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Understanding

C-REACTIVE PROTEIN

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A Simple Test to Help Predict Risk of Heart Attack and Stroke

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Of the 1.5 million heart attacks and 600,000 strokes that occur in the United States each year, almost half will affect apparently healthy men and women with normal or even low cholesterol levels. Older age, smoking, diabetes, and high blood pressure all contribute to risk of heart disease. However, you may well have family members or friends who suffer from heart disease yet have few, if any, of these traditional risk factors.

For many years cholesterol was pinpointed as the leading, singular cause of heart disease, but researchers knew that 50 percent of heart attacks occurred in people with normal cholesterol levels. Pioneering laboratory work by several Brigham and Women's Hospital scientists pointed to the hypothesis that inflammation plays a key role in heart disease and in the late 1990s, the team began research with a two-part goal - to provide evidence that inflammation (an immune-system reaction in the arteries) caused heart attacks and to seek a method for doctors to detect inflammation for clinical use.

In a series of landmark studies, the group achieved the results they needed and revealed that the inflammatory biomarker C-reactive protein (CRP) could be used to detect and measure inflammation in the arteries as well as predict first ever heart attacks and strokes and developed a simple blood test for the detection and measurement of CRP.

In an effort to better determine risk of heart disease and prevent clinical events, many physicians have begun to measure CRP as a routine part of global risk assessment. This inexpensive and simple approach to heart disease evaluation has recently been endorsed by both the Centers for Disease Control and Prevention and by the American Heart Association.

CRP testing, however, is not a replacement for cholesterol evaluation. Rather, CRP testing should be used along with cholesterol and other traditional risk factors to determine individual risk.

WHAT IS CRP?

CRP is a critical component of the immune system, a complex set of proteins that our bodies make when faced

with a major infection or trauma. CRP was discovered nearly 70 years ago by scientists exploring the human inflammatory response. The role CRP plays in heart disease, however, has only recently been uncovered.

Everyone makes CRP, but in different amounts depending on a variety of factors, including genetics as well as lifestyle habits. On average, individuals who smoke, have high blood pressure, are overweight, and fail to exercise tend to have high levels of CRP, whereas thin, athletic individuals tend to have lower levels. Nonetheless, almost half of the variation in CRP levels between different people is inherited and thus reflects levels that your parents and grandparents have passed on to you through their genes. This is not surprising given the fundamental role that CRP plays in inflammation, an extremely important process for wound healing, for

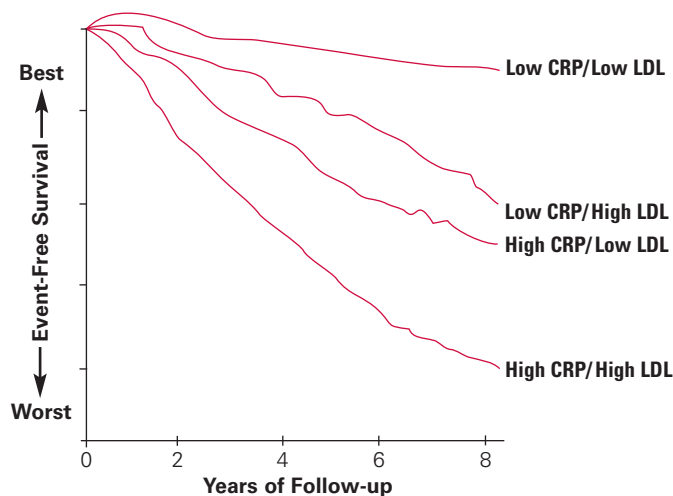


Figure 1. Cardiovascular event-free survival based on combined hs-CRP and LDL cholesterol measurements. Adapted from Ridker et al (*N Engl J Med.* 2002;347: 1557-1565)

warding off bacteria and viruses, and for many key processes critical for survival. Research over the past decade has shown that too much inflammation in some circumstances can have adverse effects, particularly on the blood vessels that carry oxygen and nutrients to all the tissues of the body. Scientists now understand that atherosclerosis (the process that leads to cholesterol accumulation in the arteries) is in many ways an

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inflammatory disorder of the blood vessels, just as arthritis is an inflammatory disorder of the bones and joints.

Many studies have found that blood markers that reflect the inflammatory process are elevated among individuals at high risk for future heart disease. Inflammation is important in all phases of heart disease, including the early initiation of atherosclerotic plaques within the arteries, as well as the acute rupturing of these plaques that results in heart attack and, all too often, sudden death. Until recently, available markers of inflammation were not suitable for use in physicians' offices. By contrast, CRP is very stable and quite easy to measure.

