Development of Predictive Models for Long-Term Cardiovascular Risk Associated With Systolic and Diastolic Blood Pressure

Robert J. Glynn, Gilbert J. L’Italien, Howard D. Sesso, Elizabeth A. Jackson, Julie E. Buring

Abstract—Most existing risk prediction models have not considered the joint contribution of systolic and diastolic blood pressure to cardiovascular risk, and some suggest that there are thresholds below which further reductions of blood pressure yield no additional benefit. We developed multivariate risk prediction models that quantify the risk associated with both systolic and diastolic blood pressure and that can be used to infer the benefits of antihypertensive therapy in populations. Two large clinical trial cohorts, the Physicians’ Health Study, composed of 22,071 males (mean age, 53.2 years; median follow-up, 13.0 years), and the Women’s Health Study, composed of 39,876 females (mean age, 53.8 years; median follow-up, 6.2 years), were used to develop gender-specific predictive models via Cox regression. End points included myocardial infarction, stroke, coronary artery bypass, angioplasty, and cardiovascular death. Risk reduction estimates were derived by computing reductions associated with incremental lowering of systolic and diastolic blood pressures. In both populations, lower levels of blood pressure predicted lower event rates, with no evidence of a plateau or a J-shaped curve. In males, both systolic and diastolic blood pressures were significantly associated with events (P < 0.001), whereas in females, only systolic blood pressure (P < 0.001) predicted outcome after multivariate adjustment. Correction for measurement error in blood pressure increased risk estimates by 50%. Differences in systolic blood pressure yielded greater relative risk reductions than did differences in diastolic blood pressure in a combined population of males and females. These predictive models may be useful for risk estimation associated with hypertension in similar populations and may also be used to infer the benefits of antihypertensive therapy.

Key Words: blood pressure • coronary disease • epidemiology • hypertension, essential • models, statistical • stroke

Hypertension is a major risk factor for cardiovascular disease, and randomized trials have proven that antihypertensive drug therapy decreases risks of stroke, coronary heart disease, heart failure, and total mortality.1–3 Data from observational studies4–6 provide complementary information on the risks associated with hypertension in a wide variety of populations and have been used to infer the benefits of treatment in persons who have not been included in trials, eg, those with borderline levels of blood pressure.7,8 However, some observational studies have suggested that the relation of blood pressure to cardiovascular risk is not linear, with no further reduction in risk or perhaps even an increased risk associated with low blood pressure.9,10 This apparent nonlinearity in the relation of blood pressure to cardiovascular risk may also be an artifact of comorbid influences on blood pressure.11,12

The availability of effective antihypertensive therapies provides a rationale to develop risk prediction models that can contribute to the development of risk assessment/management guidelines.13–15 An important question is whether the joint consideration of systolic and diastolic blood pressure (SBP and DBP, respectively) will lead to enhanced prediction. Inclusion of both measures allows for an evaluation of whether some linear combination of SBP and DBP, such as pulse pressure (PP) or mean arterial pressure (MAP), predicts risk better than does either SBP or DBP alone. Predictive risk equations derived from the Framingham Heart Study include blood pressure terms for SBP or DBP in separate models,16 or they use both SBP and DBP as broadly ranged categories in the same model.17 Although useful for estimating absolute risk, this last approach may underestimate therapeutic benefit by ignoring blood pressure differences within each category.
Another important issue is the dilution of estimated risks due to errors in measuring blood pressure reliably, resulting in regression dilution bias.\(^5\),\(^6\),\(^12\)

The goal of the present study was to develop cardiovascular risk prediction models based on blood pressure that can be used to estimate absolute risk among hypertensive subjects and relative risk reductions resulting from antihypertensive therapies.

