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ORIGINAL ARTICLE

C-Reactive Protein—A Screening Test for Coronary Disease?

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C-reactive protein (CRP) is one of a number of substances termed ''acute phase reactants,'' biologic substances that appear in the circulation when an active inflammatory process occurs. Although traditionally used to monitor or detect major infectious or inflammatory conditions, elevations of CRP levels within the conventional range of ''normals'' has been intensively studied as a marker for coronary disease and risk of future coronary events. Sensitive assays that can be performed on a high-volume, commercial basis are now available. CRP appears to be a valuable marker for the prediction of future events in individuals who have known coronary artery disease. CRP has been proposed as a coronary disease–screening test for healthy individuals; however, available data suggest that use of CRP in this context may be premature. This paper reviews published research concerning CRP and the prediction of cardiovascular and total mortality risk, then outlines the current ''state of the art'' for the application of CRP to the risk assessment process.

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C-reactive protein (CRP) is one of a number of substances termed ''acute phase reactants,'' biologic substances that appear in the circulation when an active inflammatory process occurs. In clinical practice, the traditional use of CRP has been in detecting or monitoring serious inflammatory processes such as rheumatologic disorders or chronic infections. Several thousand–fold increases in CRP levels in these circumstances are well-established ''abnormal'' values.[1]

Inflammation has been found to have a major role in the development of atherosclerotic plaque in coronary artery disease. Injury to vascular epithelium can be initiated by a number of insults including oxidative stress, altered lipids, and hemodynamic forces.[2] In response, injured vascular epithelial cells initiate a protective response. Up-regulation of adhesion molecules and cytokines mediates increased adhesion of monocytes, and their migration into intercellular space. Uptake of LDL-cholesterol by these cells, which have become macrophages, transforms them into lipid-laden ''foam cells,'' the first recognizable component of an advanced atherosclerotic lesion. Mononuclear cells within this inflammatory infiltrate of the endothelial wall release additional cytokines including interleukin-1 and interleukin-6 that reinforce the inflammatory process as well as the oxidation and uptake of LDL. Release of other substances, mitogens, stimulates the proliferation of smooth muscle cells and contributes to the maturation of the fatty streak to an intermediate atherosclerotic lesion. Later, a fibrous cap forms over this developing inflammatory mixture of inflammatory and smooth muscle

cells, intracellular and extracellular lipid, necrotic cellular debris to form the advanced, complex atherosclerotic plaque. Particular attention has been directed to the fibrous cap at the edge or shoulder of the atheromatous lesion, where inflammatory cells continue to accumulate, and plaque rupture frequently occurs. Plaque rupture, with sudden exposure of atheroma contents, promotes thrombus formation and results in acute infarction.

Since the inflammatory process is active at every stage of atherosclerosis, CRP has been intensively studied as a risk marker in coronary disease. CRP is produced by the liver in response to circulating interleukin-6, a ''cytokine'' or chemical messenger that is released from the site of active inflammation such as a coronary artery. (Interleukin-6 has also been evaluated as a coronary risk marker.[3])

Elevations in CRP levels conventionally regarded as in the ''normal'' range have been shown to be related to risk for future coronary events.[2] High-sensitivity assays (hsCRP) have been developed to detect variations of CRP within this range of CRP (generally <5 mg/L). CRP has several characteristics that make it a particularly attractive candidate marker. Its concentration remains stable over long periods in the absence of new stimuli. Circulating levels depend almost entirely on the rate of hepatic production rather than protein clearance. Reliable assay techniques, well-established standards, and the ability to fully automate production testing are also attractive features.

In this article we will review published studies that evaluate the predictive value of CRP, and point out areas where more knowledge is needed before CRP is considered a ''gold-standard'' CAD predictor (see Table).

