

Medical Policy



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Title: High-Sensitivity C-Reactive Protein

Professional

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DESCRIPTION

C-reactive protein (CRP) is an acute phase reactant produced by the liver that has long been used to monitor inflammatory processes, such as infection and autoimmune diseases. Recent studies have suggested that low-level chronic inflammation may play a role in atherogenesis, and thus measurement of CRP has been investigated in various settings of cardiovascular disease, i.e., in patients with known cardiovascular disease, in patients with risk factors for cardiovascular disease, and as a general risk assessment tool for cardiovascular disease. Conventional methodologies for measuring CRP in acute inflammatory diseases have a detection limit of 3-5 mg/L. However, in the setting of the low levels of chronic inflammation in otherwise healthy individuals, this level of detection is not adequate. To be used as a risk assessment tool, a greater precision at lower levels of CRP is needed such that the range of values collected in epidemiologic studies can be subdivided into quartiles and quintiles; in this way, the data from large epidemiologic studies can be applied to individual patients. Such new technologies, collectively known as high-sensitivity C-reactive protein (hs-CRP) include enzyme linked immunoabsorbent assays (ELISA) and various other techniques based on monoclonal antibodies. While the ELISA test is still primarily used as a research tool, various immunoassays have been automated and are commercially available. Several of the high-sensitivity C-reactive protein tests have received 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA).

POLICY

Measurement of high-sensitivity C-reactive protein is considered **investigational** as a method of cardiac risk stratification.

Determination of high-sensitivity C-reactive protein (hs-CRP) may be included as a component of a comprehensive cardiovascular risk assessment offered by reference laboratories. Comprehensive risk assessment may include evaluation of small low-density lipoproteins, subclassification of high-density lipoproteins, evaluation of apolipoprotein E genotype or phenotype, total plasma homocysteine, apolipoprotein B, and lipoprotein a.

RATIONALE

Evaluation of the clinical utility of a risk factor involves the following steps:

1. Standardization of the measurement of the risk factor.
2. Determination of its contribution to risk assessment. As a risk factor, it is important to determine whether the novel risk factor (i.e., high-sensitivity C-reactive protein [hs-CRP]) independently contributes to risk assessment compared to established risk factors. In addition, it is important to understand the relationship of any novel risk factor with other "emerging" risk factors. There are many potential novel risk factors that could be incorporated into existing risk assessment guidelines. These include measurements of lipid subclasses (e.g., apo B, low density lipoprotein [LDL] size, etc.), inflammatory markers (e.g., CRP, fibrinogen, plasminogen activator, etc.), as well as other potential cardiac-related measurements (e.g., B-natriuretic protein [BNP], homocysteine, etc.). Any one of these markers may individually contribute to risk assessment models. However, the optimal combination of markers for risk assessment can only be understood by evaluating multiple potential markers in a multivariate fashion.
3. Determination of how the novel risk assessment will be used in the management of the patient, compared to standard methods of assessing risk, and whether any subsequent changes in patient management result in an improvement in patient outcome.

The above attributes are reviewed in relation to hs-CRP.

- 1 Standardization of the measurement of the risk factor.

Several studies have evaluated automated methods of measuring hs-CRP and compared them to enzyme-linked immunoabsorbent assays (ELISA), considered the gold standard. (1, 2) These studies suggest a high correlation between the automated assays and the ELISA assay. In addition, serial measurement levels of hs-CRP have shown minimal variability among healthy adults. (3)

2. Determination of its contribution to risk assessment.

Several prospective epidemiologic studies have suggested that measurement of hs-CRP is an independent risk factor for cardiovascular disease in a variety of clinical settings. For example, results of the Multiple Risk Factor Intervention Study (MRFIT) demonstrated that among male smokers there was a correlation between hs-CRP and coronary heart disease mortality. (4) Similarly, a direct positive correlation between hs-CRP and future coronary events was observed among apparently healthy men participating in the Physicians Health Study. (5, 6) Results from the Women's Health Study report similar findings in women. (7) These studies also suggest levels of hs-CRP were independent of other recognized cardiovascular risk factors, and that risk models incorporating measurements of lipids and hs-CRP were better at predicting risk than risk assessment based on lipid levels alone. Elevated levels of hs-CRP have also been found to be independent risk factors of cardiovascular risk in those with both chronic stable and unstable angina. (8, 9)

A TEC Special Report completed in 2002 (10) concluded that a large body of well-done observational cohort studies demonstrates an association between C-reactive protein levels and risk of future coronary heart disease (CHD) events. There are, however, uncertainties as to the exact role C-reactive protein plays in the pathogenesis of CHD and the reliability of C-reactive protein assessment.

