Clinical Update: C-reactive protein: A marker for assessing and managing cardiac risk

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Inflammation plays a major role in coronary artery disease (CAD), whereby inflammatory changes develop in the blood vessel walls. This observation has spurred interest in exploring the connection between CAD and markers of inflammation, including C-reactive protein (CRP), fibrinogen, serum amyloid A, and many other novel markers.

CRP is one such marker that, in the wake of extensive and varied types of studies, has been shown to be directly related to a patient's risk of sustaining a coronary event (see "C-reactive protein: An overview"). The data are so compelling that use of CRP testing has been endorsed for assessing risk in select patient groups in a scientific statement from the American Heart Association (AHA) and the CDC. Nonetheless, many questions remain concerning CRP, its role in CAD, and its clinical value in identifying patients at increased risk for cardiac events. For instance, does CRP cause atherosclerosis directly, or does it simply reflect atherosclerotic damage? Should all patients be screened for elevated CRP levels? Are CRP levels more accurate than lipid levels for identifying patients who are likely to have a myocardial infarction (MI)? Should patients with elevated levels of CRP but no history of heart disease be treated any differently than patients in whom CRP levels are normal? Another area of speculation and exploration is the relationship between CRP and various drugs used to treat CAD. Statins, for example, produce greater clinical benefit in patients with elevated levels of CRP. Statins also lower CRP levels independently of their effect on low-density lipoprotein cholesterol (LDL-C). This suggests that statins may have important anti-inflammatory properties. If so, the effect of statins on CRP levels may be as important as their effect on LDL-C levels.

To further explore this theory, we evaluated CRP levels and outcomes after statin therapy (see "C-reactive protein and response to statins"). In this Clinical Update, I will review our findings and those of other recent studies and discuss the clinical implications.

**PROVE IT-TIMI 22**

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)-Thrombolysis in Myocardial Infarction (TIMI) 22 trial showed a significantly lower risk of cardiovascular death or recurrent MI in patients with LDL-C levels below 70 mg/dL than in patients with higher LDL-C levels. This was the first validation of the new, lower LDL-C "optional therapeutic target" set by the National Cholesterol Education Program (NCEP) expert panel.

For each group, we examined the impact on cardiac risk of the post-treatment CRP level. Overall, in patients with a CRP level below 2 mg/L, the incidence of cardiac death or recurrent MI was much lower than in patients with a CRP level above 2 mg/L. In patients with LDL-C levels below 70 mg/dL and CRP levels below 2 mg/L, the risk of death or MI was 20% to 25% lower than it was in patients in whom either of these 2 parameters was not met and about 50% lower than it was in patients with LDL-C levels over 70 mg/dL and CRP levels over 2 mg/L.

We performed a post hoc analysis to see what happens when the LDL-C level is below 70 mg/dL--which is very desirable according to the new NCEP guidelines--and the CRP level is below 1 mg/L. The results showed that patients with such levels would have a 45% lower coronary risk than patients with LDL-C levels below 70 mg/dL but CRP levels above 2 mg/L. These findings indicate that CRP provides more information than LDL-C about a patient's cardiac risk. Also, reducing the CRP level to below 1 mg/L--even when the LDL-C level is optimal--is associated with a lower risk of cardiac death or MI.

Our study was the first to examine prospectively the concept that lowering CRP levels would be
beneficial. The results point to the potential impact of targeting treatment—in this case, with statins—to reduce CRP levels, just as we routinely do with LDL-C. Considering our findings, we are now evaluating a dual goal of treatment, targeted at reducing both CRP and LDL-C levels. Although everyone in our trial received statins, the intensive statin regimen helped more patients achieve desirably low levels of CRP and LDL-C than the regular statin regimen. Therefore, physicians should consider implementing high-dose statin therapy whenever possible. REVERSAL

Recently, Nissen and colleagues reported on a study in which 502 patients with angiographically documented CAD underwent intravascular ultrasonography. Patients were randomly treated with intensive or regular-dose statins, then had another ultrasonographic examination to see how their atherosclerosis had progressed.

Their findings were similar to ours in documenting the benefit of intensive versus regular statin treatment. Patients who took high-dose statins had the least progression of atherosclerosis; they also had the lowest LDL-C and CRP levels. The new analysis found that patients who had the greatest reduction in CRP levels had the slowest progression of atherosclerosis. Those who had the greatest reduction in both LDL-C and CRP levels had the least progression of all. In fact, by some indices, there was regression of atherosclerosis in these patients.

These findings help demonstrate how keeping LDL-C and CRP levels down prevents atherosclerotic plaques from progressing or destabilizing and from causing clinical events. These 2 studies have confirmed the connection between high CRP levels and progression of heart disease. They suggest that this might apply to new drugs: if a new drug can reduce CRP levels, it may also reduce atherosclerosis and cardiac events. Many ongoing trials are testing this hypothesis with different classes of drugs. The link between CRP and LDL

The relationship between LDL-C and CRP is very weak. LDL-C and CRP levels do not correlate for any given patient. In some patients, the LDL-C level declines significantly while the CRP level remains the same; in others, however, the opposite scenario occurs. Clinically, this means that we need to check both LDL-C and CRP levels during statin treatment. We cannot assume that because LDL-C levels have dropped, CRP levels have also dropped. Conversely, you do not want a patient with a low CRP level to have an LDL-C level of 160 mg/dL, which can happen.

