## Review Article:

# C-reactive protein and coronary heart disease - risk marker or risk factor?

**J. Fiddy Davis,[1] Sudha Vidyasagar,[2] G. Arun Maiya[1]**

*Department of [1]Physiotherapy, Manipal College of Allied Health Sciences, Karnataka and Department of [2]Medicine, Kasturba Medical College, Manipal, Karnataka*

## ABSTRACT

Cardiovascular diseases are gaining a dubious distinction of becoming the leading cause of death. Thus, the search for new risk markers and risk factors of cardiovascular disease continue, in an attempt to predict the risk of cardiovascular events with greater precision. Of all the risk markers available, high sensitivity C-reactive Protein (hsCRP) is considered to be the most robust tool with test characteristics desirable and conducive for clinical use. Pharmacological intervention trials were successful in reducing hsCRP in individuals with elevated levels, following which its status as a therapeutic target has taken a big leap. Numerous pharmacologic and non-pharmacologic interventions are presently being investigated for their efficacy in reducing this inflammatory marker. This review discusses the stability of hsCRP, factors affecting the concentration, independent predictive ability as compared to the traditional risk factors and its role in atherogenesis.

**Key Words:** *Inflammation, Cardiovascular diseases, Primary prevention, Atherosclerosis*

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Cardiovascular diseases (CVD) accounted for more than 17 million deaths worldwide in 2008.[1] India is predicted to have the largest burden of CVD in the world by 2015.[2] About 64 million people in India may be afflicted with CVD in the year 2015, of which 61 million would constitute coronary artery disease (CAD).[3] Population based studies indicate that the prevalence of CAD is estimated to be 3% to 5% in rural areas and 8% to 10% in urban areas among individuals aged 20 years and above.[4]

CAD is a manifestation of atherosclerosis. Earlier, atherosclerosis was considered to be a bland condition associated lipid storage that reduces the arterial lumen. However, it is now believed to be a chronic inflammatory condition that starts at a very young age.[5] Empirical evidence suggest that inflammation plays a critical role in all the stages of atherosclerosis, from a nascent lesion to a fully grown atheromatous plaque.[6] The greatest danger with the atheromatous plaque is its thrombogenic potential and not just the magnitude of stenosis,[7] which accounts for the manifestation of acute coronary syndrome.

### Inflammatory markers

Inflammation associated with CAD is subclinical in nature and can be diagnosed using various inflammatory markers. The inflammatory markers can be grouped into three categories namely, cytokines and chemokines, soluble adhesion molecules and acute phase reactants.[8] The C-reactive protein (CRP), an acute phase reactant, is a novel inflammatory marker that is very sensitive to systemic inflammation, infection and tissue damage.[9] It is synthesized by the hepatocytes in response to one of the stimuli mentioned above.[10] Level of CRP increases from about 6 hours and reaches the peak value within 48 hours. Given the long half-life period (approximately 19 hours) of CRP, the only determinant of its concentration is the rate of synthesis, which is a reflection of the magnitude of the underlying pathology.[11]

### High sensitivity CRP

The term *high sensitivity* CRP (hsCRP) denotes the measurement of CRP using immunoassay methods that have adequate sensitivity to quantify CRP throughout its normal range. Methods like radioimmunoassay, immunonephelometry, immunoturbidimetry,

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**Corresponding Author:** Dr Sudha Vidyasagar, Professor and Head, Department of Medicine, Kasturba Medical College, Karnataka. **e-mail:** vsagar33@yahoo.com

immunoluminometry and enzyme linked immuno sorbent assay (ELISA) are used to measure hsCRP.[8] The Centers for Disease Control and Prevention (CDC) along with American Heart Association (AHA) has put forth the recommendations (Table 1) for the measurement of hsCRP.[12]

