

## C-Reactive Protein test to screen for heart disease: Why Do We Need Another Test?

(This article was first printed in the February, 2003 issue of the *Harvard Health Letter*. For more information or to order, please go to <http://health.harvard.edu/health>.)

*The predictive powers of a cholesterol test only go so far. If your LDL is low, your C-reactive protein may be a better sign of impending heart trouble.*

The gap between knowing what's good for you and actually doing it can be huge, especially when it comes to something like getting exercise. (Never underestimate the appeal of the sedentary life.) Many of us need a warning—some might say a bit of a kick in the pants—before we'll change our ways and get with a heart-healthy program.

### Cholesterol Tests

For decades, cholesterol testing has served as that warning for many. An elevated level of "bad" LDL cholesterol has been just the warning people needed to change their ways. It has played that role for several reasons. People like tests because the results seem objective. Reliable measurement of cholesterol is easy and relatively inexpensive. It makes sense biologically. *LDL cholesterol*, a protein-wrapped package containing fat and cholesterol, tends to slip out of the bloodstream and lodge in blood vessel walls, forming the *plaque* that leads to clots and heart attacks.

And it makes sense statistically. The correlation between lowering your LDL and lowering your chances of having a heart attack or developing other forms of heart disease is well documented. Indeed, exercise and dietary changes are good for the heart partly because they lower LDL cholesterol levels.

### The Blind Spot

But for all its virtues, cholesterol testing is seriously flawed. Research has shown that only about 50% of the people who have heart attacks have high LDL. If LDL levels are supposed to be an alarm, then it's not going off for half of those who might benefit from a wake-up call.

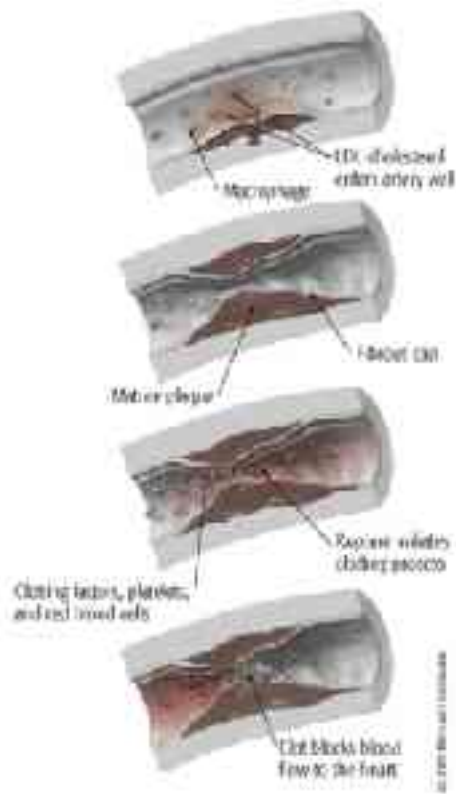
This shortcoming presents two problems. First, and most obviously, many people at risk are being missed. So there's a need for a different test that will "capture" those who slip through the fingers of cholesterol screening.

Second, because cholesterol screening does miss so many incipient heart attacks, it suggests that cholesterol doesn't adequately explain heart disease.

Inflammation seems to be that explanation, and C-reactive protein (CRP), a by-product of inflammation, may provide the test.

### Inflammation Causes Heart Attacks

Experts who study blood vessels, plaque, and heart attacks in minute detail have been developing an inflammatory explanation for heart attacks. They've described a process quite different from the clogged plumbing analogy. Blood vessels aren't solid pipes, but slender tubes of layered, living tissue, some of it quite delicate. LDL cholesterol doesn't simply lodge in arterial walls—it injures them. And like injuries elsewhere in the body, this stirs up an inflammatory response. Swarms of cytokines, macrophages, and other cells swoop in. They enlarge and transform deposits of LDL cholesterol into accumulations of fat-laden foam cells sealed by fibrous caps of collagen.



Other inflammatory molecules can so weaken a fibrous cap that eventually it bursts open. The contents of the plaque spill out and activate clotting factors in the blood. A massive blood clot forms. The result: a blocked artery and a heart attack.

## Why C-Reactive Protein?

If inflammation explains heart attacks, then a test that helps doctors gauge inflammatory activity inside the blood vessels might be valuable. CRP is nothing new to medical science. The protein was discovered over 70 years ago.

Researchers quickly figured out that it was part of the immune or inflammatory response because levels soared in response to *Streptococcus A* infection. In fact, doctors have used CRP measurements for decades to monitor patients with lupus, rheumatoid arthritis, and other conditions related to the immune system.

