C-Reactive Protein (CRP), an exquisitely sensitive marker of systemic inflammation, has emerged as a powerful predictor of cardiovascular diseases, in particular of coronary heart disease (CHD). The availability of high-sensitivity (hs) assays has enabled the detection of even low-grade inflammatory responses that have previously been regarded as clinically not meaningful.

In this issue of the Journal, Rifai and Ridker propose an algorithm using CRP concentrations together with the total cholesterol: HDL-cholesterol ratio, the most powerful predictor among lipoproteins, for cardiovascular risk assessment. They suggest risk stratification based on two consecutive hs-CRP measurements and categorizing subjects according to quintiles of hs-CRP and total cholesterol: HDL-cholesterol ratio. These quintiles were derived from ongoing population-based surveys, whereas risk estimates were taken from prospective studies in men and women.

CRP fulfills most of the requirements needed to serve as a new risk factor for CHD: (a) The consistency of results from 11 prospective population-based studies in initially healthy subjects has been remarkable. (b) The association between CRP and future coronary events is strong. The combined risk ratio for CHD from metaanalysis is 2 if subjects with baseline CRP concentrations in the upper tertile of the population distribution are compared with those in the lower tertile. This holds true in initially healthy subjects as well as in patients with manifest atherosclerotic disease, in men and in women, and for both the short term and for time periods >10 years. Compared with a variety of other inflammatory markers and lipid variables, in univariate analyses CRP turned out to be the best predictor for future coronary events. (c) The association between CRP and coronary risk has been demonstrated to be independent of a wide variety of potential confounders in prospective studies, including social class in some of them. (d) To date, two studies have demonstrated that the addition of CRP to total cholesterol dramatically improves risk prediction. (e) CRP is relatively stable; it can be measured in plasma or serum, and therefore preanalytical handling of the samples is easy. The measurement procedure is standardized, and automated hs-CRP assays are available with low analytical intra- and interassay variability. (f) The reproducibility is, however, only moderate over time, as clearly must be expected from a protein that is part of the acute phase response and that increases unspecifically in response to many different stimuli. Nonetheless, the between-subject variability is sufficiently large compared with the intraindividual variation, and an index of individuality derived from these components compared favorably with total cholesterol in one study. (g) Although the underlying mechanisms that trigger the low-grade inflammatory response in atherosclerosis are essentially unknown, increased CRP in the context of this disorder is biologically plausible, and it indeed may be causally involved in the pathophysiology of atherosclerosis and its complications. However, the available evidence is indirect, and thus causality has not been demonstrated yet. At present, CRP must be regarded primarily as a surrogate marker for cytokine-mediated inflammation, and there is a sound experimental and pathologic basis that these molecules are directly involved in various processes of atherogenesis. In addition, CRP may act as a procoagulant, as it is known to induce the expression of tissue factor in monocytes. Furthermore, there are accumulating data in favor of several direct vascular endothelial effects: CRP is found in the vessel wall, even in the very early stages of plaque formation. It fulfills most of the requirements needed to serve as a new risk factor for CHD: (a) The consistency of results from 11 prospective population-based studies in initially healthy subjects has been remarkable. (b) The association between CRP and future coronary events is strong. The combined risk ratio for CHD from metaanalysis is 2 if subjects with baseline CRP concentrations in the upper tertile of the population distribution are compared with those in the lower tertile. This holds true in initially healthy subjects as well as in patients with manifest atherosclerotic disease, in men and in women, and for both the short term and for time periods >10 years. 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the emergency room or the intensive care unit in patients presenting with the syndrome of unstable angina. Proper exclusion criteria for interpretation have yet to be defined. Finally, there is no agreement to date on which cutpoints should be used in the primary and the secondary care setting. Quantiles (tertiles, quintiles) are sample-dependent and population-dependent and therefore are not universally applicable. More data from general populations are needed to resolve this issue (15). Meanwhile, the proposal put forward by Rifai and Ridker (2) represents a first step in the right direction, and one hopes it will initiate further studies to answer these remaining important questions.

References


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