Systolic and Diastolic Blood Pressure, Pulse Pressure, and Mean Arterial Pressure as Predictors of Cardiovascular Disease Risk in Men

Howard D. Sesso, Meir J. Stampfer, Bernard Rosner, Charles H. Hennekens, J. Michael Gaziano, JoAnn E. Manson, Robert J. Glynn

Abstract—We compared systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), and mean arterial pressure (MAP) in predicting the risk of cardiovascular disease (CVD), stratifying results at age 60 years, when DBP decreases while SBP continues to increase. We prospectively followed 11 150 male physicians with no history of CVD or antihypertensive treatment through the 2-year questionnaire, after which follow-up began. Reported blood pressure was averaged from both the baseline and 2-year questionnaires. During a median follow-up of 10.8 years, there were 905 cases of incident CVD. For men aged <60 years (n = 8743), those in the highest versus lowest quartiles of average SBP (≥130 versus <116 mm Hg), DBP (≥81 versus <73 mm Hg), and MAP (≥97 versus <88 mm Hg) had relative risks (RRs) of CVD of 2.16, 2.23, and 2.52, respectively. Models with average MAP and PP did not add information compared with models with MAP alone (P > 0.05). For men aged ≥60 years (n = 2407), those in the highest versus lowest quartiles of average SBP (≥135 versus <120 mm Hg), PP (≥55 versus <44 mm Hg), and MAP (≥99 versus <91 mm Hg) had RRs of CVD of 1.69, 1.83, and 1.43, respectively. The addition of other blood pressure measures did not add information compared with average SBP or PP alone (all P > 0.05). These data suggest that average SBP, DBP, and MAP strongly predict CVD among younger men, whereas either average SBP or PP predicts CVD among older men. More research should distinguish whether MAP, highly correlated with SBP and DBP, better predicts CVD. (Hypertension. 2000;36:801-807.)

Key Words: blood pressure ■ coronary artery disease ■ stroke ■ epidemiology ■ aging

The positive association between either systolic blood pressure (SBP) or diastolic blood pressure (DBP) and the risk of cardiovascular disease (CVD) is well established. Blood pressure is also characterized by its pulsatile and steady components. The pulsatile component, estimated by pulse pressure (PP), represents blood pressure variation and is affected by left ventricular ejection fraction, large-artery stiffness, early pulse wave reduction, and heart rate. The steady component, estimated by mean arterial pressure (MAP), is a function of left ventricular contractility, heart rate, and vascular resistance and elasticity averaged over time.

It remains unclear which measures of blood pressure, either alone or in combination, best predict the risk of CVD. Data from the Framingham Heart Study and other studies indicate that SBP increases continuously across all age groups, whereas DBP increases until age 60 years and then begins to decrease steadily. As a result, PP may become a more important blood pressure measure associated with CVD in older individuals. MAP, which has been extensively studied, with positive associations in some, but not all, studies with CVD.

Therefore, we considered the use of SBP, DBP, PP, and MAP in a large cohort of men aged 40 to 84 years at baseline with no history of antihypertensive treatment. Using self-reported average blood pressure values on the baseline and 2-year questionnaires, we compared the associations of each blood pressure measure with the risk of incident CVD. We further examined potential differences in CVD risk by age dichotomized at 60 years, when DBP levels decrease while SBP continues to increase.

Methods

Study Population and Data Collection

The subjects and methods of the Physicians’ Health Study, a 2×2 factorial trial of aspirin and β-carotene for the primary prevention of
CVD or cancer, have been described previously. Briefly, 22 071 US male physicians, aged 40 to 84 years at entry, were enrolled and were free from prior myocardial infarction (MI), stroke, transient ischemic attack, cancer (except non-melanoma skin cancer), current renal or liver disease, peptic ulcer, and gout. Among the 22 071 randomized men, subjects were excluded if they had CVD (n=520), any past or current history of antihypertensive medication use (n=540), or any missing data on blood pressure (n=5). Among the 22 071 men, 9192 (41.6%) had a history of hypertension, 2041 (9.3%) had diabetes mellitus, and 1004 (4.6%) had underwent coronary angioplasty. Table 1 compares the blood pressure parameters and other baseline characteristics of men aged <60 years and ≥60 years. There were 5.3% and 16.8% of men aged <60 years and ≥60 years, respectively, who had an average SBP ≥140 mm Hg or DBP ≥90 mm Hg despite reporting no history of antihypertensive treatment.

