C-Reactive Protein:

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Now that the role of inflammation in the pathogenesis of cardiovascular disease has been recognized, biomarkers of inflammation have become the subject of intense research interest. Once considered a novel cardiovascular risk factor, the inflammatory biomarker C-reactive protein (CRP) is currently believed to improve global risk prediction in patients not previously deemed at high risk.

Now that the role of inflammation in the pathogenesis of cardiovascular disease (CVD) has been recognized, biomarkers of inflammation have become the subject of intense research interest. Once considered a novel cardiovascular risk factor, the inflammatory biomarker C-reactive protein (CRP) is currently believed to improve global risk prediction in patients not previously deemed at high risk. Strong epidemiologic evidence indicates that CRP predicts future cardiovascular events and is a better predictor of risk than even low-density lipoprotein cholesterol (LDL-C) levels.1-3

In this article, I review the most recent evidence concerning the role of inflammation in CVD and the utility of measuring CRP in clinical practice. I also answer questions clinicians often ask about CRP measurement (Box). INFLAMMATION IN CARDIOVASCULAR DISEASE

Atherosclerosis is no longer considered solely a disease of lipid accumulation. Rather, the various stages of atherosclerosis, including initiation, development, and complications of the atherosclerotic plaque, are described as an inflammatory response to injury of the vessel wall.4,5 Previously recognized cardiovascular risk factors--such as smoking, hypertension, dyslipidemia, and hyperglycemia--are now thought to be proinflammatory triggers that initiate endothelial dysfunction. These risk factors promote secretion of leukocyte soluble adhesion molecules, which facilitate attachment of monocytes to endothelial cells, and of chemotactic factors, which promote migration of monocytes into the subintima. Fatty streaks form when monocytes are transformed into macrophages and take up oxidized LDL-C. Continuing injury and the accumulation of inflammatory mediators and chemotactic factors occur within the growing atherosclerotic lesion. Inflammation also contributes to the weakening of the protective fibrous cap of the atherosclerotic plaque and to its physical disruption, which results in acute thrombotic complications. Oxidized LDL-C causes loss of vascular smooth muscle cells in the cap, and activated macrophages release enzymes that degrade its collagen content. These inflammatory processes weaken the cap, making it vulnerable to rupture. Plaque rupture exposes the atherosclerotic core to blood, inducing thrombosis. As outlined in the Table, CRP is actively involved in several mechanisms that contribute to the development and progression of atherothrombosis.6,7

| Mechanisms by which CRP contributes to the development and progression of atherothrombotic processes |
| Localizes in atherosclerotic intima but not normal intima |
| Induces production of cell adhesion molecules (eg, MCP-1, endothelin-1) |
| Induces production of tissue factor in monocytes |
| Promotes monocyte recruitment into arterial wall |
| Attenuates production of nitric oxide and decreases expression of endothelial nitric oxide synthase |
| Induces expression of PAI-1 and stabilizes PAI-1 mRNA |
| Triggers oxidation of LDL-C |
| Mediates uptake of LDL-C by macrophages |
| Blunts endothelial reactivity |
| Induces complement activation |
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ADVANTAGES OF CRP
Population-based studies have shown that elevated levels of inflammatory mediators among apparently healthy men and women predict future vascular events. Of the many potential inflammatory biomarkers (eg, cytokines, adhesion molecules, acute phase reactants), CRP appears most clinically promising.\(^1,4-6\) CRP is an acute phase protein whose levels increase during systemic inflammation; however, CRP has no specificity for particular diseases. In low-grade infections, the CRP level is greater than 3 mg/L; in acute infections or inflammation, it is greater than 10 mg/L. Characteristics of CRP that make it a clinically useful marker include:

- A relatively long half-life and stable levels that do not demonstrate day-to-day variation.
- The availability of a commercial, standardized high-sensitivity assay that can be used in outpatient settings.
- The existence of population norms to guide interpretation of results.
- Its independence from established cardiovascular risk factors.
- Its association with CVD clinical end points.
- The generalizability of results to various population groups.

Until recently, CRP was measured to assess severe inflammatory conditions. Traditional tests, however, cannot measure CRP levels within the small range necessary for cardiovascular risk assessment. Instead, a high-sensitivity CRP (hsCRP) assay was developed that has the required sensitivity to detect the lower levels of CRP (less than 1 to more than 3 mg/L) needed for CVD risk prediction.\(^1\) Throughout this article, the results of studies that used the hsCRP assay will be described using this term.

