Blood Pressure and Risk of Secondary Cardiovascular Events in Women

The Women’s Antioxidant Cardiovascular Study (WACS)

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Background—In apparently healthy people, the relation between blood pressure and risk of subsequent cardiovascular disease (CVD) is linear. In persons with CVD, the relation is uncertain.

Methods and Results—We conducted a prospective study of 5218 older women with CVD who reported their blood pressure at baseline in the Women’s Antioxidant Cardiovascular Study (WACS), an ongoing double-blind, placebo-controlled secondary prevention trial of the benefits and risks of antioxidant vitamins, folic acid, vitamin B6, and vitamin B12 among women with CVD or ≥3 coronary risk factors. A total of 661 confirmed CVD events (nonfatal myocardial infarction, nonfatal stroke, coronary artery bypass graft procedure, percutaneous coronary angioplasty, or CVD death) occurred during a median follow-up of 6.5 years. After controlling for age, randomized treatment assignment, antihypertensive medication use, and coronary risk factors, we found that systolic blood pressure (SBP) was a strong predictor of CVD events and that the relation between SBP and CVD risk was positive, continuous, and linear (P for linear trend=0.001). For each 10-mm Hg increment in SBP, there was a 9% (95% CI 4% to 15%) increase in risk of secondary CVD events. Diastolic blood pressure, mean arterial pressure, and pulse pressure were weaker predictors of CVD risk in this cohort, and joint consideration of SBP and diastolic blood pressure found that only SBP significantly predicted risk. Use of antihypertensive medication did not modify the relationship of SBP with CVD events.

Conclusions—In this population of women with CVD, we observed a strong, continuous, and linear association between SBP and risk of secondary CVD events. SBP was the blood pressure measure most strongly related to CVD risk. (Circulation. 2004;109:1623-1629.)

Key Words: hypertension ■ cardiovascular diseases ■ prevention ■ women

Hypertension is a strong independent risk factor for the development of cardiovascular disease (CVD). In primary prevention, the relationship between blood pressure (BP) and cardiovascular risk appears to be positive, graded, and continuous.1,2 Current guidelines in primary and secondary prevention reflect these findings.3-5 Most of the evidence in support of BP treatment guidelines comes from primary prevention trials6,7 and observational studies in patients without CVD,8-11 although recent trials show benefit of antihypertensive therapy in patients with preexisting CVD.12,13

In secondary prevention, the relationship between BP and CVD events is less certain. Although the argument for a linear relation is strong, it is based primarily on data in primary prevention clinical trials involving a restricted range of BP values and extrapolations that assume the validity of the linear logistic model. Nonlinear relations have been reported14-17 but not widely accepted.6,7 Previous work also suggests that joint consideration of systolic BP (SBP) and diastolic BP (DBP), as well as consideration of nonlinear relationships with CVD risk, may improve prediction.18-20 Despite the apparent uncertainties, the traditional view that the relationship between BP and CVD risk is linear generally prevails in clinical practice.3,5 Whether this assumption is correct with respect to secondary prevention remains unproven.

The objective of this analysis was to examine the relationship between BP and secondary cardiovascular events in a population of older women with CVD. We systematically tested for both linear and nonlinear relationships between various measures of BP and CVD risk.
Methods

Study Population
The Women’s Antioxidant Cardiovascular Study (WACS) is an ongoing randomized, double-blinded, placebo-controlled secondary prevention trial of the benefits and risks of antioxidant vitamins, folic acid, vitamin B₆, and vitamin B₁₂ that is being conducted among US female health professionals 40 years and older with known CVD or ≥3 coronary risk factors.²³ CVD was defined as a self-reported history of myocardial infarction (MI), angina pectoris, coronary revascularization, stroke, transient cerebral ischemia, carotid endarterectomy, or peripheral artery surgery on the baseline questionnaire. Primary exclusion criteria for enrollment were history of cancer (except for nonmelanoma skin cancer), active liver disease or cirrhosis, chronic kidney failure, current use of warfarin or other anticoagulant, or unwillingness to comply with study medications or to withhold use of out-of-study vitamin supplements.

