Should C-Reactive Protein Be Added to Metabolic Syndrome and to Assessment of Global Cardiovascular Risk?

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Abstract—Of novel risk factors for cardiovascular disease currently under investigation, high-sensitivity C-reactive protein (hsCRP) is the most promising. To date, more than 20 prospective epidemiologic studies have demonstrated that hsCRP independently predicts vascular risk, 6 cohort studies have confirmed that hsCRP evaluation adds prognostic information beyond that available from the Framingham Risk Score, and 8 cohort studies have demonstrated additive prognostic value at all levels of metabolic syndrome or in the prediction of type 2 diabetes. In contrast to several other biomarkers that also reflect biological aspects of inflammation, hypofibrinolysis, and insulin resistance, hsCRP measurement is inexpensive, standardized, widely available, and has a decade-to-decade variation similar to that of cholesterol. Given the consistency of prognostic data for hsCRP and the practicality of its use in outpatient clinical settings, we believe the time has come for a careful consideration of adding hsCRP as a clinical criterion for metabolic syndrome and for the creation of an hsCRP-modified coronary risk score useful for global risk prediction in both men and women. Toward this end, we believe experts in the fields of epidemiology, prevention, vascular biology, and clinical cardiology should be convened to begin discussing the merits of this proposal. (Circulation. 2004;109:2818-2825.)

Key Words: inflammation ■ risk factors ■ prevention ■ diabetes mellitus ■ atherosclerosis

The identification of individuals who are at high risk for developing cardiovascular disease but who currently lack symptoms is a critical issue in primary prevention. For more than 30 years, cardiovascular risk prediction algorithms have relied on blood pressure, smoking status, hyperlipidemia, and the presence or absence of diabetes. These core traditional risk factors for heart disease and stroke derive largely from the groundbreaking Framingham Heart Study that first provided the conceptual basis for cardiovascular risk factors in the early 1960s.1 With corroborating evidence from major cohort studies performed worldwide, these risk factors and their interactions with age and sex were formally codified in the 1980s into the Framingham Risk Score.2,3 This scoring system, along with its European counterpart,4 has been highly successful and forms the basis for most coronary risk detection and prevention programs.5 In current practice, those with 10-year Framingham coronary heart disease (CHD) risk estimates that are less than 5% are considered to be at low risk, those with 10-year estimates between 6% and 20% are considered at intermediate risk, and those with 10-year risks of 20% and higher (or who have diabetes) are considered to be coronary risk equivalents.6,7

Despite the success of the Framingham Risk Score, there are limitations to this approach. First, it is widely recognized that a fifth of all events occur among individuals in whom traditional risk factors have not been identified.8 Moreover, the specificity of traditional risk factors is limited.9 Multiple studies additionally confirm that most vascular events occur among individuals without evidence of very high cholesterol levels10 and that the intermediate-risk group is large, heterogeneous, and in need of better methods for risk stratification.11 Finally, the relationship between Framingham scores and absolute risk for CHD varies across populations.12-14

For all of these reasons, there has been considerable interest in developing novel risk factors that might improve global risk prediction. To be useful in a clinical setting, the biomarker of interest should provide information on risk or prognosis beyond that available from standard global assessment tools. Successful screening techniques should also be inexpensive and available to primary care practitioners to ensure appropriate interpretation and follow-up. Thus, imaging techniques, including MRI, carotid ultrasonography, and coronary calcium detection, are unlikely to be useful as first-level screening tools. Similarly, metabolic evaluations, such as oral glucose tolerance testing, may be impractical given the time constraints of daily clinical practice. By contrast, simple blood tests that can be sent at the time of cholesterol evaluation are more likely to succeed.
Of potential novel risk factors presently available, high-sensitivity C-reactive protein (hsCRP), a marker of low-grade vascular inflammation, is among the most promising. Prospective epidemiologic studies consistently demonstrate that hsCRP adds independent prognostic information at all levels of LDL cholesterol and at all levels of the Framingham Risk Score. The Centers for Disease Control and Prevention (CDC) and the American Heart Association (AHA) published in January of 2003 the first set of guidelines to endorse use of hsCRP as an adjunct to traditional risk factor screening. The CDC/AHA report also endorsed hsCRP as the only inflammatory biomarker currently available with adequate standardization and predictive value to justify use in outpatient clinical settings. On the basis of data from available investigations, levels of hsCRP <1, 1 to 3, and >3 mg/L have been defined as lower, moderate, and higher cardiovascular risk. Taking a conservative approach, the CDC/AHA report suggested that the best use of hsCRP was in patients at intermediate Framingham risk.