**Prediction of increased cardiovascular risk.** Several prospective epidemiologic studies have demonstrated that persons with no known coronary disease who had hsCRP levels in the top quartile generally had twice the risk of major coronary events as those in the lowest quartile.\(^1\) The increased risk was evident in various population groups, including men, women, and elderly persons, and was independent of other cardiovascular risk factors and smoking status.\(^1\) Elevated hsCRP levels predict new coronary events in patients with unstable angina or acute myocardial infarction (MI); they also predict both short- and long-term recurrent CVD and death.\(^4\) In addition, elevated CRP levels are associated with increased risk of restenosis following revascularization procedures, a worse prognosis in patients with peripheral arterial disease, and a worse prognosis--both early and late--for those with acute coronary syndromes.\(^5\)

Elevated hsCRP levels, independent of other cardiovascular risk factors, appear to provide important information on other conditions associated with inflammation. For example, elevated hsCRP levels furnish prognostic information about relative risk at all degrees of severity of the metabolic syndrome, based on the number of components,\(^9\) and are an independent predictor of risk for type 2 diabetes mellitus.\(^10-12\) Elevated hsCRP levels are significant predictors of future stroke and/or transient ischemic attack.\(^13,14\)
Elevated hsCRP levels are one of the strongest predictors of future cardiovascular events. Among 28,262 postmenopausal women enrolled in the Women's Health Study, elevated hsCRP levels were a stronger predictor of future cardiovascular events than LDL-C levels (Figure 1). In fact, of the lipid and nonlipid parameters evaluated, hsCRP alone was the strongest predictor of risk after the combination of hsCRP and the total cholesterol:high-density lipoprotein cholesterol ratio, and its predictive value was evident at all lipid levels.

Improved global risk assessment. Recent studies have found that hsCRP levels correlate significantly with calculated 10-year Framingham risk scores, and that assessment of hsCRP is clinically useful in determining risk of future cardiovascular events across a full spectrum of hsCRP values and Framingham scores. For example, in the Women's Health Study, the risk of future cardiovascular events increased linearly across the range of hsCRP levels from very low (less than 0.5 mg/L) to very high (more than 10 mg/L), with no evidence of a threshold level in persons who had 10-year Framingham risks of less than 10% (low risk) or 10% to 20% (intermediate risk) (Figure 2).

The Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Augsburg cohort study also demonstrated that hsCRP enhances the assessment of global risk as measured by the Framingham risk score, particularly in persons at intermediate risk for coronary heart disease. WHEN TO MEASURE CRP

The correlation of hsCRP levels with cardiovascular risk is as follows:

- Low risk: below 1 mg/L.
- Moderate risk: 1 to 3 mg/L.
- High risk: above 3 mg/L.

Generally, only one hsCRP measurement is necessary to determine risk, provided the patient does not have an acute inflammatory disorder (eg, infection or trauma). When the hsCRP level is higher than 10 mg/L, rule out the possibility of a noncardiovascular cause of the inflammation and measure the hsCRP level again in 2 weeks.

Guidelines from the American Heart Association and CDC state that although evidence from multiple randomized clinical trials is lacking, hsCRP measurement may be used to help guide further evaluation or therapy in patients without known CVD who are at intermediate risk according to global risk assessment (a 10% to 20% risk of coronary heart disease within 10 years). These persons may then be targeted for cardioprotective therapies, including lifestyle changes. The hsCRP level may be used as a marker for recurrent events—including death, MI, and restenosis—in those with stable coronary disease or acute coronary syndromes after percutaneous
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Coronary intervention.\textsuperscript{4} It may also be used in combination with the lipid profile to assess global risk in smokers and in persons with hypertension, the metabolic syndrome, or a family history of premature coronary artery disease.

An elevated hsCRP level predicts the onset of diabetes, and inflammation appears to be an important link between diabetes and atherothrombosis. It may be useful to measure hsCRP levels in patients with insulin resistance or increased levels of asymmetric dimethyl arginine or in patients who are morbidly obese.\textsuperscript{19} The addition of hsCRP to global risk assessment may identify patients at high risk who are not identified by cholesterol evaluation alone--that is, persons with CRP levels higher than 3 mg/L but normal or low LDL-C levels. In the Women's Health Study, women in this subgroup were at substantially higher absolute risk for cardiovascular events than were women with high LDL-C and low hsCRP levels.\textsuperscript{20} In this study, 77\% of first cardiovascular events occurred in women with LDL-C levels below 160 mg/dL. Lifestyle and pharmacologic interventions aimed at lowering CRP and LDL-C levels in these apparently healthy at-risk persons have the potential to greatly improve cardiovascular health and outcomes. **Strategies to lower hsCRP**

Several therapeutic interventions can lower hsCRP levels, thereby potentially decreasing cardiovascular risk. In one study, weight loss through diet and exercise reduced hsCRP levels in obese women.\textsuperscript{21} Other research has shown that treatment with aspirin and clopidogrel successfully prevented cardiovascular events in patients with elevated hsCRP levels.\textsuperscript{22,23} In the Physicians' Health Study, aspirin treatment decreased the risk of MI by 56\% in participants with the highest hsCRP levels, compared with a reduction of only 14\% in those with the lowest levels.\textsuperscript{24} Most evidence that supports an association between lower hsCRP levels and lower cardiovascular event rates comes from clinical trials of statins. In the secondary-prevention Cholesterol and Recurrent Events (CARE) trial, hsCRP levels predicted recurrent cardiovascular events in post-MI patients with average total cholesterol levels (below 240 mg/dL), and the risk associated with hsCRP was independent of baseline lipid levels and smoking status.\textsuperscript{25} The benefit of statin therapy for reduction in cardiovascular events was greatest in the group with the highest hsCRP level at baseline. During the 5-year follow-up period, median hsCRP levels decreased by 17\% with pravastatin therapy; this effect was not related to reductions in LDL-C level.\textsuperscript{26}