An expert panel of National Academy of Clinical Biochemistry, opined that hsCRP is the only marker that fulfills all the criteria to be accepted as a biomarker for risk assessment in primary prevention of CVD.[13] The normal range of CRP is between 0 - 6 mg/L. However, individuals are categorized to different risk categories based on the concentration of hsCRP within the normal range (Table 2).[12]

**Table 1: Recommendations by CDC and AHA for clinical measurement of hsCRP**

- hsCRP can be measured both in fasting and non-fasting state
- When the test values are more than 10 mg/L the results should be discarded and test has to be repeated after 2 weeks.
- For a reliable estimate, an average of two assays performed 2 weeks apart should be considered
- When hsCRP levels are > 10 mg/L on two consecutive tests, search for other infections and inflammation has to be performed.

hsCRP = high sensitivity C-reactive protein ; CDC = Centers for Disease Control and Prevention AHA = American Heart Association

**Table 2: Categorization of patients using standard hsCRP assays to different risk strata**

| Concentration of hsCRP (mg/L) | Risk stratification |
|---|---|
| < 1.0 | Low risk |
| 1.0 - 3.0 | Average risk |
| > 3.0 | High risk |

hsCRP = high sensitivity C-reactive protein

## Stability of hsCRP

Stability of hsCRP over a period of time was investigated on 8901 participants who were allocated to the placebo group in an intervention trial. The hsCRP was measured at baseline and was repeated at 13 weeks, 1, 2, 3 and 4 years. Investigators found that the concentration remained high throughout the trial duration.[14] This finding is in line with another trial which investigated the reproducibility of hsCRP with an intention to determine if this marker can be used as a marker of future CVD in community based risk screening. Seventy Australian cohort dwelling in the community were followed-up for 829 days. At follow up, it was observed that the concentration remained stable.[15]

## Factors affecting concentration of hsCRP

There are a variety of factors that can influence the concentration of hsCRP. Elevated blood pressure, obesity, smoking, diabetes mellitus, metabolic syndrome, dyslipidaemia and hormone use are the individual characteristics that can increase level of hsCRP along with chronic infection of inflammation. Moderate alcohol consumption, improved fitness, weight loss and medications like statins, fibrates, niacin, aspirin, and non steroidal anti-inflammatory drugs (NSAIDs) can decrease the level of hsCRP.[12] Extraneous factors that can influence the concentration are seasonal variation, diurnal influence, age, gender and ethnic differences.

### *Seasonal variation*

A couple of cross sectional studies indicate that there could be seasonal variation in the concentration of hsCRP with an increase during fall and winter as compared to summer.[16-18] A longitudinal trial[16] on 641 white overweight participants measured hsCRP at baseline and repeated the measurement every three months till one year, Mean hsCRP of 1.72 mg/L varied by about 9% across seasons. The highest values were witnessed in the month of November and December and the lowest was found in June. The results of all the trials are consistent with this study.

### *Diurnal influence*

Interleukin-6 is a cytokine responsible for the synthesis of CRP and has been proven to have diurnal variation.[19,20] In a study aimed at determining if hsCRP also would exhibit similar

variation, 13 healthy participants (10 men) in the age group of 21-35 years were observed for 24 hours with eight hours of sleep in the night. Blood samples were withdrawn on an hourly basis and were analyzed. Results of the analysis revealed that there was no diurnal variation.[21] Clinical implications of this result would be that, hsCRP can be measured at any time of the day without any concern of circadian influence.

### *Age and gender influence*

Age and gender difference in hsCRP concentration has been observed by many cross sectional studies.[22-24] CRP has been found to increase with age and has been found to be more in women. The third National Health and Nutrition Evaluation Survey (NHANES III) data of more than 22,000 individuals show that there is a linear relationship between age and CRP.[22] As the relationship was strong, they generated an equation to estimate the upper limit of CRP based on age. The equations provided were: age/50 for males, and (age/50) + 0.6 for females. The equations clearly suggest high levels in women and an increase with age.[22] However the National Academy of Clinical Biochemistry, CDC and AHA in their guidelines did not mention about age adjusted or gender adjusted normal values. This could possibly be because of a difference in hsCRP that is clinically not significant.

