Brief Rapid Communication

Prospective Study of C-Reactive Protein and the Risk of Future Cardiovascular Events Among Apparently Healthy Women

Paul M. Ridker, MD; Julie E. Buring, ScD; Jessie Shih, PhD; Mathew Matias, BS; Charles H. Hennekens, MD

Background—C-reactive protein (CRP) predicts risk of myocardial infarction (MI) and stroke among apparently healthy men, but in women, virtually no data are available.

Methods and Results—CRP was measured in baseline blood samples from 122 apparently healthy participants in the Women’s Health Study who subsequently suffered a first cardiovascular event and from 244 age- and smoking-matched control subjects who remained free of cardiovascular disease during a 3-year follow-up period. Women who developed cardiovascular events had higher baseline CRP levels than control subjects (P=0.0001), such that those with the highest levels at baseline had a 5-fold increase in risk of any vascular event (RR=4.8; 95% CI, 2.3 to 10.1; P=0.0001) and a 7-fold increase in risk of MI or stroke (RR=7.3; 95% CI, 2.7 to 19.9; P=0.0001). Risk estimates were independent of other risk factors, and prediction models that included CRP provided a better method to predict risk than models that excluded CRP (all P values <0.01). In stratified analyses, CRP was a predictor among subgroups of women with low as well as high risk as defined by other cardiovascular risk factors.

Conclusions—In these prospective data among women, CRP is a strong independent risk factor for cardiovascular disease that adds to the predictive value of risk models based on usual factors alone. (Circulation. 1998;98:731-733.)

Key Words: C-reactive protein ▪ inflammation ▪ cardiovascular diseases

C-reactive protein (CRP) is a marker for inflammation that appears to predict cardiovascular events among apparently healthy men. For example, in the prospective Physicians’ Health Study (PHS), high plasma concentration of CRP was associated with a 2-fold increase in risk of stroke, a 3-fold increase in risk of myocardial infarction (MI), and a 4-fold increase in risk of developing peripheral vascular disease.1,2 Moreover, CRP adds to the predictive value of total and HDL cholesterol such that the risk of future MI for men with elevated levels of CRP and hyperlipidemia appears to be greater than the product of the risks associated with either abnormality alone.3 Finally, CRP has been associated with increased risks of fatal coronary events among high-risk male smokers,4 incident coronary disease among the elderly,5 and recurrent coronary events among those with known coronary disease.6–8

In women, prospective data evaluating CRP are sparse. We therefore sought to determine whether CRP was also an independent predictor of future vascular disease among currently healthy women.

Methods
The study population consisted of participants in the Women’s Health Study (WHS), a primary prevention trial being conducted among 39 876 postmenopausal female health professionals with no prior history of MI, stroke, or transient ischemic attack.9 Among these women, 28 263 (70.9%) provided baseline blood samples collected in EDTA, which, after cold overnight shipping, were centrifuged and frozen at −170°C until analysis.

Questionnaires are sent to WHS participants to elicit information on risk factors and incident health events. For all cases of MI, stroke, PTCA, CABG, or cardiovascular death reported after enrollment, hospital records are obtained and reviewed. Reported MI was confirmed if symptoms met World Health Organization criteria and the event was associated with elevated cardiac enzymes or characteristic ECG changes. Reported stroke was confirmed if the patient had a new neurological deficit with signs and symptoms persisting for >24 hours; CT scans were available in most cases. Reported revascularization procedures were confirmed by hospital records. Coronary deaths were confirmed by autopsy reports, death certificates, and circumstances of death.

For each case subject who provided a baseline blood sample, 2 control subjects of the same age (±1 year) and smoking pattern (current, past, never) who also provided a baseline plasma sample and who remained free of reported vascular disease during follow-up were selected; 122 women who suffered a first cardiovascular event during a 36-month follow-up period and 244 who remained free of disease were included in this analysis. Plasma samples for each subject were thawed and assayed for CRP with a high-sensitivity ELISA (Abbott Laboratories).10

We used Student’s t test to evaluate differences in means and the χ2 statistic to evaluate differences in proportions. Because the...
distribution of CRP levels was skewed, differences in medians were tested with the rank sum test. Logistic regression was used to estimate relative risks (RRs) and 95% CIs. Tests for trend were used to assess relationships of increasing levels of CRP with risk after the cohort was divided into quartiles defined by the distribution of the control subjects. Likelihood ratio tests were used to determine whether prediction models that included CRP provided a better fit than did models limited to traditional risk factors alone. All P values were 2-tailed.