In the year since publication of the CDC/AHA report, abundant data have emerged not only confirming the ability of hsCRP to add prognostic information to the Framingham Risk Score but also linking hsCRP to metabolic syndrome and the development of incident type 2 diabetes. Moreover, accumulating data suggest that both very low and very high levels of hsCRP seem to provide independent prognostic information across a full spectrum of Framingham risk. At the same time, cost-effectiveness studies have found that, given the low cost of screening for hsCRP, simultaneous evaluation of hsCRP at the time of lipid screening may be more efficient than a selective policy of hsCRP use that requires a return visit to the primary care physician as well as an additional outpatient phlebotomy.

All of these new data raise the possibility that hsCRP testing may improve CHD risk assessment, and clinicians within the prevention community have begun considering the use of hsCRP as a core part of global risk assessment, both in terms of Framingham risk evaluation and in terms of a modified metabolic syndrome evaluation. We thus review here evidence for hsCRP as a potential adjunct to both the Framingham Risk Score and as an additional clinical criterion for diagnosis of metabolic syndrome.

Evidence That hsCRP Is Independent of and Adds Predictive Value to the Framingham Risk Score
To date, 22 prospective studies of hsCRP and risk of future cardiovascular disease have been presented, and all are positive. Furthermore, 6 major prospective studies have demonstrated that hsCRP adds prognostic information on cardiovascular risk beyond that available using the Framingham Risk Score alone. Four investigations—the Physicians’ Health Study (PHS), the Women’s Health Study (WHS), the Atherosclerosis Risk in Communities Study (ARIC), and the Air Force/Texas Atherosclerosis Prevention Study (AFCAPS/TexCAPS)—were performed in the United States, and 2 studies, the Monitoring of Trends and Determinants of Cardiovascular disease (MONICA) study and the Reykjavik Study, were performed in Europe. In addition, the Framingham Heart Study itself has provided evidence that hsCRP independently predicts thrombotic events in the cerebral circulation, and the Pravastatin Inflammation/CRP Evaluation (PRINCE) database has provided evidence that hsCRP picks up risk information that cannot be gleaned from the individual Framingham covariates.

The largest of the American cohorts is the WHS, a prospective evaluation of 27 939 initially healthy American women who underwent hsCRP evaluation along with a full lipid panel and Framingham risk assessment and were monitored over a period of 8.3 years for the occurrence of first-ever cardiovascular events. When this study was first presented, 571 first-ever nonfatal myocardial infarctions, nonfatal strokes, coronary revascularizations, or cardiovascular deaths had accrued. Following the National Cholesterol Education Program Adult Treatment Panel III (ATP III) guidelines, the WHS emphasized hard cardiovascular end points and did not include angina pectoris.

Overall, baseline hsCRP levels in the WHS were a strong predictor of future vascular events; the relative risks for those with lowest to highest quintiles of hsCRP at baseline were 1.0, 1.8, 2.3, 3.2, and 4.5 ($P<0.001$). After adjustment for age, smoking, diabetes, blood pressure, and hormone replacement therapy, the risk in the top quintile of hsCRP was 2.3 (95% CI, 1.6 to 3.4). The hsCRP levels minimally correlated with LDL in the WHS, and a combined approach, using both lipids and hsCRP, provided improved prediction of cardiovascular event-free survival (Figure 1).

Most importantly, hsCRP levels remained a highly significant predictor of risk in the WHS after adjustment for the Framingham Risk Score. After taking into account all components of the Framingham Risk Score, the relative risks for those with lowest to highest hsCRP quintiles at baseline were 1.0, 1.3, 1.4, 1.7, and 1.9 ($P<0.001$) for all participants and 1.0, 1.6, 1.5, 1.8, and 2.2 ($P<0.001$) for those not taking...
hormone replacement therapy. The addition of data on hsCRP provided qualitatively important information on risk at all levels of LDL cholesterol after adjustment for usual risk factors (Figure 2, right) and at all levels of estimated 10-year risk based on the Framingham Risk Score (Figure 2, left). These latter analyses were based on levels of hsCRP <1, 1 to 3, and >3 mg/L, the cut points suggested for use by the CDC/AHA guidelines.

