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High-Sensitivity C-Reactive Protein as a Risk Assessment Tool for Cardiovascular Disease

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Summary: Almost half of first cardiovascular events occur in individuals with no known risk factors. Attempts in the last decade to predict cardiovascular risk more accurately have led to the emergence of a novel risk factor, C-reactive protein (CRP), which has proved to be as good a risk predictor as low-density lipoprotein cholesterol. C-reactive protein is an index of inflammation that is now believed to promote directly all stages of atherosclerosis, including plaque rupture. As measured by high-sensitivity assays, high-sensitivity CRP (hs-CRP) also independently predicts recurrent events in patients with known coronary artery diseases. Recent evidence implicates hs-CRP, and thus inflammation, in the metabolic syndrome and diabetes mellitus, particularly in women. As a clinical tool for cardiovascular risk assessment, hs-CRP testing enhances information provided by lipid screening or global risk assessment. Statin therapy and other interventions can lower hs-CRP. Whether or not such reductions can prevent cardiovascular events is under investigation.

Key words: cardiovascular risk assessment, C-reactive protein, inflammation, metabolic syndrome, statins

Introduction

Traditional cardiovascular risk factors fall short in identifying individuals at high risk for cardiovascular disease (CVD). In a study of 27,939 healthy American women, 77% of first cardiovascular events occurred in those with only moderately elevated low-density lipoprotein (LDL) cholesterol (< 160 mg/dl) and 46% occurred among those with "normal" levels of LDL cholesterol (< 130 mg/dl).[1] Moreover, as many as 50% of first cardiovascular events occur in individuals with neither elevated cholesterol nor any other traditional risk factor.[2, 3]

The attempt to identify other possible causes for CVD has spurred a continuing search for novel risk factors. The most extensively studied is a plasma marker of inflammation known as C-reactive protein (CRP), the centerpiece of a well-grounded theory that sees atherosclerosis as a disease of chronic inflammation as well as lipid accumulation.[4, 5] In prospective epidemiologic studies of apparently healthy populations, CRP has predicted future vascular events independent of traditional risk factors and is as good a risk factor as LDL cholesterol.[1, 6, 7] C-reactive protein has predicted new and recurrent events in patients with established atherosclerosis and is linked increasingly to the metabolic syndrome and diabetes mellitus.[8–10] It now appears that CRP plays a direct role in atherogenesis,[11, 12] and approaches to the medical management of CRP are being studied, even as its optimal role in risk assessment is taking shape.

C-Reactive Protein and Cardiovascular Risk Prediction

C-reactive protein is one of several acute-phase reactants, a major category of circulating biomarkers of inflammation. It is synthesized mainly in the liver in response to interleukin-6, interleukin-1β, and other inflammatory cytokines. It has a long plasma half-life, no diurnal variation or dependence on age or gender, and good stability over time. C-reactive protein is present in trace levels in healthy individuals and at extremely high levels in the presence of infections, autoimmune diseases, and cancer.[12, 13] Levels of CRP that may be predictive of cardiovascular risk can be as low as 1 mg/l and are measured by widely available high-sensitivity assays.[12, 14]

High-sensitivity CRP (hs-CRP) has shown strong predictive ability in patients with known CVD. In one of the earliest studies, patients with unstable angina and levels of CRP and serum amyloid A ≥ 3 mg/l averaged 4.8 ischemic episodes

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during hospitalization, significantly more than those with acute-phase reactants < 3 mg/l, who averaged only 1.8 episodes (p = 0.004).[8] Baseline hs-CRP predicted overall 5-year mortality in the Scandinavian Simvastatin Survival Study, which enrolled subjects with a history of angina pectoris or acute myocardial infarction (MI). Even after adjustment for other risk factors, participants in the highest quartile of hs-CRP were 2½ times more likely to die than those in the lower three quartiles (p = 0.005).[15] Recently reported post-hoc analyses from the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) and Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trials suggest improved clinical outcomes in patients with lower versus higher hs-CRP levels after statin therapy, regardless of LDL cholesterol levels.[16, 17] In PROVE IT, patients with acute coronary syndromes who had hs-CRP < 2 mg/dl after statin therapy had lower rates of recurrent cardiac events than did patients with higher levels (2.8 vs. 3.9 events per person years, p = 0.006), no matter the value of LDL cholesterol (Fig. 1).[17] In REVERSAL, post-treatment low hs-CRP levels were independently associated with slower rates of atherosclerosis progression assessed by intravascular ultrasound.[16] The most favorable outcomes in both trials were associated with the greatest reductions in both LDL cholesterol and hs-CRP.