Results
Baseline characteristics of study participants are shown in Table 1. As expected, case subjects had higher rates of usual cardiovascular risk factors than control subjects. Because of matching, age and smoking status were virtually identical between study groups.

Case subjects had higher median CRP levels at baseline than control subjects (P = 0.0001). In age- and smoking-matched analyses, the risk of future vascular events increased with each increasing quartile of CRP (P for trend = 0.0001) such that women with the highest levels had a 5-fold increase in risk of any vascular event (RR = 4.8; 95% CI, 2.3 to 10.1; P = 0.0001) and a 7-fold increase in risk of MI or stroke (RR = 7.3; 95% CI, 2.7 to 19.9; P = 0.0001); estimates were minimally altered after control for other risk factors (Table 2).

To evaluate whether CRP adds to usual risk factors in predicting future vascular events, likelihood ratio tests were used to compare the fit of prediction models that specifically included or excluded log-normalized CRP. In these analyses, the simultaneous assessment of CRP and traditional risk factors provided an improved ability to predict risk over models limited to traditional factors alone (all P values < 0.01). For example, models that used CRP in addition to hyperlipidemia, hypertension, diabetes, a family history of coronary disease, and body mass index provided a significant improvement in prediction (P = 0.005) compared with models that excluded CRP.

Baseline levels of CRP predicted risk of vascular disease among women with and without other cardiovascular risk factors. These effects were most striking among women who appeared to be at low baseline risk; elevated levels of CRP were associated with a 4-fold increase in risk in analyses limited to nonsmokers (RR = 4.5, P = 0.001) or to those with no history of hyperlipidemia (RR = 3.9, P = 0.002). Similarly, elevated levels of CRP were associated with increased risk among women with no history of hypertension (RR = 2.8, P = 0.03), no evidence of diabetes (RR = 4.9, P = 0.001), or those with no family history of premature atherosclerosis (RR = 6.6, P = 0.001) (Table 3).

Discussion
These prospective data indicate that baseline CRP concentration is an independent risk factor for cardiovascular disease.

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**TABLE 1. Baseline Characteristics of Study Participants**

<table>
<thead>
<tr>
<th>Case Subjects (n=122)</th>
<th>Control Subjects (n=244)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>59.3±8.4</td>
<td>59.3±8.4</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>27.9</td>
<td>27.9</td>
</tr>
<tr>
<td>Never</td>
<td>42.6</td>
<td>42.6</td>
</tr>
<tr>
<td>Past</td>
<td>29.5</td>
<td>29.5</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.1±4.8</td>
<td>26.0±5.2</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>45.9</td>
<td>28.3</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>55.5</td>
<td>31.3</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>9.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Family history of CAD, %</td>
<td>21.3</td>
<td>12.8</td>
</tr>
<tr>
<td>CRP, mg/L, median</td>
<td>6.45</td>
<td>3.75</td>
</tr>
</tbody>
</table>

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**TABLE 2. Relative Risks of Future Cardiovascular Events Among Apparently Healthy Women According to Baseline Concentration of CRP**

