



## Clinical Application of C-Reactive Protein for Cardiovascular Disease Detection and Prevention

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In an attempt to improve global cardiovascular risk prediction, considerable interest has focused on C-reactive protein (CRP), a marker of inflammation that has been shown in multiple prospective epidemiological studies to predict incident myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death. CRP levels have also been shown to predict risk of both recurrent ischemia and death among those with stable and unstable angina, those undergoing percutaneous angioplasty, and those presenting to emergency rooms with acute coronary syndromes. These highly consistent clinical data are supported by abundant laboratory and experimental evidence that demonstrate that atherothrombosis, in addition to being a disease of lipid accumulation, also represents a chronic inflammatory process. In terms of clinical application, CRP seems to be a stronger predictor of cardiovascular events than LDL cholesterol, and it adds prognostic information at all levels of calculated Framingham Risk and at all levels of the metabolic syndrome. Using widely available high-sensitivity assays, CRP levels of <1, 1 to 3, and >3 mg/L correspond to low-, moderate-, and high-risk groups for future cardiovascular events. Individuals with LDL cholesterol below 130 mg/dL who have CRP levels >3 mg/L represent a high-risk group often missed in clinical practice. The addition of CRP to standard cholesterol evaluation may thus provide a simple and inexpensive method to improve global risk prediction and compliance with preventive approaches.

### Evidence Supporting CRP Use in Primary Prevention

Composed of five 23 kDa subunits, C-reactive protein (CRP) is an hepatically derived pentraxin that plays a key role in the innate immune response. CRP has a long plasma half-life and is now understood to be a mediator as well as a marker of atherothrombotic disease. To date, over a dozen prospective epidemiological studies carried out among individuals with no prior history of cardiovascular disease demonstrate that a single, non-fasting measure of CRP is a strong predictor of future vascular events<sup>1-14</sup> (Figure 1). The relationship between a patient's baseline level of CRP and future vascular risk has been consistent in studies from the United States and Europe, and in most cases has proven independent of age, smoking, cholesterol levels, blood pressure, and diabetes, the major "traditional" risk factors evaluated in daily practice. These effects are present among women as well as men, among the elderly as well as those in middle age, among smokers and non-smokers, and among those with and without diabetes. CRP levels have long-term predictive value. In one recent study, CRP was a strong predictor of risk even 20 years after initial blood samples were obtained.<sup>15</sup>

Very recently, event-free survival data have become available that allow clinicians to interpret CRP levels either in terms of population-based quintiles (Figure 2, left) or in terms of simple clinical cut-points (Figure 2, right).<sup>6</sup> Although the

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Dr Ridker is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory bio-markers in cardiovascular disease.