In the primary-prevention Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) of persons with normal cholesterol levels, elevated baseline hsCRP levels were associated with a significant increase in cardiovascular events. After adjustment for other risk factors, the risk of acute coronary events increased by 17\% with each increase in hsCRP quartile.\textsuperscript{27} After 1 year of treatment with lovastatin, median hsCRP levels decreased by 15\% and major coronary events were reduced by 37\% (both, \(P < .001\)). The benefit of statin therapy was significant in those with baseline LDL-C and hsCRP levels above the median values. A noteworthy finding was that statin therapy was also highly effective in persons with LDL-C levels below the median ($149 \text{mg/dL}$) and hsCRP levels above the median ($1.6 \text{mg/L}$), which suggests that the benefit of statin therapy may be related to anti-inflammatory as well as cholesterol-lowering effects.

Other investigators have also demonstrated an anti-inflammatory effect with statin therapy. In one study of patients with hyperlipidemia, the significant ($P < .025$) reduction in hsCRP levels (range, 20\% to 28\%) after 6 weeks of therapy with pravastatin, simvastatin, or atorvastatin was independent of the LDL-C lowering effect.\textsuperscript{28} The Pravastatin Inflammation/CRP Evaluation (PRINCE) study, which included both primary- and secondary-prevention cohorts, found significant ($P < .001$) reductions of approximately 14\% to 15\% in median hsCRP levels after 12 and 24 weeks of statin therapy, independent of lipid-lowering effects.\textsuperscript{29}

**Recent and ongoing trials**

The evidence to date strongly supports a link between lower hsCRP levels and better clinical outcomes. However, no direct evidence demonstrates that a reduction in hsCRP levels lowers the risk of cardiovascular events. **The CHARISMA trial.** Two ongoing trials are designed to address the possible link between lowered hsCRP levels and reduced cardiovascular risk. The clinical significance of the effectiveness of clopidogrel in lowering CRP levels is being assessed in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, a secondary- and high-risk primary-prevention, double-blind, placebo-controlled trial.\textsuperscript{23,30} The 15,200 recruited patients have either previous cardiovascular, neurovascular, or peripheral arterial manifestations of atherothrombosis or multiple recognized risk factors for atherosclerosis, and are receiving low-dose aspirin therapy. In addition to the primary outcome of prevention of major cardiovascular events, levels of anti-inflammatory mediators, including hsCRP, are being measured at baseline and study end (maximum follow-up, 3.5 years) in order to determine the magnitude of the anti-inflammatory effect of clopidogrel.\textsuperscript{23,30}
JUPITER. The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) is an ongoing prospective, randomized, placebo-controlled study designed to assess the role of statins in primary prevention and of inflammation as a cause of CVD. The primary objective of JUPITER is to determine whether long-term treatment with rosuvastatin, 20 mg/d, reduces the rate of first major cardiovascular events (combined end point of cardiovascular death, stroke, MI, hospitalization for unstable angina, or arterial revascularization) in men 55 years or older and women 65 years or older who have no history of coronary artery disease, low to normal LDL-C levels (below 130 mg/dL), and elevated hsCRP levels (higher than 2 mg/L). The secondary objectives of the trial are to evaluate the safety of long-term rosuvastatin treatment (total mortality, noncardiovascular mortality, adverse events) and to determine whether rosuvastatin reduces the incidence of type 2 diabetes. In addition, inflammation appears to be an important link between diabetes and atherothrombosis.

Patients enrolled in JUPITER are at increased risk for CVD because of their elevated hsCRP level despite a low to normal LDL-C level. Approximately 25 to 30 million adults in the United States belong to this high-risk group of patients; therefore, findings from the approximately 3.5-year JUPITER have the potential to greatly expand the use of statin therapy for aggressive lowering of LDL-C levels and for primary prevention of CVD events. The 20-mg dose of rosuvastatin used in this trial is expected to result in a reduction of about 50% in LDL-C levels and a substantial reduction in hsCRP levels. However, because rosuvastatin markedly lowers both LDL-C and hsCRP levels, researchers in JUPITER will not be able to determine whether a reduction in hsCRP levels alone leads to a reduction in vascular events.

The ANDROMEDA study. In this study, rosuvastatin lowered hsCRP by 34% and 40% at doses of 10 and 20 mg, respectively, compared with reductions of 21% and 34% with atorvastatin, 10 and 20 mg, a nonsignificant difference.

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