Blood Pressure, C-Reactive Protein, and Risk of Future Cardiovascular Events

Gavin J. Blake, MD, MPH, MRCP; Nader Rifai, PhD; Julie E. Buring, ScD; Paul M Ridker, MD, MPH

Background—Accumulating data suggest a link between blood pressure and vascular inflammation.

Methods and Results—We examined the relationship between blood pressure, C-reactive protein (CRP), and incident first cardiovascular events among 15,215 women followed prospectively over a median of 8.1 years. In cross-sectional analyses at baseline, median levels of CRP for women with blood pressure <120/75, 120 to 129/75 to 84, 130 to 139/85 to 89, 140 to 159/90 to 94, and ≥160/95 mm Hg were 0.96, 1.42, 2.20, 2.82, and 3.34 mg/L, respectively (P for trend <0.0001). Increasing categories of blood pressure were significant predictors of CRP levels at baseline. In prospective analyses, both elevated CRP levels (≥3 mg/L) and increasing categories of blood pressure were independent determinants of future cardiovascular events, and CRP had incremental prognostic value at all levels of blood pressure. The adjusted hazard ratio for women with blood pressure ≥160/95 mm Hg and CRP levels ≥3 mg/L was 8.31 (95% CI, 4.44 to 15.55, P<0.0001) compared with those with blood pressure <120/75 and CRP levels ≤3 mg/L. After participants had been divided into 4 groups on the basis of CRP levels (<3 or ≥3 mg/L) and blood pressure levels (<130/85 or ≥130/85), the risk factor–adjusted hazard ratios were as follows: low CRP/low blood pressure, 1.0; high CRP/low blood pressure, 1.87 (P=0.002); low CRP/high blood pressure, 2.54 (P<0.0001); and high CRP/high blood pressure, 3.27 (P<0.0001).

Conclusions—CRP and blood pressure are independent determinants of cardiovascular risk, and their predictive value is additive. (Circulation. 2003;108:2993-2999.)

Key Words: blood pressure ■ risk factors ■ inflammation

Hypertension is a central risk factor for cardiovascular events. The precise pathophysiological mechanisms through which elevated blood pressure leads to cardiovascular disease, however, remain uncertain. Basic data suggest that increasing levels of blood pressure may stimulate a proinflammatory response and that endothelial inflammation may also herald the changes in arterial wall that characterize the hypertensive state.1–4

Inflammatory processes are now recognized to play a fundamental role in atherogenesis.5 C-reactive protein (CRP) has been found to be a robust predictor of incident cardiovascular disease.6–15 In this regard, the American Heart Association and the Centers for Disease Control and Prevention have recently issued a class IIa recommendation for the measurement of CRP in primary prevention among those at intermediate risk.16

Despite accumulating data, the clinical relevance of the relationship between blood pressure and vascular inflammation is largely unknown. Cross-sectional studies have suggested that levels of CRP and other markers of inflammation, such as interleukin-6, and soluble intercellular adhesion molecule-1 may be related to levels of blood pressure, but these studies have been limited by their small numbers or lack of use of high-sensitivity assays for CRP.17–23

To address these issues, we sought to determine the relationship between CRP and blood pressure in a large cohort of women and to determine whether blood pressure was an independent determinant of CRP levels. Furthermore, we sought to determine the predictive value of these 2 measures for future cardiovascular events.

Methods

The Women’s Health Study is an ongoing evaluation of aspirin and vitamin E for the primary prevention of cardiovascular events among women ≥45 years of age. At enrollment, all participants were asked to provide information regarding demographic, behavioral, and lifestyle factors, including self-reported blood pressure measurements. The baseline characteristics of the Women’s Health Study cohort have been described elsewhere.24 The proportion of women

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Dr Ridker is named as a coinventor on patents filed by Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes.

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who were overweight and had elevated blood pressure, elevated cholesterol, or the metabolic syndrome was similar to that in the general US population. Before randomization, 28,345 study participants provided blood samples in EDTA-containing tubes that were stored in liquid nitrogen until the time of analysis. Because recent randomized trial evidence indicates a net hazard in association with hormone replacement therapy, 27 we elected to increase the generalizability of our data by limiting our analysis to the 15,745 participants who were not using hormone replacement therapy at enrollment. The present study cohort of 15,215 is composed of all women who were not using hormone replacement therapy for whom baseline measures of systolic blood pressure, diastolic blood pressure, body mass index, and CRP were all available. CRP was measured with a validated high-sensitivity assay (Denka Seiken). The methods for this assay have been described previously. 28 The percentage coefficients of variation are as follows: 0.087 mg/dL, 2.75%; 1.139 mg/dL, 2.01%; and 5.243 mg/dL, 2.79%.

