Two-Year Changes in Blood Pressure and Subsequent Risk of Cardiovascular Disease in Men

Howard D. Sesso, ScD, MPH; Meir J. Stampfer, MD, DrPH; Bernard Rosner, PhD; J. Michael Gaziano, MD, MPH; Charles H. Hennekens, MD, DrPH

Background—It is unclear whether, given a current blood pressure level, the previous 2-year change in blood pressure adds important predictive information for cardiovascular disease (CVD).

Methods and Results—We conducted a prospective cohort study of 11,150 middle-aged and older men reporting blood pressure in the Physicians’ Health Study. These men had no history of CVD or antihypertensive medication use through the time of the 2-year follow-up questionnaire; after this time, follow-up for the current study began. A total of 905 incident cases of CVD (705 cases of coronary heart disease and 200 cases of stroke) occurred during a median follow-up of 10.8 years. After controlling for current blood pressure and other coronary risk factors, we found that previous 2-year changes in systolic blood pressure were not associated with the risk of CVD. A similar lack of association was found for individual end points of coronary heart disease and stroke. However, previous 2-year changes in diastolic blood pressure (DBP) may be inversely associated with the risk of CVD (linear trend, \( P=0.049 \)) independent of coronary risk factors and current DBP. In subgroup analyses, previous 2-year blood pressure changes only added information in leaner men (body mass index <24.39 kg/m²).

Conclusions—In this normotensive population of men, the prior 2-year change in DBP, but not systolic blood pressure, may add information to current levels in relation to the risk of CVD. Clinicians may need to consider the previous pattern of DBP change when considering the risk associated with the current DBP level. These data require confirmation in other studies in which blood pressure is measured. (Circulation. 2000;102:307-312.)

Key Words: blood pressure • myocardial infarction • heart diseases • epidemiology • stroke

Although the association between blood pressure and increased risk of cardiovascular disease (CVD) is well documented,\(^1,2\) individual blood pressure change has also been postulated as an important predictor of CVD.\(^3\) Previous studies focusing on changes in either systolic blood pressure (SBP) or diastolic blood pressure (DBP) have reported an inconsistent, wide range of relative risks in relation to the subsequent risk of CVD.\(^4–11\) These studies have been limited by the small numbers of subjects and end points, which diminishes their power to detect moderate magnitudes of effect. In addition, these studies primarily adjusted for the baseline level of blood pressure, which examines the importance of the future 2-year change in blood pressure on the risk of CVD. However, such an analytic approach would be expected to demonstrate a positive association between changes in blood pressure and risk of CVD because changes in blood pressure determine subsequent blood pressure, which in turn predicts the risk of CVD.

In this study, we were instead interested in whether, given a level of blood pressure, the change in blood pressure over the previous 2 years independently predicts CVD risk. In other words, does it matter whether the current blood pressure level used to be higher, lower, or the same as it was 2 years ago? We examined this question using data from the Physicians’ Health Study, a large cohort of apparently healthy men, and excluded those with a current or past history of antihypertensive medication use.

Methods

Physicians’ Health Study

The subjects and methods of the Physicians’ Health Study, a 2×2 factorial trial of aspirin and beta-carotene for the primary prevention of CVD or cancer, have been described previously.\(^12\) Briefly, 22,071 US male physicians, aged 40 to 84 years of age at entry, were enrolled in the study. They were free from prior myocardial infarction (MI), stroke, transient ischemic attack, cancer (except for nonmelanomatous skin cancer), and other major chronic diseases at entry. The primary end points of the study were nonfatal MI or stroke. The study population was followed for a median of 10.8 years, with a mean follow-up of 12.2 years. During follow-up, 905 incident cases of CVD (705 cases of coronary heart disease and 200 cases of stroke) occurred. The PCI was used to calculate the hazard ratio (HR) and its 95% confidence interval (CI). The HR was adjusted for the following covariates: age, smoking status, body mass index, total and HDL cholesterol, and systolic blood pressure.
non-melanoma skin cancer), current renal or liver disease, peptic ulcer, and gout.