Since publication of these results, there has been continued accrual of cardiovascular end points within the WHS as well as ongoing analysis of the utility of hsCRP as a risk predictor. For example, within the WHS, evidence is now available that demonstrates predictive value both for extremely low levels of hsCRP (<0.5 mg/L) and for extremely high levels of hsCRP (>10 mg/L). This new analysis is important because it shows that dividing hsCRP levels into five categories (<0.5, 0.5 to <1.0, 1.0 to <3.0, 3.0 to <10.0, and ≥10.0 mg/L) may improve risk discrimination at both low and high levels of the Framingham Risk Score, potentially leading to a superior way to code hsCRP for use in CRP-modified algorithms (Figure 3). These data are also consistent with the hypothesis that very low levels of hsCRP may protect against acute vascular events. On the other hand, chronic inflammation from any source leads to excess risk, a hypothesis consistent with evidence about direct mechanisms by which CRP may affect both atherosclerotic development and acute thrombosis.

Data from the WHS demonstrate the additive value of hsCRP to the Framingham Risk Score and provide confirmation of data that had been presented earlier for men in the PHS. In that cohort of healthy middle-aged men, baseline levels of hsCRP were independently predictive of future myocardial infarction and thromboembolic stroke but not of venous thrombosis. Furthermore, the PHS demonstrated that the relative benefit of aspirin was greatest in preventing vascular events among those with the highest hsCRP levels, an intriguing observation given the antiinflammatory properties of aspirin. That hsCRP is an independent predictor beyond the Framingham Risk Score is also evident in those early original data. Specifically, after adjustment for all components of the Framingham Risk Score, the relative risks of future myocardial infarction in the PHS for those with hsCRP levels <1, 1 to 3, and >3 mg/L were 1.0, 1.7, and 2.2 (95% CI for those with hsCRP >3.0 mg/L, 1.2 to 3.8).

Data on hsCRP from the PHS and WHS have been corroborated by similar analyses from other large cohorts from the United States and Europe. In a case-cohort analysis of 12,819 apparently healthy middle-aged men and women participating in the ARIC study over a 6-year follow-up period, the relative risks of incident coronary heart disease for those with baseline hsCRP levels <1.0, 1.0 to 3.0, and >3.0 mg/L were 1.0, 1.6, and 2.5 after adjusting for age, sex, and ethnicity. After full adjustment for the Framingham covariates and additionally for diabetes, these risk estimates were...
1.0, 1.2, and 1.8, respectively (95% CI for those with hsCRP >3.0, 1.0 to 3.0). Almost identical data derive from a prospective evaluation of 3435 German men participating in the MONICA-Augsberg Cohort Study in which 191 incident coronary events occurred during 6.6 years of follow-up.24 In this study of men, as in the WHS study of women, hsCRP levels at baseline were independently associated with incident coronary events. These effects remained significant \((P<0.001)\) after adjustment for the Framingham Risk Score, such that persons with hsCRP levels of <1, 1 to 3, and >3 mg/L had fully adjusted relative risks of 1.0, 1.5, and 2.5, respectively (95% CI for those with hsCRP >3.0, 1.8 to 3.7).

The exceptional consistency of these Framingham-adjusted findings for hsCRP across the PHS, WHS, ARIC, and the MONICA studies using the AHA/CDC established cut points for hsCRP of <1, 1 to 3, and >3 mg/L are shown in Figure 4.

