C-reactive protein (CRP) is an independent determinant of risk of stroke among both men and women. For instance, in the Framingham Study, the relative risk for future stroke for the highest quartile of CRP compared with the lowest was 2.0 for men and 2.7 for women. The association between CRP and risk of stroke among men and women in this cohort persisted after adjustment for age, smoking, total cholesterol: HDL cholesterol ratio, systolic blood pressure, and diabetes. Similarly, in the Physicians’ Health Study, men in the highest quartile of CRP also had a 2-fold increased risk of stroke compared with the lowest quartile, while in the Women’s Health Study women in the top quartile of CRP had a more than 3-fold increased risk of stroke.

While the association between CRP and hard cardiovascular events seems robust, the relationship between CRP and subclinical atherosclerosis is less clear. Thus, the report by Wang and colleagues regarding CRP and carotid atherosclerosis in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, and a recently published companion report from the same group regarding CRP and coronary artery calcification, are valuable additions to this field.

In the present report, Wang and colleagues describe the association between CRP and carotid atherosclerosis as assessed by ultrasonography among 3173 men and women enrolled in the Framingham Offspring Study. Overall, they found that increasing levels of CRP were predictive of carotid stenosis (≥25%) in both crude and adjusted analyses. However, in analyses stratified by gender, the association between CRP and carotid atherosclerosis appeared stronger among women; in age-adjusted analyses, the top quartile of CRP was associated with an increased risk of carotid stenosis of 1.6 among men and 3.9 among women. After adjustment for other cardiovascular risk factors, this association remained significant only in the women studied. The gender-specific results were similar when internal carotid intima-media thickness (IMT) was used as the outcome. In these authors’ companion article regarding coronary artery calcification, CRP was associated with coronary artery calcification in both men and women, and this association persisted after adjustment for age and Framingham risk score. Both these studies are valuable as they help explain conflicting data from previous studies.

From a clinical perspective, the most important issue is how well any marker of subclinical atherosclerosis predicts future cardiovascular events. There are accumulating data to show that carotid IMT is a strong predictor of future cardiovascular events. For instance among 4476 subjects over the age of 65, the relative risk for myocardial infarction or stroke for the top quintile of IMT compared with the bottom quintile was 3.15, after adjustment for traditional risk factors. The separate results for myocardial infarction and stroke paralleled those for the combined end point, suggesting that this marker of subclinical atherosclerosis in the cerebral circulation can predict risk in other vascular territories.

The association between coronary calcification and future cardiovascular events in less clear. Calcification occurs as part of the development of atherosclerosis and is not present in the normal coronary arterial wall. Available data suggest, however, that mature and stable plaque is most often calcified, while vulnerable plaque is typically not. Data regarding the value of detection of coronary calcification by electron beam tomography for prediction of future cardiovascular events among asymptomatic individuals are somewhat conflicting. One study found that the presence of coronary calcium predicted future coronary death, myocardial infarction, and the need for revascularization, while another suggested that coronary calcium was a weak predictor of death and myocardial infarction, but that its predictive value was better for the need for revascularization. A further analysis reported that electron beam coronary calcium score did not add significant incremental information to that of traditional risk factors. These data would support the concept that coronary calcification may reflect atherosclerotic disease burden, but it may fail to identify which atherosclerotic lesions are prone to instability.

In contrast, there are convincing data that CRP is an independent predictor of future cardiovascular events, including cardiovascular death, myocardial infarction, stroke, revascularization, the development of peripheral vascular disease, and sudden cardiac death. Indeed, several previous reports have suggested that the associations between CRP and measures of atherosclerosis burden are more modest than the association with hard cardiovascular events. Thus, it is possible that elevated levels of CRP may reflect the presence of vulnerable plaque that is at high risk for rupture, as opposed to solely reflecting the burden of atherosclerosis. While the pivotal role of inflammation in determining plaque stability may support this concept, further studies are required to directly explore this hypothesis.

Emerging data, however, suggest that CRP may be a mediator as well as a marker of atherosclerosis. CRP induces expression of cellular adhesion molecules, interleukin-6, and endothelin-1 by endothelial cells. CRP also mediates monocyte chemoat-
tractant protein-1 induction, and it has been shown to mediate uptake of LDL by macrophages. Furthermore, smooth muscle cells and macrophages in arterial tissue have been shown to produce CRP, a process that is substantially upregulated in atherosclerotic plaque.

Very recently, Verma and colleagues have reported that CRP, at concentrations known to predict future cardiovascular events, directly quenches the production of NO, in part through post-translational effect on endothelial NO synthase mRNA stability. Diminished NO bioactivity, in turn, was shown to inhibit angiogenesis, an important compensatory mechanism in chronic ischemia. These data suggest that by suppressing NO synthesis, CRP plays a direct role in the pro-atherogenic process.

To be of potential clinical utility, any marker of subclinical atherosclerosis must be shown to predict cardiovascular risk in several large prospective studies, and the marker should improve on traditional means of risk prediction. While CRP and carotid IMT seem to meet these criteria, further large-scale studies of coronary calcification are required before clinical application of this technique can be recommended. The cost and ease of administration of any screening test are also of paramount importance, and in this regard, a simple inexpensive blood test such as CRP may hold advantages over more sophisticated noninvasive imaging modalities for widespread clinical application.

References


C-Reactive Protein, Subclinical Atherosclerosis, and Risk of Cardiovascular Events
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