



## Is CRP A Better Predictor of Heart Attack Risk than Serum Cholesterol?

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1 CPE hour for RDs and DTRs ♦ Good through December 2013.

It is now scientifically well established that inflammation plays a role in the initiation, growth and destabilization of atherosclerotic plaques that lead to clogged arteries and most heart attacks. The rupture of unstable, cholesterol-filled plaques triggers the formation of a blood clot inside the artery that can suddenly block blood flow to tissues down stream from that clot.[1] [2] [3] Inflammation promotes blood clot formation.[4] There seems to be little doubt that inflammation plays some role in both the growth of atherosclerotic plaques and their subsequent rupture and clot formation. The question is how can this inflammation be accurately measured and what steps should be taken clinically if inflammatory markers are elevated.

There is growing interest about using blood markers for chronic low levels of inflammation such as high-sensitivity, C-reactive protein (hs-CRP) to determine a person's future risk of having a heart attack. Current National Cholesterol Education Program (NCEP) guidelines for assessing the future risk for cardiovascular disease (CVD) put the emphasis on low density lipoproteins (LDL) levels based on data from the Framingham Heart Study and do not recommend the use of hsCRP. However, it is unknown whether or not elevated hsCRP levels directly contribute to the pathogenesis of either atherosclerosis or thrombosis or is simply correlated with factors that promote atherosclerosis and thrombosis.[5]

A recent large prospective study of 27,939 women age 45 and older examined the risk for a first-time cardiovascular disease event (eg, heart attack or stroke) over an eight-year follow-up period. At the start of the study both LDL and hsCRP levels were measured. Women with either higher levels of hsCRP or higher levels of LDL in their blood were much more likely to suffer a first cardiovascular event than were women who had lower levels of both hs-CRP and LDL in their blood. Indeed, the women with higher levels of CRP were actually somewhat more likely to experience a heart attack or stroke than were women with higher levels of LDL-cholesterol compared to those with the lowest levels.[6] ♦

### Increased hs-CRP correlates with CVD but does it cause it?

While inflammation clearly plays a role in CVD this does not mean that biological markers of inflammation are independent risk factors for coronary heart disease as is total cholesterol, LDL-cholesterol, non-high-density lipoprotein (HDL)-cholesterol and the ratio of total cholesterol to HDL-cholesterol in the blood. High blood pressure, diabetes and cigarette smoking are all well-established

risk factors for the development of CVD and fatal myocardial infarcts. However, data from the Framingham Heart Study found that the association between higher hs-CRP levels and having neck (carotid) arteries blocked by atherosclerotic plaque was significant only in women but not men.[7] ♦

Another research study found that inflammatory markers including hs-CRP are indeed correlated with the extent of atherosclerotic disease and the risk of a myocardial infarct or stroke but that CRP itself is not an independent risk factor and does not provide much discriminatory diagnostic power over better-established CVD risk factors.[8]

Others have noted that hs-CRP can increase acutely in response to walking or jogging[9] but no one suggests that such activities actually increase the risk of having a heart attack. It has also been suggested that higher levels of hs-CRP may simply reflect more biological aging.[10]

## **Should doctors start screening their patients for hs-CRP levels?**

Before CRP becomes a widely accepted test for screening individual patients for their risk of cardiovascular disease, it must be of proven value. CRP still has a ways to go before it is widely accepted as an effective screening tool.

One problem with hs-CRP is that it varies a lot more than LDL levels when measured repeatedly in the same patient even though they have made no significant change in their diet, exercise level or had changes in medications. Hs-CRP levels can also increase with infections or inflammatory conditions such as arthritis. Studies of apparently healthy people have found hs-CRP levels vary at least 4 to 5 times as much as do LDL levels.[11] Another study found that hs-CRP levels measured repeatedly in the same individual varied on average by 42%. By contrast, the variability in repeated LDL levels is less than 10%.[12] ♦ Some of this variability is due to measurement error and some to real variation. If someone with a high risk LDL level of 200 mg/dl were measured a week later the chances are the next reading would be more than 180 mg/dl and less than 220 mg/dl and most of the time between 190mg/dl and 210. All these values suggest a very high risk of atherosclerosis and a much greater risk of a heart attack over time. What if LDL levels varied by 42% on average instead of less than 10%? Then a 200 mg/dl level one day could easily be as low as 120 the next day or week even though no changes were made in diet, lifestyle or medication. Clearly this would not be acceptable for clinical use because 120 mg/dl suggest below average risk and 200 mg/dl level suggests very high risk of CVD. Another problem with using hs-CRP as a marker for successful treatment of atherosclerotic disease is that we have no convincing evidence that simply lowering CRP levels with diet and/or drugs will lead to reduced heart attacks and strokes. We know this is the case if LDL-cholesterol or non-HDL-cholesterol levels are lowered with diet and/or drugs.