Methods

Populations, Measures, and End Points

The populations studied have been described elsewhere.\(^1\),\(^8\),\(^19\) Briefly, the Physicians’ Health Study (PHS) was a randomized, double-blind, placebo-controlled trial that tested the effects of aspirin and \(\beta\)-carotene on the primary prevention of cardiovascular disease and cancer among 22,071 US male physicians, aged 40 to 84 years. The present study includes 17,862 men with no prior cardiovascular event who provided complete information on important cardiovascular risk factors on their mailed baseline questionnaires.

The Women’s Health Study (WHS) is an ongoing, randomized, double-blind, placebo-controlled trial evaluating the balance of benefits and risks of low-dose aspirin and vitamin \(E\) therapy in the primary prevention of cardiovascular disease and cancer in 39,876 female health professionals aged >45 years. The present study includes 36,944 women with no prior cardiovascular event who provided complete information on important cardiovascular risk factors on their mailed baseline questionnaires.

The end point for the current analyses was a first occurrence of cardiovascular disease, defined as myocardial infarction, stroke, death from cardiovascular causes, percutaneous transluminal coronary angioplasty, or coronary artery bypass graft surgery. For data from the PHS, we used all confirmed events occurring up to the end of the trial, with a median follow-up of 13.0 years. For analyses in the WHS, we used all confirmed events between randomization into the trial (beginning in April 1993) and March 2000, with a median follow-up of 6.2 years.

Statistical Analysis

We used Cox proportional hazards regression to develop separate prediction models in females and males. For the PHS, specific values of SBP and DBP were used, whereas for the WHS, the midpoint of DBP and SBP categories was used. To determine whether SBP and DBP had linear relationships with cardiovascular risk, we fitted models with the use of natural cubic splines\(^20\) and models that included a priori clinical blood pressure categories. We used likelihood ratio tests to compare the fit of alternative models and to rank the models containing a single blood pressure measure.

To account for the dilution of the effects of blood pressure on risk due to measurement error, we used the approach of Spiegelman et al.\(^21\) Specifically, in the PHS, 14,664 of the participants in our study provided complete information on important risk factors on their mailed baseline questionnaires.

The derived models were also used to compute estimates of relative risk reduction (%RR) associated with specified differences in DBP and SBP. These were based on the interpretation of the coefficients in the model as measures of relative hazard:

\[
\%\text{RR} = 1 - \left\{ \exp(-d\beta_{\text{DBP}} - s\beta_{\text{SBP}}) \right\}
\]

where \(\beta_{\text{DBP}}\) and \(\beta_{\text{SBP}}\) correspond to the coefficients for SBP and DBP, respectively, and \(d\) and \(s\) are the specified differences in SBP and DBP, respectively. According to the proportional hazards model, this risk reduction is independent of the levels of all other risk factors.

An expanded Methods section can be found in an online data supplement available at http://www.hypertensionaha.org.

Results

Patient Demographics and Cardiovascular Events

The distributions of cardiovascular risk factors were similar between the 2 study populations, with a few exceptions (Table 1). Men tended to exercise more frequently than did women, they reported a higher level of alcohol intake, and they were less likely to have a history of myocardial infarction in their parents before age 60 years. Women reported slightly lower mean blood pressure levels in spite of higher mean body mass index. During the follow-up periods, there were 2356 combined events in the PHS versus 536 combined events in the WHS. In males, revascularization was the most frequent event, followed by myocardial infarction and stroke. In females, strokes predominated, followed by revascularization and myocardial infarction.
Models based on cubic splines and controlling for potential confounding variables revealed that men and women with lower SBP levels had lower risk of cardiovascular disease, with no apparent risk threshold (Figures 1 and 2). In men, lower DBP reduced the risk of cardiovascular disease until \( \approx 65 \) mm Hg, below which there was a slight nonsignificant increase in risk. In women, DBP had little independent association with risk of cardiovascular disease. In both men and women and for both SBP and DBP, likelihood ratio tests indicated that the cubic splines did not provide a significantly better fit to the data than a simple linear fit for each blood pressure measure (each \( P > 0.05 \)). Consideration of clinically defined categories of SBP and DBP also indicated that risk increased linearly across blood pressure categories (Table 2).

