CRP Has a Big Role in Heart Disease

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This *Heartbeat* will discuss two articles from the January 6, 2005 *New England Journal of Medicine* concerning the role of CRP in heart disease. They confirm that reducing the inflammatory component of coronary artery disease, reflected by decreasing C-reactive protein (CRP) levels, through the use of statin therapy, improves clinical outcome independently of the reduction in cholesterol. These two studies provide the strongest evidence yet that CRP plays a large role in heart disease and that it is a slightly better indicator of coronary events than is low-density lipoprotein cholesterol (LDL-C). Both groups of authors suggest statins provide benefits not only through LDL-C lowering but also through anti-inflammatory (plaque stabilizing) actions, and that strategies to lower cardiovascular risk with statins should include monitoring of CRP as well as LDL-C. The investigators suggest that for secondary prevention, statin therapy should be adjusted to maintain *hs*-CRP* < 2mg/L as well as LDL-C < 70mg/dL.

In the original **PROVE-IT** (Pravastatin or Atorvastatin Evaluation and Infection Therapy) and **REVERSAL** (Reversal of Atherosclerosis with Aggressive Lopid-lowering) statin trials, the investigators compared an aggressive LDL-C lowering program (atorvastatin 80mg) with a moderate LDL-C lowering program (pravastatin 40mg). Both showed a clear superiority of the more aggressive treatment—ushering in a new era of intensive statin therapy—for the lowering of LDL-C and a modification of the National Cholesterol Education Program (NCEP) guidelines last July. PROVE-IT[1] showed a 16% reduction of clinical events in the atorvastatin group, and REVERSAL[2] demonstrated that intensive lipid-lowering with atorvastatin 80mg halted the progression of coronary atheroma, whereas pravastatin 40mg was associated with continued coronary atherosclerosis progression.

PROVE-IT proves it for inflammation

In the PROVE-IT sub-study, investigators examined relationships between the LDL cholesterol and CRP levels achieved after treatment with 80 mg of atorvastatin or 40 mg of pravastatin per day and the risk of recurrent myocardial infarction or coronary death in 3,745 patients with acute coronary syndromes (ACS).[3] Dr Paul Ridker and his colleagues point out that the difference in the rate of clinical events between patients with LDL < or > 70 mg/dL is "almost identical" to the difference in clinical events in patients with a CRP < or > 2 mg/L. Results also showed that those in whom statin therapy resulted in CRP levels of < 2 mg/L, in general, had better clinical outcomes regardless of the level of LDL cholesterol achieved.

Patients with LDL-C levels of < 70 mg/dL during statin therapy had lower event rates than did those with higher LDL levels (2.7 vs 4.0 age adjusted events per 100 person-years; P = .008). Similarly, those patients achieving CRP levels of < 2 mg/L after statin therapy had lower event rates than did those with higher levels (2.8 vs 3.9 age adjusted events per 100 person-years; P = .006), regardless of LDL cholesterol level. Less than 3% of the variation in achieved CRP levels was attributable to the variation in achieved LDL cholesterol levels (Table 1).

Table 1. Age-adjusted Event Rates According to LDL and CRP Level Achieved with Statin Therapy.

Individually		Together	
LDL-C >70	4.0	LDL-C > 70, CRP > 2	4.6
LDL-C< 70	2.7	LDL-C < 70, CRP > 2	3.1
CRP > 2	3.9	LDL-C > 70, CRP < 2	3.2
CRP < 2	2.8	LDL-C < 70, CRP < 2	2.4

For patients with post-treatment LDL-C levels of > 70 mg/dL, the rates of recurrent events were 4.6 per

100 person-years for those with CRP levels of > 2 mg/L and 3.2 events per 100 person-years for those with CRP levels of < 2 mg/L. For those with LDL-C levels < 70 mg/dL, the respective rates were 3.1 and 2.4 events per 100 person-years ($P < .001$) [Table 1].

The lowest rate of recurrent events (1.9 per 100 person-years) occurred in patients with LDL cholesterol levels < 70 mg/dL and CRP levels < 1 mg/L after statin therapy. Patients receiving atorvastatin were more likely to achieve low levels of LDL cholesterol and CRP than were those receiving pravastatin. However, meeting these targets was more important in determining outcome than the specific choice of therapy. The authors conclude, "Patients who have low CRP levels after statin therapy have better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL cholesterol. The data provide strong evidence to support the hypothesis that *early* therapies designed to reduce inflammation after acute coronary ischemia may also improve cardiovascular outcomes."