The most effective use of CRP may be in the setting of primary risk prediction. In a cohort of initially healthy men in the Physicians' Health Study who were followed for more than 8 years, men with baseline CRP in the highest quartile had three times the risk of future MI (relative risk [RR] 2.9, 95% confidence interval [CI] 1.8–4.6, p < 0.001) and twice the risk of future ischemic stroke (RR 1.9, 95% CI 1.1–3.3, p = 0.02) than men in the lowest quartile.[7] These risk levels held over time and after adjustment for both lipid- and nonlipid-related risk factors. High-sensitivity CRP also significantly predicted sudden cardiac death over 17 years in this study population, whereas LDL cholesterol and other lipids did not.[6]

Among postmenopausal women in the Women's Health Study, the adjusted RR of a cardiovascular event for women in the highest versus lowest hs-CRP quartiles was 1.5 over 3 years (95% CI 1.1–2.1, p = 0.02).[3] Elevated hs-CRP was the strongest risk predictor among a dozen risk factors and inflammatory markers considered in this study (Fig. 2); most notably, it retained its predictive strength even in women with LDL cholesterol < 130 mg/dl. In a 20-year follow-up of the Honolulu Heart Study, elevated CRP independently predicted future ischemic stroke in middle-aged Japanese-American men, particularly in nonsmokers and in those ≤ 55 years.[18] Similarly, hs-CRP independently predicted a first stroke or transient ischemic attack in elderly men and women (mean age 70 years) in the original Framingham Study cohort.[19]

C-Reactive Protein versus Low-Density Lipoprotein Cholesterol

Although hs-CRP predicts vascular events independent of LDL cholesterol, these two risk factors enhance each other as prognosticators. For example, in survival analyses of 27,939 subjects in the Women's Health Study, who were assessed for the occurrence of MI, ischemic stroke, coronary revascularization, or cardiovascular death over a mean of 8 years, hs-CRP surpassed LDL cholesterol in predicting the risk of all study endpoints, even after adjustments for age, smoking status, diabetes, blood pressure, and use of hormone replacement therapy (which is associated with increased CRP).[1] The analyses also showed that hs-CRP and LDL cholesterol correlated minimally (r = 0.08); each had a strong linear relationship with cardiovascular risk. However, the two factors together were superior to either factor alone in predicting risk. Survival was worst for women with high levels of both markers and best for

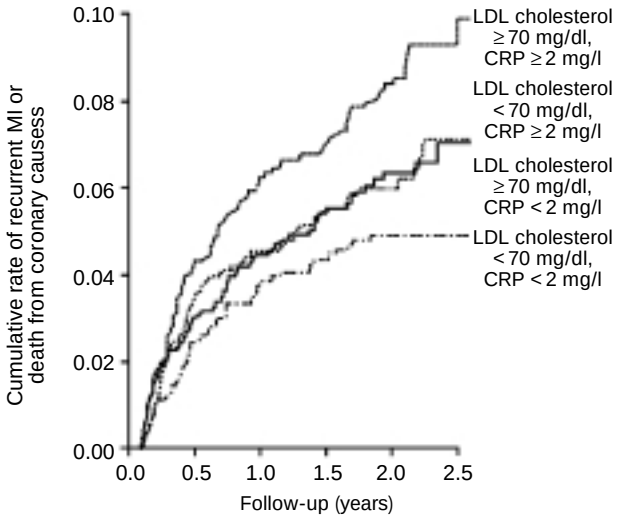

FIG. 1 Cumulative incidence of recurrent myocardial infarction (MI) or death from coronary causes, according to achieved levels of both C-reactive protein (CRP) and low-density lipoprotein (LDL) cholesterol in the PROVE IT study. Reprinted from Ref. No. 17 with permission.

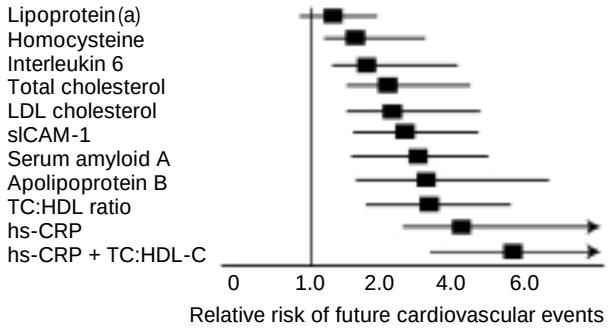

FIG. 2 Comparison of C-reactive protein to lipid and nonlipid risk factors for prediction of future cardiovascular events. HDL= high-density lipoprotein, HDL-C = high-density lipoprotein cholesterol, hs-CRP = high-sensitivity C-reactive protein, LDL = low-density lipoprotein, sICAM-1 = soluble intercellular adhesion molecule-1, TC = total cholesterol. Reprinted from Ref. No. 26 with permission.