In men, a model including both SBP and DBP was significantly better than a model including either measure alone (\( P < 0.001 \) by likelihood ratio test, Table 2). A 10 mm Hg higher level of SBP was associated with a 14% increased risk of cardiovascular disease (95% confidence interval [CI], 9% to 19%), and a 10 mm Hg higher level of DBP was associated with a 17% increased risk of cardiovascular disease (95% CI, 9% to 25%). The best single blood pressure measure to predict cardiovascular disease in the PHS was MAP, and a model including MAP was not significantly different from the model including both SBP and DBP (\( P = 0.16 \)). MAP was the weakest single predictor of cardiovascular disease in men.

In women, a model with both SBP and DBP was not significantly better than a model with only SBP (\( P = 0.72 \)), whereas models including only DBP, only PP, or only MAP each provided significantly poorer predictions of relative risk compared with the model including both SBP and DBP (each \( P < 0.001 \)). A 10 mm Hg higher level of SBP was associated with a 30% increased risk of cardiovascular disease (95% CI, 22% to 38%). DBP was the weakest predictor of cardiovascular risk in women.

Additional analyses, controlling for the effects of hyperlipidemia, found similar effects of blood pressure on cardiovascular risk in both men and women (data not shown). Further control for menopausal status and use of hormone replacement therapy in women also had little impact on the effects shown in Table 2. Evaluation of potential interactions between SBP and DBP revealed no significant modification of the effects of SBP by categories of DBP. We also found no significant interactions of age with SBP, DBP, or PP. Results of the analyses used to test the proportional hazards assumption indicated that the assumption was tenable for all models. Bootstrap validation results indicated that all model coefficients were stable.

### Impact of Blood Pressure Reduction on Population Risk

Table 3 provides estimates of the risk reduction (%RR) associated with particular changes in SBP and DBP derived from the PHS and WHS models. These were computed by using the %RR equation in Methods and were corrected for regression dilution bias. This correction increased the risk reduction estimates by a factor of \( \approx 1.5 \). Risk reduction estimates were obtained for males only, females only, and for a mixed population with the assumption of a male to female ratio of 1:1. The data in Table 3 can be used to illustrate the
TABLE 2. Comparison of Multivariate Relative Risks and 95% CIs from Cox Proportional Hazards Models for Risk of Cardiovascular Disease in Men and Women

<table>
<thead>
<tr>
<th>Variable/Tests</th>
<th>SBP Only</th>
<th>DBP Only</th>
<th>Both SBP and DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>SBP (per 10 mm Hg)</td>
<td>1.20 (1.16–1.24)</td>
<td>1.30 (1.22–1.38)</td>
<td>...</td>
</tr>
<tr>
<td>DBP (per 10 mm Hg)</td>
<td>...</td>
<td>...</td>
<td>1.32 (1.24–1.40)</td>
</tr>
<tr>
<td>(-2 ) Log likelihood (df)</td>
<td>1766.86 (14 df)</td>
<td>653.15 (15 df)</td>
<td>1753.28 (14 df)</td>
</tr>
</tbody>
</table>