Recent literature has focused on the predictive ability of CRP when considered together with other emerging risk factors. These studies examined different combinations of potential risk factors, and used different methods of analyzing the predictive relationship among these factors. Ridker and colleagues (11) evaluated the predictive ability of hs-CRP in relationship to the emerging lipid measures apo B and apo A-I in 15,632 women enrolled in the Women's Health Initiative. This study concluded that hs-CRP added significant predictive information above that of apo B or apo A-I. However, these analyses of "additional predictive ability" were performed individually for each of the lipid measurements rather than in a fully integrated multivariate model.

Wang and colleagues (12) evaluated 10 potential biomarkers (i.e., hs-CRP, BNP, N-terminal pro-atrial natriuretic peptide, aldosterone, renin, fibrinogen, D-dimer, plasminogen-activator inhibitor type I, homocysteine, and the urinary albumin/creatinine ratio) in 3,209 participants in the Framingham Heart Study. In a multivariate model including all 10 potential biomarkers, CRP was not an independent predictor for cardiovascular events, but was an independent predictor of overall mortality. This study also included an analysis of the incremental predictive ability of these markers for classification accuracy, using the C-statistic (similar to receiver-operating characteristic [ROC] analysis). For cardiovascular events, the C-statistic (analogous to "area under the curve" in ROC analysis) was 0.76 in a model including age, sex, and conventional risk measurements. This C-statistic rose only slightly to 0.77 when the experimental biomarkers were entered into the model. The authors therefore concluded that the additional predictive ability of these novel biomarkers was modest at best.

3. Determination of how risk assessment will be used in the management of the patient. Currently, no clinical studies have focused on how measurements of hs-CRP will be used in the management of the patient, and whether such management changes will reduce the subsequent incidence of cardiovascular events. There are no data on how knowledge of hs-CRP levels should influence current management strategies, such as diet, weight control, or cholesterol-lowering therapies. Data have suggested that both aspirin and statin therapies modulate the inflammatory response, and thus may be particularly effective in patients with elevated hs-CRP. For example, Ridker and colleagues reported that among patients with primary hypercholesterolemia, 8 weeks of cerivastatin therapy was associated with a reduction in CRP levels independent of reduction in lipid levels. (13) However, all of these patients were candidates for statin therapy based on their lipid status, and it is unclear whether statin therapy should be recommended in patients with elevated hs-CRP without an associated increase in LDL. Some authors have suggested that elevated hs-CRP levels may lead to improved compliance with physician recommendations regarding diet,

exercise, and smoking cessation, but this hypothesis is still untested. (14) There are no studies of how hs-CRP may be used in the management of patients with known cardiovascular disease.

hs-CRP has been included as an outcome in interventional studies. (15-19) For example, Ridker and colleagues evaluated the relationships between the LDL cholesterol and CRP levels achieved after treatment with statin drugs and the risk of recurrent myocardial infarction or cardiovascular death in 3,745 patients with acute coronary syndromes. (18) Patients who had low CRP levels after statin therapy had better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL cholesterol. Nissen and colleagues examined the outcomes of moderate and intensive statin therapy in patients with documented coronary artery disease. (19) Lipoprotein and CRP levels were measured at baseline and at follow-up. The primary outcome was the progression of atherosclerosis, as assessed by ultrasonography. The decrease in CRP levels was independently and significantly correlated with the rate of progression.

Both of these articles confirm that reducing the inflammatory component of cardiovascular disease (as evidenced by a reduction in hs-CRP), through the use of statin therapy, improves the clinical outcome independently of the reduction in serum cholesterol levels. The independent effect of CRP and LDL levels suggest that two different pathways are at work. However, there are still no trials in which levels of CRP have been used to direct therapy. In both of the studies reviewed here, patients were recruited based on their clinical history and cholesterol levels, and the treatment did not vary according to changes in CRP levels. These studies raise the question of whether CRP levels will emerge as a therapeutic target and whether the effects of statins on CRP should be considered in decisions regarding therapy. There is currently an ongoing clinical trial assessing the use of CRP levels to guide therapy in patients who do not have elevated LDL cholesterol. (20)

The 2002 TEC Special Report offered the following conclusions:

- While the existing observational evidence suggests that using CRP as a component of a risk assessment tool will result in a more accurate cardiac risk prediction, at this point in time, there appears to be no scientific literature that directly and experimentally tests the hypothesis that measurement of C-reactive protein to assess CHD risk results in improved patients outcomes. In addition, there appears to be no generally accepted risk assessment tool available using C-reactive protein that translates into risk estimates to which established treatment guidelines can be applied (e.g., Adult Treatment Panel III sponsored by the National Cholesterol Education Program).
- There is no general agreement on how management of the patient would be changed in patients with high C-reactive protein levels.