Spearman correlations between average SBP and DBP were 0.70 and 0.61 in men aged <60 and ≥60 years (both P<0.001). Average SBP and DBP were each highly correlated with MAP, with Spearman correlations ranging from 0.88 to 0.94 (all P<0.001) in all men. Average DBP was weakly correlated with PP, with Spearman correlations of 0.03 and 0.06 in men aged <60 and ≥60 years, respectively. All other combinations of blood pressure measures were highly correlated.

During 112 384 person-years of follow-up (median follow-up, 10.8 years), we identified 905 total cases (<60 years, 509 cases; ≥60 years, 396 cases) of incident CVD. To reduce any potential bias due to underlying illnesses that may have affected their blood pressure levels, the exclusion of men with CVD during the first 3 years of follow-up did not materially alter the results. Additional adjustment for coronary risk factors other than age had a small relative impact on the RRs for blood pressure. There were 204 men (22 cases of CVD) had little effect on the results. We calculated relative risks (RRs) and 95% CIs, assuming a 10-mm Hg increase in each blood pressure measure. All probability values were 2-tailed α=0.05. Nested blood pressure models were compared with the χ² test statistic from likelihood ratio tests.

Our second analysis strategy examined the individual effects of average SBP, DBP, PP, and MAP. Each blood pressure measure was categorized into quartiles for each subgroup of men. Cox proportional hazards models were used to calculate the RR of CVD, with the first quartile as the reference group. We also compared the >95th versus <25th percentiles. Multivariate models adjusted for the same coronary risk factors as before. The assumption of proportional hazards was confirmed in all models (all P>0.05) by Wald tests for the interaction of time with each measure of blood pressure. A linear trend across quartiles of blood pressure was tested with an ordinal variable, using median blood pressure levels within each quartile.

We also considered joint models of average SBP and DBP. Average SBP was categorized into <120, 120 to <130, 130 to <140, and ≥140 mm Hg, and average DBP was categorized into <70, 70 to <80, 80 to <90, and ≥90 mm Hg. The reference group included men with average SBP <120 mm Hg and average DBP <70 mm Hg. In sensitivity analyses, we considered other cut points besides age 60 years. Separate multivariate models for each blood pressure measure were considered for men aged 40 to 49, 50 to 59, 60 to 69, and ≥70 years. Effect modification by age was assessed by examining the interaction between age (classified as an ordinal variable using median values from categories of 40 to 49, 50 to 59, 60 to 69, and ≥70 years) and each average blood pressure measure in multivariate models. We then examined whether the association between blood pressure and risk of CVD was similar for men with any history of hypertension treatment. Finally, the RRs for stroke (200 cases) were compared with the overall results for CVD.

Results

The mean (±SD) levels of average SBP, DBP, PP, and MAP for all 11 150 men (mean age, 52.3 years) were 124.1±11.1, 77.5±7.1, 46.6±8.8, and 93.0±7.6 mm Hg, respectively. Table 1 compares the blood pressure parameters and other baseline characteristics of men aged <60 and ≥60 years. As expected, men aged ≥60 years had higher levels of average SBP, DBP, and MAP than men aged <60 years. Average DBP in men aged ≥60 years was similar to that in men aged <60 years. There were 5.3% and 16.8% of men aged <60 and ≥60 years, respectively, who had an average SBP ≥140 mm Hg or DBP ≥90 mm Hg despite reporting no history of antihypertensive treatment.