SBP categories

<table>
<thead>
<tr>
<th>SBP categories</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120 mm Hg</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>...</td>
<td>...</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>120–129 mm Hg</td>
<td>1.20 (1.04–1.39)</td>
<td>1.59 (1.20–2.09)</td>
<td>...</td>
<td>...</td>
<td>1.13 (0.97–1.32)</td>
<td>1.52 (1.12–2.05)</td>
</tr>
<tr>
<td>130–139 mm Hg</td>
<td>1.72 (1.49–1.98)</td>
<td>2.39 (1.81–3.15)</td>
<td>...</td>
<td>...</td>
<td>1.52 (1.29–1.78)</td>
<td>2.35 (1.72–3.22)</td>
</tr>
<tr>
<td>140–159 mm Hg</td>
<td>1.82 (1.56–2.12)</td>
<td>2.80 (2.08–3.76)</td>
<td>...</td>
<td>...</td>
<td>1.51 (1.26–1.81)</td>
<td>2.86 (2.02–4.03)</td>
</tr>
<tr>
<td>≥160 mm Hg</td>
<td>2.39 (1.85–3.10)</td>
<td>4.18 (2.64–6.63)</td>
<td>...</td>
<td>...</td>
<td>1.92 (1.45–2.54)</td>
<td>4.41 (2.64–7.38)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DBP categories</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65 mm Hg</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1.00 (0.75–1.35)</td>
<td>1.15 (0.72–1.84)</td>
</tr>
<tr>
<td>65–74 mm Hg</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1.35 (1.02–1.78)</td>
<td>1.74 (1.11–2.74)</td>
</tr>
<tr>
<td>75–84 mm Hg</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1.71 (1.27–2.29)</td>
<td>1.72 (1.06–2.79)</td>
</tr>
<tr>
<td>85–89 mm Hg</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>1.84 (1.37–2.47)</td>
<td>2.00 (1.21–3.31)</td>
</tr>
<tr>
<td>≥90 mm Hg</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>(P), linear trend</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Multivariate models included age, body mass index, current hypertension treatment, diabetes, parental history of MI before 60 y, smoking status (never, former, current), exercise (none, <2 times/wk, ≥2 times/wk), and alcohol intake (<1 drink/wk, 1–6 drinks/wk, ≥1 drink/d). Additional variables for women in the WHS included randomized aspirin treatment and randomized \(\beta\)-carotene treatment. Additional variables for men in the PHS included randomized aspirin treatment, randomized vitamin E treatment, and randomized \(\beta\)-carotene treatment. Ranges in parentheses are 95% CIs.

The impact of blood pressure lowering in populations similar to WHS and PHS and with a 1:1 gender ratio. For example, the risk reductions associated with SBP in those with DBP were greater in magnitude than those associated with DBP. Differences in SBP from 5 to 20 mm Hg and a difference in DBP of 5 mm Hg yielded corrected risk reduction estimates from 19.7% to 48.3%, whereas a difference in DBP from 5 to 20 mm Hg and a difference in SBP of 5 mm Hg resulted in risk reduction estimates from 19.7% to 33.2%.

Absolute Risk Prediction Model

The full multivariate Cox model, after correction of regression dilution bias in SBP and DBP, allows estimation of absolute risk for these and similar populations (Table 4, which includes all covariates that potentially confound the effects of SBP or DBP).

Discussion

The present study used 2 large cohorts to develop gender-specific risk prediction models with continuous values of both SBP and DBP in 1 model. The findings have corroborated the prognostic importance of SBP in the subsequent development of cardiovascular disease.\(^5\)\(^,\)\(^6\) While also suggesting that DBP may contribute independent information. We also found that lower levels of blood pressure predicted lower event rates with no evidence of a plateau or a J-shaped curve.

Our finding that SBP and MAP were better single measures to predict cardiovascular risk than were PP and DBP is consistent with results from other healthy primarily middle-aged populations.\(^5\)\(^,\)\(^22\) The low prevalence of risk factors including diabetes and cigarette smoking in these populations may contribute to this finding. PP emerges as a more important predictor in older populations and in those with prevalent disease.\(^23\)\(^,\)\(^24\)

Risk reduction estimates derived from the models were greater for unit differences in SBP than for unit differences in DBP. The magnitude of these reductions is consistent with estimates reported elsewhere for cardiovascular events such as stroke and coronary heart disease.\(^25\) Estimates of risk reductions derived from models without correction for regression dilution are suitable for risk classification based on a single blood pressure assessment; if multiple blood pressure measurements over repeated visits are available, then corrected estimates are more appropriate.