Existing Guidelines and Specialty Society Recommendations

The American Heart Association/Centers for Disease Control and Prevention (AHA/CDC) Scientific Statement was published in January 2003. (21) The recommendations of the

AHA/CDC are summarized in the table below. In their report, the AHA/CDC offered several recommendations classified according to the following criteria:

Class I

Conditions for which there is evidence and/or general agreement that a given procedure is useful and effective.

Class II

Conditions for which there is conflicting evidence and/or divergence of opinion about the usefulness / efficacy of a procedure or treatment.

Class IIa

Weight of evidence / opinion is in favor of usefulness/efficacy

Class IIb

Usefulness / efficacy is less well established by evidence/opinion

Class III

Conditions for which there is evidence and/or general agreement that the procedure / treatment is not useful/effective and in some cases may be harmful.

Recommendation of AHA/CDC Regarding Role of hs-CRP Measurements in Clinical Practice

Class IIa Recommendations

- Measurement of hs-CRP is an independent marker of risk, and, in those judges at intermediate risk by global risk assessment (10%–120% risk of CHD per 10 years), at the discretion of the physician, may help direct further evaluation and therapy in the primary prevention of cardiovascular disease (CVD). The benefits of such therapy based on this strategy remain uncertain.
- In patients with stable coronary disease or acute coronary syndromes, hs-CRP measurement may be useful as an independent marker of prognosis for recurrent events, including death, myocardial infarction (MI), and restenosis after percutaneous cardiac interventions. The benefits of therapy based on this strategy remain uncertain.

Class IIb Recommendations

- Measurement of hs-CRP is an independent marker of risk and may be used at the discretion of the physician, as part of a global coronary risk assessment in adults without known CVD. The benefits of this strategy remain uncertain. (Compared to the Class IIa recommendation above, this statement includes a broader population of patients.)
- hs-CRP levels may be useful in motivating patients to improve lifestyle behaviors. The benefits of this strategy remain uncertain.

As noted here, none of the recommendations received a Class I recommendation, and the AHA/CDC recognize that the benefits of using hs-CRP as a cardiac risk assessment tool are uncertain. The policy statement in this BCBSA policy, indicating that hs-CRP is investigational, is based on this acknowledged lack of direct evidence linking a risk assessment incorporating hs-CRP to changes in therapy and ultimately to improvement in health outcomes. The strongest recommendation by the CHD/AHA (i.e., IIa) suggests that the results of hs-CRP may help identify patients at intermediate risk who may benefit from primary prevention of CVD. It is estimated that some 30%–40% of the population may fall into this intermediate risk group. If the results of the hs-CRP measurement are considered high, patients may then be offered various interventions, frequently including the initiation of statin therapy. Therefore, the use of hs-CRP as one component of a risk assessment tool may ultimately result in considerably more patients being placed on life-long drug therapy.

Evaluation of any risk assessment tool for primary prevention is complicated by the fact that, in general, recommendations for primary prevention are in part based on cost-effective analyses. Risk assessment typically involves setting cut-off points to determine candidacy for an intervention, since the population of patients that could benefit from primary prevention is quite broad. These cutoff points for interventions are typically based in part on cost effectiveness. For example, lowering LDL-cholesterol through lifestyle changes or drug therapy appears to be an effective prevention strategy regardless of the particular risk factors a person has for CVD or their absolute risk of CHD. Nevertheless, the guidelines of the National Cholesterol Education Program (NCEP), which have been widely adopted to identify candidates for risk reduction, do not target the general population but focus on those with a higher baseline risk of CVD who will achieve a greater absolute reduction in risk with an intervention. These NCEP guidelines are in part based on concepts of cost effectiveness. Cost-effective analysis of using hs-CRP as part of the risk assessment tool may be particularly important given that some 30%–40% of the population may fall into an intermediate risk group, and a certain proportion of those may be considered for primary intervention when hs-CRP is used as part of the assessment tool.

The CDC/AHA Scientific Statement includes the following statement:

“...The next question is: ‘When and in whom should [hs-CRP] be measured?’ Key to this discussion are the purpose for its measurement and the likelihood that further diagnostic and therapeutic plans might change on the basis of the test results. No clinical trials have been completed in which a population has been randomly allocated to screening for hs-CRP screening with a control population group not allocated to hs-CRP screening and both groups followed up prospectively to determine the benefits and harms of the screening. In particular, there continue to be few data on the cost effectiveness of screening with inflammatory markers, taking into account further testing and treatment of persons classified as having high risk for CVD or the possibility of reduced testing and treatment of persons classified as being at low risk.”

