High-Sensitivity C-Reactive Protein: A Useful Marker for Cardiovascular Disease Risk Prediction and the Metabolic Syndrome

Every year, 1.3 million Americans suffer a myocardial infarction with only one half of them exhibiting evidence of dyslipidemia. The identification of additional risk factors for cardiovascular disease is therefore of paramount importance. Of the examined novel biochemical markers, high-sensitivity C-reactive protein (hs-CRP) is the most promising. To date, 22 prospective epidemiologic studies have demonstrated that hs-CRP is a strong predictor of future vascular disease, 6 cohort studies have shown that hs-CRP measurements add prognostic value beyond that available from the Framingham risk score, and 8 cohort studies have confirmed that hs-CRP adds prognostic information in the metabolic syndrome and in the prediction of type 2 diabetes (1). These studies, done by various groups in Europe and the United States, examined middle-aged and elderly men and women, and some included different ethnic and racial groups. As a result of these findings and the fact that hs-CRP can be reliably and accurately measured by clinical laboratories, the American Heart Association (AHA) and the CDC issued joint guidelines about the implementation of hs-CRP measurement as part of the global risk assessment of cardiovascular disease (2).

In this Journal, Levinson et al. (3) recently questioned the validity of using hs-CRP to predict future cardiovascular disease. These authors relied in their argument on data from the Women’s Health Study (WHS) (4) and the recently published article from the Reykjavik Study by Danesh et al. (5). We would like to point out some of the important issues regarding these two studies.

Using the WHS cohort, we directly compared the ability of hs-CRP and LDL-cholesterol to predict future coronary events in 27,939 participants over a follow-up period of 8 years (4). Our data clearly showed that hs-CRP was superior to LDL-cholesterol in its ability to predict risk (fully adjusted relative risks, 2.3 for hs-CRP and 1.5 for LDL-cholesterol; both \( P < 0.001 \)). In addition, we demonstrated that hs-CRP provided additional prognostic information at all LDL-cholesterol concentrations and Framingham risk scores. After adjustment for all components of the Framingham risk score, hs-CRP remained a strong predictor of future risk. It is surprising that Levinson et al. (3), using these data, questioned the ability of hs-CRP, but not LDL-cholesterol, to predict future cardiovascular disease risk.

We also examined 3597 of those women who have metabolic syndrome, as defined by the National Cholesterol Education Program, and have been followed for 8 years for first-ever cardiovascular events (6). The probability of cardiovascular event-free survival in these women was markedly affected by their hs-CRP values (Fig. 1). Baseline hs-CRP concentration was able to differentiate between low, moderate, and high risk of future cardiovascular events among those with metabolic syndrome, indicating the clinical benefit from its measure-
States and could have contributed to the increased risk associated with cholesterol and the reduced risk associated with hs-CRP seen in that report (8). In addition, the odds ratios and the areas under the ROC curves were almost identical for hs-CRP, cigarette smoking, and hypertension. Therefore, if the authors of that report and Levinson et al. (3) doubt the ability of hs-CRP to predict future cardiovascular events, they must also believe that cigarette smoking and hypertension are unimportant risk factors.

In summary, we find the arguments and conclusions reached by Levinson et al. (3) to be misleading because they are not supported by scientific evidence. However, we agree with them that investigators from the major prospective studies, epidemiologists, cardiologists, and laboratorians should together reexamine current guidelines because a tremendous amount of data has become available since the AHA/CDC expert panel was convened in March 2002. We believe that the consistency of the data will lead to a further widening of the use of hs-CRP as a clinical criterion for metabolic syndrome and as part of a modified cardiovascular risk score useful for global risk assessment in both men and women.

### References


### Table 1. Comparison between the Reykjavik and the WHS risk predictions.

<table>
<thead>
<tr>
<th></th>
<th>Reykjavik*a</th>
<th>WHS*b</th>
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<tbody>
<tr>
<td>CRP (top vs low tertile)c</td>
<td>1.5 (1.3–1.7)</td>
<td>1.7 (1.4–2.2)</td>
</tr>
<tr>
<td>CRP (top vs low quintile)</td>
<td>1.7 (1.4–2.0)</td>
<td>1.9 (1.6–3.4)</td>
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<tr>
<td>CRP (first 10 years)</td>
<td>1.8 (1.5–2.3)</td>
<td>1.8 (1.4–2.4)</td>
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<tr>
<td>Blood pressure</td>
<td>1.5 (1.3–1.7)</td>
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<tr>
<td>Current smoking</td>
<td>1.9 (1.6–2.2)</td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>2.3 (2.0–2.7)</td>
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</tbody>
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*a Adjusted for age, sex, cholesterol, smoking, blood pressure, diabetes, triglycerides, body mass index, and forced expiratory volume (1 s).

*b Adjusted for Framingham risk covariates.

c Cut points, >2 mg/L vs <0.78 mg/L.

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