WACS randomized 8171 women between April 1995 and October 1996. For the purposes of the present analysis, we excluded women with ≥3 coronary risk factors but without known CVD (n=2933) and those who did not provide complete baseline BP information (n=20), which yielded a study population of 5218 women.

Assessment of BP
Self-reported BP measurements were obtained from prerandomization questionnaires. Participants reported SBP in 1 of 9 categories: <110, 110 to 119, 120 to 129, 130 to 139, 140 to 149, 150 to 159, 160 to 169, 170 to 179, and ≥180 mm Hg. DBP was reported in 1 of 7 categories: <65, 65 to 74, 75 to 84, 85 to 89, 90 to 94, 95 to 104, and ≥105 mm Hg. In health professionals, self-reported BP has good reliability, reproducibility, and construct validity.²²−²⁴ Continuous BP values were assigned to each participant by taking the midpoint value for their reported BP category. Participants with SBP <110 or ≥180 mm Hg were assigned the values 95 or 190 mm Hg, respectively; those with DBP <65 or ≥105 mm Hg were assigned the values 55 or 110 mm Hg, respectively. We calculated mean arterial pressure (MAP; 2/3 DBP+1/3 SBP) and pulse pressure (PP; SBP−DBP) using the generated values of SBP and DBP.

Assessment of Other Risk Factors
Prevalent CVD was determined from WACS prerandomization questionnaires and categorized hierarchically: MI, stroke, revascularization procedure (PTCA, CABG, carotid endarterectomy, and peripheral artery surgery), and symptomatic vascular disease (angina pectoris and transient cerebral ischemia). Questionnaires also asked about baseline characteristics (age at randomization, race, weight, height, alcohol use, exercise frequency, menopausal status, serum cholesterol level, and current use of BP, cholesterol, or diabetes medications) and coronary risk factors (current tobacco use, parental history of MI at age <65 years, history of diabetes, history of elevated cholesterol, and history of hypertension).

End-Point Ascertainment and Confirmation
The primary outcome measure in WACS is a combined end point of nonfatal MI, nonfatal stroke, coronary revascularization procedure (CABG or PTCA), or CVD mortality. Participants received questionnaires every 6 months for the first year after randomization and annually thereafter; the response rate for the most recently completed follow-up questionnaire (48 months) was 90%, and vital status was known for 99% of participants. On all questionnaires, participants reported cardiovascular outcomes since completion of the preceding questionnaire. An end-points committee reviewed all reported events; only confirmed events are included in the present analysis. MI was confirmed if symptoms were consistent with World Health Organization criteria and the event was associated with elevation of serum cardiac enzymes or diagnostic changes on ECG.²² Stroke was confirmed if the participant experienced a new neurological deficit that persisted longer than 24 hours. Revascularization procedures were confirmed by review of medical records. CVD death was confirmed if a cardiovascular mechanism was suggested from autopsy reports, death certificates, and medical records.

Statistical Methods
Baseline variables were summarized as means and SDs (continuous variables) or proportions (categorical variables). We used Cox proportional hazards regression to determine the relative risk (RR) and 95% CI of first postrandomization CVD events according to categories of SBP and DBP. SBP category 120 to 129 mm Hg and DBP category 75 to 84 mm Hg were defined as the reference groups for their respective comparisons. Initial models adjusted for age and randomized treatment assignment, and multivariate models also included terms for body mass index, past or current tobacco use, alcohol use, exercise frequency, history of elevated cholesterol, diabetes, current antihypertensive medication use, prior MI, prior stroke, and prior revascularization. Additional adjustment for parental history of MI at age <65 years, menopausal status, serum cholesterol level, and hormone replacement therapy had little effect on the results, and these variables were not included in the final models.

