

## Proposed Cardiovascular Risk Assessment Algorithm Using High-Sensitivity C-Reactive Protein and Lipid Screening

Several prospective epidemiologic studies from the United States and Europe have demonstrated that high-sensitivity C-reactive protein (hs-CRP) is a predictor of future coronary events among apparently healthy men and women. For example, findings from the Multiple Risk Factors Intervention Trial demonstrated a correlation between hs-CRP and coronary heart disease mortality among male smokers followed over a 17-year period [relative risk (RR) = 2.8; 95% confidence interval (CI), 1.4–5.4] (1). A similar positive association between hs-CRP and future coronary events was noted in the Cardiovascular Health Study and Rural Health Promotion Project, which included elderly men and women with subclinical cardiovascular disease (2). A direct positive association between hs-CRP and future coronary events was also reported in apparently healthy men from the Physician's Health Study (PHS); those in the highest quartile of hs-CRP had twice the risk of future stroke (RR = 1.9; 95% CI, 1.1–3.3), three times the risk of future myocardial infarction (RR = 2.9; 95% CI, 1.8–4.6), and four times the risk of future peripheral vascular disease (RR = 4.1; 95% CI, 1.2–6.0) (3, 4). Furthermore, both the MONICA-Augsburg cohort (5) and the Helsinki Heart Study (6) showed that compared with those with low hs-CRP, individuals with the highest hs-CRP concentrations were at approximately three times the risk of developing future coronary events. Finally, two reports from the Women's Health Study (WHS) showed that hs-CRP is also a strong predictor of future cardiovascular events in women (RR = 4.4; 95% CI, 2.2–8.9) (7, 8). In fact, in that study, which directly compared several novel risk factors to

standard lipid screening, hs-CRP was the single strongest predictor of future vascular risk (8). Specifically, as shown in Fig. 1, the relative risk associated with being in the top vs the bottom quartile for hs-CRP in the WHS was substantially greater than that associated with other "novel" risk factors such as homocysteine and lipoprotein(a) [Lp(a)], and in fact was greater than that associated with the usual lipid markers of risk. In almost all of these prospective studies, risk estimates associated with hs-CRP were independent of other recognized cardiovascular risk factors.

Data from both the PHS and WHS demonstrate that the joint effects of hs-CRP and lipid screening are greater than the product of the individual effects of each risk factor considered alone (8, 9). Furthermore, when study participants were stratified according to the quintile of hs-CRP and the quintile of the ratio of total cholesterol to HDL-cholesterol (TC:HDL-C ratio), the relative risk of first coronary events in those in the highest quintiles of both hs-CRP and TC:HDL-C ratio was approximately eight- to ninefold higher than that of those in the lowest quintiles of these analytes. In all of these analyses, risk prediction models that incorporated TC:HDL-C ratio were significantly better ( $P < 0.001$ ) than those based on hs-CRP alone (8, 9).

For the purpose of assessing risk of first coronary events, hs-CRP concentration should be interpreted using cut points established by prospective clinical studies. As the distribution of hs-CRP concentrations is (rightward) skewed, each patient should be classified into a quintile (or quartile) based on the measured hs-CRP concentra-

