C-Reactive Protein: A New Risk Assessment Tool for Cardiovascular Disease

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Recent research has focused on the use of high-sensitivity C-reactive protein (hs-CRP), a marker of inflammation, in the detection of patients at increased risk for cardiovascular disease. Several prospective studies have demonstrated that hs-CRP is an independent predictor of future risk for cardiovascular events among healthy individuals, as well as among patients with acute coronary syndromes.

In addition, because half of all cardiovascular events occur in persons with low to average levels of low-density lipoprotein cholesterol, hs-CRP may aid in identifying patients at high risk for a first cardiovascular event who might otherwise be missed by lipid screening alone. Thus, hs-CRP is a potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. The Centers for Disease Control and Prevention and the American Heart Association have therefore proposed joint guidelines for the use of hs-CRP in determining cardiovascular disease risk. The author reviews numerous studies examining the prognostic value of hs-CRP and outlines ongoing efforts to assess the effect of statin therapy in healthy individuals with low levels of low-density lipoprotein cholesterol and high levels of hs-CRP.

Up to half of all events associated with cardiovascular disease (CVD) are reported to occur in apparently healthy individuals who have few or none of the traditional risk factors, including dyslipidemia. As a result, attention has increasingly turned to the role of other factors, such as inflammation, in the development of atherosclerosis and CVD. These efforts have led to the search for inflammatory biomarkers to improve the detection of coronary and cardiovascular risk among seemingly healthy individuals.

Prominent among the possible candidates for a clinically useful biomarker of CVD risk is C-reactive protein (CRP) as measured by high-sensitivity (hs) assay. This article reviews the evidence to date that hs-CRP levels can add important prognostic information to patient risk assessment. The article also examines the role of therapy with hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) in lowering elevated levels of hs-CRP.

Methods

I searched the United States National Library of Medicine’s MEDLINE database for all relevant English-language studies and clinical trials of C-reactive protein published between January 1990 and February 2005. The following Medical Subject Heading terms and keywords were used: randomized, controlled clinical trials, clinical trials, or cohort studies and (+) C-reactive protein, and (+) coronary disease or cardiovascular diseases. These terms were then combined with the following terms: acute coronary syndromes, drug effects, endothelial cells, hydroxymethylglutaryl CoA reductase inhibitors, inflammation, LDL cholesterol, lipoproteins, metabolic syndrome, myocardial infarction, risk factors, and type 2 diabetes mellitus.

Review of Studies Examining Prognostic Value of hs-CRP

Atherosclerosis, Inflammation, and C-Reactive Protein

Research over the past decade has led to the current understanding of atherosclerosis as an inflammatory disease that occurs in response to endothelial dysfunction. The earliest identifiable lesion is the fatty streak, an inflammatory lesion that consists of monocyte-derived macrophages (foam cells) and T lymphocytes. As a fatty streak progresses to an intermediate and advanced lesion, it forms a fibrous plaque—a process that involves a complex interaction between the endothelium, inflammatory cytokines, and numerous blood elements. C-reactive protein, an acute-phase reactant synthesized in the liver in response to the cytokine interleukin-6, is also a factor in the development of atherosclerotic plaque. Although CRP was initially believed to be only a marker of vascular inflammation, recent research indicates that it also plays an active role in atherogenesis. It is detectable in the early stages of plaque development and is believed to be involved throughout the atherogenic process, facilitating everything from the initial recruitment of leukocytes to the arterial wall to the eventual rupture of the plaque.

Calabro et al have proposed that the smooth muscle cells of the human coronary arteries may also produce CRP as a local

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response to inflammatory cytokines. They further noted that this locally produced CRP may participate in the atherogenic process. In addition, Khreiss et al have suggested that loss of the pentameric symmetry of CRP can result in a modified or monomeric CRP, which may be the major CRP promoter of the proinflammatory response in the coronary arteries.

The recent standardization of the hs-CRP assay allows acceptable precision down to and below 0.3 mg per liter. It is within these lower, previously “normal” ranges, that hs-CRP levels seem to have predictive abilities for coronary heart disease (CHD) events.

C-Reactive Protein as an Independent Risk Factor

A number of large, prospective epidemiologic studies have indicated that hs-CRP is a strong independent predictor of future cardiovascular events, including myocardial infarction, ischemic stroke, peripheral vascular disease, and sudden cardiac death among individuals without known CVD.