To assess the shape of the relationship between BP and CVD risk, we used 3 complementary approaches. For each approach, we used likelihood ratio tests to compare the competing model with the simpler model that assumes a linear relationship between BP and the log hazard. First, we used the traditional test for deviation from linearity that compares the linear model to the model that includes indicator variables for BP categories. Second, we considered curvilinear relations by adding a quadratic term to the linear model. Third, we used flexible spline methodology to compare models using splines with simpler linear models.²⁶ We constructed piecewise linear spline models using knots at 130 and 160 mm Hg, thus generating 3 SBP groups below 130 mm Hg (<110, 110 to 119, and 120 to 129 mm Hg), 3 groups between 130 and 160 mm Hg (130 to 139, 140 to 149, and 150 to 159 mm Hg), and 3 groups above 160 mm Hg (160 to 169 mm Hg, 170 to 179, and ≥180 mm Hg). For DBP, we used a single knot at 80 mm Hg. All piecewise linear spline models included terms for both SBP and DBP. We examined potential effect modification by age, type of CVD, and antihypertensive therapy. In models that examined interactions, joint relations between 2 BP variables, and stratification according to antihypertensive therapy, we used collapsed categories of SBP (quintiles) and DBP (quartiles). Tests of the proportional hazards assumption found no evidence for violation of the assumption of a uniform relative hazard over the duration of follow-up. Additionally, we calculated the RR of CVD for categories of MAP and PP, respectively. Ten subjects (3 CVD events) were excluded from the multivariate analyses because of missing data on covariates.

Results
Baseline Characteristics
The mean age of women in the present study was 62.1±8.7 years. Means for SBP and DBP were 133.9±17.3 and 80.4±10.4 mm Hg, respectively (Table 1). Before randomization, 1327 women experienced an MI, 611 had a stroke, 738 had undergone a revascularization procedure, and 2542 reported angina or other symptomatic vascular disease. Women with angina or other symptomatic vascular disease had lower rates of self-reported hypertension, elevated cholesterol, diabetes, tobacco use, and BP-lowering or cholesterol-lowering medication use than women with prior MI, stroke, or revascularization procedure. During 31 714 person-years of follow-up (median follow-up 6.5 years), there were 871 confirmed CVD events among 661 women: 118 CVD deaths, 131 MIs, 138 strokes, 182 CABG procedures, and 302 PTCA procedures.
SBP and CVD Risk

In the age-adjusted model (Figure 1), we found a continuous, positive, graded relation between SBP and CVD risk \((P \text{ for linear trend} < 0.0001)\). Below the reference category of 120 to 129 mm Hg, there was a modest, nonsignificant decrease in risk. All women reporting SBP values \(\geq 130\) mm Hg had a significant increase in risk of CVD events. Risk was increased most markedly in women who reported SBP values \(\geq 160\) mm Hg, as follows: 160 to 169 mm Hg—RR 2.45, 95% CI 1.73 to 3.47; 170 to 179 mm Hg—RR 2.72, 95% CI 1.55 to 4.75; and \(\geq 180\) mm Hg—RR 3.83, 95% CI 2.23 to 6.48. The addition of covariates did not alter the overall relation between SBP and CVD risk (\(P \text{ for linear trend} = 0.004\)), and there were no significant differences between slopes in the different regions (Figure 2). However, after controlling for other covariates, only the third group (SBP values \(\geq 160\) mm Hg) had a slope that was significantly different from zero \((P=0.009)\). When likelihood ratios were used for comparison, the piecewise linear spline model was not significantly better than the simpler, multivariate-adjusted linear model \((P=0.4)\).

DBP and CVD Risk

DBP was a weaker predictor of CVD risk, as indicated by the smaller likelihood ratio statistic (Table 2). In the age-adjusted analysis, DBP had a significant positive linear relationship with CVD risk \((P \text{ for linear trend} < 0.001)\), and no substantial deviation from linearity was apparent. On further control for potential confounding variables, this trend was no longer significant \((P=0.19)\). No J-shaped relation between DBP and CVD risk was apparent in either age-adjusted or fully adjusted analyses. The age-adjusted and multivariate-adjusted

### TABLE 1. Baseline Characteristics for Participants With Prevalent CVD in WACS

|                  | MI  
|                 | (n=1327) | Stroke  
|                 | (n=611) | Procedure*  
|                 | (n=738) | Angina or Other Symptomatic CVD†  
|                 | (n=2542) | Total  
|                 | (n=5218) |
| Age, mean±SD, y | 63.3±8.5 | 61.3±8.8 | 63.8±8.1 | 61.3±8.8 | 62.1±8.7 |
| BMI, kg/m²      | 28.8±6.1 | 28.0±5.9 | 28.0±5.8 | 28.9±6.3 | 28.6±6.2 |
| White, %        | 94.1      | 93.8      | 95.8      | 93.1      | 93.8      |
| History of hypertension, % | 67.2 | 66.1 | 70.3 | 60.1 | 64.0 |
| Antihypertensive therapy, % | 55.8 | 56.5 | 60.0 | 49.4 | 53.4 |
| Mean SBP, mm Hg | 134.1±17.6 | 134.4±17.2 | 135.1±16.8 | 133.2±17.2 | 133.9±17.3 |
| Mean DBP, mm Hg | 80.3±10.8 | 80.9±9.8 | 80.3±9.7 | 80.4±10.5 | 80.4±10.4 |
| History of high cholesterol, % | 72.3 | 58.1 | 81.7 | 61.4 | 66.7 |
| Cholesterol-lowering therapy, % | 34.1 | 17.2 | 46.4 | 16.3 | 25.2 |
| Diabetes, %     | 22.5      | 15.4      | 19.7      | 12.5      | 16.4      |
| Current cigarette smoking, % | 20.8 | 17.4 | 21.3 | 13.3 | 16.8 |
| Current alcohol use, % | Rarely/never | 71.1 | 66.8 | 63.8 | 65.6 | 66.9 |
|                  | Weekly   | 20.1      | 24.6      | 24.4      | 25.4      | 23.8      |
|                  | Daily    | 8.8       | 8.7       | 11.8      | 9.0       | 9.3       |
| Parental history of MI at <65 y, % | 41.7 | 32.4 | 42.4 | 37.7 | 38.7 |
| Exercise frequency, % | <120 kcal/wk | 24.5 | 27.8 | 24.5 | 25.4 | 25.3 |
|                  | 120–449 kcal/wk | 23.0 | 26.6 | 26.4 | 25.8 | 25.3 |
|                  | 450–1200 kcal/wk | 26.6 | 22.5 | 23.3 | 25.1 | 24.9 |
|                  | >1200 kcal/wk | 25.9 | 23.2 | 25.8 | 23.8 | 24.5 |
| Postmenopausal, % | 85.1 | 78.7 | 86.7 | 79.0 | 81.6 |
| Current HRT, %   | 41.7      | 45.0      | 49.3      | 50.7      | 47.6      |

BMI indicates body mass index; HRT, hormone-replacement therapy.

*Women reporting prior CABG, PTCA, carotid endarterectomy, or peripheral artery surgery.
†Women reporting angina pectoris or transient cerebral ischemia but no prior MI, stroke, or CABG/PTCA.
piecewise linear models for DBP and CVD risk generated a similar-shaped relationship between DBP and CVD risk compared with the simpler linear models (Figure 2).

SBP, DBP, and CVD Risk
The association between SBP and CVD risk was not appreciably altered in models that considered SBP and DBP simultaneously (Table 2). When likelihood ratios were used for comparison, the addition of DBP did not improve the model that already contained SBP ($P_{H_0:.5}$. For DBP, the inclusion of SBP in the model attenuated an already modest effect and significantly improved the overall model ($P_{H_0:.004}$. We also found no significant interaction between linear SBP and linear DBP ($P_{H_0:.8}$).