But as a way to screen for heart disease risk? That was a different story. All the momentum and much of the science used to be behind cholesterol testing. Now, however, CRP testing seems ready to catch on for several reasons.

### People have heard or read about the reasoning behind it.

The inflammatory explanation of atherosclerosis and heart attacks has trickled down from rarefied research circles to doctors and the public. Dozens of newspaper, magazine, and newsletter articles have been written about it. People are more likely to get a test-maybe even demand one-if they have some understanding of what's being measured and why. The same goes for doctors.

### It's a good predictor of heart disease.

Even if heart attacks were caused by inflammation, CRP testing wouldn't be useful unless it's proved to be a good predictor. In other words, studies have to show that there's a tight correlation between high C-reactive protein levels and the chances of having a heart attack.

To make a long story short, that's just what a series of studies published in prestigious journals has shown. One, in the Nov. 14, 2002, *New England Journal of Medicine*, concluded that CRP outperforms LDL cholesterol as a predictor of cardiovascular risk. In addition, the authors found that the two tests identify different high-risk groups, so using both is better than relying on either alone. (If you're interested in the details of this and other CRP studies, visit our Web site at <http://www.health.harvard.edu/health>.)

### It's a better predictor than other measures of inflammation.

There are other ways to measure inflammation. But a study in the March 23, 2000, *New England Journal of Medicine* concluded that C-reactive protein was a better predictor of cardiovascular events (heart attacks, strokes, bypass surgery, or angioplasty) than other inflammatory markers.

### **It's sensitive.**

Until fairly recently, the test available to doctors couldn't reliably measure low (below 10 milligrams per liter) CRP levels. Tests are now sensitive enough to measure levels of 1 milligram per liter or less. That's a crucial development because it's fairly minor differences at those low levels that sort out cardiovascular risk.

### **It's practical.**

The test costs \$12-\$16, and it takes only a small amount of blood. In fact, the same blood sample could be sent to a lab for both cholesterol and C-reactive protein testing.

### **Some cutoffs have already been established.**

Without preset cutoffs, doctors wouldn't know how to interpret CRP test results. Dr. Paul Ridker, a Harvard researcher, was principal investigator on most of the crucial CRP studies and is co-inventor on related patents. He says it's now possible to classify CRP levels in terms of low, moderate, or high risk.

Less than 1 milligram per liter of blood corresponds to a low risk for heart attack or other cardiovascular problems; 1-3 milligrams per liter corresponds to moderate risk; and over 3 milligrams, to high risk. These cutoffs might change with more research (as have those for cholesterol), but they're a starting point.

### **You can do something about high levels.**

Imagine your doctor telling you that a newfangled test of inflammation shows that you have a worrisome level of a telltale protein, but, um, there isn't much you-or she-can do about it. That wouldn't be a popular or helpful test, even if it were a perfect prognosticator of heart attacks.

A big reason behind the growing enthusiasm for C-reactive protein tests is that levels can be lowered. The statin drugs (Lipitor, Zocor, other brands) made their name by lowering LDL; research has shown that they also lower C-reactive protein levels. Exercise is a great way to bring down your CRP level; losing weight also seems to work.

## **What's Next?**

C-reactive protein "hawks" think the time has come when everyone should get the test and that it may eventually supplant cholesterol testing. "Doves" say that there just isn't enough evidence about how doctors should treat high levels, even if there is a link to cardiovascular risk.

As we went to press (2003), neither the American Heart Association (AHA) nor the American College of Cardiology had made a formal recommendation on C-reactive protein. Published comments from AHA leaders hint that it might stake out a middle ground and suggest testing people who fall into an intermediate-risk group because of their age (60 and older), weight, or blood pressure. AHA and other guidelines will influence how doctors will use the CRP test during the next year or so. Ultimately, though, the fate of the test rests with prospective, randomized studies of CRP-lowering interventions still in progress.

## **High CRP/Low LDL**

Dr. Ridker's November 2002 study comparing C-reactive protein and LDL found that cardiovascular risk was actually greater for people in the high CRP/low LDL group than for those in the low CRP/high LDL group. Clearly, cholesterol testing would have missed people in the high CRP/low LDL group.

If these results hold up, CRP testing might be most advisable for people with low LDL levels. Because the test is inexpensive, doctors might just order both tests right off the bat rather than wait for the cholesterol results.

## **Coming Full Circle**

No test, no matter how good it is, changes anyone's health. It's what we do in response that matters. Statins have put a pharmaceutical face on heart disease prevention, but the old truths about getting exercise, eating right, and not smoking still hold. If the CRP test gets more people to follow that advice, then it may be worthwhile.