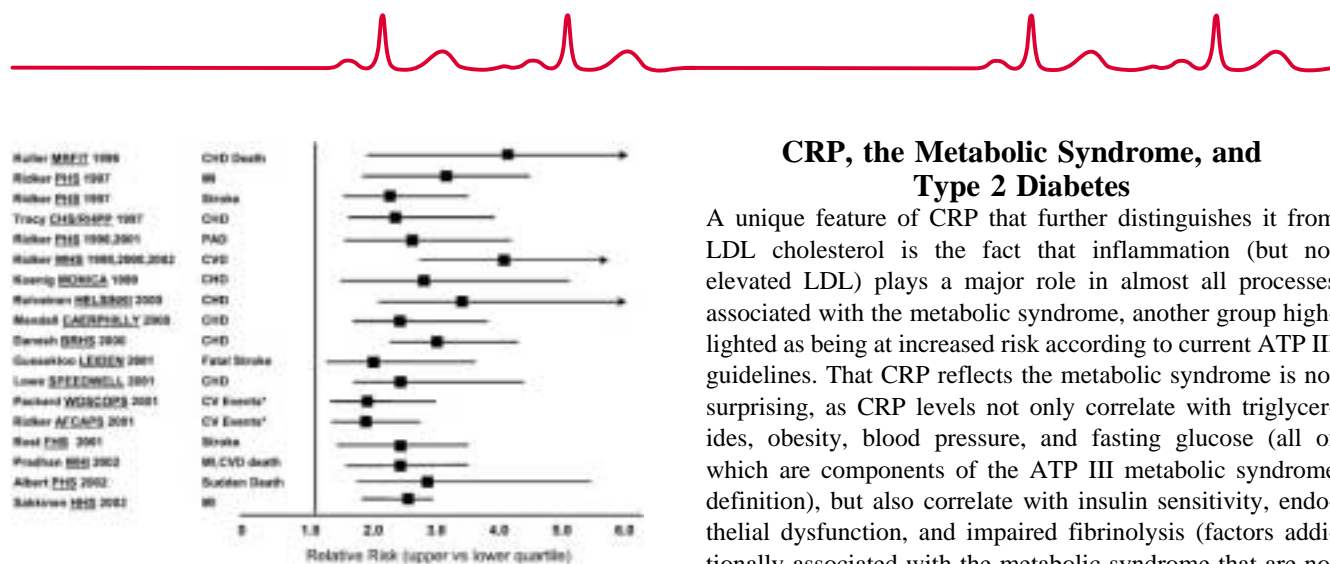
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**Figure 1.** Prospective studies relating baseline CRP levels to the risk of first cardiovascular events. CHD indicates coronary heart disease; MI, myocardial infarction; PAD, pulmonary artery disease; CV, cardiovascular; MRFIT, Multiple Risk Factor Intervention Trial; PHS, Physicians' Health Study; CHS, Cardiovascular Health Study; RHPP, Rural Health Promotion Project; WHS, Women's Health Study; MONICA, MONitoring trends and determinants In Cardiovascular disease; HELSINKI, Helsinki Heart Study; CAERPHILLY, Caerphilly Heart Study; BRHS, British Regional Heart Study; LEIDEN, Leiden Heart Study; SPEEDWELL, Speedwell Heart Study; WOSCOPS, West of Scotland Coronary Prevention Study; AFCAPS, Air Force Coronary Atherosclerosis Prevention Study; FHS, Framingham Heart Study; WHI, Women's Health Initiative; and HHS, Honolulu Heart Study.

former approach demonstrates the robust linear relationship between inflammation and vascular disease, the latter approach (in which levels of <1, 1 to 3, and >3 mg/L represent low-, moderate-, and high-risk groups) is likely to have greater clinical appeal.

Prospective data also demonstrate that CRP is a stronger predictor of risk than is low-density lipoprotein (LDL) cholesterol. In the largest study to date, both the area under the receiver operator characteristic (ROC) curve (0.64 versus 0.60) and the population attributable risk percent (40 versus 19) were significantly greater for CRP than for LDL cholesterol.<sup>6</sup>

CRP levels minimally correlate with lipid levels and there is virtually no way to predict CRP levels on the basis of either total cholesterol, high-density lipoprotein cholesterol, or LDL cholesterol. In evaluations including over 25 000 patients, the variance in CRP that can be ascribed to LDL cholesterol has consistently been less than 3% to 5%.<sup>4,6,16</sup> Thus, CRP levels do not supplant lipid evaluation, but must be considered as an adjunct to lipid evaluation. The additive value of CRP to lipid screening in terms of coronary risk prediction has been demonstrated in several settings.<sup>1,3,4,6,17</sup> A simplified clinical approach to this issue based on the Adult Treatment Panel III (ATP III) cut-points for LDL of <130, 130 to 160, and >160 mg/dL and on CRP levels of <1, 1 to 3, and >3 mg/L is shown in Figure 3, as is evidence that CRP adds prognostic information at all levels of the Framingham Risk Score.