CRP IN INDIVIDUALS WITH KNOWN CORONARY DISEASE

A number of studies have evaluated the relationship between CRP levels and the risk of subsequent cardiac events in individuals diagnosed with angina or myocardial infarction (MI). Increased CRP levels are associated with twofold increased risk of coronary events within 2 years in individuals diagnosed with angina.[1] Similar to one of the earlier studies suggesting a connection between CRP and cardiac risk, the authors felt that the modest CRP response was owing to ongoing inflammation rather than acute myocardial necrosis. CRP measured on hospital discharge following treatment for unstable angina was highly predictive of 90-day occurrence of angina or MI.[4] Receiver-operating curve (ROC) analysis of these results yielded an area of 0.84 under the ROC curve, which indicated a high predictive value for CRP measurement. (An ROC area of 0.5 indicates that the test cannot discriminate between the presence and absence of disease better than chance; an ROC area of 1.0 indicates that the test always discriminates between the presence and absence of disease.) In another series of patients with unstable angina and rest chest pain, CRP predicted long-term (6 months) but not short-term risk for mortality, MI, or performance of cardiac revascularization. The ROC analysis in this study indicated a threshold value of 10 mg/L or more maximized predictive value.[5] CRP levels have also been correlated with a history of self-reported MI in a broad population survey.[6] Based on a voluntary population survey, the relation between self-reported angina pectoris and CRP level was not shown in a separate analysis in the same paper. A gradual rise in CRP levels over time has been shown to correlate with slow, steady progression of coronary stenosis. CRP was not found to predict sudden stenosis related to acute thrombosis during the course of a hospitalization.[7] This supports the hypothesis that mild elevations of CRP reflect the chronic underlying atherosclerotic process, rather than tissue injury resulting from coronary ischemia.

CRP IN HEALTHY MEN

Evidence for the predictive value of CRP in healthy men is based on several prospective studies of coronary risk. The Physician's

Summary of Coronary Risk and C-Reactive Protein (CRP) Studies

Population Studied	Author/Study Group	Endpoint Assessed	CRP Range (or Median/ Mean for High-Risk Group) (mg/L)	Relative Risk of Event for Highest Risk Group
Angina pectoris diagnosis	Haverkate ECAT[1]	Sudden cardiac death and Myocardial infarction (MI)	>3.6	2.25
Hospital admission for angina	Ferreiros[4]	Cardiac death, MI, or ''re-fractory'' angina	>1.5	3.16
Unstable angina	Heeschen CAPTURE[5]	Mortality and MI	>10	1.97
US Population Health Survey	Ford NHANES[8]	Self-reported MI history	>0.55	1.6
Healthy males	Ridker PHS[8]	MI, stroke, venous thrombosis	≥2.11	2.9
Healthy males	Koenig MONICA[9]	MI or sudden cardiac death	>4.53	2.6
Healthy males	Gram Danish Health Survey[10]	MI, cardiac hospital admit, sudden cardiac death	2.26 (mean)	Not reported—see text
Population-Hoorn study	Jagar-Hoom Study[13]	Cardiovascular mortality	>2.84	1.32–3—see text
Healthy females*	Ridker WHS[14]	Coronary death, stroke, MI, coronary revascularization	0.85 (median)	4.4
Healthy females	Ridker WHS[15]	Coronary death, stroke, MI, coronary revascularization	>7.3	4.8
Elderly, age 70–85	Strandberg Helsinki Aging Study[17]	Total and cardiovascular mortality	>5	1.2

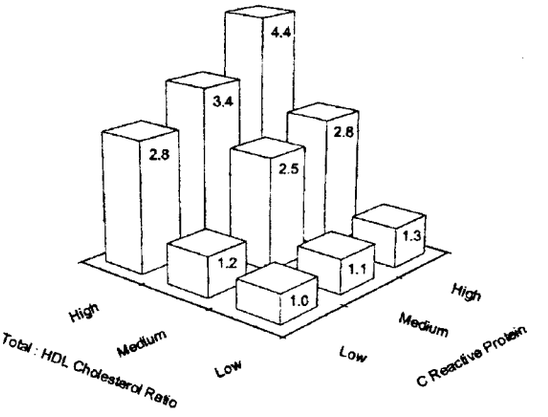
* Same population, study group, and outcomes as in Ridker et al.,[14] CRP measured with different technique.

