Editorial

The Inflammatory Hypothesis
Any Progress in Risk Stratification and Therapeutic Targets?

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About a decade ago, the prevailing wisdom was that conventional risk factors explained only about half of the risk for a myocardial infarction or stroke. However, most studies did not assess some of the newer lipid markers (such as the apolipoproteins) or measures of abdominal obesity, diet, or psychosocial factors and moreover did not try to quantify the population-attributable risk. Consequently, efforts to identify novel risk factors were undertaken to improve cardiovascular risk prediction.

The hypothesis that inflammation is a central contributor to atherothrombosis has stimulated sustained efforts to characterize the specific molecules and pathways that may be involved and to identify biomarkers in humans that enable detection of underlying inflammatory activation to improve cardiovascular risk prediction. Ridker and coworkers reported that systemic low-grade inflammation assessed by measurements of the acute-phase reactant C-reactive protein (CRP) is associated with future cardiovascular events in apparently healthy individuals. This intriguing concept stimulated intense interest in further investigating the ability of inflammatory markers to add information for cardiovascular risk stratification beyond that obtained from traditional risk factors.

CRP as Predictor for Cardiovascular Events

The value of CRP for cardiovascular risk prediction has been assessed in 3 different clinical settings: apparently healthy individuals, stable patients at risk for cardiovascular events or with documented coronary heart disease, and patients presenting with acute coronary syndromes.

The utility of CRP for risk stratification has been proposed mainly in healthy individuals. Several large, prospective cohort studies have consistently reported that higher levels of CRP are associated with an increased risk for cardiovascular disease (CVD). Whereas earlier work reported a relative risk of 2.3 in the upper quintile of CRP versus the lowest, using a multivariable model including age, smoking status, diabetes, hypertension, and LDL cholesterol, recent observational studies typically report much more modest relative risks of 1.3 to 1.7. In the current issue of Circulation, Bos and coworkers evaluate the value of CRP as a risk factor and risk predictor of future stroke. Based on 6430 participants of the Rotterdam study, the results confirm an association between CRP levels and stroke using univariate analyses; however, CRP was not a statistically significant predictor of stroke after adjustment for traditional risk factors. The authors therefore concluded that CRP measurement does not contribute materially to the assessment of stroke risk. The present study adds valuable knowledge to the current discussion because no previous studies have examined the impact of CRP on stroke as a unique endpoint. Of further importance, discrimination between the subtypes ischemic and hemorrhagic strokes revealed similar results. This is of particular interest because strokes are a very heterogeneous condition. Ischemic strokes include small- and large-vessel disease and embolic processes, each of which may have different causes and pathogenesis.

In addition to studies targeting initially healthy individuals, the predictive value of CRP has been investigated in patients with stable angina or individuals harboring multiple risk factors at high risk for future cardiovascular events. On the basis of evaluations of multiple biomarkers in a large subgroup of the Heart Outcomes Prevention Evaluation (HOPE) study, CRP levels were only moderately associated with future cardiovascular risk, which is similar to the findings from other US and European population-based studies. Data from the AtheroGene study further support the result obtained from the HOPE study indicating that CRP is not independently related to recurrent cardiovascular events in patients with stable angina pectoris.

Other studies suggested a prognostic association between increased CRP production and outcome in acute coronary syndrome. However, data providing evidence that CRP or any other inflammatory marker adds value for diagnosis or risk stratification beyond traditional risk factors, troponin levels, and clinical variables are still missing, and unpublished analyses from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study do not suggest an independent role of any inflammatory risk marker, including CRP, in predicting future clinical events (S. Mehta, S. Blankenberg, M. McQueen, and S. Yusuf, unpublished data).