## CRP, the Metabolic Syndrome, and Type 2 Diabetes

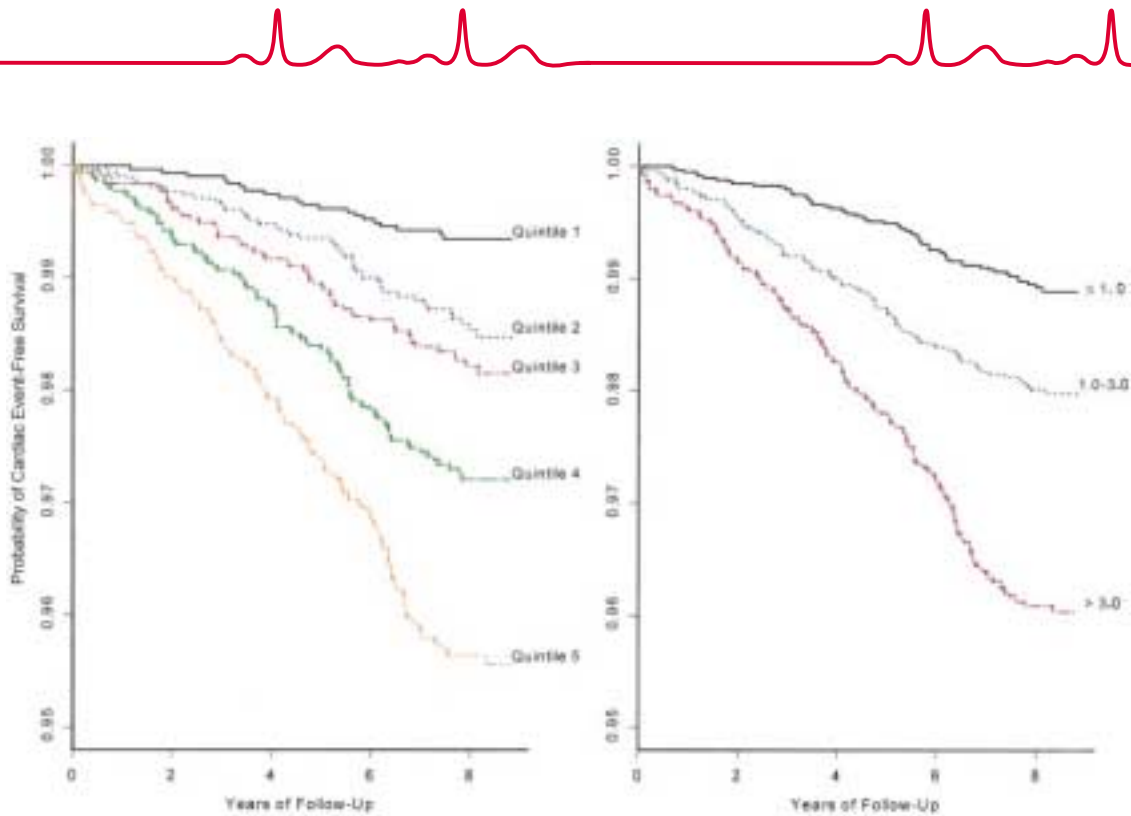
A unique feature of CRP that further distinguishes it from LDL cholesterol is the fact that inflammation (but not elevated LDL) plays a major role in almost all processes associated with the metabolic syndrome, another group highlighted as being at increased risk according to current ATP III guidelines. That CRP reflects the metabolic syndrome is not surprising, as CRP levels not only correlate with triglycerides, obesity, blood pressure, and fasting glucose (all of which are components of the ATP III metabolic syndrome definition), but also correlate with insulin sensitivity, endothelial dysfunction, and impaired fibrinolysis (factors additionally associated with the metabolic syndrome that are not easily discerned in usual clinical practice).<sup>18</sup> Although cardiac event-free survival is similar for those with CRP levels above or below 3.0 mg/L and for those with and without the metabolic syndrome, it is also clear that CRP adds independent prognostic information on risk at all levels of severity of the metabolic syndrome.<sup>18</sup> Thus, the metabolic syndrome is a heterogeneous condition; as shown in Figure 4, CRP levels of <1, 1 to 3, and >3 mg/L differentiate low, moderate, and high risk even when applied to those already defined as having the metabolic syndrome.<sup>18</sup>

Several prospective studies demonstrate that CRP levels additionally predict incident type II diabetes.<sup>19,20</sup> These data further link inflammation, atherothrombosis, and diabetes as tightly interrelated disorders of the innate immune system and may help to explain why diet and exercise are so important to the prevention of both diseases.