Strong supportive evidence for the addition of hsCRP to Framingham risk evaluation also comes from the large Reykjavik Study that included 2459 incident events during an 18-year follow-up period.25 Although this prospective study used an hsCRP cut point of 2.0 rather than 3.0 and thus would tend to underestimate effects compared with other cohorts, a highly significant fully adjusted odds ratio of 1.5 was nonetheless observed. In fact, this 50% increase in risk associated with hsCRP was observed not only after control for typical Framingham covariates but also after additional control for diabetes, triglycerides, body mass index, and indices of pulmonary function. Moreover, the odds ratio for hsCRP observed in the Reykjavik Study was exactly the same as the adjusted odds ratio observed for hypertension and statistically similar to that of smoking. Furthermore, the fully adjusted odds ratio for hsCRP during the initial 10 years of follow-up was 1.84, a risk estimate consistent with all prior studies.

Although there has been controversy about the relative importance of hsCRP compared with cholesterol in the Iceland analysis, it is important to recognize that the Reykjavik population studied had a mean total cholesterol of 247 mg/dL compared with the United States average of 213 mg/dL. Thus, the Icelandic data not only confirm prior reports that hsCRP significantly predicts risk after adjustment for Framingham covariates but also demonstrate the additive clinical value of hsCRP in a population with much higher baseline cholesterol levels than those observed in contemporary American and European studies.

In addition to these 5 major cohorts, supportive evidence for the addition of hsCRP to Framingham risk evaluation also comes from other sources. Within the AFCAPS/TexCAPS analysis of 5742 apparently healthy individuals enrolled in a randomized primary prevention trial of lovastatin versus placebo, each quartile increase in baseline hsCRP was associated with a 21% increase in the risk of a first cardiovascular event (95% CI, 4% to 41%), an effect that again persisted after control for all individual components of the Framingham Risk Score.23 Similarly, in an analysis of 1666 individuals free of cardiovascular disease enrolled in the PRINCE study, hsCRP levels correlated modestly with 10-year Framingham Risk Scores yet showed minimal relation to any individual component of the score itself.27 Thus, as in the prospective cohort evaluations, the PRINCE data suggest that hsCRP detects a component of vascular risk not readily obtained from the Framingham covariates themselves.

Finally, within the Framingham Heart Study, data have also been presented that demonstrate the ability of hsCRP to predict stroke risk independently of the Framingham covariates.26 After adjustment for age, smoking, blood pressure, diabetes, and total and HDL cholesterol, the risk of future stroke in the Framingham Heart Study increased 25% in men \((P=0.036)\) and 29% in women \((P=0.008)\) for each increasing quartile of hsCRP. These latter data are consistent with
Evidence from several studies showing that hsCRP also predicts first-ever thromboembolic stroke.\(^{10,20,21}\) With regard to hard coronary heart disease end points within Framingham, power is limited because of a small number of events. However, the age-adjusted relative risks of hard coronary heart disease within Framingham for those with baseline levels of hsCRP < 1, 1 to 3, and \(> 3 \text{ mg/L} \) are 1.0, 1.47, and 1.63, data fully consistent with those from the other larger studies.

Although a predictor of vascular events, hsCRP levels do not track closely with subclinical atherosclerosis, as measured by cardiac catheterization, intimal-medial thickness, the ankle-brachial index, or coronary calcification.\(^{28-30}\) This observation likely reflects the fact that inflammation is more tightly associated with plaque vulnerability and rupture than with total plaque burden per se. Clinically, this observation also helps to explain why hsCRP levels not only add to the Framingham Risk Score but also add to coronary risk prediction based on coronary calcification; in the South Bay Heart Study, elevated hsCRP levels resulted in a doubling of risk at low, moderate, and high levels of coronary calcification.\(^{31}\) Thus, measures of inflammation such as hsCRP seem to provide independent and complementary information on risk beyond that achievable by direct measures of atherosclerotic burden.

**Evidence That hsCRP Correlates With and Adds Prognostic Information to Formal Definitions of Metabolic Syndrome**

Part of the clinical interest in adding hsCRP to current risk algorithms derives from the fact that inflammation also plays a major role in the development of diabetes and is intimately related to several difficult-to-measure components of the metabolic syndrome.\(^{32}\) In cross-sectional studies, hsCRP levels have been found to correlate with elevated triglycerides, low HDL levels, midline obesity, elevated blood pressure, and high fasting glucose levels, the key easily measured components of the ATP III definition of metabolic syndrome.\(^{33,34}\) However, hsCRP levels also correlate with insulin resistance and impaired fibrinolysis, major components of the metabolic syndrome that are not easily evaluated in an outpatient practice setting. In one study of women, hsCRP and body mass index were the only independent correlates of fasting insulin levels when modeled as a continuous dependent variable.\(^{35}\)

In other investigations, hsCRP levels have been found to correlate with direct measures of insulin resistance and endothelial dysfunction.\(^{36,37}\) Among nondiabetic participants in the Insulin Resistance Atherosclerosis Study (IRAS), the correlation coefficients between hsCRP and fasting glucose, fasting insulin, and insulin sensitivity were 0.18, 0.33, and −0.37, respectively (all \(P \) values < 0.001).\(^{33}\) The IRAS investigators also found correlations between hsCRP and plasminogen activator inhibitor, indicating interrelationships between inflammation and hypofibrinolysis.\(^{38}\) Not all of these effects are attributable to obesity, as insulin resistance per se appears responsible for higher production of cytokines.\(^{39}\)

Thus, because of its relation to these additional pathophysiological components of risk, it has been hypothesized that hsCRP evaluation might also add prognostic information as an additional clinical criterion for diagnosis of the metabolic syndrome.\(^{40}\)

Evidence supporting this hypothesis is now available from several major prospective studies, of which the WHS and the West of Scotland Coronary Prevention Study (WOSCOPS) are the largest. In the WHS, levels of hsCRP were shown to correlate with the major components of the metabolic syndrome, and in univariate analyses, the finding of an hsCRP level greater than 3 mg/L had almost identical prognostic value in terms of cardiovascular event-free survival, as did a full assessment of the metabolic syndrome (area under the receiver-operating characteristic curve, 0.77 for hsCRP alone and 0.78 for having at least 3 of 5 ATP III components of the metabolic syndrome).\(^{34}\) More importantly, in this large-scale prospective evaluation, hsCRP levels were found to add prognostic information to the metabolic syndrome definition. As shown in Figure 5, those who had hsCRP levels <3 mg/L without metabolic syndrome had the best vascular survival, whereas those who had hsCRP levels \(> 3 \text{ mg/L} \) with the metabolic syndrome had the worst vascular survival.

![Figure 5. Cardiovascular event-free survival according to hsCRP levels above or below 3 mg/L among individuals with and without metabolic syndrome. Reprinted with permission from Reference 34.](image-url)

An almost identical additive interaction between hsCRP, metabolic syndrome, and subsequent vascular risk was observed in WOSCOPS, a randomized intervention trial of pravastatin that monitored 6447 middle-aged men over a 5-year period. In WOSCOPS, hsCRP levels above and below 3 mg/L at baseline were highly predictive of incident vascular events after stratification by the presence or absence of the metabolic syndrome.\(^{41}\) Specifically, the observed relative risks of future coronary events in the low CRP/metabolic syndrome–absent, high CRP/metabolic syndrome–absent, low CRP/metabolic syndrome–present, and high CRP/metabolic syndrome–present subgroups within WOSCOPS were 1.0 (referent), 1.6, 1.6, and 2.8, respectively (all \(P \) values < 0.05).

Additional evidence of the interrelationships between inflammation and metabolic syndrome derive from 6 prospective studies that have reported hsCRP levels to predict the onset of type 2 diabetes, often after controlling for obesity and other diabetes-related risk factors. In the WHS, those
With hsCRP levels in the top quartile were more than 4 times as likely to develop diabetes compared with those with hsCRP levels in the lowest quartile (multivariate adjusted relative risk, 4.2; 95% CI, 1.2 to 12.0). Similarly, in WOSCOPS, those with the highest levels of hsCRP at study entry had a 3-fold increase in risk of incident diabetes during the 5-year follow-up period (multivariate adjusted relative risk, 3.1; 95% CI, 1.3 to 7.1). Smaller but consistent effects were observed in the Cardiovascular Health Study, which included 5888 older individuals where the multivariate adjusted relative risk of incident diabetes for those with the highest quartile of baseline hsCRP was 1.8 (95% CI, 1.2 to 2.9). Finally, in the MONICA cohort of 2052 middle aged men, the Insulin Resistance Atherosclerosis Study (IRAS) of 1047 middle-aged men and women, and the Nurses Health Study of middle-aged women, significant age-adjusted associations between baseline hsCRP and incident diabetes were observed. hsCRP levels have additionally been found to predict cardiovascular risk among those with diabetes; in a prospective cohort of 746 men with type 2 diabetes who were free of cardiovascular disease at study entry, those with hsCRP levels in the top quartile were 3 times as likely to develop cardiovascular events even after control for all available covariates (95% CI, 1.3 to 5.3).