All participants were followed for occurrence of first cardiovascular events, including nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization procedures (either coronary artery bypass grafting or percutaneous coronary revascularization), and death from cardiovascular causes. The occurrence of myocardial infarction was considered confirmed if symptoms met the criteria of the World Health Organization and if the event was associated with diagnostic ECG criteria or with abnormal levels of cardiac enzymes. Stroke was confirmed if the participant had new neurological deficits that persisted for $>24$ hours. Computed tomographic scans or magnetic resonance images were available for the vast majority of events and were used to distinguish hemorrhagic from ischemic stroke. The performance of coronary artery bypass grafting or percutaneous coronary revascularization was confirmed by review of hospital records. Deaths from cardiovascular causes were confirmed by review of autopsy reports, death certificates, medical records, and information obtained from family members. The median follow-up was 8.1 years.

**Statistical Analysis**

The study cohort was divided into groups according to category of blood pressure as defined by Framingham risk models ($<120/75$, 120 to 129/75 to 84, 130 to 139/85 to 89, 140 to 159/90 to 94, and $\geq 160/\geq 95$ mm Hg). 29 All analyses were repeated after exclusion of those women who were receiving treatment for hypertension at baseline (12.8%: $n=1949$).

Levels of CRP were assessed according to baseline categories of blood pressure. Because of the right skew in CRP distribution, levels of CRP were log-transformed for linear regression models that were used to determine whether increasing categories of blood pressure were independent determinants of CRP levels in models adjusted for age only and models adjusted for age, body mass index (as a continuous variable), current smoking, LDL cholesterol, HDL cholesterol, and diabetes. In addition, these models were used to estimate adjusted geometric mean CRP levels according to levels of blood pressure. These analyses were repeated after stratification according to median levels of body mass index.

Cox proportional-hazard models were used to estimate hazard ratios for future cardiovascular events according to CRP levels ($<3$ or $\geq 3$ mg/L) and according to categories of blood pressure. The cutpoint of 3 mg/L for CRP was based on the recent American Heart Association/Centers for Disease Control and Prevention scientific statement suggesting that levels $>3$ mg/L be considered high. 16 Hazard ratios were estimated in crude models, models adjusted for age only, and models adjusted for age, body mass index (as a continuous variable), current smoking, LDL cholesterol, HDL cholesterol, and diabetes.

To evaluate joint effects, we assessed the relative risks of future cardiovascular events in Cox proportional-hazard models after dividing the cohort into 10 groups according to levels of CRP ($<3$ or $\geq 3$ mg/L) and categories of blood pressure. Finally, we constructed Kaplan-Meier curves for event-free survival according to levels of CRP ($<3$ or $\geq 3$ mg/L) and blood pressure category ($<130/\leq 85$ or $\geq 130/\geq 85$ mm Hg). All models were adjusted for random allocation to aspirin or vitamin E. All probability values are 2-tailed.

**Results**

At enrollment, the mean age of the 15,215 women was 54.1±7.7 years, 24.9% had a history of hypertension, 12.8% were receiving treatment for hypertension, 12.2% were current smokers, and 3.3% had diabetes. Over a median follow-up of 8.1 years, 321 women developed first cardiovascular events. Thirty-three women died from cardiovascular causes, 97 had nonfatal myocardial infarction, 85 had nonischemic stroke, and 106 underwent coronary revascularization procedures.

Figure 1 shows cross-sectional analyses of crude median levels and interquartile ranges of CRP according to Framingham blood pressure category at enrollment. A similar linear increase in levels of CRP was also seen as levels of systolic...
blood pressure or diastolic blood pressure increased. Table 1 shows cross-sectional data regarding baseline blood pressure categories as predictors of log-transformed CRP levels. In both age-adjusted and risk factor–adjusted models, increasing categories of blood pressure were significant predictors of CRP levels (both, \( P \) for trend <0.0001). The age-adjusted and risk factor–adjusted geometric mean levels of CRP showed stepwise increases as blood pressure category increased. For example, after adjustment for other risk factors, geometric mean levels of CRP were 1.33 mg/L among those women with blood pressure <120/75 mm Hg, compared with 1.84 mg/L for those women with blood pressure \( \geq 160/95 \) mm Hg (\( P <0.0001 \)).