These findings can not be generalized beyond situations involving secondary prevention because all the participants had a myocardial infarction or had high-risk unstable angina and therefore had a clear indication for long-term statin therapy. Benefit with statin treatment was suggested by post hoc analysis of a recent primary prevention trial (AFCAPS/TEXCAPS).[4] But presently, statin therapy used for primary prevention among persons with high CRP but low LDL-C is very controversial and is the subject of an ongoing multinational trial (JUPITER).[5]

Confirmation from REVERSAL

This angiographic ultrasound study included 502 patients with angiographically documented coronary artery disease (CAD) who were randomized to receive moderate treatment (40 mg pravastatin orally per day) or intensive treatment (80 mg atorvastatin orally per day), with intravascular ultrasonography performed at baseline and after 18 months to measure the progression of atherosclerosis.[6] The mean LDL cholesterol level decreased from 150.2 mg/dL at baseline to 94.5 mg/dL at 18 months ($P < .001$) for all participants, and the geometric mean CRP level decreased from 2.9 to 2.3 mg/L ($P < .001$). The sub-study of REVERSAL focuses on the CRP results and notes that after adjustment for the reduction in lipid levels, the decrease in CRP levels was independently and significantly correlated with the rate of progression of atheroma. Patients with decreases in both LDL-C and CRP that were greater than the median had significantly slower rates of progression of atheroma than patients with reductions that were less than the median. Reductions in the levels of atherogenic lipoproteins were not closely correlated with reductions in CRP levels, showing that statin-mediated reductions in CRP are largely unrelated to the decrease in LDL cholesterol levels.

The REVERSAL authors, led by Dr Steven Nissen, write: "These findings confirm the work of other investigators and strongly suggest that the statin-mediated reduction in CRP is unlikely to be a secondary consequence of a reduction in LDL cholesterol but rather is potentially mediated by independent pathways." They reach a similar conclusion to the PROVE-IT authors: "For patients with coronary artery disease, the reduced rate of progression of atherosclerosis associated with intensive statin treatment, as compared with moderate statin treatment, is significantly related to greater reductions in the levels of both atherogenic lipoproteins and CRP." They add: "Our study raises the provocative question of whether the effects of statins on CRP, as well as LDL cholesterol, should be considered in decisions regarding therapy." But they caution, "We do not believe that these data are sufficient to recommend routine serial measurement of CRP in order to modulate statin therapy, but further study is warranted."

Take Home Points:

- CRP levels correlate with the progression of coronary atherosclerosis and clinical outcomes in patients with CAD, who receive statin therapy, and they seem to be slightly better markers of CAD outcome risk than LDL-C.
- Cardiovascular risk factors, particularly LDL-C and CRP, decrease endothelial cell production of nitric oxide, leading to vasoconstriction[7] and other adverse effects on endothelial function. These include development of a procoagulant environment, platelet activation, and increased production of monocytes adhesion molecules and other inflammatory mediators which are related to plaque instability.[8] The accumulated data provide strong evidence to support the hypothesis

that therapies like statins, which reduce inflammation and stabilize plaque through lipid dependent (decreasing LDL-C) and lipid independent or pleiotropic (decreasing CRP) mechanisms, improve cardiovascular outcomes. The early improvement in endothelial cell biology with high dose statins plays an important role in explaining clinical benefit.

- The most important point comes from the accompanying editorial.[9] Statins may play a role in improving a number of autoimmune/inflammatory disease states extending from multiple sclerosis and neurodegenerative disorders to rheumatoid arthritis, systemic lupus erythematosus and HIV infection. Determining the mechanism of action of the anti-inflammatory effect of statins could help find or design other therapies for CAD.
- One statin does not appear to be more advantageous over another as long as goal levels of treatment are met.
- Serial measurement of CRP in order to regulate statin therapy is not yet ready for "prime time." We agree with Dr Nissen that further study is warranted. (Baseline measurement to access ACS risk is fine.) In ACS patients (as studied in PROVE-IT) the utility of serially measuring *hs*-CRP is problematic. All of these patients should already be on intensive treatment, including statins, to get to an LDL-C goal of < 70mg/dL. Assuming LDL-C is at goal on atorvastatin and CRP remains high, what would be the next step? Do we go to combination therapy by adding adjunctive agents like ezetimibe to further lower *hs*-CRP? Or should we treat other co-existing lipid abnormalities with niacin for HDL-C raising or a fenofibrate for triglyceride lowering, both of which also lower *hs*-CRP? What do we do if the *hs*-CRP mg/L is < 1 but the LDL-C is still > 70mg/dL on maximal statin treatment? More information is needed before serial testing of *hs*-CRP can be recommended to follow clinical response and adjust treatment.
- It is reasonable to measure *hs*-CRP as an adjunct to other major risk factors to further assess absolute risk for coronary heart disease (CHD) in primary prevention. The decision to use this study is optional, at the physician's discretion, and in this role this independent marker of inflammation seems best used to detect enhanced risk in those projected to be in the moderate 10-year CHD category as recommended in the guidelines.[10] If high, this would bump them into the high-risk moderate category where more aggressive lipid lowering (goal LDL-C of 100mg/dL) should be considered. It would seem prudent to check *hs*-CRP levels in all overweight couch potatoes who think they are safe because their cholesterol levels are low. If their CRP levels are high, they should be encouraged to lose weight, exercise and stop smoking to bring down those protein levels. Use of statins awaits further study in primary prevention.

[* *hs*-CRP: high sensitivity or cardio CRP; test developed by Paul Ridker MD to specifically measure this cardiac inflammatory marker.]

Table 1. Clinical Application of *hs*-CRP for Cardiovascular Risk reduction.

Risk level	***hs*-CRP ****
Low	< 1
Average	1.0-3.0
High	3.0-10.0

**Levels of > 10mg/L should prompt the clinician to look for other causes of infection or inflammation.

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