CRP AND THE RISK OF CARDIOVASCULAR DISEASE

Over a dozen major studies demonstrate that baseline levels of CRP in apparently healthy men and women are highly predictive of future risk of heart attack, stroke, sudden cardiac death, and the development of peripheral arterial disease. Doctors also know that CRP levels predict recurrent coronary events among patients who already suffer from heart disease and that the prognosis of patients in the acute phase of a heart attack is tightly linked to CRP levels. However, the most important current use of CRP is in primary prevention, that is, in the detection of high risk among individuals not yet known to have a problem.

Individuals with elevated levels of CRP have a risk about two to three times higher than the risk of those with low levels. It is important that your physician request a "high-sensitivity" test for CRP if he or she is using CRP for the purpose of cardiovascular risk assessment. This is because older tests for CRP, which are adequate for monitoring severe inflammatory conditions, do not have the ability to measure levels accurately within the range needed for cardiac risk detection. To remind doctors of this issue, many outpatient laboratories now specifically note on the laboratory request form that the test offered is for "high-sensitivity CRP" or "hs-CRP." Like the cholesterol test, the test for hs-CRP is nothing more than a simple, inexpensive blood test. The easiest way to assess overall risk—and avoid an additional needle stick—is simply to add a CRP evaluation at the time of cholesterol screening.

WHY DO I NEED BOTH CRP AND CHOLESTEROL MEASURED?

Both cholesterol and CRP predict risk, but you cannot predict your CRP level on the basis of your cholesterol level (or vice versa). That is because each of these blood tests picks up a different component of the disease process. This independent and additive effect is demonstrated in Figure 1, which shows cardiovascular event-free survival for initially healthy individuals according to levels of

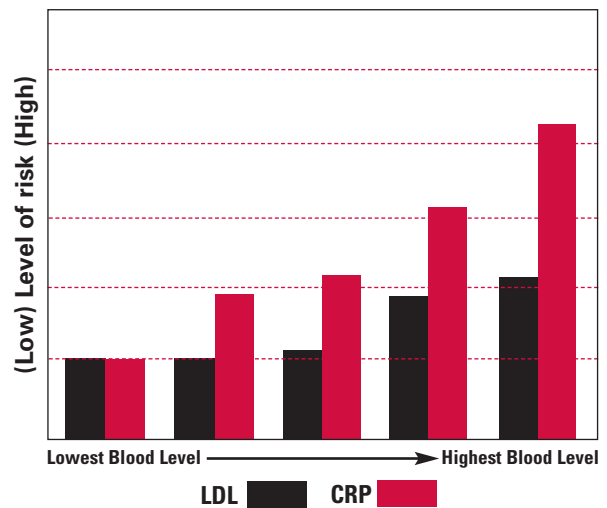


Figure 2. hs-CRP is a stronger predictor of heart attack and stroke than LDL cholesterol. Adapted from Ridker et al (*N Engl J Med.* 2002; 347:1557-1565)

both CRP and the so-called "bad cholesterol" or LDL cholesterol. As shown, the worst survival (highest risk) is seen among those with high levels of *both* LDL and CRP, while the best survival (lowest risk) is among those with low levels of both markers. However, one person in four will be in the high CRP/low LDL group. Such individuals are at a level of risk greater than that of individuals in the low CRP/high LDL category.

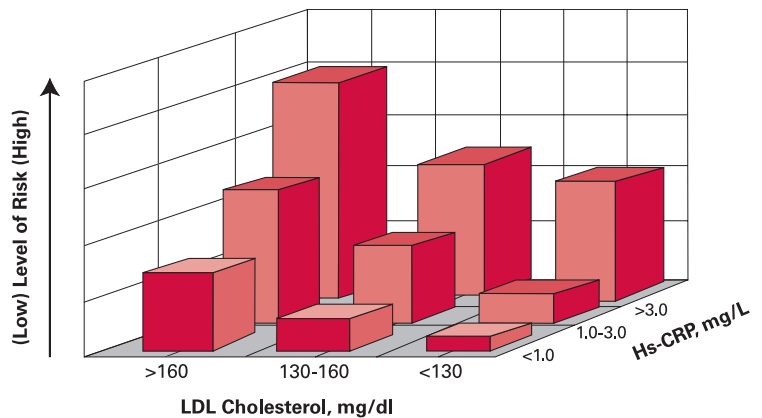


Figure 3. hs-CRP improves risk prediction at all levels of LDL cholesterol. Adapted from Risker et al (*N Engl J Med.* 2000; 342: 836-843)

Without CRP evaluation, such individuals would be missed if their physicians relied on cholesterol screening alone.