### *Racial differences*

Data from Dallas heart study,[25] in which 6,101 multi-ethnic participants were studied, showed that black subjects had higher values as compared to whites. This has been supported by the data from NHANES III, which revealed that black participants had higher values as compared to Mexican-Americans and non-Hispanic whites.[26] A systematic review of population based studies[27] included 15 studies to assess the ethnic difference in CRP; 14 of them found an ethnic variation and the results clearly show that Hispanics and south Asians had the highest CRP.

## hsCRP in Indians

There is enough evidence through large observational studies to suggest that the concentration of hsCRP is high in Indians.[28-32] Further, Indian Asians living in the United Kingdom has been found to have 17% higher CRP values as compared to Europeans,[29] the same have been found in Indians living in the United States as compared to Caucasians[28] and in Singapore as compared to Chinese and Malays.[30]

A recent population based trial recruited 334 participants with metabolic syndrome and 342 healthy urban citizens of Chennai to investigate the relationship between inflammatory markers in people with and without metabolic syndrome. Concentration of hsCRP in healthy individuals was found to be high at 2.19 mg/L and even higher for people with metabolic syndrome.[31]

## Utility of hsCRP as a predictor of risk

Elevated hsCRP has been associated with many non-communicable diseases like CAD,[33] ischemic stroke,[34] insulin resistance,[35] hypertension,[36] metabolic syndrome[37] and peripheral artery disease.[38] The most extensively studied area is its risk for CAD, there are about 25 large observational studies published since the late 90s which confirm the independent predictive ability of hsCRP in estimating risk for CAD.

In one study[39] CRP and LDL were measured at baseline for 29,939 American women and were followed for eight years for cardiovascular events. Investigators determined relative risk for CVD according to quintiles of CRP and LDL. After adjustment of traditional risk factors the relative risk reported according to increasing quintiles compared against the lowest quintile of CRP were 1.4, 1.6, 2.0 and 2.3. Similar relative risks were estimated using LDL too: the values were 0.9, 1.1, 1.3 and 1.5. The difference between the relative risks measured was statistically significant, suggesting that CRP

is a more powerful marker of risk than LDL. Another meta-analysis pooled the existing data from large observational studies to determine the predictive ability of hsCRP. Investigators found that the people in the top of the quartile have an odds ratio of about 1.5 for cardiovascular events compared to people at the lowest quartile even after adjusting other established risk factors.[40]

Another exhaustively researched area now is the predictive ability of hsCRP and its association with metabolic syndrome, which is a predisposing factor for CAD. International Diabetes Federation (IDF) believes that the risk for major CVD in people with metabolic syndrome is approximately twice as high as for those without the metabolic syndrome. Results of numerous cross sectional studies reveal that hsCRP is strongly associated with metabolic syndrome.[41-44] It has been demonstrated that the association is very strong in young overweight and obese girls with a mean age of about 12 years.[43] In a cross-sectional study to investigate the association of hsCRP with metabolic syndrome in 4066 urban Indians, the risk of metabolic syndrome increased in a dose dependent manner with an increase in hsCRP.[42] Given the predictive ability of hsCRP in estimating risk for metabolic syndrome, IDF recommends the inclusion of this inflammatory marker as an additional criterion for diagnosing metabolic syndrome in research setting.[45]

**hsCRP and global cardiovascular risk tools**

Framingham CHD risk score, Systematic Coronary Risk Evaluation (SCORE) and Reynolds risk score are the tools to evaluate an individual's cardiovascular risk. These tools estimate the 10 year absolute risk for cardiovascular events based on the traditional risk factors (age, gender, diabetes mellitus, dyslipidaemia, smoking and hypertension) and stratify the patients to "low risk", "intermediate risk" and "high risk". Guidelines for low and high risk is very clear but not for intermediate risk (people who have a risk of 10 to 20%). Moreover it has been noted that a significant number of people could not be classified appropriately based on the established risk factors alone.[46] Forty percent of deaths due to CAD happen in people with normal lipid profile[47] and a few develop cardiovascular events with one or less than one risk factor. Thus the search for newer markers of risk continues unabated. Given the proven ability of CRP as an independent risk predictor, researchers investigated the comparative efficacy of CRP against the global tools for risk assessment and also investigated if addition of CRP to the global risk assessment scores would enhance the tool's sensitivity to identify people at risk.