Health Study was a large trial (22,000 male participants) evaluating primary prevention strategies for cardiovascular disease and cancer. The CRP levels at entry were compared between a group of physicians that went on to have MI and a group that remained free of vascular disease (over a period of up to 14 years). Men with the highest CRP levels had three times the risk of MI of those with the lowest CRP levels. Importantly, this study showed that the predictive value of CRP was not altered when an analysis that adjusted for other risk factors such as body mass index, diabetes, family history, plasma lipids, or homocysteine was performed.[8]

In another long-term (over 8 years) prospective study of cardiovascular risk (MONICA—Augsburg), those with the highest CRP levels had a 2.6-fold increased risk of first MI. Adjustment for age and smoking status had only a minor impact on risk prediction in this study.[9] In a subgroup of the Danish National Hospital Register, CRP correlated with other risk factors, but was not shown to be a strong independent risk factor in this analysis (an ROC curve area of 0.59).[10]

CRP enhances the strength of predictive models incorporating CRP and either total cholesterol or HDL cholesterol.[11] Increased CRP has also been correlated with the number of conventional coronary risk factors present in an individual case[12] (see Figure).

Others suggest that the independent predictive power of CRP may not be as strong. In a separate population–based study, elevated CRP was associated with a threefold increase in cardiovascular mortality risk. However, when adjusted for a series of other risk factors including age, sex, presence of glucose intolerance or diabetes, hypertension, current smoking, low HDL, total cholesterol, obesity, and presence of peripheral vascular disease, the relative cardiovascular mortality risk was reduced to 1.32. These investigators concluded that CRP was not necessarily independent of other coronary risk factors.[13] This study included both male and female subjects that were healthy or had diagnosed diabetes mellitus.



Relative risks of first myocardial infarction among apparently healthy men associated with high (>5.01), middle (3.78–5.01), and low (<3.78) tertiles of the total cholesterol/HDL-cholesterol ratio and high (>1.69 mg/L), middle (0.72–1.69 mg/L), and low (<0.72 mg/L) tertiles of C-reactive protein. Printed with permission Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. CIRCULATION. 1998;97:2007–2011.

Whether CRP is clearly independently related to risk of coronary events still needs to be established. Additionally, the suggestion that the risk impact of CRP may be more than additive when it is considered with other established coronary risk factors needs to be proven and defined.

CRP IN HEALTHY WOMEN

CRP has also been evaluated for the coronary risk assessment of healthy women. In a prospective study that involved over 28,000 healthy postmenopausal women followed for a mean of 3 years (Women's Health Study), a comparison was made of the CRP levels between a group of women that had cardiovascular events and a set of matched controls. A commercial hsCRP assay was used. CRP was the study's strongest individual predictor of cardiovascular events; the highest CRP group had 4.4 times the risk of the lowest CRP group.[14] In an analysis of the ability of other risk factors to predict coronary risk, only CRP and the total cholesterol/HDL ratio emerged as independent predictive factors. CRP was even demonstrated to be an indicator of increased coronary risk in women

with normal LDL cholesterol levels based on standards of the National Cholesterol Education Program. A previous study of the same group using an experimental CRP assay showed a sevenfold increase in the risk of MI or stroke.[15] For comparison, in a separate analysis of the same group, women with the highest homocysteine levels had a twofold increase in the risk of any cardiovascular event.[16]

For healthy women, CRP also appears to be an independent predictor of cardiovascular events. Coronary event risk related to CRP may also be more than additive when considered with established cardiovascular risk factors, and may be a stronger factor than homocysteine in the assessment of relative cardiovascular risk of women.

CRP AND THE ELDERLY

While all the publications described above consider risk in population-based cohorts of men and women with a mean age of approximately 60 years, Strandberg et al have studied three older-aged groups aged 75, 80, and 85. Ten-year mortality data were available for each age group. In this study,[17] baseline CRP over 10 mg/dL significantly predicted total mortality and cardiovascular mortality in the group that was aged 75 at the outset. The predictive value of CRP in the 80- and 85-year–old groups was clearly attenuated and was not statistically significant.