It is important to recognize that high levels of LDL cholesterol remain a critical risk factor and that aggressively lowering LDL cholesterol is a fundamental goal of cardiovascular disease prevention. However, as shown in Figure 2, CRP is actually a stronger overall predictor of heart disease and stroke than is LDL cholesterol. Thus, recent practice recommendations have been to measure cholesterol levels and CRP together and to base interventions on the combined information each provides (see below and in Figure 3).

In many ways, a decision to test for CRP is similar to the decision to test for cholesterol; knowledge that levels are high should motivate you to lose weight, to diet, to exercise, and to stop smoking. All of these lifestyle changes are well known to reduce the risk of ever getting heart disease, and they all lower CRP levels.

HOW DOES CRP COMPARE WITH OTHER “NOVEL RISK FACTORS”?

CRP is a powerful predictor of risk, particularly when combined with cholesterol evaluation. Some physicians choose to measure CRP along with a panel of other “novel” risk factors including homocysteine and lipoprotein(a). Others may elect to measure CRP along with more expensive tests that measure specific cholesterol subfractions. However, in all direct comparisons, the predictive value for CRP has been substantially greater than that observed for these alternative “novel” markers of risk. Further, only CRP has proven to add important prognostic information to that already available from standard cholesterol screening.

In some communities, imaging techniques including “whole-body scans” that detect calcification in the heart arteries and the aorta have been advocated as screening techniques. While the presence of calcification does increase cardiovascular risk, such scans are not recommended by the American Heart Association and currently are very expensive. An additional concern for these imaging techniques is that results are often misinterpreted by patients and physicians and can lead to unnecessary coronary interventions, including angioplasty and bypass surgery. While CRP levels also have been shown to add prognostic information at all levels of coronary calcium, this should be used primarily to motivate at-risk individuals to adopt more heart-healthy lifestyles, not to seek aggressive interventional cardiac procedures.

HOW DOES CRP AFFECT DIABETES AND THE METABOLIC SYNDROME?

Unlike LDL cholesterol, CRP predicts not only heart disease, but also the risk of developing type 2 diabetes. Individuals with CRP levels greater than 3 mg/L have a risk of getting diabetes four to six times higher than individuals with lower levels of CRP. Part of the link between heart disease and diabetes is due to inflammation, and for many patients that inflammation in turn is the result of obesity, particularly “central obesity” or the tendency to put on weight around the stomach. This is because fat cells or “adipocytes” produce messenger proteins that turn on the production of CRP itself.

The metabolic syndrome is a condition known to predispose patients to diabetes and heart disease. Physicians classify patients as having the metabolic syndrome if they have at least three of the following

five conditions: low HDL cholesterol, central obesity, high triglycerides, increased blood sugar levels, and high blood pressure. However, the metabolic syndrome also entails a number of less easily measured abnormalities that include insulin resistance and problems with blood clotting. CRP levels increase as the number of components of the metabolic syndrome increase. Even among individuals known to have the metabolic syndrome, CRP levels add important prognostic information on risk. Thus, many physicians now also measure CRP as part of the process of defining the metabolic syndrome. This practice is increasingly common among endocrinologists and other physicians interested in the prevention of diabetes as well as heart disease.

IS CRP SPECIFIC FOR CARDIOVASCULAR DISEASE?

Because CRP is an “acute-phase reactant” and goes up during major trauma and infection, some physicians have worried that CRP testing might be too nonspecific for clinical use. However, multiple studies show that CRP, when measured appropriately with high-sensitivity assays in stable individuals, is quite specific for the prediction of future cardiovascular events. In one recent study, elevated CRP levels were associated with an 8-fold increase in cardiovascular mortality, but had no predictive value for death from other causes. Other studies show that CRP levels predict heart attack and stroke, but not cancer or other major disorders. Thus, a persistently elevated CRP level is indicative of the risk of heart disease and of the accelerated atherosclerosis that affects individuals with diabetes.

AT WHAT AGE SHOULD I BE TESTED?

The first time to consider CRP evaluation is probably in your mid-30s, the same age that most physicians check cholesterol levels. There is good evidence that CRP levels in your teens and 20s are very predictive of levels later in life. Elevated CRP levels predict risk over the next 30 to 40 years. This is good news from a prevention perspective because ample time is available to institute lifestyle changes and, where appropriate, initiate pharmacological interventions to prevent first-ever heart attack and stroke.

Unlike cholesterol testing, CRP evaluation does not require you to fast and can be done at any time of the day.