The association between elevated hs-CRP levels and future CHD events has generally been consistent among these studies: subjects in the top quartile of hs-CRP levels have a 2 to 3 times greater relative risk of a future coronary event than do those in the bottom quartile. For example, in a cohort of 1086 apparently healthy middle-aged men in the dataset of the Physicians’ Health Study, subjects with baseline levels of hs-CRP that were in the highest quartile had a twofold increase in risk of ischemic stroke or peripheral vascular disease (P=.02) and a threefold increase in risk of myocardial infarction (P<.001), relative to subjects in the lowest quartile. These effects were independent of other cardiovascular risk factors, including lipid levels and tobacco use.

The Honolulu Heart Program analyzed frozen serum samples to assess the relationship of hs-CRP to the development of myocardial infarction in clinically healthy men over a follow-up period of 20 years. Overall, hs-CRP levels in this study were associated with coronary events that occurred as many as 15 years later. As early as five years into follow-up, the risk of myocardial infarction grew with increasing hs-CRP levels (P=.009). At 10 to 15 years into follow-up, the relative odds of myocardial infarction in the highest hs-CRP quartile were 2.1 times that of the lowest quartile, after adjustment for such risk factors as total cholesterol, hypertension, and type 2 diabetes mellitus (P=.016). The strongest correlation between hs-CRP and risk of myocardial infarction occurred in those men without other risk factors.

Levels of hs-CRP have also been associated with CVD events in women. In the primary prevention Women’s Health Study, 122 initially healthy postmenopausal women who subsequently suffered a first cardiovascular event were paired with 244 controls matched for age and tobacco use who remained CVD event–free over a three-year follow-up period. Women with the highest baseline hs-CRP levels had 5 times greater risk of suffering a vascular event (relative risk [RR], 4.8; 95% confidence interval [CI], 2.3–10.1; P<.001) and 7 times the risk of myocardial infarction or stroke (RR, 7.3; 95% CI, 2.7–19.9; P<.001) than did control subjects. A more recent analysis from the Women’s Health Study reported that in 15,632 women, hs-CRP added prognostic information beyond that noted by standard lipid measurements—even after adjusting for age, blood pressure, smoking, diabetes mellitus, and obesity.

Nested case-control analyses of 121,700 women in the Nurses’ Health Study and 51,529 men in the Health Professionals Follow-up Study recently supported the results of the Women’s Health Study, finding that hs-CRP is a predictor of CHD that is independent of other cardiovascular risk factors.

In contrast to the results of these and many other trials, a nested sample of 157 subjects from the Rotterdam Study in 2003 raised concerns about whether hs-CRP adds predictive value to traditional risk factors. This concern was raised again in 2004 by a cohort study of the Reykjavik trial that questioned the usefulness of CRP over more established risk markers. In this study, 2459 patients diagnosed with CHD after enrollment were matched with 3969 controls who did not have a CHD event. After adjustments for smoking status and other established CHD risk factors, patients whose baseline hs-CRP levels were in the top tertile (cutoff value=2.0 mg/L) had an odds ratio for CHD of 1.45 (95% CI, 1.25–1.68) compared with those in the bottom tertile (cutoff value=0.78 mg/L).

The Reykjavik investigators concluded that hs-CRP added only marginally to the predictive value of established risk factors. However, the adjusted odds ratio of 1.45 for elevated hs-CRP in this study should be considered in the context of other odds ratios reported in the same group of patients: 1.87 for individuals who were current smokers versus those who had never smoked, and 1.50 for individuals with elevated systolic blood pressure versus those with normal blood pressure. Because the increased risk associated with elevated hs-CRP was comparable to that of well-established CVD risk factors, this study confirmed the value of hs-CRP as a strong, independent predictor of future heart disease.

Providing additional support for the predictive value of hs-CRP, the Cardiovascular Health Study evaluated protein levels in an elderly population without a history of vascular disease. In this study of 3971 men and women aged 65 years or older, a single instance of elevated hs-CRP levels was associated with an increased 10-year risk of CHD beyond traditional risk factors, especially in moderate high-risk men and in high-risk women.

C-Reactive Protein With Established Coronary Heart Disease

Elevated hs-CRP has been shown to be a strong predictor of future cardiovascular risk in patients with established CHD, with or without a previous myocardial infarction. In the Scandinavian Simvastatin Survival Study, elevated hs-CRP levels predicted mortality in patients with stable ischemic heart disease. Patients in the highest quartile for hs-CRP levels had the highest risk of death, compared with those in the first through
C-Reactive Protein, Diabetes Mellitus, and the Metabolic Syndrome

Recent evidence suggests that hs-CRP plays a major role in the physiologic processes associated with the metabolic syndrome.5 High levels of hs-CRP have been shown to be an independent predictor of cardiovascular risk for all degrees of severity of the metabolic syndrome.32 Furthermore, elevated hs-CRP has been correlated with abdominal obesity in middle-aged, healthy men with atherogenic dyslipidemia, an important clinical characteristic of the metabolic syndrome.33