## The Population Distribution of CRP

When measured with high-sensitivity assays, the population distribution of CRP has generally been consistent across sex and ethnic groups, and values of 0.3, 0.6, 1.5, 3.5, and 6.6 mg/L have been reported as estimates of the 10th, 25th, 50th, 75th, and 90th percentile cut-points for middle-aged Americans.<sup>6</sup> In 4 major cohort studies performed in the United States, the Physicians Health Study, the Women's Health Study, the Women's Health Initiative, and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),<sup>2,3,4,6,10</sup> the quintile distributions of CRP for men and for women not taking hormone replacement therapy (HRT) are remarkably similar, and in practice approximate quintile cut-points of <0.5, 0.5 to 1.0, 1.0 to 2.0, 2.0 to 4.0, and >4.0 mg/L have been suggested for use. An alternative approach, as suggested above, is simply one that emphasizes levels <1, 1 to 3, and >3.0 mg/L as low-, moderate-, and high-risk groups.

Because women taking HRT will have higher levels of CRP,<sup>21,22</sup> risk estimates for such women may need to be calibrated downward. As recently demonstrated in analyses of CRP and HRT in the Women's Health Initiative,<sup>10</sup> however, these effects in terms of actual event prediction are not as large as anticipated. Further, these data suggest that it is the



**Figure 2.** Cardiovascular event-free survival among apparently healthy individuals according to baseline CRP levels. Data are shown using population-based quintiles for CRP (left) and using 3 simple clinical cut-points for CRP, <1, 1 to 3, and >3 mg/L (right). Adapted from reference 6.

expressed level of CRP that determines a given woman’s vascular risk. Finally, in the Women’s Health Study,<sup>3,6</sup> there was no substantive difference in risk estimates for women taking HRT when cut-points were determined among users of HRT rather than non-users. Taken together, these large outcome analyses suggest little value in having separate clinical cut-points for CRP either by sex or by HRT use.

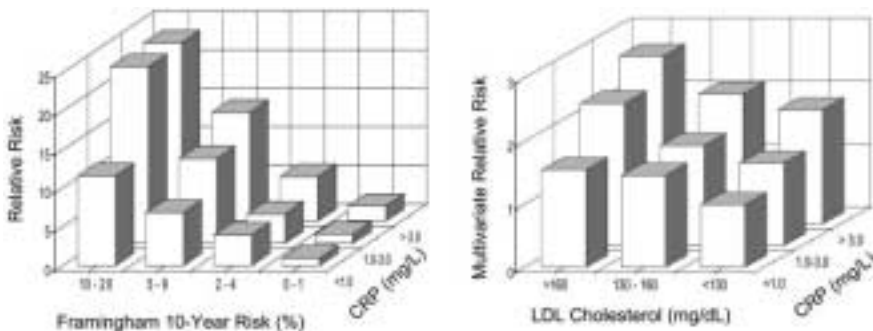
The sparse population data available for blacks is consistent with these findings. However, the total number of individuals evaluated in this group remains small.

**Interpreting CRP Assays, Cost-Effectiveness, and Serial Assessment**

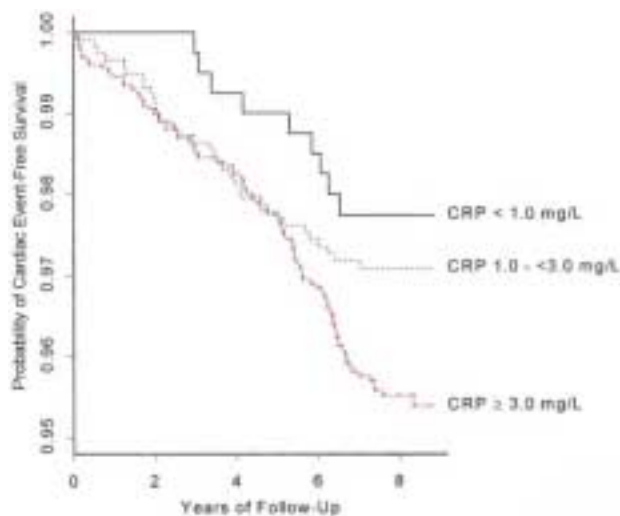
In most clinical settings, a single CRP assessment is likely to be adequate as long as levels less than 10 mg/L are observed. Because major infections, trauma, or acute hospitalizations can elevate CRP levels (usually 100-fold or more), levels

greater than 10 mg/L should initially be ignored and the test repeated at a future date when the patient is clinically stable. Many investigators have recommended 2 measures of CRP, with the lower value or the average being used to determine vascular risk, a practice consistent with recommendations for cholesterol evaluation. In rare instances where levels of CRP are markedly elevated, alternative sources of systemic inflammation such as lupus, inflammatory bowel disease, or endocarditis should be considered. In such cases, there is usually an accompanying elevation in the erythrocyte sedimentation rate. Accumulated experience in outpatient settings has shown such values to be infrequent.