CRP AND THERAPY

CRP as an ''acute phase reactant'' may reflect the presence of active inflammation from ongoing coronary atherogenesis. An intriguing possibility is the use of CRP as a criterion for initiating and monitoring therapeutic interventions. Several studies have evaluated possible relationships between CRP and therapies.

CRP AND ASPIRIN THERAPY

One goal of the Physician's Health Study was to assess the potential benefit of aspirin in primary prevention of coronary disease, a benefit that was clearly demonstrated. The men who had the highest CRP levels had the most benefit from aspirin therapy. Randomized assignment to aspirin therapy was associated with a 46% reduction in MI risk among men with the highest baseline levels of CRP.[8] This result lends support to the view that there is a direct relationship between CRP levels and an active atherosclerotic process. It also suggests that high CRP levels could be used to identify patients for aggressive preventive therapies.

CRP AND PRAVASTATIN THERAPY

The cholesterol-lowering ''statin'' drug pravastatin has been studied as a secondary preventive strategy in patients who have suffered a first MI. Pravastatin was shown to have a beneficial effect in reducing the risk of recurrent MI in treated patients. For patients who had CRP measured, the reduction of risk for a second MI was greatest in those that had the highest CRP levels.[18] This effect was independent of any lipid-lowering effect of the drug. This supports the view that ''statins'' have an anti-inflammatory effect in addition to their lipid-lowering effect, and provides additional evidence that CRP levels could be used as a basis for initiating preventive therapies. In post–first-MI patients receiving long-term (5 years) pravastatin therapy, CRP levels were found to be 21.6% lower than in an untreated patient group.[19] Unfortunately, the risk of MI or death was not assessed in this study.

CRP AND HORMONE REPLACEMENT THERAPY

The possibility that hormone replacement therapy (HRT) for postmenopausal women may increase cardiovascular risk has been an ongoing concern. Median CRP levels were increased twofold in healthy postmenopausal women taking HRT in a subgroup of the Women's Health Study.[20] Risk of cardiac events was not evaluated in this report.

Though, in the opposite sense, this observation highlights the potential use of CRP for monitoring the effects of therapy that, in the case of HRT, may increase cardiovascular risk.

CRP AND AN INFECTIOUS ETIOLOGY FOR CORONARY DISEASE

CRP has also been used as a tool to investigate low-grade or occult intravascular infections as a potential etiology of coronary atherosclerosis. This hypothesis suggests that infection is the initial event that triggers the inflammatory cascade in the coronary artery endothelium (as described above). Chronic periodontal disease, *Chlamydia pneumoniae,* cytomegalovirus, and *Helicobacter pylori* have been investigated as possible etiologies of coronary artery disease. A relationship between CRP and the presence of periodontal disease, or multiple positive serologies to these agents has been demonstrated. However, this connection is not conclusive evidence for a direct cause-effect relationship of a specific organism as a cause of coronary disease.[21,22]

LABORATORY ISSUES

Though much has been written about the development of hsCRP assays to measure CRP in the conventional ''normal'' range, several authors have concerns regarding the use of hsCRP for population screening. Relatively little has been written about the variability of CRP measurements. It has been observed that hsCRP levels vary little over time and are generally at the low end of the measurement range (0.5–3 mg/L) for a single individual.[23] However, there is a relatively large variability in ''normal'' hsCRP values from one person to another. Combined, these 2 observations mean that many individuals can have coronary disease–associated changes in CRP, but have hsCRP values that do not exceed the reference interval. A parameter called ''critical difference,'' has been calculated for hsCRP as 118 and 175%[24,25] in 2 different analyses. This implies a change in an individual's CRP of at least this magnitude is required before it can be concluded that a risk or disease related change has occurred, suggesting that risk assessment based on a single measurement may be problematic. Serial hsCRP measurements (in the same individual) have been related to change in status over time.[7]

SUMMARY

CRP is a highly promising marker for cardiovascular risk because its levels are relatively stable over time, is affected by little other than inflammation, and appears to predict cardiovascular event risk independent of other known risk factors.

