants who attended the first (1971-1975), second (1979-1982), third (1984-1987), and fourth (1987-1990) examination cycles (1971-1990; used for slope and mean BP calculations) were eligible for the present study (n=3214). Participants were excluded for the following reasons: age younger than 50 years at the last baseline examination (n=1391), major CVD at or before the last baseline examination (n=96), systolic BP 140 mm Hg or higher or diastolic BP 90 mm Hg or higher at the first baseline examination (n=397), and antihypertensive therapy at any of the baseline examinations (n=290). After these exclusions, 1040 individuals (mean age, 58 years; 57% women) remained eligible for this investigation.

MEASUREMENT OF BP AND COVARIATES

At each examination, a routine medical history was obtained, participants underwent physical examination including anthropometry, and laboratory assessment of CVD risk factors was performed. Systolic and diastolic BP measurements were obtained in the supported left arm of the resting seated partici-pants using a mercury column sphygmomanometer, and were recorded to the nearest even number using standardized methods. The mean of 2 separate readings by the examining physician was considered the examination BP.

Body mass index was calculated as weight in kilograms divided by height in meters squared. “Cigarette smoking” was defined as self-report of smoking at least 1 cigarette daily within the preceding year. “Diabetes” was defined as presence of a nonfasting blood glucose concentration of 200 mg/dL or greater (to convert glucose to millimoles per liter, multiply by 0.0555) (earlier period) or a fasting plasma glucose concentration of 126 mg/dL or greater (later period), or use of insulin or oral hypoglycemic agents (both periods). Previous nonmajor CVD included angina pectoris, transient ischemic attack, intermittent claudication, coronary insufficiency, questionable congestive heart failure, or unrecognized or questionable myocardial infarction.

FOLLOW-UP AND OUTCOME EVENTS

All study participants were under continuous surveillance for CVD events and death through review of outside medical records, hospitalization records, Framingham Heart Study clinic visits, and communication with personal physicians. A panel of 3 experienced investigators reviewed all suspected CVD events. Follow-up extended for up to 16 years after the last baseline examination (through 1984 in the earlier period and through 2003 in the later period). The primary outcome was incidence of a “first major CVD event,” defined as fatal or nonfatal stroke, cardiovascular death, definite congestive heart failure, or fatal or nonfatal recognized acute myocardial infarction. Diagnostic criteria have been detailed elsewhere. The secondary outcome was all-cause mortality.

STATISTICAL METHODS

Long-term systolic and diastolic BP slope (in milligrams of mercury per year) was calculated from the 4 baseline examinations using linear regression. Mean systolic and diastolic BP was calculated as the mean of the BP measurements at these examinations (Figure). Means of BP variables in the earlier period vs the later period were compared using the t test. Pairwise Pearson product moment correlation coefficients were estimated for the interrelations between the BP measurements. The percentages of individuals with hypertension (systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, or use of an-
shihypertensive therapy), individuals with hypertension receiving antihypertensive therapy, and individuals with controlled hypertension (systolic BP <140 mm Hg and diastolic BP <90 mm Hg in individuals with hypertension) were calculated from the last available clinic examination during follow-up for the 2 periods separately and were compared using the χ² test.

Multivariate-adjusted (age, sex, body mass index, smoking status, the presence of diabetes mellitus, previous nonmajor CVD, atrial fibrillation at baseline, and total cholesterol concentration) Cox proportional hazards model analyses were used to investigate associations of various BP variables with outcome separately for the 2 periods. We estimated hazard ratios (HRs) and their 95% confidence intervals (CIs) for a 1-SD increment of each BP variable. The standardization of variables was sex-specific. Likelihood ratio χ² statistics for the models were calculated to indicate overall model fit. Nonlinear associations were excluded by examining incidence rates for tertiles of BP variables. The assumption of proportionality of hazards was confirmed by examining interactions of BP variables and survival time in Cox models. We used 3 sets of models in a hierarchical fashion: (1) including each BP variable separately; (2) paired systolic and diastolic BP components jointly entered; and (3) multivariate models with backward elimination including all significant BP variables with an individual threshold of P < .05 for retention. The clinical covariates were forced into this model. The HRs in the earlier vs later periods were compared using χ² scores. We repeated the analyses after excluding participants with nonmajor CVD or atrial fibrillation at or before the last baseline examination (eligible samples, n = 1499 in the earlier period and n = 1032 in the later period) and participants receiving antihypertensive therapy after the first baseline visit (eligible samples, n = 1833 in the earlier period and n = 1278 in the later period).