Figure 1. High-sensitivity C-reactive protein adds prognostic information on vascular risk at all levels of the Framingham Risk Score (left) and all levels of low-density lipoprotein (LDL) cholesterol (right). (Adapted from Ridker PM, for the JUPITER Study Group. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: Rationale and design of the JUPITER trial [review]. Circulation. 2003;108[19]:2292–2297.)
nondiabetic women, providing additional evidence for the association between subclinical inflammation and the risk of type 2 diabetes mellitus and CVD.25 The odds ratio for having elevated fasting insulin increased with each tertile of hs-CRP. The odds ratio for the highest versus lowest tertile of hs-CRP was 4.4 (95% CI, 1.9–10.1).25 Similarly, the West of Scotland Coronary Prevention Study indicated that high hs-CRP levels are an independent predictor for future diagnosis of type 2 diabetes mellitus in healthy middle-aged men.26 Patients in the highest hs-CRP quintile (>4.18 mg/L) in this study had more than a threefold increased risk of diabetes mellitus after five years (95% CI, 1.9–10.1).25

Using hs-CRP Values for Risk Assessment

C-Reactive Protein Adds to Global Risk Scoring

Using traditional risk factors, clinicians can predict approximately 50% to 60% of the variation in the absolute risk of a future coronary event in individual patients.28 The addition of hs-CRP to current strategies for global risk assessment, such as the Framingham Risk Score (FRS), may therefore have the potential to increase the accuracy of cardiovascular risk prediction (Figure 1). Albert et al29 demonstrated that hs-CRP levels are correlated with the calculated 10-year FRS in men, as well as in women not taking hormone replacement therapy. Data from the Augsburg cohort of the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study also showed that hs-CRP enhances the assessment of global coronary risk as measured by the FRS, particularly in persons at intermediate risk for CHD.30 In the Women’s Health Study, both very low (<0.5 mg/L) and very high (>10 mg/L) levels of hs-CRP were useful for risk prediction across a full range of FRS.31 Women with hs-CRP levels of less than 0.5 mg per liter had the lowest risk of future cardiovascular events. Women with hs-CRP levels of greater than 20 mg per liter had a risk almost 8 times higher (crude RR, 7.6; 95% CI, 4.7–12.1) than the women at lowest risk.31

C-Reactive Protein Adds to Value of Lipid Profile

The addition of hs-CRP levels to standard cholesterol evaluation protocols improves clinicians’ abilities to predict CVD risk.32 In the Physicians’ Health Study, hs-CRP added to the predictive value of lipid parameters for determining future risk of myocardial infarction.32 Men with high levels of both hs-CRP and total cholesterol had a 5.3 times greater relative risk of a first myocardial infarction (P = .0001) than did men with either high total cholesterol or high hs-CRP levels alone (Figure 2).32

Measurement of hs-CRP in the Women’s Health Study added predictive value to all low-density lipoprotein cholesterol (LDL-C) cutoff points, as defined in the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines.33,34 Furthermore, women with high hs-CRP and low LDL-C levels had a higher absolute risk of a future CVD event than did women with low hs-CRP and high LDL-C levels, despite the fact that high LDL-C is traditionally targeted for aggressive intervention in primary prevention (Figure 3).33,34 Levels of LDL-C and hs-CRP were minimally cor-
Relationship Between Statin Therapy and hs-CRP

Clinical trials have shown that statins reduce patient levels of CRP by 15% to 28% as early as six weeks after treatment begins, independent of the magnitude of reduction in LDL-C levels. Data from a posthoc analysis of the secondary prevention Cholesterol and Recurrent Events (CARE) trial suggest that risk reduction of coronary events is greatest among patients with high baseline levels of hs-CRP. In this analysis, the risk reduction attributable to pravastatin therapy among patients with high levels of hs-CRP and another marker of inflammation, serum amyloid A (SAA), was substantially greater (54%) than in patients with lower levels of hs-CRP and SAA (25%). This finding held true even though total cholesterol, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were almost identical in the two groups.

Guidelines for Use of hs-CRP in Risk Assessment

In January 2003, joint guidelines from the Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) named hs-CRP as the inflammatory marker of choice to assess cardiovascular risk. The guidelines support the use of hs-CRP in primary prevention and set cutoff points according to relative risk categories: low risk (<1.0 mg/L), average risk (1.0–3.0 mg/L), and high risk (>3.0 mg/L). These cutoff points approximate the tertiles of hs-CRP observed in the adult population.