**Study Population and Data Collection**

On both the baseline and 2-year follow-up questionnaires, subjects reported their current blood pressure and antihypertensive treatment history. We excluded men who were ever treated for hypertension, had missing data on blood pressure, or were diagnosed with CVD before the 2-year questionnaire. This left 11,150 men for the present analysis. We believe self-reported blood pressure by these physicians is reliable and valid. A single measurement of self-reported blood pressure in a different study of physicians was highly correlated with measured SBP (r=0.72) and DBP (r=0.60).13 Another study of the correlation similar to that for 2 measurements of blood pressure was reliable and valid. A single measurement of self-reported blood pressure found a correlation similar to that for 2 measurements of blood pressure within a year.14

We calculated the 2-year change in blood pressure as the difference between the blood pressure reported at 2 years and baseline. Blood pressure change was categorized a priori to better differentiate nominal, moderate, and large decreases or increases in blood pressure over 2 years. Therefore, we constructed 7 categories of SBP change and 5 categories of DBP change. For SBP, the categories were a change (in mm Hg) of ≤−15, −14 to −7, −6 to −3, −2 to 2, 3 to 6, 7 to 14, and ≥15; for DBP, the categories were a change (in mm Hg) of ≤−10, −9 to −3, −2 to 2, 3 to 9, and ≥10. On the baseline questionnaire, participants also provided information on age, smoking status, vigorous exercise, history of diabetes mellitus, parental history of MI at <60 years, and alcohol intake. Body mass index (in kg/m²) was calculated from height and weight.

Follow-up of the 11,150 participants began after completion of the 2-year questionnaire. On annual follow-up questionnaires, participants were asked whether they had experienced any CVD event since the return of the last questionnaire. CVD events included coronary heart disease (CHD), which included MI, angina pectoris, coronary artery bypass graft surgery, and percutaneous transluminal coronary angioplasty, and stroke. For men reporting MI or stroke, relevant medical records were obtained from >95% of the participants. Nonfatal MI was diagnosed using World Health Organization criteria.13 Nonfatal stroke was defined as a typical neurological deficit, sudden or rapid in onset, lasting >24 hours. CVD death was documented by convincing evidence of a cardiovascular mechanism from death certificates and medical records. All analyses are based on the first confirmed CVD event. At the end of follow-up, 99.2% of men still provided morbidity information; mortality follow-up was 99.99% complete.16 In all, 905 cases of confirmed CVD occurred over a median follow-up of 10.8 years (maximum, 11.2 years).

**Data Analysis**

We first compared subjects according to categories of blood pressure change using mean values or proportions of baseline risk factors. Spearman correlation coefficients were computed to compare baseline, 2-year, and 2-year change in blood pressure. We fitted Cox proportional hazards models to determine the relative risk (RR) and 95% confidence intervals of CVD for categories of blood pressure change, using the −2 to 2 mm Hg category as the referent. Models first included age (in years) and then further controlled for the 2-year level of blood pressure (in mm Hg). Multivariate models included aspirin treatment (yes/no), beta-carotene treatment (yes/no), smoking status (never/past/current), vigorous exercise ≥1 time/week (yes/no), history of diabetes mellitus (yes/no), parental history of MI at <60 years (yes/no), alcohol intake (<1 drink/week, 1 to 6 drinks/week, and ≥1 drink/day), and body mass index (in kg/m²).

A linear trend across categories of blood pressure change was tested with an ordinal variable in the model, using the median value from each category. The proportional hazards assumption was confirmed for both SBP change (P=0.18) and DBP change (P=0.80). The RRs for total CHD (705 cases) and stroke (200 cases) were also determined. Stratum-specific estimates were calculated for baseline coronary risk factors to test for interactions between each factor and changes in blood pressure. We also investigated whether the RRs differed among subjects who never initiated antihypertensive treatment during follow-up and before censoring.

**Results**

Among the 11,150 men with no current or past history of antihypertensive medication who comprised the study population, the average SBP at baseline was 123.7 mm Hg (SD, 10.7 mm Hg); at 2 years, it was 124.1 mm Hg (SD, 11.2 mm Hg). DBP also did not change considerably, with averages at baseline and 2 years of 77.3 (SD, 7.0) and 77.5 (SD, 7.3) mm Hg, respectively. Tables 1 and 2 compare subjects according to categories of 2-year changes in SBP and DBP, respectively. Men in higher categories of 2-year blood pressure change had lower baseline blood pressures and higher 2-year blood pressures compared with men in lower categories of 2-year blood pressure change. The Spearman correlation coefficients were computed to compare baseline, 2-year, and 2-year change in blood pressure.
RRs, because the 2-year SBP was strongly associated with both 2-year SBP change and the risks of CVD, CHD, and stroke. Additional control by coronary risk factors did not appreciably change the RR estimates, nor did adding 2-year DBP into the model (data not shown). We found no overall appreciable change in risk estimates. Previous 2-year changes in DBP were inversely associated with the subsequent risk of CVD after adjustment for 2-year DBP and coronary risk factors (trend, $P=0.02$). The association was attenuated with additional adjustment for 2-year SBP (trend, $P=0.049$). In other words, when assessing the current DBP in men, the previous 2-year change in DBP may add information in determining an individual’s subsequent risk for CVD, independent of coronary risk factors and SBP. Given the current DBP level, men with a previously large 2-year decrease in DBP ($\leq -10$ mm Hg) retained a nonsignificant 16% increased risk of CVD compared with men who had no change in DBP ($-2$ to $2$ mm Hg). In addition, men with a previously large 2-year increase in DBP ($\geq 10$ mm Hg) retained a nonsignificant 15% decreased risk of CVD.