<table>
<thead>
<tr>
<th>Quartile of CRP (range, mg/L)</th>
<th>1 (≤1.5)</th>
<th>2 (1.5–3.7)</th>
<th>3 (3.8–7.3)</th>
<th>4 (&gt;7.3)</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (crude)</td>
<td>1.0</td>
<td>2.4</td>
<td>2.5</td>
<td>4.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>95% CI</td>
<td>...</td>
<td>1.1–5.2</td>
<td>1.1–5.6</td>
<td>2.3–10.1</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>...</td>
<td>0.03</td>
<td>0.02</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>RR (adjusted)</td>
<td>1.0</td>
<td>2.0</td>
<td>2.3</td>
<td>4.1</td>
<td>0.001</td>
</tr>
<tr>
<td>95% CI</td>
<td>...</td>
<td>0.8–4.7</td>
<td>1.0–5.6</td>
<td>1.7–9.9</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>...</td>
<td>0.1</td>
<td>0.06</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>MI or stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR (crude)</td>
<td>1.0</td>
<td>3.5</td>
<td>4.5</td>
<td>7.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>95% CI</td>
<td>...</td>
<td>1.2–10.0</td>
<td>1.6–12.6</td>
<td>2.7–19.9</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>...</td>
<td>0.02</td>
<td>0.005</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>RR (adjusted)</td>
<td>1.0</td>
<td>2.7</td>
<td>3.5</td>
<td>5.5</td>
<td>0.002</td>
</tr>
<tr>
<td>95% CI</td>
<td>...</td>
<td>0.9–8.1</td>
<td>1.1–10.4</td>
<td>1.8–16.6</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>...</td>
<td>0.08</td>
<td>0.03</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

All models age- and smoking-matched. Adjusted models controlled for body mass index, diabetes, hypertension, hypercholesterolemia, exercise, family history, and treatment assignment.
among apparently healthy middle-aged women. Moreover, in these data, the predictive value of models that include CRP is significantly better than those limited to usual risk factors. Finally, these data indicate that CRP predicts vascular events even among low-risk subgroups of women with no readily apparent markers for disease.

Previous studies of CRP in healthy populations have almost exclusively been limited to men.\textsuperscript{1–4} As such, the present data extend prior observations concerning the potential clinical utility of CRP as a marker for vascular disease. Our primary prevention data in women are also consistent with subgroup observations from the Cardiovascular Health Study, in which CRP levels were found to predict risk among 41 elderly women with evidence of subclinical cardiovascular disease, as well as observations from the Rural Health Promotion Project, in which CRP levels were higher among 65 elderly women at risk for vascular events.\textsuperscript{5} In both of these prior subgroup analyses, the risks of vascular disease associated with CRP were greater for women than for men. This also appears to be the case for our data, in which the adjusted RR of either MI or stroke for women with CRP levels in the highest quartile was 5.5, compared with 2.8 for men participating in the PHS.\textsuperscript{6} Whether these differences reflect chance or effect modification by sex requires investigation.

It is also of interest that median levels of CRP in the present study of women are higher overall than levels observed in previous studies of men.\textsuperscript{1–3} Although this may further reflect sex-specific effects, it is important to recognize that the CRP assay techniques and the methods of blood collection and storage in the present study are somewhat different from those used in previous studies. The higher median CRP levels observed in the present data may also reflect the fact that, at least compared with men evaluated in the PHS,\textsuperscript{1–3} women in the present analysis were more likely to be current smokers, were heavier, and had a higher prevalence of hypertension, hyperlipidemia, and family history of premature atherosclerosis; all of these factors are associated with increased CRP levels\textsuperscript{1–7} and thus might contribute to a higher overall distribution of baseline values.

These data support the hypothesis that low-grade inflammation is a marker for subsequent cardiovascular disease. Whether CRP has direct vascular or prothrombotic effects, reflects underlying endothelial dysfunction due to prevalent atherosclerosis, leads to increased lipid peroxidation, or is simply a marker resulting from an as yet undefined environmental and/or infectious stimulus remains to be elucidated.\textsuperscript{11,12}

Acknowledgments
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References

\begin{table}
\centering
\caption{Relative Risks of Future Cardiovascular Events Among Low-Risk Subgroups of Women According to Baseline Concentration of CRP.}
\begin{tabular}{|c|c|c|c|c|}
\hline
\multicolumn{2}{|c|}{Quartile of CRP (range, mg/L)} & 1 & 2 & 3 & \textit{P} for Trend \\
\hline
No hyperlipidemia & 1.0 & 1.7 & 2.0 & 3.9 & 0.002 \\
No hypertension & 1.0 & 1.7 & 2.0 & 2.8 & 0.04 \\
No current smoking & 1.0 & 2.0 & 2.3 & 4.5 & 0.0004 \\
No diabetes & 1.0 & 2.5 & 2.6 & 4.9 & 0.0001 \\
No family history & 1.0 & 3.3 & 3.2 & 6.6 & 0.0001 \\
\hline
\end{tabular}
\end{table}
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