Plasma Concentration of C-Reactive Protein and the Calculated Framingham Coronary Heart Disease Risk Score

Michelle A. Albert, MD, MPH; Robert J. Glynn, PhD; Paul M Ridker, MD, MPH

Background—Although C-reactive protein (CRP) predicts vascular risk, few data are available evaluating the relation between CRP and the Framingham Coronary Heart Disease Risk Score (FCRS).

Methods and Results—CRP levels were compared with calculated 10-year FCRS in a cross-sectional survey of 1666 individuals free of cardiovascular disease. Among men and women not using hormone replacement therapy (HRT), CRP levels were significantly related to 10-year Framingham Coronary Heart Disease Risk categories [total cholesterol (TC) score for men and women: \( r = 0.29 \) and \( r = 0.22 \), respectively; LDL cholesterol score for men and women: \( r = 0.29 \) and \( r = 0.22 \), respectively, all probability values <0.01]. However, CRP levels correlated minimally with individual components of the FCRS, which included age (\( r_{\text{men}} = 0.17, r_{\text{women}} = -0.003 \)), TC (\( r_{\text{men}} = -0.02, r_{\text{women}} = -0.006 \)), HDL-C (\( r_{\text{men}} = 0.13 \)), LDL-C (\( r_{\text{men}} = -0.0002, r_{\text{women}} = 0.012 \)), blood pressure (\( r_{\text{men}} = 0.18, r_{\text{women}} = 0.22 \)), diabetes (\( r_{\text{men}} = 0.10, r_{\text{women}} = 0.07 \)), and smoking (\( r_{\text{men}} = 0.16, r_{\text{women}} = 0.14 \)) status. For women taking HRT, no significant relation was observed between CRP and the FCRS, although the power to detect effects in this subgroup is limited.

Conclusions—Our data demonstrate that CRP levels significantly correlate with calculated 10-year Framingham Coronary Heart Disease Risk in men and women not taking HRT but correlate minimally with most individual components of the FCRS. These data provide additional support for continued evaluation of CRP as a potential adjunct in the global prediction of cardiovascular risk. (*Circulation*, 2003;108:161-165.)

Key Words: prevention ■ inflammation ■ risk factors

The Framingham Coronary Heart Disease Risk Score (FCRS) is a simplified coronary prediction tool developed to enable clinicians to estimate cardiovascular risk in middle-aged individuals.1,2 Although it is an important clinical tool, it is recognized that not all persons at high coronary heart disease risk are identified by the FCRS. For example, recent evidence indicates that the c statistic for the area under the receiver operator characteristic curve associated with the FCRS varies between 0.63 to 0.83 in different populations.3 In an effort to improve coronary heart disease risk prediction, several novel cardiovascular risk markers have been evaluated as potential adjuncts to lipid screening in primary prevention. Of these, C-reactive protein (CRP), a marker of low-grade inflammation, has been extensively studied in several large, prospective, epidemiological studies.4–7 However, few data are available directly comparing CRP levels with calculated FCRS. Although both CRP and the FCRS each predict vascular risk, the extent to which CRP reflects any individual component of the FCRS is unclear.

Methods
We measured CRP levels and calculated the FCRS among 932 men and 734 women participating in the primary prevention arm of the Pravastatin Inflammation/CRP Evaluation (PRINCE) Study,8,9 a multicenter, community-based study of the effect of 40 mg pravastatin or placebo on CRP levels over a 6-month follow-up period. At study entry, in addition to providing a blood sample for CRP and lipid evaluation, 1666 of a total of 1702 participants provided data on age, gender, smoking status, and diabetes history. Data on weight, height, and blood pressure were measured by the participant’s physician at study entry. None of the participants had a history of myocardial infarction, stroke, or coronary revascularization. Participants all provided written informed consent, and all procedures followed were in accordance with institutional guidelines.