Spearman correlations between average SBP and DBP were 0.70 and 0.61 in men aged <60 and ≥60 years (both P<0.001). Average SBP and DBP were each highly correlated with MAP, with Spearman correlations ranging from 0.88 to 0.94 (all P<0.001) in all men. Average DBP was weakly correlated with PP, with Spearman correlations of 0.03 and 0.06 in men aged <60 and ≥60 years, respectively. All other combinations of blood pressure measures were highly correlated.

Two separate analysis strategies sought to determine which measures of average blood pressure predicted the risk of CVD. We first compared equivalent multivariate Cox proportional hazards models that only differed by the measures of average blood pressure used. Seven main models were compared, including SBP only, DBP only, both SBP and DBP, PP only, both PP and DBP, MAP only, and both PP and MAP. Other joint models included SBP and PP, SBP and MAP, and DBP and MAP. Models included terms for age, body mass index (in kg/m²), randomized aspirin treatment (yes, no), randomized †-carotene treatment (yes, no), smoking status (never, past, current <1 pack/d, current ≥1 packs/d), vigorous exercise ≥1/wk (yes, no), alcohol consumption (<1 drink/wk, 1 to 6 drinks/wk, ≥1 drink/wk), parental history of MI at <60 years (yes, no), and history of diabetes mellitus (yes, no). Use of finer categories of physical activity did not appreciably change the results. Although we did not control for self-reported lipid levels because data were missing in >10% of participants, additional control for history of hyperlipidemia (self-reported or measured cholesterol >260 mg/dL)
Among men aged <60 years, the addition of any single measure of blood pressure added significantly to the multivariate model (all P<0.05 with 1 df) (Table 2). An increase of 10 mm Hg in average SBP, DBP, PP, and MAP had corresponding RRs of 1.31, 1.46, 1.23, and 1.48, respectively. In model 3, including both SBP and DBP did not add information compared with SBP alone ($\chi^2$=2.96, 1 df, $P=0.09$) but did add information compared with DBP alone ($\chi^2$=8.53, 1 df, $P=0.003$). Finally, a model with average MAP alone was virtually as good as models with MAP and either SBP, DBP, or PP (all $P<0.05$). In model 5, including both DBP and PP did add information compared with either DBP or PP alone (both $P<0.05$).

Among men aged ≥60 years, the addition of average SBP, PP, and MAP added significantly to the multivariate model (all $P<0.05$ with 1 df) (Table 3), with corresponding RRs for 10-mm Hg increases in average SBP, PP, and MAP of 1.21, 1.24, and 1.28, respectively. Average DBP was not significantly associated with the risk of CVD in men aged ≥60 years. In model 3, including both SBP and DBP did not add significantly to the model 1 with SBP alone ($\chi^2=0.57, 1 df, P=0.45$). In addition, the parameter estimate for average DBP was essentially zero. Models with SBP or PP alone were not improved with the addition of any other blood pressure measure (all $P>0.05$). The RRs for a model with both SBP and MAP were 1.29 and 0.89, respectively.

We next examined similar multivariate models in Table 4 but based on quartiles of average SBP, DBP, PP, and MAP. In men <60 years, average SBP, DBP, and MAP all had strong associations with CVD risk. Men in the highest versus lowest quartiles of average SBP (≥130 versus <116 mm Hg), DBP (≥81 versus <73 mm Hg), and MAP (≥97 versus <88 mm Hg) had RRs of CVD of 2.16, 2.23, and 2.52, respectively. An increased risk of CVD was evident in men aged <60 years in the second quartile of SBP, DBP, and MAP. In men aged ≥60 years, increasing quartiles of SBP and PP were strongly associated with the risk of CVD. Comparing the highest versus lowest quartiles of average SBP (≥135