The main goals of the present study were clarification of the relation of blood pressure to cardiovascular risk and the development of prognostic models for the assessment of cardiovascular risk reduction. Although applicable for patient
TABLE 3. Estimates of 5-Year Risk Reduction Associated With Differences in SBP and DBP

<table>
<thead>
<tr>
<th>Difference in SBP</th>
<th>Difference in DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>−5 mm Hg</td>
</tr>
<tr>
<td>Males</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21.5%</td>
</tr>
<tr>
<td>Females</td>
<td>17.8%</td>
</tr>
<tr>
<td>All*</td>
<td>19.7%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>31.9%</td>
</tr>
<tr>
<td>Females</td>
<td>17.8%</td>
</tr>
<tr>
<td>All*</td>
<td>24.8%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>40.8%</td>
</tr>
<tr>
<td>Females</td>
<td>17.8%</td>
</tr>
<tr>
<td>All*</td>
<td>29.3%</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>48.6%</td>
</tr>
<tr>
<td>Females</td>
<td>17.8%</td>
</tr>
<tr>
<td>All*</td>
<td>33.2%</td>
</tr>
</tbody>
</table>

 Estimates of 5-y risk reduction are corrected for regression dilution bias. *Assumes 1:1 ratio of males to females.

risk assessment, these models can also provide insight into the clinical benefit of therapeutic blood pressure lowering according to guidelines such as the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI),13 the World Health Organization/International Society of Hypertension Survey (WHO/ISH),15 and the Joint British Hypertension Committee.14 The risk reduction estimates derived from these models can, in turn, be used to infer long-term cost-effectiveness of antihypertensive therapies.26 The new models described in this report offer some advantages over the existing Framingham risk equations used in a variety of cost-effectiveness analyses to estimate the benefit of therapy.27 In many of these studies, risk estimates were based exclusively on DBP and failed to account for the additional and substantial risk reduction attributable to SBP lowering.

Although the original Framingham risk equations included DBP and SBP in separate models, the recently revised equations17 include both SBP and DBP as broadly ranged JNC-VI categories in a single model. This model is appropriate for the assessment of baseline risk. However, risk reduction estimation is problematic because the blood pressure categories are too broad to estimate risk changes due to blood pressure differences within a category. Another limitation of the revised Framingham equations for these purposes is that the blood pressure categories are based on JNC-VI guidelines only.13 Other antihypertensive guidelines, such as the UK Joint British Guidelines and the 1999 WHO/ISH guidelines, use different blood pressure categories.14,15 Thus, the risk functions used in the present study appear to be more adaptable to a variety of guidelines.

There are some limitations in the development of these models. For example, blood pressure was self-reported in these cohorts. However, a single measurement of self-reported blood pressure in physicians is strongly associated with measured SBP and DBP and does not differ significantly from measured levels.28 In health professionals, correlations between self-reported and measured blood pressures are similar to those for 2 measurements of blood pressure within a year.29 Self-reports of hypertension in nurses have good sensitivity and specificity.30 Furthermore, any misclassification due to self-reporting would be random and would therefore tend to underestimate the association between blood pressure and cardiovascular disease incidence.

Consideration of stroke and coronary events together in a composite cardiovascular end point would be problematic if blood pressure had different effects on these different components. In both the PHS and the WHS, SBP had slightly stronger effects on stroke than on myocardial infarction, but the differences were not significant. Moreover, the composite cardiovascular end point is more relevant from a public health perspective. Another limitation involves the generalizability of the cohorts. Although restricted to health care professionals, study subjects were recruited across the entire United States, which would enhance generalizability. However, certain racial subgroups, such as African Americans, are underrepresented. Consistent with other risk prediction models, including the Framingham study, these models should be applied to individuals who are similar to persons in the populations from which the models were derived.

In conclusion, the prediction models described in the present report provide reliable estimates of incident cardiovascular disease associated with SBP and DBP in populations
of otherwise healthy persons. These functions, in turn, can be used to infer the clinical benefit of antihypertensive regimens that target the various stages of hypertension.

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References
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