EDITORIAL

C-Reactive Protein: Potential Use for the Future

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Studying the effect that a difficult-to-quantify lifestyle factor such as alcohol consumption has on a general inflammatory marker such as C-reactive protein is far from a simple task.[1] Methodologic problems are inherent in design, implementation, and analysis of any such study. Not surprisingly, then, these concerns can be raised with the study by Stewart et al that appears in this issue of the *Journal*.[2] Initial sample size (and therefore the response rate) of the population receiving the survey questionnaire is not specified, nor are criteria used for the variables required to qualify for receiving the survey. Selection of a value of 0.30 mg/dL as indicative of the upper limit of normal for the C-reactive protein reading in this study appears to be retrospectively determined and therefore not necessarily reflective of an abnormal value in populations differing in any way from specifically surveyed study group respondents.

Use of a C-reactive protein assay with limited range is also potentially problematic (a lower cutoff of 0.21 mg/dL was reported in this study for anyone with a C-reactive protein value of 0.21 mg/dL or below; C-reactive protein values less than this lower cutoff value have been associated with increased cardiovascular risk).[3,4] Proof of a cause-and-effect relation between alcohol consumption and reduced likelihood of C-reactive protein elevation as a mechanism for coronary protection cannot be established from retrospective analysis. Finally, the fundamental parameter being looked at in this study (alcohol consumption) is not optimally assessed by self-report, with implications based on drinking frequency but without attention to quantity not necessarily reflecting the relation between alcohol use and any effect it might have on an inflammatory marker such as C-reactive protein.

That said, the evolving concept of using a highly sensitive assay for C-reactive protein (hs-CRP) as a marker of coronary artery disease risk is enticing, and the message suggested by results of this study is both provocative and in line with the increasing body of literature rapidly accumulating in the exciting field of preventive cardiology.

Hardly a week passes without report of a new potential association between C-reactive protein values and some commonly encountered medical condition, physiologic state, or cardiac risk factor. Examples include cardiac arrhythmias (C-reactive protein tends to increase with atrial fibrillation, especially when the rhythm is persistent rather than paroxysmal)[5]; exercise (more frequent physical activity appears to correlate with a lesser chance of C-reactive protein elevation)[6]; estrogen use (hormone replacement is associated with an increase in C-reactive protein regardless of whether estrogen is given alone or in combination with progesterone)[7]; and obesity and smoking (both associated with increased C-reactive protein values).[3,4]

Accumulating data suggest that even modest hs-CRP elevation is associated with increased risk of future cardiovascular events.[4,8–10] The theory behind this association is fascinating: coronary artery disease is now thought to be the manifestation of an inflammatory process.[11] Patients most vulnerable to acute ischemic events are more likely to have unstable atherosclerotic plaques that are at increased risk of developing fissure, rupture, and thrombogenesis, which at any time can lead to acute thrombotic occlusion of a major coronary vessel. Patients with high-risk lesions might be expected to manifest signs of increased inflammatory activity. Such inflammation appears to occur not only locally (in the affected vessel wall), but also systemically, as suggested by increased circulating levels of inflammatory markers, such as cytokines and C-reactive protein.[1] In fact, many patients at highest risk, including those who have acute coronary syndromes, manifest evidence of surprisingly widespread rather than localized inflammation in several areas of the coronary vasculature.[12]

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In view of this new evidence favoring a more generalized and ongoing acute inflammatory process extending beyond the limits of a single vulnerable plaque, focal revascularization procedures (by percutaneous intervention or bypass surgery) would seem unlikely to correct completely the underlying problem for such patients.[11] Intriguingly, use of an easily measurable systemic marker of inflammation (such as hs-CRP) might hold the key for determining which patients with coronary artery disease are most at risk. Although the full relation between C-reactive protein elevation and cardiovascular risk is not yet completely known, the finding of C-reactive protein elevation in certain physiologic states might be a marker for individuals with an exaggerated inflammatory response that might in turn accelerate atheroma progression and facilitate thrombogenesis.[4] More active intervention in the form of primary and secondary preventive measures might then be targeted to these high-risk persons.

hs-CRP assay is far from a perfect test. Specificity of C-reactive protein for inflammation is clearly not infallible, with noninflammatory states such as chronic fatigue, high-protein diet, depression, and aging itself all being associated with increased likelihood of C-reactive protein elevation.[13] While adequate data are now available to document an overall increase in relative risk for cardiovascular events in patients with C-reactive protein elevation, data are still lacking with respect to absolute risk and the positive predictive value that C-reactive protein elevation might have in patients with acute and less acute manifestations of coronary artery disease, as well as in asymptomatic populations of men and women with cardiac risk factors. Data are also lacking to show that interventions aimed at reducing C-reactive protein levels will lower the risk of subsequent cardiovascular events. Without this information, use of hs-CRP assay either acutely or as a screening modality will be limited. In particular, routine inclusion of hs-CRP assay in risk factor profiling of otherwise healthy, asymptomatic persons could result in a disproportionate number of patients with false-positive C-reactive protein elevations that are unrelated to prediction of future cardiovascular events.[13]

What, then, is a clinician to do? Realizing the controversy that surrounds this issue, and the absence at this time of a uniformly agreed-upon, evidenced-proven approach, the following might be reasonable:

1. Risk factor assessment with attention to optimizing primary and secondary preventive measures for cardiovascular disease should remain the essential objective of primary care clinicians. In most cases, assessment of standard risk factors should suffice to determine most patients who are at greatest risk.
2. Interventions aimed at enacting healthy lifestyle changes should benefit all patients. These changes include smoking cessation, moderation of alcohol intake, achieving and maintaining appropriate body weight through proper dietary selection, and regular exercise. C-reactive protein levels will generally decrease as a natural consequence of implementing and enhancing beneficial lifestyle changes.
3. Cardiovascular risk might be further reduced by interventions aimed at correcting additional risk factors (ie, enhancing control of diabetes, lipid abnormalities, and blood pressure).
4. Potential preventive measures, such as aspirin and clopidogrel, angiotensin-converting enzyme inhibitors, β-blockers, and folate-vitamin B_{12} supplementation, should be actively considered and encouraged when appropriate.[14,15]
5. Hormone replacement should no longer be viewed as a cardioprotective measure for postmenopausal women.[16–18]

After considering these five points, additional means of risk stratification might then be contemplated for selected patients in whom our clinical approach is still uncertain. An example might be for assessment of an asymptomatic young adult who has a strong family history of premature coronary disease but no other risk factors. The finding of a baseline C-reactive protein value in the upper quintile for those of the same age and sex would suggest a much higher risk of a future cardiovascular event than would be the case if the C-reactive protein value was in a lower quintile for that person's age and sex.[4] This increased relative risk of future cardiovascular events appears to hold true even if low-density cholesterol is within the normal range (ie, <130 mg/dL).[19] Primary prevention with aspirin and use of a statin drug, in addition to intense effort at enacting beneficial lifestyle changes, *would* be appropriate considerations for treating this person

in the hope of reducing cardiovascular risk by attenuating the inflammatory response. Statin therapy appears to lower hs-CRP assay findings *independent* of the patient's lipid profile.[19]

Whether these interventions in a asymptomatic person with strong family history can then be monitored by changes in hs-CRP values with time as the mechanism for cardiovascular risk reduction is among the fascinating questions to be answered during the next few years in this exciting and rapidly evolving field.

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