### TABLE 1. Summary of Self-Reported Coronary Risk Factors According to Age (<60 and ≥60 Years)

<table>
<thead>
<tr>
<th>Coronary Risk Factor</th>
<th>Age &lt;60 y (n=8743)</th>
<th>Age ≥60 y (n=2407)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average* SBP, mm Hg</td>
<td>122.7±9.2</td>
<td>128.3±10.7</td>
</tr>
<tr>
<td>Average* DBP, mm Hg</td>
<td>77.2±6.2</td>
<td>78.3±6.0</td>
</tr>
<tr>
<td>Average* PP, mm Hg</td>
<td>45.5±6.6</td>
<td>50.0±8.5</td>
</tr>
<tr>
<td>Average* MAP, mm Hg</td>
<td>92.3±6.7</td>
<td>95.0±6.8</td>
</tr>
<tr>
<td>Age, y</td>
<td>48.5±5.7</td>
<td>66.0±5.2</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.8±3.0</td>
<td>24.7±2.8</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td>53.1</td>
<td>45.9</td>
</tr>
<tr>
<td>Former</td>
<td>36.2</td>
<td>44.2</td>
</tr>
<tr>
<td>Current, &lt;1 pack/d</td>
<td>4.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Current, ≥1 pack/d</td>
<td>6.7</td>
<td>6.8</td>
</tr>
<tr>
<td>Vigorous exercise ≥1/wk, %</td>
<td>75.0</td>
<td>73.3</td>
</tr>
<tr>
<td>Alcohol intake, %</td>
<td>26.1</td>
<td>26.9</td>
</tr>
<tr>
<td>&lt;1 drink/wk</td>
<td>53.3</td>
<td>41.9</td>
</tr>
<tr>
<td>1–6 drinks/wk</td>
<td>20.5</td>
<td>31.2</td>
</tr>
<tr>
<td>History of diabetes, %</td>
<td>1.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Parental history of MI &lt;60 y, %</td>
<td>13.8</td>
<td>8.8</td>
</tr>
</tbody>
</table>

Values are mean±SD unless indicated otherwise.

*Averages of self-reported values on the baseline and 2-year follow-up questionnaires.

who were excluded from multivariate models because of missing coronary risk factor data besides age; however, a comparison of age-adjusted models with and without these subjects did not affect the RRs. For all Cox proportional hazards models in Tables 2 and 3, adjustment for coronary risk factors introduced 12 degrees of freedom (df). Average blood pressure measures were then added to the multivariate model as follows: model 1, SBP; model 2, DBP; model 3, SBP and DBP; model 4, PP; model 5, DBP and PP; model 6, MAP; and model 7, PP and MAP.

### TABLE 2. Comparison of RRs (95% CIs) From Cox Proportional Hazards Models* of Cardiovascular Disease Among Men Aged <60 Years

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1 Average SBP (per 10 mm Hg)</th>
<th>Model 2 Average DBP (per 10 mm Hg)</th>
<th>Model 3 Average SBP and DBP (per 10 mm Hg)</th>
<th>Model 4 Average PP (per 10 mm Hg)</th>
<th>Model 5 Average DBP and PP (per 10 mm Hg)</th>
<th>Model 6 Average MAP (per 10 mm Hg)</th>
<th>Model 7 Average PP and MAP (per 10 mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average SBP</td>
<td>(1.19–1.43)</td>
<td>(1.07–1.37)</td>
<td>(1.26–1.69)</td>
<td>(1.09–1.40)</td>
<td>(1.07–1.37)</td>
<td>(1.03–1.23)</td>
<td>(1.25–1.66)</td>
</tr>
<tr>
<td>Average DBP</td>
<td>(1.19–1.43)</td>
<td>(1.07–1.37)</td>
<td>(1.26–1.69)</td>
<td>(1.09–1.40)</td>
<td>(1.07–1.37)</td>
<td>(1.03–1.23)</td>
<td>(1.25–1.66)</td>
</tr>
<tr>
<td>Average PP</td>
<td>(1.26–1.69)</td>
<td>(0.98–1.45)</td>
<td>(1.25–1.66)</td>
<td>(1.07–1.37)</td>
<td>(1.07–1.37)</td>
<td>(1.03–1.23)</td>
<td>(1.25–1.66)</td>
</tr>
<tr>
<td>Average MAP</td>
<td>(1.09–1.40)</td>
<td>(1.07–1.37)</td>
<td>(1.07–1.37)</td>
<td>(1.07–1.37)</td>
<td>(1.07–1.37)</td>
<td>(1.03–1.23)</td>
<td>(1.25–1.66)</td>
</tr>
<tr>
<td>−2 Log likelihood</td>
<td>259.56</td>
<td>253.99</td>
<td>262.52</td>
<td>238.00</td>
<td>262.52</td>
<td>261.55</td>
<td>262.52</td>
</tr>
<tr>
<td>df</td>
<td>13</td>
<td>13</td>
<td>14</td>
<td>13</td>
<td>14</td>
<td>13</td>
<td>14</td>
</tr>
</tbody>
</table>