Because CRP levels are stable over long periods of time, are not affected by food intake, and demonstrate almost no circadian variation, there is no need to obtain fasting blood samples for CRP assessment. Despite being an acute phase reactant, the variability in CRP levels in given individuals is



**Figure 3.** CRP provides prognostic information at all levels of LDL cholesterol and at all levels of the Framingham Risk Score. Data adapted from reference 6.



**Figure 4.** Cardiovascular event-free survival according to baseline CRP levels among individuals already defined as having the metabolic syndrome. Adapted from reference 18.

quite similar to that associated with cholesterol screening, as long as the CRP levels are within the clinical range defined above.<sup>23</sup>

Traditional assays for CRP do not have adequate sensitivity to detect levels required for vascular disease prediction. To alleviate this problem, high-sensitivity CRP assays have been developed and are now widely available.<sup>24</sup> The cost of CRP screening is comparable to that of standard cholesterol evaluation and far less than almost all other alternative approaches to cardiovascular screening under consideration. Both in terms of years of life saved and cost-to-benefit ratios, CRP screening seems to be highly effective.<sup>25</sup> In many settings, the inexpensive approach of adding CRP to LDL screening may yield immediate cost-savings in terms of negative predictive value and the subsequent avoidance of unnecessary clinical testing, particularly when compared with far more expensive screening approaches such as electron beam calcium tomography or MRI.

CRP levels within the range detected with high-sensitivity assays have demonstrated specificity for vascular events.<sup>26</sup> Although it has not been determined whether serial CRP assessment provides incremental clinical value, some physicians have elected to use CRP as part of their annual physical examination.

### Comparison of CRP to Other Novel Risk Factors

CRP is not the only inflammatory biomarker that has been shown to predict myocardial infarction and stroke. More sophisticated measures of cytokine activity, cellular adhesion, and immunologic function (such as interleukin-6, intercellular adhesion molecule-1, macrophage inhibitory cytokine-1, and soluble CD40 ligand) have all been shown to be elevated among those at increased vascular risk.<sup>27</sup> These approaches, however, are unlikely to have clinical utility because the assays required for

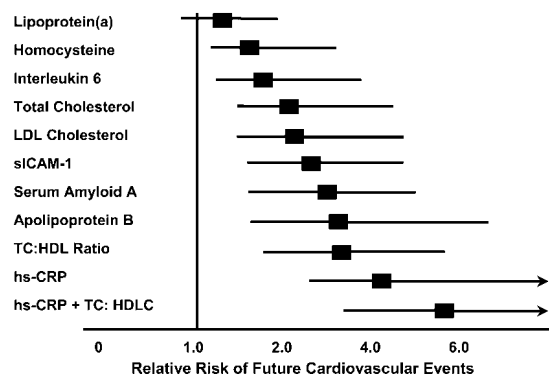
their assessment are either inappropriate for routine clinical use or the protein of interest has too short a half-life for clinical evaluation. Measures for fibrinogen, a biomarker involved in both inflammation and thrombosis, remain poorly standardized, and methodological issues limit use of this parameter despite consistent population-based data. Other broad measures of systemic inflammation, such as the white blood cell count or the erythrocyte sedimentation rate, have proven unreliable in clinical settings. By contrast, high-sensitivity assays for CRP have been standardized across many commercial platforms. Moreover, CRP is highly stable, allowing measures to be made accurately in both fresh and frozen plasma without requirements for special collection procedures. This is due in part to the stable pentraxin structure of CRP and its long plasma half-life of 18 to 20 hours.

