Inflammation appears to be an integral part of the process of atherosclerosis that leads to coronary artery disease (CAD) and acute ischemic syndromes (1, 2). Data indicate that high-sensitivity C-reactive protein (hs-CRP) and other inflammatory markers are associated with atherosclerosis and that hs-CRP decreases with statin treatment (3, 4). These are important findings that support the inflammatory disease hypothesis. Moreover, it was suggested that hs-CRP could be used to assess risk of CAD for clinical purposes (5), and several hs-CRP assays are commercially available (6).

In this Journal, Rifai and Ridker (7) suggested an algorithm for assessing risk of CAD based on hs-CRP in conjunction with the ratio of HDL-cholesterol to total cholesterol. The algorithm was later modified to use hs-CRP cutoffs of <1, 1–3, and >3 mg/L in conjunction with the LDL-cholesterol (LDLC) concentration or the Framingham 10-year risk assessment (8). Several editorials that have accompanied reports on hs-CRP cautioned that use of this test for clinical purposes was premature (9–12). In spite of these warnings, an American Heart Association/CDC Scientific Statement (13) recommended the use of this test to enhance risk evaluation in certain population groups, although they noted that the benefits of this strategy or any treatment based on it remain uncertain. The clinical recommendations of others argued for even wider use of the test, suggesting that it should be an adjunct for initial screening for global risk assessment in conjunction with conventional lipid testing (8).

We contend that because of its poor predictive value, until its use is better demonstrated, hs-CRP should not be recommended for defining risk. As discussed below, our argument is based on recently published reports and reassessment of previously published reports.

We have shown that hs-CRP exhibits a very low Bayesian positive predictive value when used alone as a marker for predicting CAD (14). The positive predictive value in the highest quartile for hs-CRP was calculated to be 0.86%. hs-CRP varies with many conditions, e.g., acute infections, chronic diseases, smoking, hormone replacement therapy, obesity, age, diabetes, and atrial arrhythmias, and it is associated with the metabolic syndrome that is strongly linked to a proinflammatory state (14, 15).

A recent report in this Journal indicated that 40% of women between ages 30 and 39 years have hs-CRP concentrations >3.5 mg/L and that this high percentage was similar in healthy women and those treated with hormone replacement therapy (16). However, the risk of a coronary event in these women is very low, which is consistent with the poor predictive value of hs-CRP.

In another recent article, Danesh et al. (17), who studied 2459 persons who had suffered a coronary event, concluded that recommendations regarding the use of hs-CRP in predicting the likelihood of disease should be reviewed because the adjusted risk ratio (~1.45) was much lower than indicated in some previous reports. This conclusion was reinforced by a metaanalysis comparing earlier studies with those conducted more recently (17). On the basis of our previous calculations (14), after adjustment for conventional risk factors, this would translate into a much lower positive predictive value than the 0.86% that we calculated previously. An editorial (18) accompanying the publication by Danesh et al. (17) noted that further research is needed to clarify the usefulness of hs-CRP in the clinical setting.

In yet another recent report, risk ratios were calculated after binning of data for 27 939 women into deciles (19). For the entire cohort, after adjustment for Framingham risk factors, the risk ratios for hs-CRP values between 0.64 mg/L (third decile) and 7.73 mg/L (ninth decile) ranged between 1.7 and 2.1, with substantial overlap between confidence intervals (CIs; 1.0–2.8 for the third decile and 1.3–3.4 for the ninth decile). This indicates no significant discrimination over this wide range of hs-CRP concentrations and is in agreement with the conclusions suggesting very poor positive predictive values (14). The discrimination was even poorer when adjusted for diabetes. After results for women on hormone replacement therapy were removed from the analysis, there was some improvement in discrimination, but the fourth through eighth deciles varied between risk ratios of 1.7 and 1.8 and still indicated no significant discrimination based on CIs.