We then considered models adjusting for the average 2-year blood pressure by examining 2-year changes in blood pressure given the usual level over the previous 2-year period.

### TABLE 3. RRs (95% Confidence Intervals) of CVD, CHD, and Stroke According to Categories of 2-Year Change in SBP

<table>
<thead>
<tr>
<th>2-Year Change in SBP (mm Hg)</th>
<th>$\leq -15$</th>
<th>$-14$ to $-7$</th>
<th>$-6$ to $-3$</th>
<th>$-2$ to $2$</th>
<th>$3$ to $6$</th>
<th>$7$ to $14$</th>
<th>$\geq 15$</th>
<th>$P$, Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CVD, n</td>
<td>35</td>
<td>110</td>
<td>107</td>
<td>336</td>
<td>118</td>
<td>128</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.81 (0.57–1.15)</td>
<td>0.97 (0.78–1.20)</td>
<td>1.18 (0.95–1.47)</td>
<td>1.00</td>
<td>1.23 (0.99–1.51)</td>
<td>0.97 (0.79–1.19)</td>
<td>1.26 (0.97–1.62)</td>
<td>0.09</td>
</tr>
<tr>
<td>Age, 2-year SBP</td>
<td>0.99 (0.70–1.41)</td>
<td>1.06 (0.86–1.32)</td>
<td>1.20 (0.96–1.49)</td>
<td>1.00</td>
<td>1.13 (0.91–1.39)</td>
<td>0.84 (0.68–1.03)</td>
<td>0.86 (0.65–1.15)</td>
<td>0.07</td>
</tr>
<tr>
<td>Multivariate*</td>
<td>1.00 (0.70–1.43)</td>
<td>1.07 (0.86–1.33)</td>
<td>1.18 (0.95–1.48)</td>
<td>1.00</td>
<td>1.16 (0.94–1.44)</td>
<td>0.85 (0.69–1.05)</td>
<td>0.90 (0.68–1.19)</td>
<td>0.12</td>
</tr>
<tr>
<td>Total CHD, n</td>
<td>26</td>
<td>90</td>
<td>86</td>
<td>264</td>
<td>91</td>
<td>96</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.77 (0.52–1.16)</td>
<td>1.00 (0.79–1.28)</td>
<td>1.21 (0.95–1.54)</td>
<td>1.00</td>
<td>1.20 (0.95–1.51)</td>
<td>0.93 (0.74–1.17)</td>
<td>1.19 (0.88–1.60)</td>
<td>0.33</td>
</tr>
<tr>
<td>Age, 2-year SBP</td>
<td>0.93 (0.62–1.39)</td>
<td>1.10 (0.86–1.40)</td>
<td>1.22 (0.96–1.55)</td>
<td>1.00</td>
<td>1.12 (0.88–1.42)</td>
<td>0.82 (0.65–1.04)</td>
<td>0.86 (0.62–1.19)</td>
<td>0.09</td>
</tr>
<tr>
<td>Multivariate*</td>
<td>0.94 (0.63–1.42)</td>
<td>1.12 (0.88–1.42)</td>
<td>1.21 (0.95–1.55)</td>
<td>1.00</td>
<td>1.15 (0.90–1.46)</td>
<td>0.84 (0.66–1.07)</td>
<td>0.90 (0.65–1.25)</td>
<td>0.15</td>
</tr>
<tr>
<td>Total stroke, n</td>
<td>9</td>
<td>20</td>
<td>21</td>
<td>72</td>
<td>27</td>
<td>32</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>0.95 (0.48–1.90)</td>
<td>0.82 (0.50–1.34)</td>
<td>1.08 (0.66–1.76)</td>
<td>1.00</td>
<td>1.28 (0.82–2.00)</td>
<td>1.11 (0.73–1.68)</td>
<td>1.45 (0.87–2.41)</td>
<td>0.09</td>
</tr>
<tr>
<td>Age, 2-year SBP</td>
<td>1.22 (0.61–2.45)</td>
<td>0.92 (0.56–1.51)</td>
<td>1.09 (0.67–1.78)</td>
<td>1.00</td>
<td>1.16 (0.75–1.81)</td>
<td>0.93 (0.61–1.42)</td>
<td>0.87 (0.49–1.54)</td>
<td>0.60</td>
</tr>
<tr>
<td>Multivariate*</td>
<td>1.19 (0.59–2.40)</td>
<td>0.86 (0.52–1.44)</td>
<td>1.07 (0.65–1.76)</td>
<td>1.00</td>
<td>1.19 (0.76–1.86)</td>
<td>0.88 (0.57–1.37)</td>
<td>0.87 (0.49–1.56)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Values are RR (95% confidence intervals) or No. of cases.