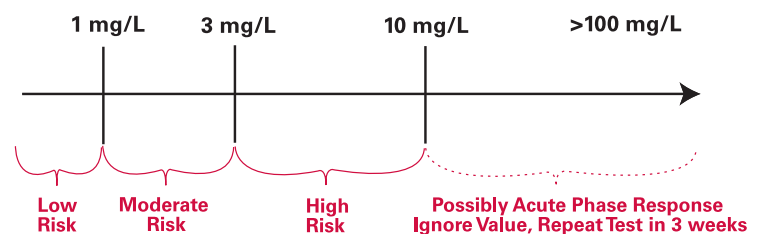


Figure 4. Clinical interpretation of hs-CRP for cardiovascular risk prediction. Adapted from Yeh and Willerson (*Circulation*. 2003;107 370-372)

WHAT IS THE BEST WAY TO LOWER CRP?

The role of CRP as a predictor of future heart attack and stroke has only recently been described, and it is important to recognize that there is no evidence yet that lowering CRP per se will necessarily lower cardiac risk. However, it took almost 20 years before definitive, randomized clinical trials showed that lowering cholesterol lowered cardiac risk. You and your physician should keep abreast of ongoing studies concerning this important issue.

The good news is that the best ways to lower CRP are already known to lower cardiovascular risk. These include diet, exercise, blood pressure control, and smoking cessation. Thus, an important role for CRP evaluation now is to identify high-risk individuals (even when cholesterol is low) and to motivate them toward heart-healthy interventions.

WHAT ABOUT ASPIRIN AND THE “STATIN” DRUGS?

Aspirin is an antiplatelet drug that, at least in men, has been shown to reduce the risk of first-ever heart attack. Aspirin, however, is also an anti-inflammatory drug, and it has been shown that the magnitude of benefit of aspirin in terms of prevention is greatest among those with high levels of inflammation as defined by elevated CRP levels. Any decision to take aspirin needs to balance potential risks and benefits and should be made in consultation with your physician.

The statin drugs are highly effective at reducing risk of first heart attacks and stroke (primary prevention) as well as reducing recurrent events (secondary prevention). While these drugs work primarily by lowering LDL cholesterol, they also reduce CRP levels in many patients, and it has been suggested that this additional “anti-inflammatory” effect may also have clinical benefit. Currently, statin therapy is warranted for those with known heart disease, those with elevated levels of LDL cholesterol (above 160 mg/dL), and those with diabetes.

Whether otherwise healthy individuals with low levels of LDL but high levels of CRP should also be on statin therapy is controversial. A major clinical trial called JUPITER has been designed to address this very question. If you are interested in participating in this study, you can call 1-888-660-8254 or go to <http://www.JUPITERstudy.com> on the Internet.

WHO SHOULD BE TESTED FOR CRP?

The Centers for Disease Control and Prevention and the American Heart Association suggest that CRP evaluation be considered as a part of overall global risk prediction for individuals concerned about vascular risk.

The test is most likely to have greatest utility among those at “intermediate” risk where additional prognostic information is likely to change overall risk estimates and motivate lifestyle change. For efficiency of clinical practice and to avoid unnecessary blood draws, many physicians simply add CRP testing to standard cholesterol evaluation. CRP testing is not considered mandatory but rather should be done at the discretion of your physician.

The Centers for Disease Control and Prevention and the American Heart Association also endorsed the use of CRP evaluation for those with a prior history of heart attack and among those admitted to hospital with acute heart disease syndromes. In the Emergency Room setting, patients coming in with chest pain syndromes may also have CRP levels checked in order to identify those at high risk for coronary disease.

HOW DO I INTERPRET CRP TEST RESULTS?

Interpreting CRP results is straightforward (Figure 4). All laboratories should report values in mg/L (milligrams per liter). Levels of CRP less than 1 mg/L are desirable and reflect a low overall cardiovascular risk. Levels of CRP between 1 and 3 mg/L are indicative of moderate risk, while levels of CRP in excess of 3 mg/L suggest quite elevated vascular risk. As noted above and described in Figures 1 and 3, this may be true even if your cholesterol levels are low.

It is possible that you will have a CRP level that is very high (above 10 mg/L). In that case, the test should be repeated in about two to three weeks as levels above 10 mg/L can reflect the presence of an acute infection (this is why it is recommended to have CRP evaluation done when you are feeling well). If on repeat testing the CRP level remains high, you are most likely in the high-risk group.

Postmenopausal women who take standard estrogen or estrogen plus progesterone oral hormone replacement therapy (HRT) tend to have elevated levels of CRP. Women in this group should discuss the relative benefits and risks of HRT since recent studies have not shown HRT to lower cardiovascular risk. Stopping oral HRT will lower your CRP levels. Topical estrogens and the selective estrogen receptor modulators (SERMS) do not seem to elevate CRP.

Levels of CRP are similar in men and women. The average CRP in middle-aged Americans is about 1.5 mg/L. Approximately 25 percent of the US population has levels of CRP greater than 3 mg/L, the cut point for high risk.

ADDITIONAL RESOURCES

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