Plasma samples were assayed for CRP by using a clinically validated high-sensitivity assay10; total cholesterol, HDL cholesterol, and LDL cholesterol levels were determined in a Centers for Disease Control and Prevention standardized laboratory. Framingham Coronary Heart Disease risk was calculated by using previously published algorithms that used baseline cardiac risk factors including age, HDL cholesterol, LDL cholesterol, total cholesterol, smoking status, blood pressure, and diabetes history.2

To assess the relation between CRP and individual components of the FCRS, we first calculated the scores corresponding to the individual components of the FCRS as well as the total score. Next, Pearson correlation coefficients relating these individual risk factor scores and the total score to the natural log of baseline CRP levels were calculated. Additionally, biserial correlation coefficients were computed for diabetic and smoking status because both of these

References
TABLE 1. Baseline Characteristics of Study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men (n=932)</th>
<th>Women (n=734)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.0 (47.0, 63.0)</td>
<td>59.0 (52.0, 69.0)</td>
</tr>
<tr>
<td>Aspirin use, %</td>
<td>29.6</td>
<td>26.6</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>45.6</td>
<td>54.3</td>
</tr>
<tr>
<td>Current</td>
<td>15.2</td>
<td>15.3</td>
</tr>
<tr>
<td>Past</td>
<td>39.2</td>
<td>30.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.5 (26.0, 31.5)</td>
<td>28.6 (25.0, 33.4)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>130.0 (120.0, 140.0)</td>
<td>130.0 (120.0, 140.0)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>80.0 (76.0, 86.0)</td>
<td>80.0 (70.0, 84.0)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>38.7</td>
<td>68.4</td>
</tr>
<tr>
<td>Never/rarely</td>
<td>38.7</td>
<td>36.8</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>162.5 (117.0, 235.0)</td>
<td>158.0 (113.0, 231.0)</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>222.5 (205.0, 245.0)</td>
<td>235.0 (214.0, 256.0)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>139.4 (125.4, 156.4)</td>
<td>143.6 (126.9, 160.5)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>35.8 (30.8, 41.5)</td>
<td>43.4 (36.3, 50.4)</td>
</tr>
<tr>
<td>Exercise activity, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>6.9</td>
<td>4.8</td>
</tr>
<tr>
<td>≥2 times/wk</td>
<td>33.0</td>
<td>27.7</td>
</tr>
<tr>
<td>Once/wk</td>
<td>12.3</td>
<td>6.5</td>
</tr>
<tr>
<td>&lt;1 time/wk</td>
<td>10.1</td>
<td>9.5</td>
</tr>
<tr>
<td>Never/rarely</td>
<td>37.7</td>
<td>51.5</td>
</tr>
</tbody>
</table>

*Values are percentage or median and associated interquartile range.

The baseline characteristics of the study participants are shown in Table 1. Compared with men, women were older (59.0 versus 53.0 years), more likely to have diabetes (12.3% versus 9.3%), and had higher total cholesterol (235.0 versus 222.5 mg/dL), HDL cholesterol (43.4 versus 35.8 mg/dL), and LDL cholesterol levels (143.6 versus 139.4 mg/dL). As expected, median CRP levels were significantly higher among women (2.90 mg/L; interquartile range, 1.30 to 5.80 mg/L) than among men (median CRP=1.50 mg/L; interquartile range, 0.80 to 3.20 mg/L), an effect largely the result of HRT use. Specifically, those women who reported current estrogen therapy use (HRT) had higher baseline CRP levels (median=3.80 mg/L; interquartile range, 2.00 to 6.80 mg/L) than those women who were not taking HRT (median=2.40 mg/L; interquartile range, 1.10 to 5.00 mg/L).

We found a modest correlation between CRP levels and the FCRS in men and women not taking HRT by using both the total cholesterol (rmen=0.29, P<0.01; rwomen=0.22, P<0.01) and LDL cholesterol (rmen=0.29, P<0.01; rwomen=0.22, P<0.01) scoring algorithms. As shown in Table 2, although we also noted modest associations between CRP and HDL cholesterol (r=0.24, P<0.01) and blood pressure scores (r=0.22, P<0.01) in women not taking HRT, we found minimal additional evidence of association between CRP levels and the individual components of the FCRS.

Results

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For example, in men and women taking HRT, CRP had the largest correlation with baseline blood pressure (rmen=0.18, rwomen=0.13). Furthermore, except for the relation between diabetes and CRP among men, bireal correlation coefficients assessing the relation between diabetic status and CRP was significant (rmen=0.11, rwomen=0.11, rwomen (no HRT)=0.08) as well as between smoking status and CRP (rmen=0.22, rwomen (no HRT)=-0.004, rwomen (no HRT)=0.14) were almost identical to the corresponding Pearson correlation coefficients noted in Table 2. Likewise, plots showing median CRP levels versus individual components of the FCRS among men and women not taking HRT also demonstrate minimal association between CRP levels and the components of the FCRS (Figures 1 and 2). Specifically, among men, plots of HDL-C and CRP demonstrate a small decrease in median CRP levels with increasing HDL-C levels, whereas there is small increase in CRP concentrations at the highest levels of systolic blood pressure (Figure 1). Plots for women not taking HRT demonstrate similar findings (Figure 2).