Both CRP and LDL are valuable in predicting cardiac risk. Neither displaces the other in monitoring a patient’s cardiac risk. Monitoring CRP levels

CRP has dramatic prognostic value in the setting of secondary prevention, as we found in our study. We are starting to monitor CRP levels in patients with established heart disease, as well as in patients identified as being at cardiac risk, based on the AHA/CDC guidelines. I am starting to monitor CRP levels in patients taking statins. I check the CRP level when I check LDL-C levels, to see whether both parameters are under control.

CRP monitoring could also be useful for predicting the long-term risk of a coronary event in patients who have only a few cardiac risk factors and who are otherwise healthy. Thus, in the primary prevention setting, CRP monitoring could be quite helpful. I think that CRP monitoring will probably become a routine practice. The test is inexpensive—$30 to $50, depending on the laboratory. Frequently, the result of a test such as the CRP assay is all patients need to start changing their behavior to reduce cardiac risk.

Of course, the test also tells the clinician whether the patient needs to be considered for more intensive risk factor modification and/or statin therapy. Strategies to reduce CRP levels

Our study showed that increasing the dose of a statin increases the likelihood of reducing both LDL-C and CRP levels. Thus, intensive statin treatment is one approach to reducing CRP levels. However, although high doses of statins generally reduce CRP levels more than lower doses, there is considerable individual variation.

If the patient is already taking a high-dose statin—for example, atorvastatin, 80 mg—and he or she has not reached the LDL-C or CRP goal, many other treatments have been shown to reduce LDL-C and CRP levels individually. One is ezetimibe, a cholesterol absorption blocker. Ezetimibe can be taken with a statin to reduce both LDL-C and CRP levels.

The glitazone agents also can reduce CRP levels. Rosiglitazone and pioglitazone can reduce CRP levels by approximately 40%. These drugs are being studied to determine whether they can decrease the progression of atherosclerosis and eventually even lower the incidence of cardiac death. The endocannabinoid receptor blockers are another class of drugs under investigation. Rimonabant, which has been shown to help patients lose weight and stop smoking, can reduce CRP levels by 25%, although it has not yet been approved for this use. Studies are under way to determine whether rimonabant can decrease the progression of atherosclerosis.
Many companies are developing specific drugs targeted at reducing inflammation and CRP levels. The response to treatment with these drugs will be a test of how decreasing CRP levels improves a patient's cardiac outlook.

NSAIDs have a minimal effect on CRP levels; they lower CRP levels only by about 5% to 10%. Aspirin does not lower CRP, but it is very effective for preventing thrombosis in patients with high CRP levels.

The same lifestyle interventions that we recommend for lowering cholesterol help lower CRP levels too. Measures such as stopping smoking, controlling blood sugar, eating a healthful diet, exercising, and losing weight are all helpful.

Controlling lipid levels, by raising high-density lipoprotein levels and reducing triglyceride levels, helps keep CRP levels low as well. **CRP targets**

It is too early to adopt a CRP-based strategy for all patients. However, I have begun monitoring CRP in patients who are taking statins, with the goal of decreasing CRP levels to below 2 mg/L (ideally, below 1 mg/L). Once the patient has begun treatment, CRP levels start to decline within days. For monitoring LDL-C response (and now CRP response), I usually schedule a follow-up visit for 1 to 2 months later to make sure that the LDL-C level is less than 70 mg/dL (for any patient with CAD) and to evaluate CRP. If the CRP level is still elevated, I consider intensifying statin therapy and/or advising lifestyle modification.

For example, if the LDL-C level is controlled and that of CRP is still high, it might be a further incentive for patients to lose more weight and/or improve their diet. If LDL-C and CRP targets are not optimal, I would consider increasing the statin dose to the maximum or adding a second agent. For now, information about CRP is useful in determining whether this parameter is under control or whether more intensive treatment may be needed. **Take-home messages**

There are several take-home messages for primary care physicians (Table):

- CRP levels are useful for predicting a patient's cardiac risk and for evaluating the response to statin therapy.
- After a cardiac event, the clinician should target treatment to reduce the LDL-C level to the NCEP goal of less than 70 mg/dL and should consider monitoring CRP. I aim to reduce the CRP level to below 1 to 2 mg/L.
- Treatment with intensive doses of statins is more effective than standard treatment for lowering LDL-C and CRP levels and cardiac risk.
- CRP levels can be reduced significantly with a program of drug therapy and cardiac risk factor/lifestyle modification.

All of the means for monitoring and reducing CRP levels are within the grasp of every physician. By focusing on CRP as well as lipid levels, we may be able to improve effectively the cardiac risk profile of even more patients than we do now.

**References:**

**REFERENCES**


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