MAP, PP, and CVD Risk
Both MAP and PP had significant positive linear relationships with risk of subsequent CVD events in the present study (Table 2). However, on the basis of likelihood ratio tests, neither variable was as strong a predictor of CVD risk as SBP, and neither variable added significantly to a model that included SBP ($P_{H_0:.5}$. For DBP, the inclusion of SBP in the model attenuated an already modest effect and significantly improved the overall model ($P_{H_0:.004}$. We also found no significant interaction between linear SBP and linear DBP ($P_{H_0:.8}$).

Subgroup Analysis
In subgroup analyses that adjusted for multiple covariates, we found no evidence for interactions between BP and age ($P_{H_0:.7}$), type of CVD at entry ($P_{H_0:.24}$), or use of antihypertensive therapy ($P_{H_0:.32}$).

Discussion
BP is considered an important modifiable risk factor in both primary and secondary CVD prevention, and this is reflected in current clinical statements. Yet the shape of the relationship between BP and CVD risk is not certain and may depend on age, presence of underlying cardiovascular disease, length of follow-up, and antihypertensive treatment. The prospective data from the present study demonstrate that SBP is a strong independent predictor of CVD events among middle-aged and older women with known CVD. The relation between SBP and CVD risk was positive, graded, and continuous in both age-adjusted and multivariate-adjusted models. In the multivariate model, significant elevations in risk (RR 1.28, 95% CI 1.00 to 1.64) were noted among women with high-normal BP (130 to 139 mm Hg) relative to
might be explained in part by the slightly older and more disease. The differences compared with the present results CVD death among elderly men and women with heart U-shaped relation between BP (DBP and SBP) and biennial relation for SBP. More recently, Kannel et al reported a U-shaped relation between DBP and biennial CVD death rate and a similar but nonsignificant relation for SBP. D'Agostino et al reported a U-shaped relation between DBP and biennial CVD death rate and a similar but nonsignificant relation for SBP. More recently, Kannel et al reported a U-shaped relation between BP (DBP and SBP) and biennial CVD death among elderly men and women with heart disease. The differences compared with the present results might be explained in part by the slightly older and more heterogeneous Framingham cohort having a larger representation of patients with more severe noncardiac comorbidities and thus a larger proportion of patients with an association between ill health (causing low BP) and mortality ("reverse causality"). Furthermore, the use of an outcome defined by short-term follow-up (biennial CVD death rate) may have increased the impact of this interaction on the observed association between BP and CVD mortality.

As demonstrated previously, the length of follow-up is critically important in determining the observed relationship between BP and mortality. In men (aged 45 to 57 years) with heart disease screened for the Multiple Risk Factor Intervention Trial, there was a J-shaped relation between SBP and CVD mortality during the first 2 years of follow-up but a linear relation during 16-year follow-up. Similarly, Glynn et al reported that within an elderly population-based cohort, there was a continuous relation between BP and cardiovascular mortality after exclusion of deaths from short-term follow-up (<3 years) but a J-shaped relation when these events were included. We found no evidence for a different relationship of SBP with CVD risk in early (first 3 years) versus later follow-up. Although some have argued that the increased risk of secondary events is caused by decreased coronary perfusion in the setting of significant coronary stenosis, it seems more likely that the association is explained by the effect of noncardiac premorbid conditions on lowering the systemic BP. Regardless, J-shaped relations demonstrated from observational data need to be interpreted with caution because they may not have implications for antihypertensive therapy.