To assess for evidence of effect modification according to body mass index, we stratified according to median body mass index less than the median (\( <25.06 \) kg/m\(^2\)) or among those with body mass index equal to or above the median (\( \geq 25.06 \) kg/m\(^2\)). For example, among those with body mass index below the median, after adjustment for other risk factors, geometric mean levels of CRP were 0.79 mg/L among those with blood pressure <120/75 mm Hg, compared with 1.32 mg/L for those with blood pressure \( \geq 160/95 \) mm Hg (\( P <0.0001 \)). Among those with body mass index above the median, after adjustment for other risk factors, geometric mean levels of CRP were 2.30 mg/L among those with blood pressure <120/75 mm Hg, compared with 2.94 mg/L for those with blood pressure \( \geq 160/95 \) mm Hg (\( P <0.0001 \)).

Table 2 shows prospective data regarding the predictive value of CRP and blood pressure categories for future

<table>
<thead>
<tr>
<th>Blood Pressure Category, mm Hg</th>
<th>Age-Adjusted Model</th>
<th>Risk Factor-Adjusted Model*</th>
<th>Parameter Estimate</th>
<th>CRP, mg/L</th>
<th>P</th>
<th>Parameter Estimate</th>
<th>CRP, mg/L</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;120/\leq 75)</td>
<td>(\ldots)</td>
<td>(\ldots)</td>
<td>(1.00)</td>
<td>(\ldots)</td>
<td>(1.33)</td>
<td>(\ldots)</td>
<td>(2.51)</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>(120–129/75–84)</td>
<td>0.31</td>
<td>1.36</td>
<td>(&lt;0.0001)</td>
<td>0.06</td>
<td>1.42</td>
<td>(&lt;0.0001)</td>
<td>0.17</td>
<td>1.59</td>
</tr>
<tr>
<td>(130–139/85–89)</td>
<td>0.71</td>
<td>2.03</td>
<td>(&lt;0.0001)</td>
<td>0.17</td>
<td>1.59</td>
<td>(&lt;0.0001)</td>
<td>0.23</td>
<td>1.67</td>
</tr>
<tr>
<td>(140–159/90–94)</td>
<td>0.93</td>
<td>2.52</td>
<td>(&lt;0.0001)</td>
<td>0.23</td>
<td>1.67</td>
<td>(&lt;0.0001)</td>
<td>0.32</td>
<td>1.84</td>
</tr>
<tr>
<td>(\geq 160/\geq 95)</td>
<td>1.10</td>
<td>2.98</td>
<td>(&lt;0.0001)</td>
<td>0.32</td>
<td>1.84</td>
<td>(&lt;0.0001)</td>
<td>0.32</td>
<td>1.84</td>
</tr>
</tbody>
</table>

*Risk factor-adjusted model adjusts for the effects of age, body mass index, smoking status, LDL cholesterol, HDL cholesterol, and diabetes.

### Table 2. CRP and Blood Pressure as Predictors of Future Cardiovascular Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Crude Hazard Ratio</th>
<th>( P )</th>
<th>Age-Adjusted Model</th>
<th>Hazard Ratio</th>
<th>( P )</th>
<th>*Risk Factor-Adjusted Model</th>
<th>Hazard Ratio</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP ( \geq 3 ) mg/L</td>
<td>2.78</td>
<td>(&lt;0.0001)</td>
<td>2.51</td>
<td>(&lt;0.0001)</td>
<td>1.53</td>
<td>0.0009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure category, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;120/\leq 75)</td>
<td>1</td>
<td>(\ldots)</td>
<td>1</td>
<td>(\ldots)</td>
<td>1</td>
<td>(\ldots)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(120–129/75–84)</td>
<td>1.93</td>
<td>0.001</td>
<td>1.68</td>
<td>0.01</td>
<td>1.39</td>
<td>0.11</td>
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<tr>
<td>(130–139/85–89)</td>
<td>4.70</td>
<td>(&lt;0.0001)</td>
<td>3.36</td>
<td>(&lt;0.0001)</td>
<td>2.45</td>
<td>(&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(140–159/90–94)</td>
<td>6.50</td>
<td>(&lt;0.0001)</td>
<td>4.00</td>
<td>(&lt;0.0001)</td>
<td>2.54</td>
<td>(&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\geq 160/\geq 95)</td>
<td>12.45</td>
<td>(&lt;0.0001)</td>
<td>7.89</td>
<td>(&lt;0.0001)</td>
<td>5.30</td>
<td>(&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP, ( \geq 3 ) mg/L</td>
<td>1.94</td>
<td>(&lt;0.0001)</td>
<td>2.02</td>
<td>(&lt;0.0001)</td>
<td>1.44</td>
<td>0.005</td>
<td></td>
<td></td>
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<tr>
<td>Blood pressure category, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;120/\leq 75)</td>
<td>1</td>
<td>(\ldots)</td>
<td>1</td>
<td>(\ldots)</td>
<td>1</td>
<td>(\ldots)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(120–129/75–84)</td>
<td>1.81</td>
<td>0.004</td>
<td>1.56</td>
<td>0.03</td>
<td>1.38</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(130–139/85–89)</td>
<td>4.00</td>
<td>(&lt;0.0001)</td>
<td>2.85</td>
<td>(&lt;0.0001)</td>
<td>2.40</td>
<td>(&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(140–159/90–94)</td>
<td>5.21</td>
<td>(&lt;0.0001)</td>
<td>3.20</td>
<td>(&lt;0.0001)</td>
<td>2.45</td>
<td>(&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\geq 160/\geq 95)</td>
<td>9.57</td>
<td>(&lt;0.0001)</td>
<td>6.09</td>
<td>(&lt;0.0001)</td>
<td>5.06</td>
<td>(&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All models were adjusted for random allocation to aspirin and vitamin E.