2008 Update

A literature search was performed for the period of January 2007 through March 2008. There were a large number of publications on the topic of CRP and cardiovascular disease, most of which evaluated the predictive ability of hs-CRP for a variety of cardiovascular and related outcomes. A smaller number of studies addressed the use of hs-CRP as a treatment target, or examined genetic polymorphisms of hs-CRP and their association with hs-CRP levels and cardiovascular risk.

Several large prospective studies were identified that added to the already substantial body of literature on hs-CRP as a predictor of cardiovascular risk. Analysis of data from the Cardiovascular Health Study, consisting of 5,020 patients without baseline cardiovascular disease followed up for 12 years, examined whether hs-CRP was an independent predictor of future cardiovascular events (22). An elevated hs-CRP ($>3\text{mg/l}$) was an independent predictor of cardiovascular death in patients with pre-existing carotid atherosclerosis (RR 1.72, 95% CI 1.46-2.01), but was not an independent predictor of outcomes in patients without pre-existing carotid atherosclerosis. Ridker et al (23) published the Reynolds Risk Score, which is an empirically derived prediction model for cardiovascular outcomes based on data from 24,558 initially healthy women enrolled in the Women's Health Study and followed up for a median of 10.2 years. A total of 35 potential predictors of cardiovascular disease were considered as potential predictors in both derivation and validation models. Hs-CRP was one of 9 independent predictors of cardiovascular events that were included in the final model. Zakai et al (24) evaluated 13 potential biomarkers for independent predictive ability compared to established risk factors, using data from 4,510 individuals followed up for 9 years in the Cardiovascular Health Study. Hs-CRP was one of 7 biomarkers that had incremental predictive ability above established risk factors. The adjusted hazard ratio for each standard deviation increase in hs-CRP was 1.13 (95% CI 1.05-1.21). Kozan et al (25) evaluated the ability of hs-CRP to impact classification of cardiac risk. These authors classified 1,817 hypertensive patients from the Intensive/Initial Cardiovascular Examination Regarding Blood Pressure Levels: Evaluation of Risk Groups (ICEBERG study) into risk categories according to the European Society of Hypertension/European Society of Cardiology guidelines. The addition of hs-CRP to risk prediction models significantly increased the absolute number of patients classified into "high" or "very high" risk categories by 11%–13%.

One large prospective study reported results that differed from the above studies. Olsen et al (26) followed up 2,656 individuals from Denmark over a period of 9.4 years, and evaluated the incremental predictive ability a number of emerging risk markers including hs-CRP, N-terminal BNP, and urine albumin/creatinine ratio. When controlled for both traditional risk markers, N-terminal BNP added significant predictive information for future cardiovascular events while hs-CRP did not (HR 1.17, $p=\text{NS}$).

One large study examined the use of hs-CRP as a treatment target for lipid-lowering therapy. Sattar et al (27) used data from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) to evaluate whether hs-CRP levels were associated with degree of

response to statin therapy. While this analysis reported that hs-CRP levels were a predictor of adverse cardiovascular outcomes, there was no correlation between hs-CRP levels and response to statin therapy.

A number of studies addressed whether genetic polymorphisms of hs-CRP have an impact on its predictive ability. Kivimaki et al (28) evaluated 5 different genetic polymorphisms of the hs-CRP gene and their relation to hs-CRP levels in 1,609 patients from the Cardiovascular Risk in Young Finns Study. These authors reported that there were significant differences in hs-CRP levels according to genetic status. However, in a multivariate model, the total amount of variation in hs-CRP explained by genetic status was relatively low ($r^2=3.3-5.0\%$). In a separate publication from the same study, Eklund et al (29) found that there was a correlation between genetic polymorphisms and measures of carotid artery compliance, a surrogate marker for atherosclerotic disease.

The majority of the new studies identified for this update confirms or extends what is known about hs-CRP as a predictor of cardiovascular risk. This information alone is not sufficient to justify the use of hs-CRP in routine care without having adequate tools and guidelines to incorporate hs-CRP into routine clinical decision-making. Researchers have started to address these needs with studies such as Kozan et al (25), in which hs-CRP was used to reclassify individuals into clinically relevant risk categories, and The Reynolds Risk Score (23), which offers clinicians an alternative risk prediction model for cardiovascular disease in women that includes hs-CRP. Questions have been raised about the reclassification study because of lack of an additional step of evaluating the impact of the reclassification. Also, including revascularization as an end-point has been raised as an issue with the article on the Reynolds Risk Score. In addition, these potential tools for using hs-CRP measurements have not yet become widely disseminated nor have they been incorporated into existing clinical guidelines concerning cardiac risk assessment.

Studies still have not demonstrated if prospective use of this measure will improve patient outcomes compared to current care.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

86141 C-reactive protein; high sensitivity (hsCRP)

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