*Adjusted for age, 2-year SBP, randomized aspirin treatment, randomized beta-carotene treatment, smoking status, parental history of MI at <60 years, exercise $\geq 1$ time/week, body mass index, alcohol intake, and diabetes.
The association between previous 2-year changes in SBP and risk of CVD remained nonsignificant (trend, \( P = 0.28 \)), and the association for previous 2-year changes in DBP was attenuated (trend, \( P = 0.61 \)). We also considered traditional blood pressure change models adjusting for baseline level by examining future 2-year changes in blood pressure. The multivariate RRs for 2-year changes in SBP of ≤−15, −14 to −7, −6 to −3, −2 to 2 (referent), 3 to 6, 7 to 14, and ≥15 mm Hg were 0.62, 0.87, 1.06, 1.00 (referent), 1.28, 1.04, and 1.45, respectively (trend, \( P < 0.001 \)). For 2-year changes in DBP of ≤−10, −9 to −3, −2 to 2 (referent), 3 to 9, and ≥10 mm Hg, the corresponding multivariate RRs were 0.85, 0.98, 1.00 (referent), 1.08, and 1.22 (trend, \( P = 0.03 \)).

We then examined whether the association between blood pressure change and CVD risk differed in particular subgroups of men. We found no interactions between 2-year changes in blood pressure and coronary risk factors, except for body mass index. A significant interaction was found between levels of SBP change and body mass index \( (P = 0.011) \), which was dichotomized at the median of the study population \( (24.39 \text{ kg/m}^2) \). In leaner men only, knowledge of the previous 2-year change in SBP added important information in relation to CVD risk. Given the current SBP level, men with previous 2-year increases in SBP of 7 to 14 and ≥15 mm Hg or more had nonsignificant 22% and 37% decreased risks of CVD, respectively, compared with men with no 2-year change in SBP (−2 to 2 mm Hg). The interaction was particularly strong for stroke \( (P = 0.005) \).

Finally, 1642 men initiated antihypertensive medications during follow-up but before censoring. Among subjects without antihypertensive treatment during follow-up \( (n = 9508; 695 \text{ cases of CVD}) \), we still found no association for changes in SBP (trend, \( P = 0.38 \)) and an inverse association for changes in DBP (trend, \( P = 0.017 \)) in multivariate models.

**Discussion**

Our data suggest that for a measurement of blood pressure, the prior 2-year change in DBP, but not SBP, may add information to predict the future risk of CVD, independent of coronary risk factors. The previous pattern of DBP change may need to be considered when assessing the current DBP in relation to CVD risk. We also found that only the current SBP level, regardless of the prior pattern of 2-year SBP change, may be necessary in determining the risk of CVD. In subgroup analyses, the previous 2-year change in blood pressure only added information in leaner men.

Previous research on blood pressure change and risk of CVD has largely focused on controlling for the baseline level of blood pressure. This analysis strategy addresses the future impact of blood pressure change, highlighting the importance of primary prevention to maintain or reduce current blood pressure levels. Because changes in blood pressure determine subsequent blood pressure, which in turn predicts the risk of CVD, a positive association between blood pressure change and risk of CVD would be expected. Our study supports this hypothesis, as have others.4–6,9

Another analysis strategy, which was conducted in this study and was advocated by Hofman et al.,3 examines previ-

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**TABLE 4. RRs (95% Confidence Intervals) of CVD, CHD, and Stroke According to Categories of 2-Year Change in DBP**