Though most published studies have suggested that the risk effect of a combination of CRP and other risk factors is at least additive, more conclusive data are needed to show how CRP contributes independently to cardiovascular event and mortality prediction. The reader should be aware that a large proportion of current CRP publications originates from investigations of one group. Expansion of the number of other independently conducted assessments, as well as additional assessment of the independent predictive value of CRP, would allow a clear statement of the role of CRP in the whole context of cardiovascular risk assessment.[26,27]

Our knowledge of CRP in healthy adults is based on an analysis of relatively few events in large study groups. CRP levels and absolute population risk of cardiovascular events, as well the direct relationship of CRP to mortality risk, needs further study. Further research is also needed to assess the relationship of CRP in evolving new measures of cardiovascular disease risk (eg, other inflammation markers such as interleukin-6 and electron beam computed tomography).

Based on research published to date, the best current application of CRP for risk assessment may be in those individuals who already have identified coronary artery disease, either angina pectoris or first MI. In one study that specifically addressed the ability

of CRP to predict a cardiovascular event 90 days following admission for angina, CRP had high predictive value.[4] The association between reduction in CRP with secondary prevention therapies (aspirin or pravastatin) and cardiac event risk reduction is also compelling.

For healthy men and women, there is relatively little gradation in relative cardiovascular risk over most of the range of CRP values. There may also be considerable overlap in CRP measurements between controls and individuals who later develop disease. For healthy individuals, only those with CRP levels in the highest percentiles of a distribution of ''normal'' CRP values may represent a true high-risk group.

WHAT IS THE CURRENT STATUS OF CRP FOR UNDERWRITING?

The best use of CRP in underwriting is as a tool to more precisely classify the risk in individuals already at risk for future cardiovascular events. These situations would include applicants with prior coronary diagnosis, or those who have had an equivocal result in another test that assesses cardiac risk. CRP can provide important risk-assessment information if interpreted carefully in the context of complete cardiac history and risk factor data.

There are no data to suggest that *low* CRP values can be related to an *improvement* of cardiovascular risk status in otherwise healthy adults otherwise considered to be standard risks. Although one might infer that a ''negative'' CRP confers a mortality advantage, the use of hsCRP in this context would be speculative at this time. Any advantage is likely to be small, and the costs of widespread testing for this purpose would have to be justified in terms of mortality cost savings.

An hsCRP value at the highest end of the distribution for the ''healthy'' population might be used as a ''negative'' risk factor in this context, that is, not consistent with a risk that is better than standard. Use of hsCRP in this context would require evidence that an applicant has no current infectious or inflammatory condition. Use as a ''negative'' factor would also require development of an administrative process to deal with challenges based on these results. Subacute and relatively minor infections (eg, upper respiratory tract infections) can result in elevation in hsCRP. This fact could be used as grounds for generating retesting requests.

The availability of hsCRP assays performed on a large-scale commercial basis, combined with the potential for examining matched risk profile and outcomes data on a large study population, would provide the basis for a prospective study that could efficiently address many of these questions. This is a challenge that the insurance and laboratory industries should be well equipped to address.

REFERENCES

1. Haverkate F, Thompson SG, Pyke SDM, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. *Lancet.* 1997;349:462–466.
2. Morrow DA, Ridker PM. C-reactive protein, inflammation, and coronary risk. *Med Clin North Am.* 2000;84:149–161.
3. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation.* 2000;101:1767–1772.
4. Ferreiros ER, Boissonnet CP, Pizarro R, et al. Independent prognostic value of elevated C-reactive protein in unstable angina. *Circulation.* 1999;100: 1958–1963.
5. Heeschen C, Hamm CW, Bruemmer J, Simoons ML. Predictive value of C-reactive protein and troponin T in patients with unstable angina: a comparative analysis. *J Am Coll Cardiol.* 2000;35:1535–1542.
6. Ford ES, Giles WH. Serum C-reactive protein and fibrinogen concentrations and self-reported angina pectoris and myocardial infarction, findings from National Health and Nutritional Examination Survey III. *J Clin Epidemiol.* 2000;53:95–102.
7. Yokoya K, Takatsu H, Suzuki T, et al. Process of progression of coronary artery lesions from mild or moderate stenosis to moderate or severe stenosis. *Circulation.* 1999;100:903–909.
8. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med.* 1997;336:973–979.