In the editorial (18) accompanying the report by Danesh et al. (17), Professor Tall pointed out that it remains unclear whether hs-CRP is a marker for a low-grade inflammatory systemic state, a marker for the metabolic syndrome, or a marker for both (18). Regarding this syndrome, which is rapidly becoming the largest risk factor for CAD, after analysis of hs-CRP in 14 719 women, it was concluded by Ridker et al. (8, 20) that hs-CRP adds independent prognostic information on risk at all degrees of severity of the metabolic syndrome. After an appraisal of the data used to come to this conclusion (20), we came to a different conclusion, namely, that hs-CRP concentrations add little clinically useful prognostic information to the factors defined by the National Cholesterol Education Program (NCEP) ATP III for assessing risk (15). Table 3 from the article testing 14 719 women is partially reproduced below as Table 1.

In the third and fourth rows of Table 1, all groups show an increased risk. In addition, there is no overlap of the CI with 1.0, which indicates that this is a significant difference. We conclude from the data in these rows that all persons with metabolic syndrome should be treated to reduce its potential effects based on NCEP guidelines (15, 21) regardless of the concentration of hs-CRP. There is no evidence that treatment should be held back on the basis of this test.
with LDLC 1.0, and the CI substantially overlaps with 1.0, indicating no significant difference. This is also true for the group with LDLC <1300 mg/L. We conclude that there is no significant difference between row 2 and the controls in row 1. For the total-cohort column, the risk ratio is 1.5, and the CI in row 2 includes 1.0. This is borderline significant. A good explanation for this finding is that the total cohort includes some persons with LDLC >1600 mg/L. These people should be treated in any case.

hs-CRP may be a statistical predictor of heart disease because it reflects ongoing arteriosclerosis rather than serving as a predictor of disease that has not yet arisen, such as dyslipidemia and hypertension. Thus, not only is hs-CRP nonspecific for CAD, but it is unclear whether hs-CRP is predictive in the true sense or simply a compensatory response. For example, it has been shown that fibrinogen, another acute-phase protein that increases with risk of CAD, is a powerful antioxidant that appears to protect LDL from oxidation which is thought to be a fundamental cause of CAD (22, 23).

One reason that Ridker and associates conceived the idea of assessing risk with hs-CRP is because it has been estimated that up to one-half of all myocardial infarctions occur among persons with moderate to low risk by assessment of total cholesterol and HDL-cholesterol concentrations (5). Recent publications indicate that this estimate may be erroneous. Thus, three publications estimating the frequency of exposure to at least one risk factor from several prospective studies concluded that approximately 80–90% of persons developing CAD exhibit conventional risk factors (24–26).

In conclusion, evidence from many data sources indicates that the explanatory strength of conventional risk factors has been underestimated and that the focus of clinicians must be on lowering the burden of demonstrated, modifiable risk factors, including obesity (26). We agree with this assessment. Moreover, based on the evidence discussed above, which indicates poor discrimination for hs-CRP over a wide range of values when used in conjunction with risk factors for lipoprotein lipids, hypertension, metabolic syndrome, and diabetes, we believe that use of this test for assessment of cardiac status is economically unjustified. Furthermore, given its poor predictive value, this test is likely to lead to erroneous interpretations. We encourage clinical laboratory directors and supervisors to encourage the use of conventional risk factors and discourage use of this test for risk assessment unless its incremental usefulness is confirmed in randomized studies.

### Table 1. Relative risk of future cardiovascular events by CRP concentrations.a

<table>
<thead>
<tr>
<th>Row</th>
<th>CRP, mg/L</th>
<th>Metabolic syndrome</th>
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<th>LDLC &lt;1600 mg/L</th>
<th>LDLC &lt;1300 mg/L</th>
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<td>4.4 (2.8–7.1)</td>
<td>4.4 (2.8–7.1)</td>
</tr>
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</table>

a Partial reproduction of Table 3 from Ridker et al. (20).

### References


Stanley S. Levinson1*
James J. Miller2
Ronald J. Elin2

1 Laboratory Service
Department of Veterans Affairs Medical Center
Louisville, KY

2 Department of Pathology and Laboratory Medicine,
School of Medicine
University of Louisville
Louisville, KY

*Address correspondence to this author at: Laboratory Service, Department of Veterans Affairs Medical Center, 800 Zorn Ave., Louisville, KY 40206. Fax 502-287-6265; e-mail levinson@louisville.edu.

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