*Models additionally adjusted for age, body mass index, randomized aspirin treatment, randomized β-carotene treatment, smoking status, vigorous exercise ≥1/wk, alcohol consumption, parental history of MI at <60 years, and history of diabetes. These variables contributed 12 more df into each model.
versus <120 mm Hg) and PP (≥55 versus <44 mm Hg), the corresponding RRs were 1.69 and 1.83. MAP was also associated with the risk of CVD, but with RRs of lower magnitude.

Finally, we examined the joint effect of average SBP and DBP with the CVD risk in men aged <60 and ≥60 years after adjustment for coronary risk factors. In men aged <60 years, single category increases in average SBP (from <120 to the category 120 to <130 mm Hg) or DBP (from <70 to the category 70 to <80 mm Hg) resulted in a 2- or 3-fold increase in CVD risk. In men aged ≥60 years, there were similar patterns of an increased CVD risk but of a lower magnitude. Older men with greater PPs (average SBP 130 to <140 and DBP <70 mm Hg) had the highest RR of CVD.

In sensitivity analyses, we also considered age stratified into 4 age groups (<50, 50 to 59, 60 to 69, and ≥70 years) and compared the age-specific, multivariate RRs of CVD for 10-mm Hg increases in individual blood pressure measures (Figure). There was a pattern of declining RRs with age for average SBP, DBP, and MAP but not for average PP. These results were further supported by significant interactions found between categories of age and either SBP (P=0.004), DBP (P=0.013), or MAP (P=0.01). The largest reductions in effect sizes with age were for average DBP and MAP, which primarily occurred from ages 50 to 59 to 60 to 69 years. Among other subanalyses, the association between blood pressure and stroke (205 cases) yielded RRs similar to those for CVD, although the smaller number of strokes greatly diminished power. We then considered the associations between blood pressure measures and CVD among men with any past or present history of antihypertensive treatment at baseline. The RRs of CVD for 10-mm Hg increases in SBP (men <60 years, 1.18; men ≥60 years, 1.28), DBP (men <60 years, 1.12; men ≥60 years, 1.24), PP (men <60 years, 1.19; men ≥60 years, 1.20), and MAP (men <60 years, 1.21; men ≥60 years, 1.44) were somewhat different than the results in Tables 2 and 3.

Discussion

We found modest differences according to age for the relationship between blood pressure and CVD risk in men with no history of antihypertensive treatment after comparing models with 4 different blood pressure measures. Average SBP, DBP, and MAP were all strongly associated with an increased CVD risk in younger men. However, average DBP was not associated with CVD risk in men aged ≥60 years. Average PP was associated with the risk of CVD in both younger and older men.

This study of middle-aged and older men was sufficiently powered to examine the association between various blood pressure measures and risk of CVD. Because we excluded men with any history of antihypertensive treatment, these male physicians had a lower distribution of blood pressure values compared with other community-based cohorts. Still, in men aged <60 years, we found an increased CVD risk among men starting in the second quartile of average SBP (≥116 mm Hg), DBP (≥73 mm Hg), and MAP (≥88 mm Hg). In addition to average SBP, PP emerged with a strong positive association with the risk of CVD in men aged ≥60 years. Despite somewhat lower but elevated RRs in men aged ≥60 years, their greater incidence of CVD underscores the potentially large public health impact of elevated yet untreated blood pressure in the elderly.

