C-reactive protein: a surrogate risk marker or mediator of atherothrombosis?

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There is now compelling evidence that C-reactive protein (CRP) is a powerful independent predictor of future cardiovascular risk (15). This discovery reflects the pivotal role that proinflammatory processes play in atherogenesis and its complications (24). CRP is an acute phase reactant largely produced by the liver in response to inflammatory cytokines such as interleukin-6 that has been viewed as an inactive downstream marker of low-grade vascular inflammation. Several other more sophisticated measures of cytokine activation, cellular adhesion, and immune and enzyme function have also been found to predict risk of future cardiovascular events, including interleukin-6 and interleukin-18, tumor necrosis factor-α, soluble intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1), lipoprotein-associated phospholipase A2, and soluble CD40 ligand (3). Nevertheless, the overall weight of evidence favors CRP as the best currently available risk predictor, a finding supported by head-to-head comparisons of various inflammatory markers (2, 18, 23).

Accumulating laboratory data suggest that CRP may directly elicit a variety of proatherogenic effects in vascular tissue. However, further research is required before we can conclude that these effects are clinically relevant. As will be discussed below, the concentrations of CRP required to elicit some of these proatherogenic effects may be greater than those used for clinical cardiovascular risk prediction.

CRP predicts future cardiovascular risk in a wide variety of clinical settings, including men and women without overt cardiovascular disease, patients with stable angina and those presenting acute coronary syndromes, postmyocardial infarction patients, and patients with the metabolic syndrome (15). Furthermore, CRP predicts not only incident myocardial infarction and cardiovascular death, but also risk of ischemic stroke, sudden cardiac death, incident peripheral vascular disease, and restenosis after percutaneous coronary intervention. In primary prevention, CRP confers additional prognostic value at all levels of Framingham risk and at all levels of the metabolic syndrome (16, 22). In the setting of acute coronary syndromes, the prognostic value of CRP is independent of cardiac troponin, and CRP predicts future risk even among those with negative troponin levels (8, 9).

This robust association with future cardiovascular events reflects the underlying central role of inflammation in atherothrombosis, but also that CRP has analytic properties favorable for clinical use. CRP has a relative long half-life of 18 h, CRP levels are relatively stable over time (20), do not exhibit significant circadian variability (10), and fasting samples are not required for accurate measurement. Moreover, a recent head-to-head prospective comparison of CRP and LDL cholesterol among 27,939 women found that CRP is the stronger predictor of incident cardiovascular events and added prognostic information at all levels of the Framingham risk score (22). Perhaps even more importantly, CRP and LDL cholesterol are minimally correlated and identify different individuals at risk for cardiovascular events. Thus the combination of lipid testing and CRP adds incremental prognostic value.

Indeed in the Women’s Health Study, 77% of events occurred among those women with LDL cholesterol <160 mg/dl, a remarkable finding that highlights the urgent need for improved risk assessment. In response to these and other data from United States and European populations, the Centers for Disease Control and Prevention and the American Heart Association have recently issued guidelines including a class IIa recommendation for screening for CRP to aid in primary cardiovascular risk assessment among those at intermediate risk by Framingham risk score (13). CRP levels <1, 1–3, and >3 mg/l are used to denote low, intermediate, and high risk. CRP testing has also been given a class IIa recommendation among patients with stable coronary disease or acute coronary syndromes, although the optimal cut-points for risk stratification among this subgroup are less clear. Thus CRP testing has now entered mainstream clinical practice.

The explosion of clinical data regarding the powerful association between CRP and future cardiovascular risk has led to intense interest in potential direct proatherogenic effects of CRP. In this regard, emerging data suggest that CRP may indeed be a mediator that contributes directly to atherogenesis. CRP has been found to localize with the complement membrane attack complex in early atherosclerotic tissue (25), and levels of mRNA encoding both CRP and certain complement factors are increased in atherosclerotic plaque (29), where smooth muscle cells and macrophages appear to be the main producers of CRP. Furthermore, CRP opsonization of LDL mediates LDL uptake by

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macrophages (30), and CRP has been shown to cause ICAM-1 and VCAM-1 expression by endothelial cells and to mediate monocyte chemotactrant protein-1 induction (11, 12). These latter effects may be mediated by increased secretion of IL-6 and endothelin-1 and may be attenuated by both IL-6 and endothelin antagonism (27). In addition, CRP induces plasminogen activator inhibitor (PAI)-1 expression in human aortic endothelial cells (6), and CRP has also recently been found to quench the production of nitric oxide by endothelial cells (26, 28).

Despite these accumulating data, it remains uncertain if these potentially proatherogenic effects of CRP have direct clinical relevance. Although CRP concentrations as low as 5 mg/l have been found to decrease nitric oxide production (28), the concentrations of CRP shown to elicit many of these proinflammatory responses are typically in excess of 5 μg/ml and range between 5 and 900 μg/ml (5−900 mg/ml). As mentioned above, the plasma concentrations of CRP used to denote low, intermediate, and high risk for primary prevention are <1, 1−3, and >3 mg/l. Thus concentrations of CRP used for clinical risk prediction appear generally lower that those shown to elicit proatherogenic responses. It is possible that circulating CRP levels do not truly reflect tissue concentrations and that locally concentrated CRP may be present in a sufficient amount to promote atherogenesis. Further research is required to address these issues.

Although debate persists regarding the precise physiological role of CRP, the prognostic value of CRP as a marker of cardiovascular risk is now firmly established. Obesity, smoking, diabetes, and lack of exercise are all associated with elevated CRP levels, and thus intensification of lifestyle modification would appear appropriate for patients with high CRP. The next phase of clinical studies will assess the potential utility of CRP testing to direct future therapies. Post hoc data suggest that the benefits of both aspirin and statin therapy may be greatest among those with elevated CRP levels (17, 19, 21). In this regard, statins have anti-inflammatory effects on atherosclerotic tissue and have also been found to lower CRP levels (1). Furthermore, rosiglitazone has recently been reported to directly lower CRP levels (7), an intriguing observation as CRP predicts incident type II diabetes in addition to incident cardiovascular disease (14) and is intimately linked to the metabolic syndrome (7). Future studies assessing the benefits of these and other preventive therapies targeted to those with elevated CRP levels are required before specific interventions should be recommended for those with elevated CRP levels. If confirmed in prospective studies, available evidence suggests that the benefits of statin therapy targeted to those with high CRP may be substantial (5) and that such a strategy may be relatively cost effective, especially among those at intermediate to high risk for cardiovascular events (4).

DISCLOSURES

P. M. Ridker is the recipient of a Distinguished Clinical Scientist Award from the Doris Duke Foundation and receives support from the Donald W. Reynolds Foundation. G. J. Blake is the recipient of a Young Investigator Competitive Award grant from Glaxo Smith Kline.

REFERENCES

16. Ridker PM, Buring JE, Cook NR, and Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovas-