[A technical review]

C-Reactive Protein (CRP) High-sensitivity Test

A marker for cardiac inflammation

Introduction

The importance of factors such as age, gender, tobacco use, family history, diabetes, hypertension, and dyslipidemia in predicting risk of cardiovascular disease (CVD) is well known.[1,2] These established risk factors are largely absent in approximately half of those who develop CVD,[3] and the implication of this phenomenon is significant: there is a need for further refinements to current risk assessment schemes and stratification.

Inflammation in Atherosclerosis and CRP

Basic science and extensive studies have established an extensive body of evidence to substantiate that atherosclerosis is an inflammatory process, responsive to injurious factors such as smoking, hypertension, atherogenic lipoproteins, and hyperglycemia. C-reactive protein (CRP), an acute-phase reactant, has long been recognized as an inflammatory marker and suspected of playing a role in the atherosclerotic process. Because other sources—such as systemic inflammation (eg, connective tissue diseases) and local infections (eg, gingivitis, prostatitis, bronchitis, urinary tract infections, gastric inflammation)—can also stimulate production of CRP, its role in CVD risk assessment has not been well understood.[4]

Recognizing the confusion that surrounded the clinical utility of CRP and other inflammatory markers, the Science Advisory and Coordinating Committee of the American Heart Association (AHA) and the Centers for Disease Control (CDC) examined the best available evidence for an association between inflammatory markers and CVD. The resulting Scientific Statement from the AHA/CDC Committee recognized, among other things, that CRP was an independent predictor of increased risk for CVD and an adjunct to other major risk factors.[4] It also concluded that CRP measurement in patients at intermediate risk for CVD (estimated ten-year risk of 10% to 20% for development of coronary heart disease [CHD]), provided additional information that clinicians could use when contemplating further evaluation and therapy.[4] In contrast, CRP measurement was not recommended for individuals considered at high risk (estimated ten-year risk for CHD >20%) or low risk (estimated ten-year risk for CHD <10%) because the former should already be targeted for aggressive therapy, and the latter would not likely have elevated CRP levels.[4]

Laboratory Analysis of CRP

Initially the prospect of using CRP as an inflammatory marker was met with resistance because existing assays lacked the sensitivity to measure low concentrations of CRP in serum reliably. Manufacturers addressed the need, however, by developing high-sensitivity CRP (hs-CRP) assays with acceptable precision down to or below 0.3 mg/L—the test levels at which hs-CRP has predictive abilities for CVD. CRP testing is now standardized and automated as well as subject to proficiency testing through a program from the College of American Pathologists.[4]

The AHA/CDC Scientific Statement also shows the standardized assay CRP reference intervals that are employed by LabCorp and appear on LabCorp result reports. The reference intervals are listed in table 1 below.[4]To reduce inter-individual variability, measurements of CRP should be performed on two separate specimens, two weeks apart, from metabolically stable (fasting or nonfasting) individuals. The average of the two results should be used for risk assessment. If CRP is >10 mg/L, sources of inflammation or infection should be investigated and treated before additional samples are analyzed. A result of >10 mg/L should be disregarded. Moreover, testing should not be performed for at least two weeks following resolution of the contributing acute inflammation or infection.[4] Patients with unexplained, persistently elevated CRP levels (>10 mg/L) should be evaluated for noncardiovascular etiologies.[4] In all cases, it's important to consider results within the context of a complete clinical history.

Table 1— CRP Reference Interval

Relative Risk Category	Average hs-CRP Level
Low	<1.00 mg/L
Average	1.00 mg/L–3.00 mg/L
High	>3.00 mg/L

CRP and CVD Risk

Several national and international prospective clinical case-controlled studies[5-18] identified CRP as an independent risk factor that provides incremental value to primary and secondary prevention

strategies. Key outcomes from these studies indicate that CRP

- may be useful in identifying patients most likely to benefit from aspirin therapy;[6]
- is a modifiable risk factor, suggesting that anti-inflammatory activity from HMG-CoA therapy (pravastatin) may contribute to the drug's efficacy;[8,9]
- demonstrates positive, statistically significant correlations with other established risk factors (age, number of cigarettes smoked per day, body mass index, systolic and diastolic blood pressure, total cholesterol (TC), triglycerides, lipoprotein(a), apolipoprotein B, tissue-type plasminogen activator antigen, homocysteine, fibrinogen, and D-dimer) and an inverse correlation with exercise frequency and high-density lipoprotein cholesterol (HDL-C);[5]
- was a risk factor in apparently healthy men for fatal and nonfatal MI, ischemic stroke, and peripheral artery disease (PAD) but not venous thrombosis, suggesting its value in risk assessment may be limited to the arterial system;[6,7]
- was a risk factor in postmenopausal women for CHD death, nonfatal MI, and stroke,[10] and
- increased the overall predictive value when added to other CVD risk factors and, in particular, achieved a significant improvement in risk assessment when used with total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol in comparison to the use of each separately.[11,18]

Results from the large controlled trial, JUPITER (Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), demonstrated that there may be a strong association between lowering hs-CRP levels and risk reduction of major cardiovascular events among the patients without hyperlipidemia.[19] The trial included apparently healthy individuals from diverse populations with normal LDL-cholesterol levels and hs-CRP levels of 2.0 mg/L or higher who were treated with rosuvastatin. After a median follow-up of 1.9 years, hs-CRP levels were reduced by 37% and relative risk of major cardiovascular events was reduced by 44%.[19,20]

CRP and Primary Prevention

JUPITER study data were also the basis for a recently approved primary prevention strategy for men ≥ 50 years and women ≥ 60 years without clinically evident heart disease who have at least one additional CVD risk factor (eg, hypertension, low high-density lipoprotein (HDL) cholesterol, smoking, or a family history of premature coronary artery disease) and an hsCRP value ≥2 mg/L. Rosuvastatin (CRESTOR®) is indicated in this patient population to reduce the risk of stroke and myocardial infarction as well as the need for arterial revascularization procedures.[21]

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Relevant Assay*	
Test Name	**Test Number**
C-Reactive Protein (CRP), High Sensitivity (Cardiac Risk Assessment)	120766

*For the most current information regarding test options, including specimen requirements and CPT codes, please consult the online Test Menu at www.LabCorp.com.

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