In a study[48] the CRP levels were compared with Framingham risk score of 1666 individuals without known cardiovascular disease. Significant correlation was observed between the risk score and CRP thereby strengthening the claim of CRP as an adjunct in cardiovascular risk prediction.[48] In a study designed to determine if CRP has the potential to modify risk prediction based on Framingham risk score, 3435 German men in the age group of 45 to 74 years were followed-up for about six and half years after the baseline assessment and were monitored for fatal or non-fatal coronary events. Results of this study revealed that CRP significantly improves the predictive abilities of Framingham risk score, especially in the intermediate group (10%-20% risk).[49] Similar results were found when 3006 American men and women with a mean age of 46 years were observed for 12 years. Results of this study showed that addition of CRP helps reclassify patients who fall in intermediate risk.[50]

Predictive ability of Reynolds risk score was also investigated by including CRP and parental history. In this study[51] 10,724 American, non-diabetic men were followed up for about 11 years and 1294 cardiovascular events occurred during the study period. Two prediction models,

one with traditional risk factors and the other model that has hsCRP and parental history along with traditional risk factors were analyzed. The model which had hsCRP and parental history improved the predictive ability of the score,[51] thus is now incorporated as an integral component of Reynolds risk score. Recent recommendations from the U.S. preventive services task force suggest that adding CRP to risk prediction models improves the risk stratification.[47] We propose this algorithm for clinical decision making in using hsCRP (Figure 1). At this point of time it is the intermediate risk group which benefit from the measurement of hsCRP as it helps to reclassify patients to appropriate risk strata.

**CRP - A Potential Risk Factor**

Numerous risk factors for CVD have been identified by observational studies and the number continues to grow. One risk factor that has emerged from the status of being a marker of risk for CAD is hsCRP. Accumulating empirical evidence indicate that CRP could mediate atherosclerosis at various steps, along with other traditional risk factors.[52] In vitro analysis proved that elevated levels of CRP inhibits nitric oxide (NO) synthesis and its bioactivity in human endothelial cells.[53] Inhibition of NO can set a cascade of events leading to atherosclerosis. CRP has been shown to promote monocyte chemotaxis and tissue factor expression.[54,55] Tissue factor is a potent procoagulant, which can lead to disseminated intravascular coagulation and ultimately to thrombosis during inflammatory states. Moreover CRP induces the production of monocyte chemoattractant protein-1 (MCP-1)[56] and plasminogen activator inhibitor-1 (PAI-1) expression in endothelial cells.[57] MCP-1 is a protein responsible for the migration of monocytes to the site of lesion.[6] It has been observed that elevated CRP induces PAI-1 in human aortic endothelial cells. PAI-1 is a protease inhibitor that regulate fibrinolysis by inhibiting tissue plasminogen activator. Increased PAI-1 indicates lowered fibrinolysis and thus leads to atherogenesis.[57,58]

A few Mendelian studies question the causative role of CRP in atherogenesis demonstrating that genetic variation in the CRP gene is associated with lifelong increased CRP levels, but not with increased risk of atherothrombosis.[59,60] However association between CRP gene variants and risk of CAD could not be ascertained by the authors of this study.[52] Till this is established, CRP could be considered a causative factor for atherosclerosis and a target for therapy.