Based on current research, measuring the hs-CRP level in the individual patient has not been proven to be sufficiently accurate, reliable or beneficial in terms of preventing cardiovascular disease (CVD).[13] On the other hand LDL levels and hs-CRP levels do not correlate that closely. There are about 25-30 million Americans who may be at increased risk for cardiovascular disease despite below average LDL levels but a lot more inflammation in their arteries. The hs-CRP test would be of some value in helping to identify those people. People who have elevated hs-CRP levels despite having few or no other CVD risk factors do warrant some concern. Measuring the thickness of their intimal medial carotid arteries may

help clarify if they have more atherosclerosis than would be expected. Weight loss, particularly in overweight or obese women, may be useful for lowering hs-CRP levels and is certainly beneficial for other reasons. Poorly controlled diabetes can also increase hs-CRP levels and clearly should be treated more aggressively. Statin drugs and aspirin may lower hs-CRP levels and may well be medically justified if the IMT (define) test showed greater atherosclerotic plaque thickness. There is some evidence indicating that the risk reduction in CVD events from taking statin drugs is greater in patients with elevated hs-CRP levels and inflammation than in those with lower hs-CRP levels.[14] Recent evidence shows that statin drugs not only lower LDL-cholesterol levels but are also have potent anti-inflammatory effects as well.[15]

Based on an evaluation of the latest research on hs-CRP levels and CVD risk a joint scientific statement from the American Heart Association and the Center for Disease Control still recommend against screening the entire US population with the hs-CRP test. However, they also concluded, ♦♦ that it is reasonable to measure hs-CRP as an adjunct to the major risk factors to further absolute risk for coronary disease primary prevention. ♦ They state that the test is best used in those with a moderate CVD risk over the next 10-year period. They state that ♦ the finding of a high relative risk level of hs-CRP (> 3.0mg/L) may allow for intensification of medical therapy to further reduce risk and to motivate some patients to improve their lifestyle or comply with medication prescribed to reduce their risk.[16]

### **Could Bacterial Infection of Arteries Link Inflammation to CVD?**

While there is little debate about whether or not inflammatory processes are present in atherosclerotic arteries it is not clear whether these changes are simply a consequence of the atherosclerotic process or part of the pathogenesis of the disease.[17] [18] The idea that infections with bacteria and viruses might contribute to the growth of atherosclerotic plaque or their rupture and thrombosis has been around for many years.[19] Certainly bacteria have been found in both early and late stage atherosclerotic lesions. Data from the Helsinki Heart Study suggest that chronic infection with *Chlamydia pneumoniae* may be a significant risk factor in the development of coronary artery disease.[20] Most people are exposed to *C. pneumoniae* at some point in their life but it usually does not cause any overt symptoms. A recent study suggested that the treatment of patients with *C. pneumoniae* infections for 2 years with antibiotics slowed the thickening of carotid arteries as measured by IMT (intima-media thickness) testing. By contrast, the same antibiotic did not slow the thickening of carotid arteries of patients without *C.pneumoniae* infections. According to Dr. Dirk Sander of the Technical University of Munich, Germany who conducted this study, the small reduction in plaque growth would equate to a very modest decrease in the risk of a heart attack or stroke and more studies are needed to determine if the benefits would increase over time. Is it possible that part of the connection between increased hs-CRP levels and CVD could be due to chronic infections with *C. pneumoniae* or possibly other organisms? And would treatment of these infections with antibiotics lower hs-CRP levels and reduce the risk of future CVD? More research is needed before any firm conclusions can be drawn.

## Bottom Line:

Using the hs-CRP test in addition to LDL and other better-established risk factors may help better identify those at increased risk of heart attacks and strokes. A very-low-fat diet low in saturated fat and cholesterol with more fish, whole grains, fruits and vegetables along with regular aerobic exercise has been shown to lower body weight and both LDL and hs-CRP levels.[21] There is no harm in recommending these healthy lifestyle changes to someone with a low LDL and high hs-CRP level. However, while cholesterol-lowering statin drugs lower both LDL and hs-CRP levels they are not without risk or costs. It is, therefore, reasonable to withhold these drugs from the treatment of people who have high hs-CRP levels but low LDL levels until future research establishes a clinical benefit at a reasonable cost of treatment. In the interim patients with elevated hs-CRP levels but low LDL-cholesterol levels may be encouraged to undergo IMT testing to determine whether or not more advanced atherosclerosis is present. If IMT test shows more atherosclerotic plaque than would be predicted based on better established risk factors it may then be clinically justified to take more aggressive medical steps like statin drugs and possibly the use of antibiotics to treat suspected bacterial caused inflammation of the arteries.

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