<table>
<thead>
<tr>
<th>2-Year Change in DBP, mm Hg</th>
<th>Total CVD, n</th>
<th>Age-adjusted</th>
<th>Age, 2-year DBP</th>
<th>Multivariate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>−10 ≤ 2</td>
<td>87</td>
<td>0.94 (0.75–1.19)</td>
<td>1.18 (0.92–1.50)</td>
<td>1.16 (0.91–1.49)</td>
</tr>
<tr>
<td>−9 to −3</td>
<td>144</td>
<td>1.06 (0.88–1.28)</td>
<td>1.12 (0.93–1.36)</td>
<td>1.13 (0.93–1.36)</td>
</tr>
<tr>
<td>−2 to 2</td>
<td>429</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>3 to 9</td>
<td>150</td>
<td>1.02 (0.84–1.22)</td>
<td>0.94 (0.77–1.13)</td>
<td>0.94 (0.77–1.14)</td>
</tr>
<tr>
<td>≥10</td>
<td>95</td>
<td>0.91 (0.73–1.14)</td>
<td>0.80 (0.64–1.01)</td>
<td>0.85 (0.68–1.07)</td>
</tr>
</tbody>
</table>

Values are RR (95% confidence intervals) or No. of cases.

*Adjusted for age, 2-year DBP, randomized aspirin treatment, randomized beta-carotene treatment, smoking status, parental history of MI at ≤60 years, exercise ≥1 time/week, body mass index, alcohol intake, and diabetes.
ous blood pressure change conditional on the attained blood pressure. This approach addresses a specific clinical question: when presented with a patient at a given blood pressure, does it matter how the blood pressure changed from 2 years ago? In the Framingham Heart Study, the previous 12-year change in blood pressure among men and women was not associated with the subsequent risk of CVD when controlling for the attained blood pressure. We found a similar lack of association for the previous 2-year change in SBP. Therefore, only the current SBP level may be important. However, unlike the Framingham Heart Study, we found that the previous 2-year change in DBP was associated with CVD risk.

The observed 2-year changes in blood pressure may be due to changes in behavior, medication use, or regression to the mean. Analyses restricted to subjects having stable temporal patterns in coronary risk factors or subjects not initiating antihypertensive medications during follow-up did not appreciably alter the RR estimates. Various medications may contribute to a change in blood pressure. Because this population consists of predominantly healthy physicians, the prevalence of any such confounder should be low and result in minimal confounding. Finally, 2-year changes in blood pressure may reflect regression to the mean, indicating the usual blood pressure level over the 2-year period. Indeed, the average 2-year blood pressure had a stronger association with CVD than either the baseline or 2-year blood pressure.

Changes in SBP may accelerate or retard the progressive stiffening of the arterial wall, changes in the vascular structure, and the development of atherosclerosis. The lack of association between the previous 2-year change in SBP and the risk of CVD when controlling for the attained SBP level suggests that short-term reductions in SBP may have immediate beneficial effects. The finding that the previous 2-year change in SBP only added information in leaner men was unexpected. Given the strong association between body weight and blood pressure, increases in SBP in heavier men may have differential effects on atherosclerosis; this warrants further study.

The possible association for the previous 2-year change in DBP given the current DBP suggests a chronic effect on the risk of CVD. Acute reductions in DBP may retard the progression of atherosclerosis, as evidenced by the results from the Hypertension Optimal Treatment study and meta-analyses. Immediate benefits from DBP reduction may be limited to those with established hypertension or higher baseline CVD risk, because a change in these patients may have a greater potential to counteract the atherosclerosis. The period of DBP change may need to exceed 2 years to be clinically important given the observation that prolonged differences in DBP of 10 mm Hg conferred benefits in studies with follow-ups ranging from 6 to 25 years.

Some limitations should also be considered in light of these results. Our use of self-reported blood pressure and hypertension may be subject to misclassification. However, a single self-report of blood pressure in physicians is highly correlated with measured SBP and DBP. In a pilot study, we determined the sensitivity of hypertension diagnoses in the Physicians’ Health Study as 89%, which is consistent with results from similar cohorts of well-educated men. Second, our study consisted of men with no current or past history of antihypertensive medication use through the 2-year follow-up questionnaire. This minimized misclassification in blood pressure values and removed potential confounding by antihypertensive medication use, which may influence 2-year blood pressure changes. Third, our findings may not apply to lower socioeconomic populations and minority groups, who may be more or less susceptible to hypertension and responsive to changes in blood pressure. Finally, the lack of significant results may reflect the possibility of false-negative conclusions if the true RRs are quite modest.

We conclude that for a patient at a current level of SBP, it does not matter whether the SBP is lower, higher, or the same as it was 2 years ago. However, a clinician might usefully consider the previous 2-year change in DBP. Men with 2-year increases in DBP may retain some CVD benefit from their lower initial DBP; alternatively, men with 2-year decreases in DBP may retain some CVD risk from their higher initial DBP. Further studies using measurements of blood pressure change are needed to confirm or refute these relationships in other relevant populations.

References

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