*Risk factor-adjusted model adjusts for the effects of age, body mass index, smoking status, LDL cholesterol, HDL cholesterol, and diabetes.
cardiovascular events in crude, age-adjusted, and risk factor–adjusted models. Both elevated CRP levels (≥3 mg/L) and increasing categories of blood pressure were significant predictors in all models, and the independent predictive value of each persisted when both CRP and blood pressure categories were included together in the risk factor–adjusted model.

We further estimated the hazard ratios of future cardiovascular events after dividing the cohort into 10 groups according to baseline levels of CRP and blood pressure categories. As shown in Figure 2, after adjustment for other risk factors, the hazard ratio for those women with blood pressure ≥160/95 mm Hg and CRP levels ≥3 mg/L was more than 8-fold greater than for those with blood pressure <120/75 and CRP levels <3 mg/L (hazard ratio, 8.31; 95% CI, 4.44 to 15.55; P<0.0001).

To further assess the joint effects of CRP and blood pressure, we constructed survival curves after dividing the study participants into 4 groups on the basis of CRP levels (<3 or ≥3 mg/L) and blood pressure levels (<130/85 or ≥130/85). As shown in Figure 3, the risk factor–adjusted hazard ratios were as follows: low CRP/low blood pressure, 1.0 (this was the reference category); high CRP/low blood pressure, 1.87 (95% CI, 1.25 to 2.80; P=0.002); low CRP/high blood pressure, 2.54 (95% CI, 1.79 to 3.58; P<0.0001); and high CRP/high blood pressure, 3.27 (95% CI, 2.28 to 4.71; P<0.0001). Similar results were observed if the combination of CRP and systolic blood pressure or CRP and diastolic blood pressure was examined (Figure 4). A statistical test for multiplicative interaction between CRP and blood pressure in the Cox model was not significant (P=0.2).

Finally, we repeated these analyses after exclusion of those women who reported treatment for hypertension at enrollment (12.8%). No significant differences in these results were observed. Specifically, in cross-sectional analyses at baseline in this group, median levels of CRP for those women with blood pressure <120/75, 120 to 129/75 to 84, 130 to 139/85 to 89, 140 to 159/90 to 94, and ≥160/95 mm Hg were 0.96, 1.38, 2.10, 2.62, and 2.85 mg/L, respectively (P for trend <0.0001). In prospective analyses in this group, the risk factor–adjusted hazard ratios for incident cardiovascular events were as follows: low CRP/low blood pressure, 1.0; high CRP/low blood pressure, 1.86 (95% CI, 1.21 to 2.86; P=0.005); low CRP/high blood pressure, 2.46 (95% CI, 1.67 to 3.64; P<0.0001); and high CRP/high blood pressure, 2.94 (95% CI, 1.91 to 4.53; P<0.0001).

Discussion

In this study, among 15,215 women initially free of overt cardiovascular disease, we found a linear relationship between categories of blood pressure and CRP levels in cross-sectional analyses. This relationship was evident across the full spectrum of blood pressure levels. In prospective follow-
up, both elevated levels of CRP and increasing categories of blood pressure were strong independent determinants of future cardiovascular events, and the combination of these measures improved risk prediction on the basis of either CRP or blood pressure alone.