In selected patients, such as those with markedly premature and unexplained atherosclerosis, evaluation of other markers, such as lipoprotein(a) and homocysteine, may have clinical utility. In available population-based studies, however, the relative magnitude of these biomarkers has been small in direct comparison to CRP (Figure 5). Recent data also indicate that CRP is a stronger predictor of risk than nuclear magnetic resonance-based evaluation of LDL particle size and concentration.<sup>28</sup>

### Goals of Screening and Therapeutic Options

The primary goal of cardiovascular screening programs should be the identification of high-risk individuals who can be targeted for smoking cessation, diet, exercise, and blood pressure control. It is well established that compliance with lifestyle recommendations is directly related to the absolute risk perceived by individual patients. Thus, because the addition of CRP to lipid evaluation provides an improved prediction tool, consideration of CRP may have usefulness for this reason alone.

There is currently no definitive evidence that lowering CRP will necessarily reduce cardiovascular event rates; studies addressing this issue are only now being designed. However, many interventions known to reduce cardiovascular risk have been



**Figure 5.** Direct comparison of CRP to several other lipid and non-lipid risk factors for cardiovascular disease. sICAM-1 indicates soluble intercellular adhesion molecule-1; hs-CRP, high-sensitivity CRP; HDL, high-density lipoprotein; and HDLC, high-density lipoprotein cholesterol. Adapted from reference 3.

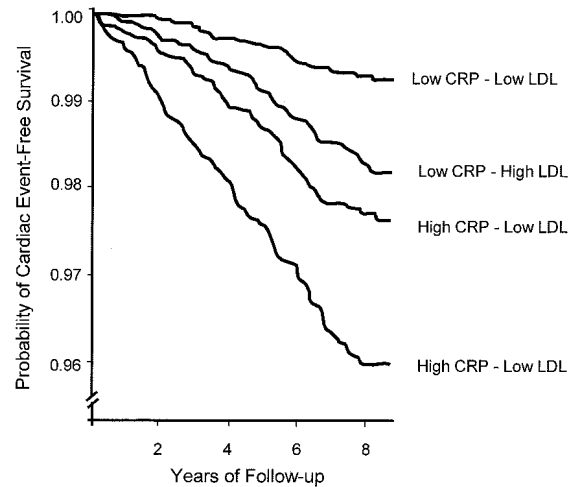
linked to lower CRP levels. In particular, weight loss, diet, exercise, and smoking cessation all lead to both reduced CRP levels and reduced vascular risk.

Several pharmacological agents proven to reduce vascular risk influence CRP levels. Of these, the statin drugs are the most important, and studies with pravastatin, lovastatin, cerivastatin, simvastatin, and atorvastatin have all shown that, on average, median CRP levels decline 15% to 25% as early as 6 weeks after initiation of therapy. As shown in the large-scale Cholesterol And Recurrent Events (CARE)<sup>29</sup> and PRavastatin INflammation/CRP Evaluation (PRINCE)<sup>16</sup> trials and subsequently confirmed in other settings, there is little evidence that the magnitude of LDL reduction predicts the magnitude of CRP reduction. On the other hand, aggressive LDL reduction remains a critical therapeutic goal, and thus serial LDL evaluation should remain the primary method to monitor statin compliance. However, whereas all subjects taking statins achieve a beneficial reduction in LDL levels, there seems to be responders and non-responders for statins in terms of CRP reduction. Whether this latter observation is important in terms of clinical event reduction is currently unknown.

Analyses of 2 randomized trials suggest that the magnitude of risk reduction attributable to statin therapy is particularly large for those with elevated CRP levels. In the CARE trial of secondary prevention, the magnitude of benefit associated with pravastatin use was nearly 55% for those with elevated CRP levels as compared with 30% for those with low CRP levels.<sup>30</sup> Similarly, in the AFCAPS/TexCAPS primary prevention trial, lovastatin use was highly effective among those with elevated CRP levels, even when LDL levels were below thresholds set by the ATP III guidelines.<sup>4</sup> Although performed on a post hoc basis and limited by relatively low event rates, the AFCAPS/TexCAPS analysis suggests that the benefit of statin therapy among those with low LDL but high CRP may be just as large as the benefit observed among those with overt hyperlipidemia.