Recently, Ridker and Cook suggested that the scope of hs-CRP values be extended from less than 0.5 mg per liter (very low) to greater than 10 mg per liter (very high). This extension of scope would provide clinicians with additional prognostic information on cardiovascular risk. The joint CDC-AHA guidelines state that the optimal use of hs-CRP is to help guide the evaluation and therapy for primary CHD prevention for patients at intermediate risk, as defined by NCEP ATP III (10%–20% CHD risk over 10 years). The joint guidelines also consider measurements of hs-CRP as a possible predictor of recurrent events in patients with stable coronary disease or ACS.

The use of hs-CRP as an adjunct to lipid screening in primary prevention is intended to improve global risk prediction in patients not clearly identified as being at high risk by cholesterol levels alone. This adjustment to the screening procedure is especially important for individuals with low LDL-C levels (<130 mg/dL) but high hs-CRP levels (>3 mg/L), an often-overlooked high-risk group. Preliminary data suggest that patients with low LDL-C and high hs-CRP levels may benefit from pharmacologic intervention, preferably with statin therapy.

In the NCEP ATP III guidelines, hs-CRP was included among the emerging risk factors whose presence might affect clinician recommendations for therapeutic options. In the primary prevention Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a posthoc analysis found that lovastatin prevented first major acute coronary events among patients with above-median hs-CRP levels and a below-median total cholesterol-to-HDL-C ratio (P=.02). In addition, the risk of future vascular events related in the study (r=0.08), suggesting that each level predicted risk in different groups.
was as great among the patients with low LDL-C and high hs-CRP levels as it was among patients with high LDL-C levels.

Several recent studies have evaluated the ability of statins to reduce hs-CRP in individuals with ACS. In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, atorvastatin (80 mg) significantly reduced CRP by 83%, versus 74% (*P < 0.001*) with placebo, at 16 weeks.39 In the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial, which compared aggressive lipid lowering with atorvastatin (80 mg) versus moderate lipid lowering with pravastatin (40 mg), atorvastatin reduced hs-CRP and LDL-C levels 38% and 35% more, respectively, than pravastatin.40 In addition, there was a resultant statistically significant 16% reduction (*P = 0.005*) in cardiovascular events at two years.40

Phase Z of the A to Z trial compared two simvastatin protocols for two years.41 One group in this trial received simvastatin, 40 mg, for one month and simvastatin, 80 mg, thereafter, while the other group received placebo for four months, then simvastatin, 20 mg, thereafter.41 The differences observed between these two treatment groups were smaller in both hs-CRP (17%) and LDL-C (18%) than were the corresponding differences observed in either the MIRACL or PROVE IT–TIMI 22 trials. These small differences may explain the lower cardiovascular event reduction—11% (*P = 0.14*)—recorded in the A to Z trial.41

An important aspect of many of the recent hs-CRP studies in patients with ACS has been the observed correlation between more powerful LDL-C lowering and greater reductions in hs-CRP. This relationship was demonstrated in the REVERSing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study, in which atorvastatin, 80 mg, lowered LDL-C by 46.3% (versus 25.2% with pravastatin, 40 mg) and hs-CRP by 36.4% (versus 5.2% with pravastatin, 40 mg; *P < 0.001* for both).42 Similarly, in the 16-week ANDROMEDA study43 of 509 patients, rosuvastatin, which was approved by the US Food and Drug Administration in August 2003, was shown to lower hs-CRP levels by 34% and 40% at doses of 10 mg and 20 mg, respectively. These results compared with observed reductions of 21% and 34% with atorvastatin, 10 mg and 20 mg, respectively.43

**Lowering hs-CRP With Statins to Reduce Coronary Risk**

In a recent analysis of 2924 patients presenting with stable or unstable angina or acute myocardial infarction requiring hospitalization and coronary artery catheterization, patients with significant coronary artery disease (coronary artery stenosis ≥70% in 1 or more coronary arteries) were stratified by baseline hs-CRP levels and observed for an average of 2.4 years to determine the effect of hs-CRP on timing and degree of benefit of statin therapy.44 Patients with baseline hs-CRP levels greater or equal to 12 mg per liter who were prescribed statin therapy at hospital discharge derived both a larger and significantly earlier (within two months) survival benefit from statins than did patients with hs-CRP levels less than 12 mg per liter. In those patients in the highest tertile of baseline hs-CRP (>17 mg/L), statin therapy conferred benefit as early as one week, compared with approximately two years in patients with baseline hs-CRP levels in the lowest tertile (<12 mg/L).44

In another retrospective analysis of patients presenting with ACS, Saab et al45 noted that patients treated with statins within 24 hours of presentation had a lower incidence of death, stroke, reinfarction, and heart failure than those whose statin therapy was delayed more than 24 hours.