In the earlier period, our power to detect an HR of 1.20 (per BP standard deviation) (α = .05) was 90% for CVD and 96% for all-cause mortality in the earlier period. In the later period, our power to detect an HR of 1.35 was 90% for CVD and 96% for all-cause mortality. We evaluated 2-way interaction terms for sex and the different BP variables for both outcomes. Two-sided P values of < .05 were considered statistically significant. All analyses were performed using commercially available software (SAS version 9.1; SAS Institute, Inc, Cary, North Carolina).

RESULTS

Baseline characteristics of the study samples are given in Table 1. The systolic and diastolic BP slopes and the mean and last baseline BP readings were lower in the later period (P < .001 for all comparisons). The percentage of individuals with hypertension at the last clinic visit during follow-up was 40% in the later period and 50% in the earlier period (P < .001). Of those with hypertension, 55% were receiving antihypertensive therapy in the later period and 49% in the earlier period (P = .08). Hypertension was controlled in 32% of patients in the later period and 23% of patients in the earlier period (P < .001). Many of the BP variables demonstrated high pairwise correlations (Table 2). The correlations were similar in the 2 study samples.

In the earlier period, 308 participants (15.8/1000 person-years at risk) had a first major CVD event and 414 (20.0/1000 person-years at risk) died during follow-up (median, 13.9 and 14.0 years, respectively). In the later period, 105 individuals (10.5/1000 person-years at risk) had a first major CVD event and 138 (13.2/1000 person-years at risk) died during follow-up (median, 10.4 years for both end points).

Of 24 examined interaction terms, 2 were significant (P < .05): systolic BP slope–sex and last baseline systolic BP–sex (both in relation to CVD incidence in the later period). The interaction terms indicated a slightly weaker association of these BP variables in women than in men; the number of CVD events in women (n = 42) was too low to enable sex-specific analyses. The directions of effect were the same in men and women.

CVD INCIDENCE

At multivariate-adjusted analyses, all BP variables except diastolic BP slope were significant predictors of incident CVD in the earlier period (Table 3). When considering paired systolic and diastolic BP components in the same

### Table 1. Baseline Characteristics of the Study Samples

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Earlier Period</th>
<th>Later Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=1644)</td>
<td>(n=1040)</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>61 (8)</td>
<td>58 (6)</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>57</td>
<td>57</td>
</tr>
<tr>
<td>Total cholesterol concentration, mg/dL</td>
<td>233 (43)</td>
<td>214 (38)</td>
</tr>
<tr>
<td>BMI</td>
<td>25.5 (3.7)</td>
<td>26.2 (4.1)</td>
</tr>
<tr>
<td>Smokers, %</td>
<td>41</td>
<td>24</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>3.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Previous nonmajor CVD, %</td>
<td>7.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>BP at first baseline examination, mm Hg</td>
<td>118 (10)</td>
<td>117 (9)</td>
</tr>
<tr>
<td>Systolic</td>
<td>118 (10)</td>
<td>117 (9)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76 (7)</td>
<td>76 (7)</td>
</tr>
<tr>
<td>BP slope, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>1.0 (1.0)</td>
<td>0.6 (1.0)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0.2 (0.6)</td>
<td>0.1 (0.6)</td>
</tr>
<tr>
<td>BP at last baseline examination, mm Hg</td>
<td>127 (12)</td>
<td>122 (11)</td>
</tr>
<tr>
<td>Systolic</td>
<td>127 (12)</td>
<td>122 (11)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>79 (6)</td>
<td>77 (6)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BP, blood pressure; CVD, cardiovascular disease.

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model, systolic BP was highly significant for all 3 BP components; diastolic BP was not significantly associated with incident CVD. When examining the relative contribution of the BP variables to CVD incidence in a multivariate model with backward elimination, only mean systolic BP remained significant in the earlier period (HR, 1.51; 95% CI, 1.35-1.69; \( P < .001 \)). All systolic BP variables were highly significant predictors of incident CVD in the later period (Table 3). When including pairs of systolic and diastolic BP components in the same models, all 3 systolic BP components were significant predictors of incident CVD, whereas the diastolic BP variables were not significantly associated with outcome. In a multivariate model with back-
ward elimination, only mean systolic BP remained significant in the later period (HR, 1.38; 95% CI, 1.14-1.67; P < .001). Although the point estimates generally were lower in the later period, no significant differences were noted in HRs for CVD between the later and earlier periods.