Conflicting Epidemiological Results

What are the explanations for the discrepancies in these findings described above? First, initial reports of the value of a new marker often tend to overestimate the true effects as a result of a number of potential biases. Therefore, we need to
examine whether subsequent reports are confirmatory or not. Most population-based studies published after the meta-analysis by Danesh et al in 2004 consistently report an independently predictive but much weaker association between CRP and other inflammatory markers with future cardiovascular events. Second, many studies do not report separate analyses with regard to coronary and cerebrovascular events, and these may have quite different pathogenesis. Third, earlier studies did not fully adjust for abdominal obesity, glucose, or other confounders. Given the strong interdependence between CRP levels and traditional risk factors, lack of full adjustment leads to overestimation of the relationship between CRP and outcomes. Fourth, most studies did not take into account the strong and consistent association between N-terminal pro-brain natriuretic peptide and vascular events. Including this biomarker in the analysis of the HOPE population nullified the impact of all inflammatory markers. Finally, most studies did not examine whether CRP adds significant information to more easily available markers or risk factors in predicting cardiovascular events. Many large, prospective, mainly population-based studies explored this question, and all failed to demonstrate an improved incremental value of CRP in predicting CVD when added to other risk factors. Therefore, in these studies, even when CRP demonstrated a relationship with CVD after univariate or even multivariate analysis, it had very little incremental prognostic value.

The attention focused on CRP mainly reflects the fact that it is a stable analyte in serum and plasma and that robust, well-standardized, and reproducible immunoassays are available at reasonable costs. Other inflammatory markers—upstream markers like cytokines or downstream markers like serum amyloid A, albumin, or erythrocyte sedimentation rate—do not provide such desirable characteristics. These properties may explain the closer and better predictions of CRP compared with other inflammatory markers. None of the inflammatory markers investigated so far provided additional information for cardiovascular risk stratification after adding to risk algorithms already containing the most relevant traditional risk factors.

However, in many diseases (infections, trauma, or malignancy, as well as inflammatory, allergic, or necrotic diseases), the circulating value of CRP reflects ongoing inflammation and/or tissue damage in multiple tissues (and not necessarily the vascular wall). No consistent data are available on whether CRP independently predicts vascular events in these populations.

**CRP: A Causal Role in Atherosogenesis?**

Traditional epidemiological methods are strained in trying to assess whether moderate relationships (eg, odds ratios <2) represent causal relationships or simply spurious associations. Often, results from observational studies and randomized controlled trials produce discordant findings. This may well be due to the confounding that persists in epidemiological studies despite extensive statistical adjustments. Recent examples of likely spurious associations reported from observational studies include the proposed protective effects of vitamin E, hormone replacement therapy, and homocysteine lowering through folic acid supplementation. Although various methods exist to prove an independent association between a variable and a disease, controlling for confounding has proved difficult when the exposure under study is related to a variety of additional factors that simultaneously influence the marker itself and disease risk.

Therefore, novel epidemiological approaches are needed to assist in elucidating whether a moderate odds ratio in an observational analysis represents a real relationship or not. An elegant opportunity to distinguish relationships that are causal versus those that are noncausal is by using genetic studies. Because acute-phase reactants like CRP are subject to confounding by simultaneous elevation of several traditional risk factors, it is impossible to clarify whether the association between CRP and CVD outcome might be the consequence of elevations of other risk factors or in itself causes CVD. If, however, we can demonstrate a relationship between a genetic variant that is associated with elevated CRP and CVD, then the link is unlikely to be secondary to confounders. This approach has been called mendelian randomization. Current genetic association studies, while demonstrating that certain gene variants like the C-1059G promoter polymorphism of the CRP gene are associated with elevated CRP, neither predict myocardial infarction or stroke nor are associated with elevations of traditional cardiovascular risk factors. Further studies testing haplotype effects of the CRP gene on CRP levels are currently underway and could shed further light.