That patients with elevated CRP but low LDL are at high vascular risk is demonstrated in Figure 6, which shows survival data from the Women's Health Study for those with LDL cholesterol above or below the study median of 124 mg/dL and CRP above or below the study median of 1.52 mg/L.<sup>6</sup> As expected, overall event-free survival was poorest for those with elevated CRP and elevated LDL, whereas the best survival was observed for those with low CRP and low LDL levels. However, event-free survival was actually worse for those with elevated CRP and low LDL when compared with those with elevated LDL and low CRP. Because of the public health implications of these data, a large-scale statin prevention trial of 15 000 patients is scheduled to begin in early 2003 specifically targeting those with native LDL <130 but a CRP above 2.0 mg/L.<sup>31</sup>

Although data are less robust, other lipid-lowering agents reported to reduce CRP include niacin, fibrates, and gemfibrozil. Aspirin also has an intriguing interaction with CRP in



**Figure 6.** Cardiovascular event-free survival according to baseline levels of CRP and LDL. Adapted from reference 6.

that the magnitude of relative risk reduction attributable to aspirin in primary prevention appears to be greatest among those with elevated CRP and declines proportionately in direct relation to CRP levels.<sup>2</sup> Observational data suggest possible differential benefits for clopidogrel and abciximab on the basis of CRP levels before percutaneous coronary interventions.<sup>32–34</sup> Thiazolidinediones also reduce CRP levels.<sup>35</sup>

### Clinical Recommendations

As documented above for primary prevention, CRP is an independent predictor of future cardiovascular events that adds prognostic information to lipid screening, to the metabolic syndrome, and to the Framingham Risk Score.

In outpatient settings, the primary use of CRP should be at the time of cholesterol screening, when knowledge of CRP can be used as an adjunct for global risk assessment.<sup>1</sup> For individuals with LDL levels above 160 mg/dL and for whom the ATP III guidelines already call for therapeutic intervention, an elevated CRP level should aggressively encourage physicians and patients to institute pharmacological therapy in those instances where none is currently being used or where compliance is poor.

For individuals with LDL levels between 130 and 160 mg/dL, the additional finding of an elevated CRP indicates an elevated global risk. In almost all cases, this information should lead to better compliance and adherence with current ATP III treatment guidelines.

For individuals with LDL levels below 130 mg/dL, the finding of an elevated CRP implies substantially higher risk than predicted on the basis of LDL alone. As shown in Figures 3 and 6, such individuals will have risk estimates as high as some individuals with overt hyperlipidemia. Patients with this profile should be advised to adhere carefully with ATP III lifestyle interventions, despite “low” LDL cholesterol levels. Individuals with the low LDL/high CRP phenotype

are at elevated risk of having the metabolic syndrome and should have fasting glucose levels measured. Large-scale, randomized trial evidence is critically needed before such patients should be considered for statin therapy.<sup>31</sup>

An alternative approach in primary prevention is to measure CRP only among those at intermediate risk as defined by the Framingham Risk Score. For example, clinicians might conservatively choose to evaluate CRP only among those with a calculated 10-year Framingham risk between 5% and 20% (see Figure 3). Although this strategy has epidemiological appeal, such an approach requires a second office visit and a second phlebotomy and thus is likely to be less efficient and perhaps less cost-effective.

In secondary prevention, the potential utility of CRP is less certain, as aggressive therapies should already be instituted and LDL evaluation provides an excellent method to assess statin efficacy.


In the setting of acute coronary ischemia and unstable angina, the role of CRP is rapidly evolving. Multiple studies demonstrate that CRP levels predict early and late mortality in acute coronary ischemia and add to the predictive value of cardiac troponin.<sup>36–41</sup> Further, knowledge of inflammatory status has been shown effective in distinguishing patient subgroups more or less likely to benefit from an aggressive versus conservative management approach.<sup>40</sup> However, appropriate clinical cut-points for CRP in the setting of acute ischemia remain uncertain, as does the timing of CRP evaluation in relation to the onset of ischemia. The most foreseeable use of CRP in the emergency room setting is thus likely to be among those with chest pain syndromes who have negative troponin levels. An elevated CRP in this setting is associated with increased short-term as well as long-term risks,<sup>39–41</sup> and thus additional evaluation modalities may be warranted. By contrast, current data suggest that patients with negative troponin and negative CRP levels in the emergency room setting are unlikely to have flow limiting coronary disease.<sup>39,40</sup>

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