**ALL-CAUSE MORTALITY**

In multivariate-adjusted analyses, all variables were significant predictors of all-cause mortality in the earlier period (Table 4). When including pairs of systolic and diastolic BP components in the same models, all 3 systolic BP components were significant predictors of mortality, whereas the diastolic BP variables were not. When examining the relative importance of the significant BP variables to all-cause mortality in a multivariate model with backward elimination, only mean systolic BP remained significant in the earlier period (HR, 1.29; 95% CI, 1.17-1.42; P < .001).

None of the BP variables was significantly associated with all-cause mortality when examining them separately or in pairs in the later period (Table 4). Because no significant associations in the single BP variable models were noted, we did not proceed with a multivariable stepwise selection model.

The HRs for all-cause mortality associated with last baseline systolic and diastolic BP were significantly lower in the later vs earlier period (P = .03 and P = .04 for comparisons of last baseline systolic and diastolic BP, respectively). No significant differences were noted for the other comparisons.

**ADDITIONAL ANALYSES**

The results for analyses after exclusion of participants with nonmajor CVD or atrial fibrillation at or before the last baseline examination were similar to those for the main analyses, although the point estimates were generally slightly higher (supplementary Table 1 and Table 2 available on request from the author). In analyses including participants receiving antihypertensive therapy after the first baseline examination (supplementary Table 3 and Table 4 available on request from the author), results for the earlier period were similar to the main results. In the later period, the associations of BP slope to outcome were no longer apparent, presumably owing to treatment effects during the baseline slope calculation period. The relations of the other BP variables to outcome were slightly weaker in the later period.

**COMMENT**

**PRINCIPAL FINDINGS**

Our study provides an opportunity to examine changes in BP progression over time and the relations of BP to major clinical outcomes in the community. Our data support the hypothesis that treatment has altered the natural
history of BP progression. First, the results are consistent with an important effect of treatment on the long-term consequences of hypertension. The HRs of BP variables, both for CVD incidence and all-cause mortality, were generally lower in the later compared with the earlier period; the attenuation was statistically significant for the relation of last baseline BP to all-cause mortality. In addition, while there were strong associations between all systolic BP variables and all-cause mortality in the earlier period, no significant associations were noted in the later period. Judging from the effect sizes and the power calculations, this change does not seem to be due to inadequate statistical power. Second, a significantly higher percentage of individuals with hypertension in the later period received treatment and achieved BP control (BP <140/90 mm Hg). Third, the BP slope was significantly less steep in the later period compared with the earlier period. Together, these observations support the hypothesis that the widespread introduction and adoption of antihypertensive therapy has altered the natural history of BP progression and the relations of BP to outcome in the community. The lower HRs associated with BP in the later period should not be interpreted to mean that BP is no longer an important contributor to outcome but that effective treatment has had a measurable effect on BP progression and, consequently, on morbidity and mortality due to hypertension in the community.

ADDITIONAL FINDINGS

In accord with most previous studies of individuals older than 50 years,2,20,21 we found that the systolic BP variables were consistently better predictors of CVD incidence than were the diastolic BP variables. We also extended these previous studies by observing the superiority of systolic BP variables for all-cause mortality. The various systolic BP components (mean and last baseline BP measurements and long-term slope) demonstrated similar associations with outcome. When including all 3 systolic BP variables in the same models, only mean systolic BP was consistently retained, indicating the superiority of repeated measures.

COMPARISON WITH PREVIOUS STUDIES

In the earlier period of our study, 23% of participants had achieved BP control at the last clinic visit during follow-up (1980-1984 for most participants). The corresponding BP control rates in the NHANES (National Health and Nutrition Examination Surveys) were 10% in NHANES II (1976-1980) and 29% in the first phase of NHANES III (1988-1991).22 In the later period of our study, 32% of participants had achieved BP control during follow-up (1999-2003 for most participants). This estimate is similar to the BP control rate of 31% reported in NHANES for 1999-2000.23 Blood pressure control rates have been reported to be lower in European countries, ranging from 5% in Spain to 10% in England during the 1990s.25