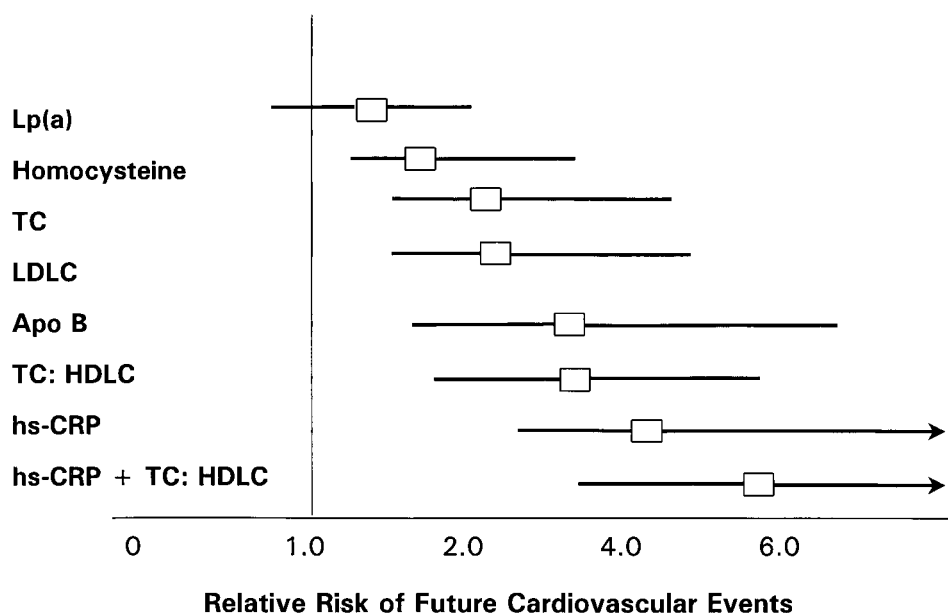


Fig. 1. RR for future cardiovascular events among apparently healthy women in the WHS according to baseline values of Lp(a), homocysteine, LDL-cholesterol (LDLC), apolipoprotein B (Apo B), hs-CRP, and TC:HDL-C ratio.

For consistency, risk estimates and 95% CIs are computed for those in the top compared with the bottom quartile for each marker.

tion. Therefore, the focus with hs-CRP reporting is what quintile a given individual is in rather than on his or her actual mass concentration. Furthermore, to provide the greatest clinical utility, hs-CRP results should be interpreted in combination with lipid values.

On the basis of these data, we present a proposed algorithm for cardiovascular risk prediction using both hs-CRP and TC:HDL-C ratio (Fig. 2). In this algorithm, hs-CRP concentrations were derived from ongoing population-based surveys using a latex-based immunoassay approved by the Food and Drug Administration for cardiovascular risk prediction (10). Lipid values for men and women as well as RRs of future cardiovascular events were derived from overview analyses using data from the PHS and WHS. Computed RRs in the proposed models

were derived from multiple logistic regression analyses in these two large-scale prospective cohort studies of currently healthy men and women in which the outcome variable is the future development of first ever myocardial infarction and stroke. In these models, risk estimates did not differ significantly between men and women; thus, a single risk assessment algorithm is currently suggested for both genders. It is important to note, however, that this is a rapidly evolving area of research. Clinical cut points used in these algorithms may require modification as more comprehensive data sets become available.

Although CRP is a classical acute phase reactant, hs-CRP concentrations are biologically stable over long periods of time. For example, in one study with 5 years of follow-up, the log-normalized correlation of baseline hs-