On the basis of the above observations, an argument can be made for including hsCRP as one of the clinical criteria for the diagnosis of the metabolic syndrome. Newly reported clinical data support this contention. Within the WHS population, 3597 women with the ATP III criteria for the metabolic syndrome were prospectively followed up over an 8-year period for first-ever cardiovascular events. In that prospective cohort, cardiovascular event-free survival among patients with metabolic syndrome was markedly different when information on hsCRP was taken into consideration. As shown in Figure 6, baseline hsCRP levels <1, 1 to 3, and >3 mg/L differentiated between low-, moderate-, and higher-risk groups among women already identified as having metabolic syndrome by ATP III criteria. Those with metabolic syndrome and the highest levels of hsCRP had a relative risk of future cardiovascular events twice that of individuals with metabolic syndrome and low levels of hsCRP (95% CI, 1.1 to 4.2; P=0.001).

The studies above demonstrate that vascular risk prediction and the prediction of type 2 diabetes can be improved by knowledge of hsCRP levels, even among those with metabolic syndrome. Recent studies relating hsCRP to incident hypertension serve to reinforce the importance of blood pressure in the metabolic syndrome complex. Whether to formally incorporate hsCRP as one criterion for diagnosis of metabolic syndrome is presently an area of intense debate. The simplicity of hsCRP evaluation strengthens the argument, particularly because direct measures of insulin resistance and hypofibrinolysis are difficult and formal oral glucose tolerance testing impractical in usual outpatient settings. From a practical standpoint, the measurement of hsCRP at the time of triglyceride, fasting glucose, and HDL assessment has appeal for improving metabolic syndrome diagnosis in daily practice.

Has the Time Come to Consider hsCRP as a Clinical Criterion for Metabolic Syndrome and as a Formal Addition to Global Risk Prediction?

Inexpensive evaluation of hsCRP in outpatient settings is now possible with the availability of standardized commercial assays capable of detecting the very low levels of CRP needed for coronary risk prediction. No circadian variation exists for hsCRP, nor does food consumption alter plasma levels, so there is no need for a fasting blood sample to be obtained. Despite being an acute-phase reactant, the decade-to-decade variation in hsCRP is similar to that of cholesterol, demonstrating long-term stability for risk prediction. Because therapy with HMG CoA reductase inhibitors lowers hsCRP as well as LDL cholesterol, many clinicians have begun measuring hsCRP at the time of cholesterol evaluation, using information on inflammation both to motivate patients for lifestyle changes and to better target statin therapy.

After publication of the CDC/AHA guidelines, outpatient use of hsCRP increased in the United States, a change that reflects the translation of the biology of inflammation into daily clinical practice. Observations that hsCRP also has predictive value in unstable angina and acute myocardial infarction have additionally encouraged some emergency room physicians to obtain hsCRP levels at the time of hospital admission. Multiple clinical trials have specified hsCRP as part of their entry criteria to identify high–cardiovascular risk patients.

In consideration of the consistency of these data, we believe the time has come to examine the possibility of incorporating hsCRP into the criteria for the diagnosis of metabolic syndrome and as a risk factor in calculation of global cardiovascular risk. To begin a dialogue on this issue and to better understand the potential role of hsCRP as an adjunct to the Framingham Risk Score, we reanalyzed data from 27 939 participants in the prospective WHS using 5 clinically defined categorical levels of hsCRP (<0.5, 0.5 to <1, 1 to <3, 3 to <10, and ≥10 mg/L) and after dividing the full WHS population into those with 10-year Framingham risks estimated as being <5%.

Figure 6. Clinical predictive value of hsCRP levels <1, 1 to 3, and >3 g/L among individuals already defined as having metabolic syndrome by ATP III criteria. Reprinted with permission from Reference 34.
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References


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