Figure 3 shows that median CRP levels increased in men with each increasing calculated Framingham 10-year coronary risk category. This significant positive trend between increasing CRP levels and progressively higher FCRS was...
noted with the use of both the total cholesterol ($P_{\text{trend}}<0.01$) and LDL cholesterol ($P_{\text{trend}}<0.01$) scoring algorithms. A similar pattern was observed for women, but this effect was attenuated in magnitude as the result of an apparent modification effect by HRT use. As shown in Figure 4 (top), among women not taking HRT, the relation between CRP and FCRS was similar to that noted in men ($P_{\text{trend}}<0.01$). By contrast, among HRT users where as reported, CRP levels were higher, the relation between CRP and FCRS was not statistically significant (total cholesterol score computation, $P_{\text{trend}}=0.18$; LDL cholesterol score computation, $P_{\text{trend}}=0.28$; Figure 4, bottom).

**Discussion**

These cross-sectional data indicate that plasma concentration of CRP is significantly associated with calculated FCRS among middle-aged men and women not taking HRT. Overall, individuals in the lowest cardiovascular risk category had CRP levels that were at least half those of individuals in the highest CHD risk category. However, despite this positive association, CRP levels correlated minimally with most individual components of the FCRS.

The dichotomy observed in our data is intriguing and suggests that whereas CRP is related to the FCRS, CRP and the individual components of the FCRS might be reflecting...
different aspects of cardiovascular risk. In support of this hypothesis are previous data from several large prospective cohorts\(^5\)–\(^7\),\(^13\),\(^14\) that indicate that CRP predicts risk of incident cardiovascular events, even after adjustment for other traditional risk factors. Furthermore, recent data from the Women’s Health Study (WHS) Cohort\(^15\) demonstrate that after adjustment for all components of the FCRS, CRP remained an independent predictor of future cardiovascular risk. Therefore, the current data are consistent with the hypothesis that the addition of CRP to the FCRS might be useful in the context of overall cardiovascular risk determination.

As previously described\(^11\),\(^12\), we also observed in our women that median CRP levels were twice as high in HRT users as compared with non-HRT users. Our data extend this observation by further demonstrating a discordance between CRP and FCRS in women taking HRT. The underlying mechanism for this effect modification by HRT is uncertain but may relate to first-pass effects of HRT on hepatic CRP production.\(^16\) These issues have clinical importance and require evaluation in experimental settings.

These data are also important because they have implications for the design of future trials of statin therapy in the primary prevention of cardiovascular disease. Previous data demonstrate that by lowering LDL levels, HMG CoA reductase inhibitors decrease the risk of future cardiovascular events.\(^17\),\(^18\) However, traditional LDL screening, a critical component of the FCRS, misses many individuals in primary prevention who are at high risk for coronary events. Because statins lower CRP levels in an LDL-independent manner,\(^9\),\(^14\),\(^19\) CRP screening in conjunction with lipid screening might help identify those individuals who may benefit from prophylactic statin therapy. For example, in AFCAPS/Tex-CAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study), individuals with below-median LDL and above-median CRP levels had a similar risk of future vascular events as did those with overt hyperlipidemia.\(^14\) In addition, lovastatin was as effective in decreasing cardiovascular event rates among individuals in the below-median LDL/above-median CRP group as it was in participants with above-median LDL levels. Furthermore, assessment of the ability of CRP and LDL-C to predict cardiovascular risk in the WHS cohort revealed that CRP was a better predictor than LDL-C in risk prediction.\(^15\) On the basis of these data, we have initiated a large-scale primary prevention trial of statin therapy among patients with low LDL but high CRP to directly test this hypothesis.\(^20\) As shown in the current analysis, such a study must include large numbers of women and detailed knowledge of HRT status at study initiation and during follow-up.

In summary, in this cross-sectional survey, whereas CRP levels were significantly associated with the level of coronary heart disease risk as calculated by the FCRS in men and women not taking HRT, CRP levels correlated only minimally with most individual components of the FCRS. These data imply that CRP may capture different components than the traditional components of coronary risk reflected in the FCRS and support the hypothesis that CRP may have an adjunctive role in the global risk prediction of cardiovascular disease.\(^4\)

**Appendix**

Components of the Framingham Cardiovascular Risk Score include age, blood pressure, total cholesterol/LDL cholesterol, HDL cholesterol, diabetes, and smoking status.

**Acknowledgments**

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References

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