In the statin studies of patients with ACS discussed in this review, lower levels of both LDL-C and hs-CRP were achieved in the more aggressively treated groups. Some investigators have speculated—though they have not yet confirmed—that the lowering of hs-CRP will confer additional benefits in decreasing cardiovascular events beyond that seen with LDL-C lowering alone.42 In fact, in a re-analysis of the PROVE IT–TIMI 22 trial, patients who achieved the dual target of LDL-C levels less than 70 mg per deciliter and hs-CRP levels less than 1 mg per liter achieved the largest event reduction.46 Moreover, patients who achieved an LDL-C level less than 70 mg per deciliter but whose hs-CRP level remained greater than 2 mg per liter had a similar event reduction to those whose LDL-C was greater than 70 mg per deciliter and whose hs-CRP was less than 2 mg per liter. The reduction of both hs-CRP and LDL-C below the median values was also significantly associated with slower progression rates of atherosclerosis in a re-analysis of the REVERSAL trial.47

**JUPITER May Answer Remaining Questions**

Many treatment modalities, in addition to statins, have been shown to lower hs-CRP levels. Among these are exercise, weight loss, multivitamins, fibrates, niacin, and thiazolidinediones.3,48,49 However, none of these modalities have correlated changes in hs-CRP with CHD event reduction, as has been suggested with statins. Research has established hs-CRP as an independent marker for CHD, but whether lowering elevated levels of hs-CRP will reduce cardiovascular events has yet to be firmly established. Moreover, a number of other questions require further investigation. For example, should future guidelines for reducing cardiovascular risk include goals for hs-CRP levels that are independent of LDL-C levels? And should there be additional treatment strategies for individuals who have achieved their LDL-C goals but still exhibit elevated hs-CRP?

The Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) is the first large-scale, prospective, randomized, placebo-controlled trial specifically designed to address these questions.4 JUPITER, which commenced subject enrollment in February 2003, is designed to assess whether long-term, aggressive daily LDL-C-lowering therapy with rosuvastatin, 20 mg, reduces the rate of first major cardiovascular events in indi-
viduals with LDL-C levels less than 130 mg per deciliter and hs-CRP levels greater than or equal to 2 mg per liter. Rosuvastatin has previously been shown to produce greater LDL-C reductions than milligram-equivalent or higher doses of other statins.50

Full enrollment for JUPITER is expected to include 15,000 men and women aged 55 years or older and 65 years or older, respectively. Subjects will be randomized to either rosuvastatin or placebo and will be followed for three to four years to observe the combined endpoints of cardiovascular death, stroke, myocardial infarction, hospitalization for unstable angina pectoris, or arterial revascularization.4 As a secondary endpoint, JUPITER will investigate whether rosuvastatin reduces the incidence of type 2 diabetes mellitus.4

The results of JUPITER are expected to provide crucial information on whether the risk of a first CVD event in individuals with low LDL-C levels but high hs-CRP levels can be decreased with aggressive statin therapy. Because as many as 30 million people in the United States are in this often-overlooked high-risk group,51 the results of the JUPITER study could have a dramatic effect on clinical practice in prevention of CVD.

Conclusions

High-sensitivity C-reactive protein, a marker of inflammation, is a strong predictor of future cardiovascular events in individuals both with and without overt CVD. Recent trials have suggested that hs-CRP may assist in stratifying risk in patients presenting with coronary artery disease, particularly those with ACS. Further studies examining hs-CRP levels may help elucidate new therapeutic strategies for the secondary prevention of CVD. High-sensitivity C-reactive protein also adds prognostic information to the calculated FRS in individuals without overt coronary disease. When combined with lipid screening, hs-CRP improves global risk prediction in patients who would otherwise not be identified for primary prevention by lipid assessment alone.

Although statin therapy has been shown to benefit individuals with elevated hs-CRP levels, it is not known whether aggressive statin therapy can reduce the risk of a first cardiovascular event in persons with low LDL-C but high hs-CRP. The ongoing JUPITER trial is the first major randomized, controlled trial to assess the effects of statin therapy on the risk of a first cardiovascular event in such subjects. A positive outcome in JUPITER would provide strong evidence supporting the use of statin therapy for the 25 million to 30 million Americans who fall outside the current NCEP ATP III treatment guidelines. This outcome would represent a tremendous step forward in CHD prevention.

Finally, preliminary data suggest that lowering hs-CRP levels may evolve as a separate, distinct therapeutic goal. However, additional prospective randomized trials are needed before targeted treatment to lower hs-CRP levels to a specific range can be endorsed.

References