women with low levels; of note, women with high hs-CRP and low LDL cholesterol were at greater risk than women with low hs-CRP and high LDL cholesterol. In the absence of hs-CRP measurement, risk in this intermediate category would have been greatly underestimated. It can be hypothesized that CRP and LDL cholesterol represent separate but equally critical aspects of the atherosclerotic process, and that both markers must be assessed to obtain a complete profile of vascular risk.

High-Sensitivity C-Reactive Protein in Clinical Practice

In 2003, the American Heart Association and Centers for Disease Control and Prevention (AHA/CDC) published guidelines on the use of CRP in the clinical setting. The authors endorsed the optional use of hs-CRP screening to guide further evaluation or therapy decisions in patients deemed at intermediate CVD risk by traditional risk factors (e.g., a 10 to 20% risk of a first event over 10 years based on the Framingham Risk Score). The guidelines maintained that hs-CRP findings would be unlikely to influence management decisions in patients with prior CVD or in patients at low primary risk (e.g., < 10% risk over 10 years) or high primary risk (> 20% risk over 10 years).[14]

The guidelines further advised that hs-CRP readings be performed twice (ideally 2 weeks apart) and averaged. Based on epidemiologic data, the guidelines recommended the following cut points for risk determination: low risk = < 1.0 mg/l, intermediate risk = 1.0–3.0 mg/l, and high risk = > 3.0 mg/l (Fig. 3), with the high-risk category representing an approximate twofold greater relative risk than the low-risk category. The guidelines also noted that tests showing an hs-CRP level > 10 mg/l should be repeated because they may reflect current infection or inflammation.[14] However, further analysis of data from the Women's Health Study cohort support the usefulness of hs-CRP across a full range of values and Framingham Risk Scores. Specifically, the analysis found that both very low (< 0.5 mg/l) and very high (> 10 mg/l) levels of hs-CRP added significant prognostic information; even levels ≥ 20 mg/l enhanced predictive ability, suggesting the absence of a threshold effect.[20]

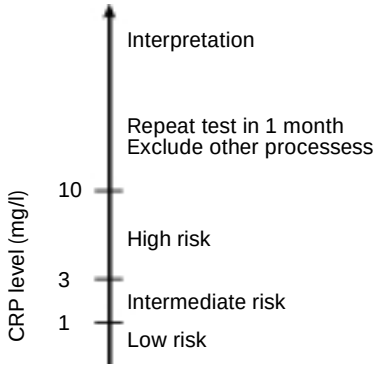

FIG. 3 Cut points for cardiovascular risk based on C-reactive protein (CRP) levels. Reprinted from Ref. No. 11 with permission.

The most efficient approach in clinical practice is to obtain hs-CRP readings at the same time as lipid determinations in apparently healthy patients. A key objective should be to identify persons whose LDL-cholesterol level is < 160 mg/dl but whose hs-CRP level is > 1 mg/l. In these individuals, dietary modification and/or aggressive lipid lowering with a 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin)—both of which can reduce CRP levels—should be initiated, with the goal of reducing LDL cholesterol to < 100 mg/dl. An elevated hs-CRP might also be used to motivate patients to adhere to or intensify an existing management plan or to begin a daily antiplatelet (e.g., aspirin) regimen. There are valid uses of hs-CRP readings in patients with existing CVD as well. For example, hs-CRP might be used in conjunction with cardiac troponin levels to identify those at high risk of recurrent events and in need of more aggressive monitoring or intervention, especially in advance of percutaneous coronary revascularization.[13]

New Developments in C-Reactive Protein and Risk Prediction

An intriguing and expanding area of research seeks to understand why CRP predicts future cardiovascular events so well: is CRP merely an index of inflammation, or does it directly drive inflammation and atherosclerotic progression? Recent laboratory observations suggest that CRP is potentially proatherogenic. For example, at concentrations associated with cardiovascular risk, CRP has induced human umbilical vein endothelial cells to express intercellular adhesion molecule (ICAM) -1, vascular cell adhesion molecule (VCAM) -1, and E-selectin, factors that attract monocytes to the vascular wall.[21] In the same model, CRP promoted the secretion of monocyte chemoattractant protein (MCP) -1, which affects transmigration of monocytes through the endothelium.[22] C-reactive protein also mediated the uptake of LDL by human macrophages[23] and decreased the synthesis of nitric oxide in human aortic endothelial cells.[11] Finally, tests with interleukin-6 and interleukin-1β, which induce hepatic expression of CRP, showed that these cytokines also produce CRP in human coronary artery smooth muscle cells.[24] Such local production could enhance the demonstrated effects of CRP and allow more direct inflammatory participation in atherogenesis.