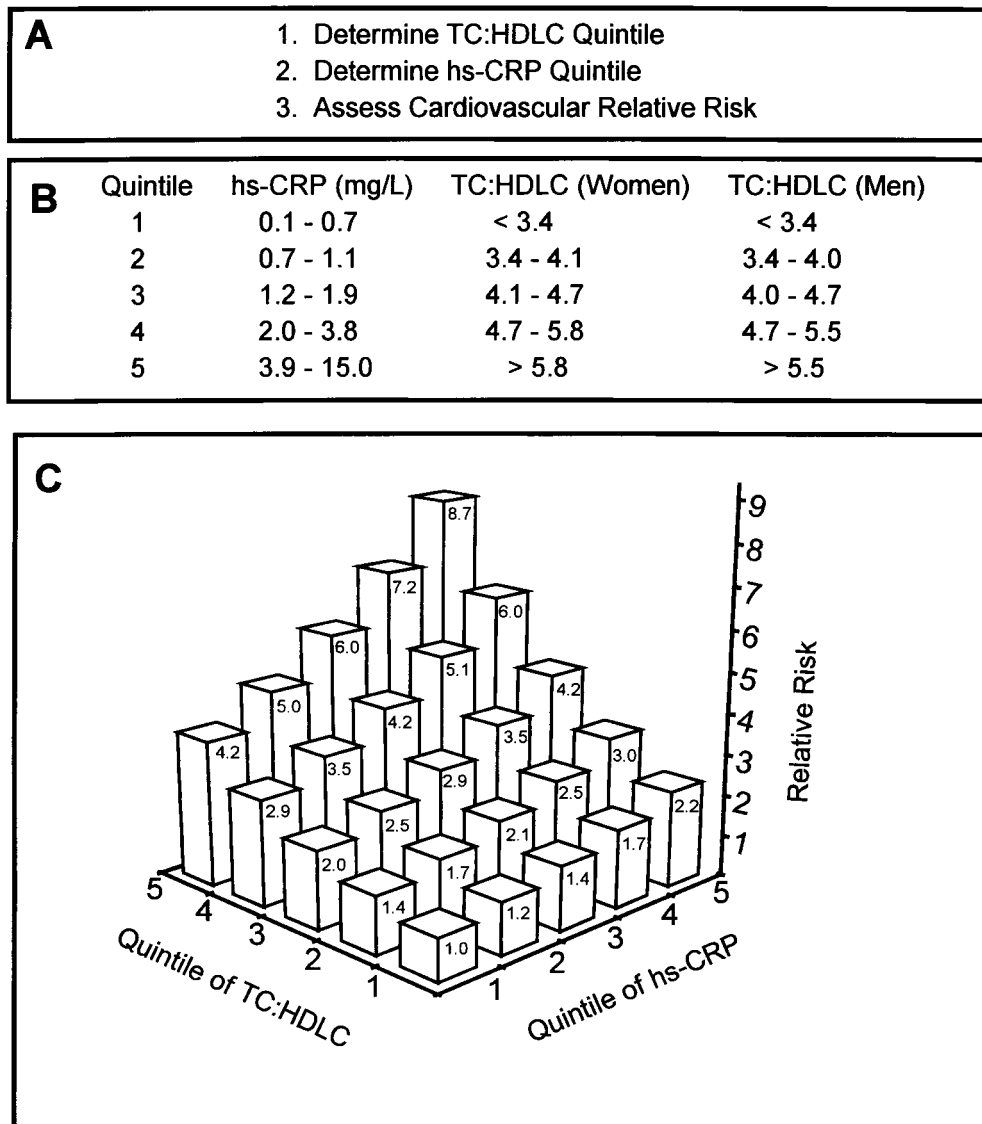


Fig. 2. Proposed cardiovascular risk assessment tool using hs-CRP and lipid screening.

(A), steps in risk assessment. (B), hs-CRP and TC:HDL-C quintiles used for the risk assessment. (C), three-dimensional column plot showing RR for future cardiovascular events based on quintile of hs-CRP and quintile of TC:HDL-C ratio. The distribution of hs-CRP was derived from ongoing population-based surveys. The lipid cutpoints and risk estimates for incident cardiovascular disease were derived from studies by Ridker and co-workers (3, 8, 9).

CRP concentrations vs those at year 5 ( $r = 0.60$ ) was greater than that associated with TC ( $r = 0.37$ ) or with LDL-cholesterol ( $r = 0.32$ ) (11). In clinical practice, hs-CRP evaluation should be avoided if there has been recent infection or trauma. A period of 2 weeks is adequate in most cases for hs-CRP concentrations increased as a result of infection to return to basal values. Values of hs-CRP  $>15$  mg/L (~99th percentile) likely indicate active inflammation or the presence of an alternative chronic inflammatory condition. The predictive value of hs-CRP is greatly improved if two measurements are made ~1 month apart and the lowest of these values is used to determine the appropriate quintile for cardiovascular risk prediction. This approach may not always be clinically feasible. At a minimum, it is therefore suggested that hs-CRP values  $>5$  mg/L be repeated to avoid misclassification because of clinically silent infection.

From a clinical perspective, the role of hs-CRP in predicting vascular risk is rapidly evolving. Current data suggest that the addition of hs-CRP to standard lipid screening can improve our ability to detect absolute coronary risk, a critical issue because one-half of all myocardial infarctions and strokes occur among individuals without overt hyperlipidemia (12). Indeed, several studies have demonstrated that increased hs-CRP concentrations are predictive of vascular events even among those without hyperlipidemia (3, 5, 8). Thus, accurate knowledge of risk can be expected to improve compliance with physician recommendations concerning diet, exercise, and smoking cessation, particularly among those with "normal" lipid concentrations.

In addition, screening for hs-CRP may have pharmacologic implications for patient treatment. At this time, evidence has been presented that suggests that both aspirin (3) and statin (11, 13) therapies modulate the inflammatory response. Thus, it has been hypothesized that hs-CRP screening may provide a method to better target these interventions. With particular regard to statin therapy, several large-scale epidemiologic evaluations are now underway specifically designed to determine whether the cost-to-benefit ratio for statin use in primary prevention can be dramatically reduced by hs-CRP screening. In addition, basic laboratory evidence suggests that angiotensin-converting enzyme inhibitors, a class of drugs now established as having potential antiatherogenic effects (14), may also function, in part, through anti-inflammatory pathways.

Finally, these data have implications for screening with regard to other novel markers of coronary and cerebral risk. As shown in Fig. 1, risk estimates associated with hs-CRP either alone or in combination with lipid screening appear to be substantially greater in magnitude than that associated with either Lp(a) or homocysteine evaluation. These data are thus consistent with the fundamental role inflammation plays in atherothrombosis (15). Indeed, within the cardiology community, acute coronary intervention studies as well as postinfarction trials are now being designed with specific screening for hs-CRP on an a priori basis.

## References

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