The present data suggest that blood pressure and CRP may work in tandem to increase cardiovascular risk. Data from basic research suggest a central role of inflammation in the genesis of hypertension and that hypertension in turn induces a proinflammatory response. Previous data from smaller studies had suggested that levels of CRP, soluble intercellular adhesion molecule-1, and interleukin-6 may be related to blood pressure measurements. Recent data also suggest that cumulative elevations of inflammation-sensitive plasma proteins (fibrinogen, α1-antitrypsin, haptoglobin, and orosomucoid) may be associated with increased risk of stroke among hypertensive men. The present data extend these observations for CRP among 15,215 women and furthermore illustrate the potential importance of both CRP and blood pressure for the prediction of incident cardiovascular events.

There are several potential mechanisms that may account for the observed relationship between blood pressure and CRP. Increased blood pressure may promote vascular inflammation by modulation of biomechanical stimuli from pulsatile blood flow. Cyclic strain has been shown to increase soluble intercellular adhesion molecule-1 and vascular cellular adhesion molecule-1 expression by endothelial cells and to upregulate endothelial cell secretion of monocyte chemoattractant protein-1. These changes, in turn, result in increased monocyte adhesion to the endothelium. Increased soluble intercellular adhesion molecule-1 expression has also been demonstrated by endothelial cells in spontaneously hypertensive rats compared with normotensive rats. Furthermore, elevated blood pressure may lead to generation of reactive oxygen species and increased oxidative stress. In this regard, levels of CRP have recently been shown to correlate with mononuclear cell oxidative stress. Thus, hypertension per se may lead to multiple proinflammatory stimuli at the vessel wall.

Hormonal stimuli may also contribute to vascular inflammation via nonhemodynamic mechanisms. Rat models of hypertension induced by angiotensin II or aldosterone are characterized by early vascular infiltration by monocytes and macrophages and increased expression of inflammatory mediators such as monocyte chemoattractant protein-1, cyclooxygenase-2, and osteopontin. Angiotensin II elicits a direct inflammatory response in smooth muscle cells by stimulation of interleukin-6 release and nuclear factor-κB activation. Interleukin-6, in turn, is a primary stimulus for CRP synthesis in the liver, and previous cross-sectional studies have observed a relationship between interleukin-6 levels and blood pressure.

Alternatively, it is possible to speculate that CRP may potentially play a more direct role in promoting hypertension. Recent data suggest that at concentrations known to predict cardiovascular events, CRP directly quenches the production of nitric oxide by endothelial cells. This, in turn, could lead to disturbance of vasomotor tone and unopposed vasoconstriction. In this regard, CRP has recently been found to upregulate angiotensin 1 receptor-mediated events in vascular smooth muscle cells. Furthermore, CRP has also been shown to augment the production of endothelin-1, a potent endothelium-derived constrictor, and may induce the expression of monocyte chemoattractant protein-1 and soluble intercellular adhesion molecule-1 via endothelin-1- and interleukin-6–dependent pathways. Recent data also suggest that cumulative elevations of inflammation-sensitive plasma proteins may predict future increases in systolic blood pressure.

Our study has limitations. It is not possible to conclude from our study whether blood pressure is stimulating heightened inflammation or whether inflammation is occurring before the development of hypertension. Indeed, it is probable that both these effects work in tandem in atherogenesis. Our study was based on observational data.
Our analyses are based on single measurements of self-reported blood pressure and CRP that may not reflect their relative contributions over time and that may increase the possibility of measurement error. This effect, however, would tend to bias the data toward the null, and blood pressure and CRP were robust predictors of future cardiovascular events in this study. The use of a composite end point may represent a potential limitation. Nonetheless, previous studies have suggested that the predictive value of CRP for these hard cardiovascular outcomes is similar.\textsuperscript{12,13,44–46} Finally, our results may be generalizable only to groups with demographics similar to those included in the Women’s Health Study.

In conclusion, among 15,215 women initially free of cardiovascular disease, CRP showed a linear relationship with blood pressure across all categories of blood pressure. Both CRP and blood pressure were independent determinants of cardiovascular risk, and in combination, each parameter had additional predictive value. Strategies targeted to lower blood pressure and reduce vascular inflammation may potentially provide increased clinical benefit.

Acknowledgments

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References


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