Another proof of causality might be obtained from animal studies. Experimental evidence implicating CRP as a potent stimulus of atherogenesis predominantly relies on data that have demonstrated CRP within the atheroma and inflammatory changes in cells and animals exposed to exogenous CRP. CRP is consistently observed within the atherosclerotic lesion; plus, CRP is produced in smooth muscle cells and macrophages within the atheroma. However, many pathogenic agents, particularly bacteria and viruses, have been identified within atherosclerotic lesions without having been attributed a causal role, nor has antibiotic therapy been associated with reduced CVD events. Another line of evidence comes from in vitro experiments testing the addition of exogenous CRP in cultured endothelial cells, smooth muscle cells, and monocytes/macrophages. Administration of CRP leads to the activation of various proatherosclerotic processes, including expression of adhesion molecules, a decrease in endothelial nitric oxide synthase, an upregulation of angiotensin I receptors, and an increase in reactive oxygen species. Despite the intriguing nature of these observations, a note of caution is necessary because it still remains unclear whether these effects can be attributed directly to CRP itself rather than to contaminants such as bacterial lipopolysaccharides.

In addition, evidence of causality derived from animal models is sparse and not necessarily applicable to humans. Several groups have developed transgenic mouse models that express human CRP. Conflicting results have been reported. For example, mouse models that express human CRP have no or only moderate increases in atherosclerotic lesions. Caution is needed in interpreting these results because CRP is a foreign protein to the mouse and because serum concentrations of CRP generated in the mouse are 30-
to 100-fold higher compared with the relevant range in humans. A better model to investigate the role of CRP would be the Watanabe heritable hyperlipidemic rabbit, which, in contrast to mice, produces CRP that is 70% homologous to humans. Currently, however, no reliable evidence exists that CRP is pathogenic in rabbits.

**CRP as a Direct Therapeutic Target and/or Therapeutic Discriminator?**

Based on the recognition that human CRP binds to ligands exposed in damaged tissue and consecutively activates complement and increases myocardial and cerebral infarct size in rats, current experiments proved that inhibition of CRP in rats undergoing acute myocardial infarction abrogates the increase in infarct size and cardiac dysfunction produced by infusion of human CRP. Thus, therapeutic inhibition of CRP might be considered an approach to cardioprotection in acute myocardial infarction and neuroprotection in stroke. However, these results need confirmation in future clinical trials.

Beside its role as a direct therapeutic target, post hoc analyses of some trials suggest that strategies to lower cardiovascular risk with statins should include monitoring CRP. In particular, high levels of CRP might act as discriminator for statin therapy even in individuals with low LDL cholesterol. Retrospective analyses generally require prospective confirmation, and very rarely have such subgroup analyses been confirmed when tested prospectively. Although a prospective trial of statins has included individuals with elevated CRP, the lack of inclusion of individuals with low CRP in the trial will preclude an assessment of whether there is a differential benefit of statins based on CRP levels.

**Conclusions**

It is still controversial whether activation of the inflammatory response simply reflects a secondary effect of an underlying atherosclerotic process and thus may represent an epiphenomenon secondary to changes in other processes involving known mechanisms. This distinction can be made only if we can intervene primarily on the inflammatory process with little effect on other important risk factors such as blood pressure, lipids, or glucose. The INTERHEART study and several others indicate that the overwhelming proportion of the population-attributable risk for AMI was predicted by a few simple modifiable risk factors. Moreover, the INTERHEART results are even likely to be an underestimate of the impact of the 9 risk factors because this study measured some risk factors crudely (eg, hypertension or diabetes) and moreover did not adjust for regression dilution biases, which tend to substantially underestimate the magnitude of the relationship of a risk factor to an outcome. In addition to reducing the levels of modifiable conventional risk factors by smoking cessation, intensive lipid lowering, and blood pressure lowering, modifying lifestyles (prudent diet and regular activity) can lead to substantial reductions in the risk of future cardiovascular events. Whether independently or additionally modifying the inflammatory response will add anything beyond current approaches to prevention is unclear. So far, the human data are still not convincing.

**Disclosures**

None.

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