Another active area of research is that linking inflammation with the metabolic syndrome and type 2 diabetes, both of which greatly increase cardiovascular risk. C-reactive protein has been associated with numerous components of the metabolic syndrome, including high triglycerides, obesity, high blood pressure, high fasting glucose, insulin resistance, endothelial dysfunction, and impaired fibrinolysis.[25] The mechanisms of these associations are not clear, but in the case of obesity, a recent study showed that adipocytes themselves secrete CRP in response to inflammatory stimuli.[26] An analysis of the Women's Health Study population found that hs-CRP,

besides correlating with components of the metabolic syndrome, added independent prognostic information on cardiovascular risk at all levels of severity of the syndrome.[9] In this same population, elevated hs-CRP predicted the development of type 2 diabetes.[10] Middle-aged men in the West of Scotland Coronary Prevention Study likewise experienced an increased risk of diabetes in association with hs-CRP.[27] However, the Mexico City Diabetes Study of middle-aged men and women found that elevated hs-CRP independently predicted the metabolic syndrome and diabetes only in women,[28] while an analysis of the Framingham Offspring Study found that age-adjusted hs-CRP levels were strongly related to components of the metabolic syndrome, but much more so in women (including those not taking hormone therapy) than in men.[29] The argument has been made that hs-CRP should be added to the current clinical criteria for diagnosis of the metabolic syndrome,[25] but that this might require adjustments along gender lines if the above findings are corroborated.

Toward Medical Management of C-Reactive Protein

At present, there is no definitive evidence that modalities aimed at lowering CRP prevent vascular events.[30] However, results of recent studies suggest an association between improved clinical outcomes and lower CRP levels after statin treatment.[16, 17] Pharmacologic and lifestyle interventions are capable of reducing both vascular risk and CRP. Statins, which appear to have direct anti-inflammatory effects, have demonstrated reductions in CRP of 25 to 50%.[13] Statins have also achieved the most sizeable risk reductions in patients with the highest levels of inflammation. In the Cholesterol and Recurrent Events trial of secondary prevention, pravastatin-treated patients with high hs-CRP at baseline experienced more than twice the reduction in RR of recurrent coronary events than patients with low hs-CRP—54 versus 25%, respectively—although the two groups had almost identical baseline lipid profiles.[31] In the Air Force/Texas Coronary Atherosclerosis Prevention Study of primary prevention, lovastatin therapy was highly effective in reducing cardiovascular events in patients with above-median hs-CRP, even in the presence of below-median LDL cholesterol.[32] In both trials, reductions in hs-CRP were independent of reductions in LDL cholesterol.

While it is tempting to base clinical decisions on such trial findings, they are derived from post-hoc analyses and involve rather small numbers of events. The Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study[33] was begun in 2003 to address these shortcomings. This randomized, placebo-controlled trial will evaluate whether long-term intensive statin therapy (rosuvastatin 20 mg/day for 3 to 4 years) can prevent first major cardiovascular events in an apparently healthy population with low LDL cholesterol (< 130 mg/dl) but at increased risk because of elevated hs-CRP (≥ 2 mg/l). The JUPITER study will follow up to 15,000 men aged ≥ 55 years and women aged ≥ 65 years, and also examine the ability of rosuvastatin therapy to decrease the incidence of type 2 diabetes. If positive, the findings are likely to extend and strengthen CRP's role as both a risk factor and treatment target and provide further justification for the use of intensive statin therapy in the primary prevention of CVD.

Conclusion

C-reactive protein has an impressive record as an independent predictor of CVD and promises to enhance our current ability to identify individuals at high risk for cardiovascular events. Little doubt remains that CRP is an active rather than passive participant in the inflammatory component of atherosclerosis, and it may well be a crucial link between atherosclerosis, the metabolic syndrome, and type 2 diabetes. Findings from current research will help determine whether intensive statin treatment can prevent cardiovascular events in a population not normally considered at high risk: patients with normal LDL cholesterol but high hs-CRP. If it can, the roles for hs-CRP in risk assessment and patient management and for statins in primary prevention will be greatly enhanced.

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