9. Koenig W, Sund S, Frohlich M, et al. C-reactive protein, a sensitive marker of inflammation predicts future risk of coronary heart disease in initially healthy middle-aged men, results from the MONICA (Monitoring Trends and Determinants In Cardiovascular Disease) Augsburg cohort study, 1984 to 1992. *Circulation.* 1999;99:237–242.
10. Gram J, Bladbjerg EM, Moller I, Sjol A, Jespersen J. Tissue-type plasminogen activator and C-reactive protein in acute coronary disease. A nested case-control study. *J Int Med.* 2000:247:205–212.
11. Ridker PM, Glynn RJ, Hennekens CH. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of first myocardial infarction. *Circulation.* 1998;97:2007–2011.
12. Rohde LEP, Henekens CH, Ridker PM. Survey of C-reactive protein and cardiovascular risk factors in apparently healthy men. *Am J Cardiol.* 1999;84: 1018–1022.
13. Jagar A, van Hinsbergh VWM, Kostens PJ, et al. von Willebrand factor, C-reactive protein, and 5-year mortality in diabetic and nondiabetic subjects, the Hoorn study. *Arterioscl Thromb Vasc Biol.* 1999;19:3071–3078.
14. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med.* 2000;342:836–843.
15. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently health women. *Circulation.* 1998;98: 731–733.
16. Ridker PM Manson JE, Burin JE, Shih J, Matias M, Hennekens CH. Homocysteine and the risk of cardiovascular disease among postmenopausal women. *JAMA.* 1999;281:1817–1821.
17. Strandberg TE, Tilvis RS. C-reactive protein, cardiovascular risk factors, and mortality in a prospective study in the elderly. *Arterioscl Thromb Vasc Biol.* 2000;1057–1060.
18. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. *Circulation.* 1998;98:839–844.
19. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. *Circulation.* 1999;100:230–235.
20. Ridker PM, Hennekens CH, Rifai N, Buring JE, Manson JE. Hormone replacement therapy and increased plasma concentration of C-reactive protein. *Circulation.* 1999;100:713–716.
21. Wu T, Trevisan M, Genco RJ, Falkner KL, Dorn JP, Sempos CT. Examination of the relationship between periodontal health status and cardiovascular risk factors: serum total and high density lipoprotein cholesterol, C-reactive protein, and plasma fibrinogen. *Am J Epidemiol.* 2000;151:273–282.
22. Anderson JA, Carlquist JF, Muhlestein JB, Horne BD, Elmer SP. Evaluation of C-reactive protein, an inflammatory marker, and infectious serology as risk factors for coronary artery disease and myocardial infarction. *J Am Coll Cardiol.* 1998;32:35–41.
23. Wilkins J, Gallimore JR, Moore EG, Pepys MB. Rapid automated high sensitivity enzyme immunoassay of C-reactive protein. *Clin Chem.* 1998;44: 1358–1361.
24. Macy EM, Hayes TE, Tracy RT. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiologic applications. *Clin Chem.* 1997;43:52–58.
25. Clark GH, Fraser CG. Biologic variation of acute phase proteins. *Ann Clin Biochem.* 1992;30:373–376.
26. Tracey RP. Inflammation in cardiovascular diseases, cart, horse, or both? (editorial). *Circulation.* 1998;97:2000–2002.
27. Shah P. Circulation markers of inflammation for vascular risk prediction, are they ready for prime time (editorial). *Circulation.* 2000;105:1758–1759.