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C-Reactive Protein as a Clinical Marker of Risk

To the Editor:

We read with great interest the article by Lagrand et al¹ in which the authors both review the role of C-reactive protein (CRP) as a marker of cardiovascular risk and propose a pathogenetic role for CRP. Although the evidence reviewed by Lagrand et al¹ convincingly suggests an association between CRP and cardiovascular risk, we are concerned that the authors appear to assume that CRP is an established, independent risk factor and that its measurement has defined clinical applications.

Although it has been shown in large epidemiological studies that high concentrations of CRP are associated with increased cardiovascular risk in both patients with coronary artery disease and apparently healthy individuals, extrapolation of findings in large epidemiological studies to the clinical setting may not be straightforward. One of the difficulties for the application of "epidemiological" results to the individual patient relates to the lack of well-established CRP levels that can be considered to represent accurate cutoff points to identify the individual patient at risk. Different studies have used different analytical assays, and therefore CRP levels vary significantly among these studies. For example, mean CRP levels in apparently healthy men who developed cardiovascular events were reported in one study to be 1.40 mg/L,² whereas another study³ in patients with unstable angina considered a value of 15.5 mg/L to represent the cutoff level between low and high risk. Another difficulty is that despite suggestions of stable CRP levels over time within individuals, there are reports indicating that the intraindividual variability of CRP may be high (between 42% and 63%).⁴ This finding of high intraindividual variability in CRP levels is important in view of the fact that in the large epidemiological studies, CRP concentrations differed only slightly, albeit significantly, between individuals with increased risk of cardiovascular events and those with low risk. The issue of intraindividual CRP variability requires further investigation in large studies. If the large variability is confirmed, strategies for the use of CRP as a prognostic marker in the individual patient should be planned carefully.

Despite the convincing evidence of a relationship between CRP concentrations and cardiovascular risk in large studies, CRP, as well as other acute-phase reactants, is a nonspecific marker of inflammation. A recent meta-analysis⁵ has shown that fibrinogen, CRP, albumin (inverse relation), and leukocyte count were all strongly related to cardiovascular risk. These observations⁵ suggest that these markers may be closely interrelated and represent only a nonspecific indication of inflammation and/or other mechanisms underlying the atherogenic process.

Lagrand et al¹ propose a most interesting pathogenetic hypothesis involving CRP in atherogenesis and rapid coronary artery disease progression. Their suggestion that CRP may have a causal role is intriguing and clearly deserves further investigation in well-designed studies. Undoubtedly, a better understanding of the pathogenic role of CRP in ischemic heart disease may help to speed up the process leading to the successful use of CRP as a clinical marker of risk. At present, however, the use of CRP as a prognostic marker in the individual patient (or the apparently healthy subject) has limitations.

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Response

Drs Kaski and Garcia-Moll address several important problems with respect to C-reactive protein (CRP) as a cardiovascular risk factor. First, they address the issue that owing to suboptimal performance of the assays, CRP levels within the normal range cannot be measured accurately enough to be useful in clinical practice. This is to some extent indeed true. In clinical practice, CRP is most often assessed to evaluate whether it is increased, eg, to monitor the response to (antibiotic) therapy. The assay methods used in clinical practice, eg, nephelometry, are able to accurately determine increased levels of CRP but have never been optimized to measure levels within the normal range. However, the recent interest in measuring CRP levels within this range will undoubtedly stimulate improvement of the assay methods. Our own experience is that normal CRP levels can be assessed by ELISA with adequate reproducibility (the variation coefficient for levels of 0.1 to 5 mg/L is 9% to 16%). Using this assay, we determined CRP levels weekly in 20 healthy laboratory workers and found that these levels may vary significantly in some persons. Increases in CRP levels were often associated with the occurrence of minor clinical symptoms such as cough or backache; eg, individuals with normal levels of about 1.5 mg/L may have increases up to 10 mg/L during intercurrent (sub)clinical disease. These slight increases of CRP were found to persist for days to weeks. Hence, a single determination of CRP may not yield reliable information about baseline levels, even when a reproducible assay is used. These observations, furthermore, emphasize the second point raised by Drs Kaski and Garcia-Moll: the intravariability (and intervariability) of CRP levels is high, as confirmed by more recent studies.¹ Possibly, repeated determinations (for example, 3 times at monthly intervals) might provide a better estimation of baseline levels.

Finally, the authors state that up to now CRP is not an established independent risk factor for cardiovascular diseases. When corrected for established cardiovascular risk factors, CRP levels still add to the prediction of adverse cardiovascular events or a worse outcome in healthy individuals, as well as in patients with manifest cardiovascular disease. Whether CRP is unique among the acute-phase proteins as a cardiovascular risk factor cannot be definitely answered at the moment. In our article, we wanted to pay attention to the fully ignored properties of CRP described in 1974 by Kaplan et al,² ie, that CRP is able to activate complement via the classic pathway after binding to a suitable ligand and hence may enhance inflammation. A proinflammatory role of CRP, in our opinion, could very well explain the observed associations with cardiovascular disease. In addition to the arguments described in detail in our article, such as the localization of CRP together with activated complement in atherosclerotic vessels³ and infarcted myocardium,⁴ we have recently found increased levels of CRP-complement complexes in infarcted tissues from patients dying of acute myocardial infarction (AMI) and in plasma of patients with AMI (manuscripts in preparation). Because these complexes are specific markers for CRP-mediated complement activation *in vivo*, these observations support such a proinflammatory role of CRP in (human) AMI.

Intervention studies should reveal whether our hypothesis is correct, ie, that the link between CRP and cardiovascular disease is based on its proinflammatory role, as described in our article.

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