### TABLE 2. Age and Multivariate Adjusted RR (95% CI) of CVD Events According to BP Category (SBP, DBP, MAP, and PP)

<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>SBP (per 10 mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted*</td>
<td>1.17 (1.12–1.22)</td>
<td>...</td>
<td>1.19 (1.13–1.26)</td>
</tr>
<tr>
<td>Multivariate†</td>
<td>1.09 (1.04–1.15)</td>
<td>...</td>
<td>1.10 (1.04–1.17)</td>
</tr>
<tr>
<td>– 2 Log likelihood</td>
<td>382.77 (17 df)</td>
<td>...</td>
<td>382.97 (18 df)</td>
</tr>
<tr>
<td>DBP (per 10 mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>...</td>
<td>1.17 (1.09–1.26)</td>
<td>0.98 (0.88–1.09)</td>
</tr>
<tr>
<td>Multivariate</td>
<td>...</td>
<td>1.06 (0.97–1.16)</td>
<td>0.98 (0.88–1.08)</td>
</tr>
<tr>
<td>– 2 Log likelihood</td>
<td>...</td>
<td>373.63 (17 df)</td>
<td>382.97 (18 df)</td>
</tr>
<tr>
<td>MAP (per 10 mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1.22 (1.14–1.29)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Multivariate</td>
<td>1.10 (1.02–1.18)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>– 2 Log likelihood</td>
<td>377.43 (17 df)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>PP (per 10 mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>...</td>
<td>1.18 (1.12–1.23)</td>
<td>...</td>
</tr>
<tr>
<td>Multivariate</td>
<td>...</td>
<td>1.10 (1.03–1.15)</td>
<td>...</td>
</tr>
<tr>
<td>– 2 Log likelihood</td>
<td>...</td>
<td>380.72 (17 df)</td>
<td>...</td>
</tr>
</tbody>
</table>

*Adjusted for age and randomized treatment assignment.
†Adjusted for age, randomized treatment assignments, body mass index, tobacco use, alcohol use, exercise frequency, diabetes, history of elevated cholesterol, prior MI, prior stroke, and prior revascularization.
‡The joint model considered linear SBP and DBP terms simultaneously in addition to age and other coronary risk factors.
Our finding that CVD risk increases with borderline elevations in SBP is consistent with previous findings in primary prevention. This finding is also consistent with recommendations from the Seventh Report of the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure that call for initiating antihypertensive therapy in patients with diabetes or chronic kidney disease with SBP ≥130 or DBP ≥80 mm Hg. Although observational, our findings suggest that among women with preexisting CVD, even borderline elevations in SBP are associated with increased risk of future CVD events.

The present study is one of the first to examine prospectively the relationship between BP and the risk of secondary CVD events exclusively in women. The prospective design and relatively large sample size allowed for a thorough examination of these associations. However, there are several limitations to our study worth noting. First, the use of self-reported BP values is subject to misclassification. Previous reports from female health professionals have demonstrated good reliability and validity of self-reported BP. However, decreased precision in the reported DBP might explain, in part, the weak and primarily positive relation observed between DBP and CVD risk and the weaker risk prediction from PP. Although the same limitation applies to SBP, it had a powerful and compelling relation with CVD risk. Second, we were unable to account for the form or dose of cardiac medications taken at baseline. Thus, we cannot comment on the potential interaction between specific medications and BP as it impacts the risk of secondary CVD events. Third, our cohort primarily consisted of white female health professionals, and thus the results might not fully apply to women with different ethnic, socioeconomic, or clinical characteristics.

In summary, the present analysis demonstrates that SBP is a strong predictor of secondary CVD events in women. These data suggest that there is a significant increase in CVD risk, regardless of antihypertensive treatment status, associated with higher SBP. The present data do not substantiate a J-shaped relationship between BP and CVD risk or the importance of joint relations between DBP and SBP with CVD risk. Although further clinical investigation is needed to explore the potential benefit of lowering BP below normal values, our data suggest that women with CVD and borderline elevations in SBP are at increased risk of future events and might benefit from a lower targeted BP.

Figure 2. Multivariate adjusted log hazard (95% CI) for joint effects of SBP and DBP, as piecewise linear splines, with CVD risk. Adjustment was for age, randomized treatment assignments, body mass index, tobacco use, alcohol use, exercise frequency, diabetes, history of elevated cholesterol, prior MI, prior stroke, and prior revascularization.
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References

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