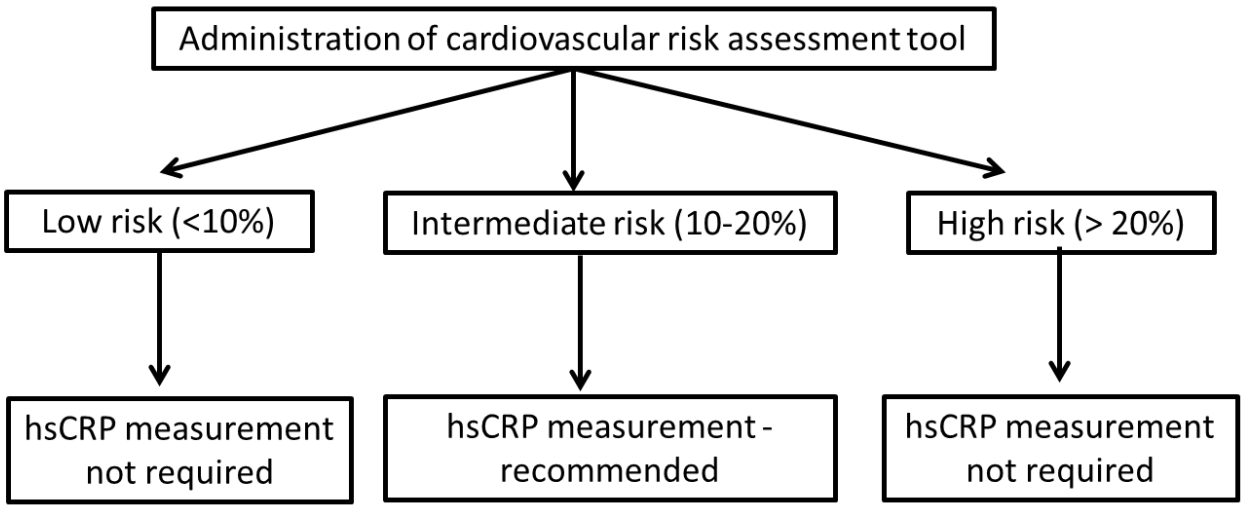


**Figure 1:** Algorithm explaining the appropriate use of hsCRP based on the score from global cardiovascular risk tools
hsCRP = high sensitivity C-reactive protein

**Is hsCRP a target for therapy?**

Evidence from statin trials supports the use of hsCRP as a therapeutic target. In a randomized controlled trial aimed at determining the effects of lovastatin in primary prevention of acute coronary events, 5742 individuals were assigned to treatment and placebo group and were followed up for about 5 years. CRP was found to be reduced in the treatment arm by about 15% and this effect was independent of the changes that happened in the lipid profile. The authors[61] concluded that statin therapy was effective in the primary prevention of CAD in individuals who had normal lipid levels but increased CRP.

A landmark study in primary prevention of CAD that strengthened the claim of CRP as a potential therapeutic target is Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial.[62] In this study[62] 17,802 apparently healthy participants, who had low density lipoprotein cholesterol (LDL-C) < 130 mg/dL but elevated hsCRP (> 2 mg/L), were randomly assigned to the treatment group which received Rosuvastatin 20 mg or placebo and the primary outcome measure was the first cardiovascular event. The trial was stopped prematurely as there was a lopsided benefit to the treatment arm, with a significant reduction (44%) in the cardiovascular events mediated by 37% reduction in hs CRP. This trial also brought to light a population with hidden risk for CHD.

In an attempt to predict the risk of CAD with greater accuracy, the search for new risk markers and their predictive ability will need to continue. At this point in time, among all the risk markers available, hsCRP appears to be the best bet as, it has assay characteristics conducive for clinical use, commercially robust assay are available widespread, it is very stable with very marginal fluctuations, more cost-effective than the emerging risk markers and more importantly has been proven to orchestrate atherosclerosis.

Even though the time has not come to screen the general public, hsCRP can be measured in patients who fall under the intermediate risk category, as it help improve accuracy of prediction and reclassify them to an appropriate strata.

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