When we considered SBP and DBP simultaneously, only SBP remained significant in multivariate models for men aged <60 and ≥60 years. During the seventh decade of life, age-specific SBP levels continue to increase, while DBP levels begin to decline. We found no independent association between average DBP and CVD risk in men aged ≥60 years. This loss of predictive value for average DBP may be due to an increasing number of men with underlying illnesses: however, we would have expected fewer such men in our cohort of apparently healthy male physicians. Isolated systolic hypertension becomes more prevalent with age and has been associated with a significant, increased risk of CVD.
Increases in PP are associated with aging, particularly after age 60 years. Higher levels of PP have been associated with carotid stenosis, left ventricular hypertrophy, MI, CVD death, and congestive heart failure in both normotensive and hypertensive populations. Studies in older men and women have found that PP remains important even after controlling for either SBP or DBP. Our results for average PP in older, but not younger, men were consistent with these findings.

Few studies have prospectively addressed the effect of MAP in relation to CVD. Dyer et al found that the steady component of blood pressure (highly correlated with MAP) was more strongly associated with CVD risk than PP in 4 Chicago epidemiological studies. Among subjects with a history of MI, one study indicated a significant 12% increase in recurrent MI for each 10-mm Hg increase in MAP. However, MAP was a weaker predictor than PP and was not associated with CVD mortality. We found that MAP may be strongly associated with CVD risk in men aged <60 years, with a RR of CVD for a 10-mm Hg increase in average MAP of 1.48. This RR was greater than a RR of 1.33 for a comparable 10-mm Hg increase among French men aged 40 to 54 years.

Any clinical advantage for MAP, which is a function of SBP and DBP, for the evaluation of CVD risk among younger men remains unclear. Models with any 2 blood pressure parameters yielded identical log likelihoods for men because of the linear relationship between blood pressure variables. In this regard, MAP when used in combination with other blood pressure parameters offers no additional ability to predict the risk of CVD. However, among models with single blood pressure parameters in men.
aged <60 years, MAP was a slightly stronger predictor of CVD than SBP based on −2 log likelihoods. Therefore, in younger men, either MAP or SBP may best predict the risk of CVD when individual blood pressure parameters are considered.

Biologically, the magnitude of RRs of CVD for average SBP in men aged <60 and ≥60 years reflects the strength of its continuous, graded relationship with CVD risk.3 Higher SBP levels may reflect the progressive stiffening of the arterial wall, changes in the vascular structure, and the development of atherosclerosis.31 Decreased DBP may indicate poor coronary flow reserve and coronary perfusion of the myocardium.32 Increases in PP reflect the stiffening of the conduit vessels. Such vessel stiffening increases pulse-wave velocity, which ultimately increases systemic load while decreasing coronary perfusion pressure.28 MAP is the steady flow of blood through the aorta and its arteries and equals the cardiac output multiplied by vascular resistance.2

Some limitations should also be considered in light of these results. First, our use of self-reported blood pressure may be subject to misclassification. For example, the weak association between DBP and CVD in men aged 60 and >60 years may be explained by an underreporting of DBP due to individual differences in recording fourth or fifth Korotkoff sounds. By averaging self-reported blood pressure on the baseline and 2-year questionnaires, we sought to further minimize any misclassification. We excluded men with any history of antihypertensive treatment to reduce any potential confounding by antihypertensive treatment on blood pressure values, although data from Framingham suggest that antihypertensive treatment may not confound the association between blood pressure and coronary heart disease.31 Next, our findings may not apply to women, lower socioeconomic groups, and non-white populations, who may be more or less susceptible to hypertension and responsive to changes in blood pressure. Finally, unaccounted biochemical, clinical, and genetic markers for the risk of CVD may introduce residual confounding.

In conclusion, among men with no history of antihypertensive treatment, SBP may be best utilized in men aged <60 years, whereas either SBP or PP may be best suited for men aged ≥60 years. DBP was a strong predictor of CVD in younger, but not older, men. Finally, more research must distinguish whether MAP, which is highly correlated with either SBP or DBP, may be an important predictor of CVD in younger men.

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References


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