To our knowledge, few previous studies have examined whether BP slope over time adds predictive information above and beyond a single baseline measurement of BP. Hofman et al.,11 using follow-up data for the Framingham Study original cohort, concluded that BP slope (assessed over 12 years) did not add predictive value above a baseline BP level. Those results were supported by another Framingham Study report that also used data for the original cohort that showed that BP slope before age 65 years was a borderline significant predictor of CVD when entered into a bivariate model including baseline BP at age 65 years.10 Reports from the Seven Countries Study have demonstrated that systolic BP slope over 10 years adds significant predictive value to models including BP at the start of the 10-year baseline, both for incident CVD and all-cause mortality.12-14 Consistent with that, the BP slope predicted outcome above and beyond the BP at the start of the slope calculation period also in the study by Hofman et al.11 These studies were conducted using BP data from several decades ago, which makes them potentially less relevant to current practice. In addition, these studies were limited by (1) evaluation in men only,13 (2) restriction to systolic BP factors,10,11,14 (3) lack of multivariate models,10 or (4) incomplete accounting for important confounders such as previous CVD or previous antihypertensive therapy.14

Sytkowski et al4 used data from the Framingham Study original cohort to assess secular trends in chronic hypertension treatment and its relation to clinical outcome. They did not examine the progression of BP in the same individuals over time but used 3 different cohorts of individuals with hypertension and found decreasing mortality in treated individuals with chronic hypertension.

CLINICAL IMPLICATIONS

Although the results of the systolic BP slope were comparable to those of mean or last baseline systolic BP measurements, the BP slope did not have an incremental predictive value over and beyond that of mean or last baseline BP measurements. Thus, the conclusion from the 1983 study by Hofman et al still holds: "For the clinician this suggests that the decision to treat high [BP] is best guided by the actual level of pressure and not by its long-term trend in the past."11(p267)

An observation in the present study that might have importance for planning future randomized clinical trials is that none of the BP variables predicted all-cause mortality in the later period. This result suggests that all-cause mortality might not be the best choice of a primary end point in future treatment trials in patients with hypertension.

STRENGTHS AND LIMITATIONS

The strengths of the present study include the large community-based samples of men and women from 2 different periods; the standardized BP measurements; and the long-term, continuous surveillance for outcome events. However, several limitations should be recognized. Our sample consists of middle-aged white persons, which limits the generalizability of our findings to other age and racial/ethnic groups. Previous studies have shown that the percentage of treated patients with hypertension who achieved BP control differed between
white and black subjects. Further, the study sample could reflect selection bias because of exclusion of individuals with previous major CVD or antihypertensive therapy, which might have influenced the comparisons of the 2 periods. However, results from additional analyses indicate that differential exclusion rates do not account for our findings. Further, the observed temporal differences in BP-outcome relations may have had explanations other than the widespread introduction of antihypertensive therapy, such as birth-cohort effects, residual confounding owing to differential use of aspirin or lipid-lowering therapy in the 2 periods, or general reductions in CVD risk factors in the population. Because ours was an observational study, we cannot establish a causal role of antihypertensive therapy for the time trends observed. The statistical power to detect associations was lower in the later period, although we had 90% and 96% power to detect an HR of 1.35 for CVD and all-cause mortality, respectively.

CONCLUSIONS

In our large community-based sample, we explored long-term BP progression and its importance for prediction of CVD and all-cause mortality in periods before and after the widespread introduction and more aggressive adoption of antihypertensive therapy. Our study demonstrates a striking temporal change in the course of BP progression and its relation to outcome in the general population. On the whole, our findings are consistent with the hypothesis that treatment of hypertension has had a profound effect on outcome at the community level. Given the low rates of BP control worldwide, our findings underscore the opportunity to improve public health by applying existing recommendations for treatment of hypertension. This may be especially true in Europe and other regions of the world where BP control rates lag behind those in the United States.

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Author Contributions: Dr Larson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Ingelsson, Gona, Larson, Lloyd-Jones, Kannel, Vasan, and Levy. Acquisition of data: Gona and Levy. Analysis and interpretation of data: Ingelsson, Gona, Larson, Lloyd-Jones, Vasan, and Levy. Drafting of the manuscript: Ingelsson, Gona, Kannel, Vasan, and Levy. Critical revision of the manuscript for important intellectual content: Ingelsson, Gona, Larson, Lloyd-Jones, Kannel, Vasan, and Levy. Statistical analysis: Gona and Larson. Obtained funding: Ingelsson and Levy. Administrative, technical, and material support: Kannel and Levy. Study supervision: Levy.

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