2-1-2005

C-reactive protein and statin benefits

Joseph A. Woelfel
University of the Pacific, jwoelfel@pacific.edu

PHARMACIST'S LETTER / PRESCRIBER'S LETTER

Detail-Document #210208

−This Detail-Document accompanies the related article published in−

PHARMACIST'S LETTER / PRESCRIBER'S LETTER

February 2005 ~ Volume 21 ~ Number 210208

C-reactive Protein and Statin Benefits

Lead author: Joseph A. Woelfel, Ph.D., FASCP, R.Ph., Assistant Editor

Background

C-reactive protein (CRP) is synthesized in the liver in response to interleukin and other cytokine polypeptides which are released from sites of inflammation. Infections, burns, tissue necrosis, wounds, surgery, stress or psychiatric conditions, and atherosclerosis can precipitate the release of CRP. CRP amounts are thought to be proportional to the extent of tissue damage.[1,2]

High-sensitivity CRP tests (hs-CRP) are preferred over classic CRP testing due to their ability to detect CRP levels below 1 mg/L.[2]

The possible beneficial effects of statins have been described for several diseases, including Alzheimer's disease, multiple sclerosis, nonischemic cardiomyopathy, prevention of bone fractures, infection, and some types of cancer. The generalized anti-inflammatory action of the statins has been proposed as a possible explanation.[3,4]

In the Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 (PROVE IT – TIMI 22) trial comparing an aggressive LDL-lowering atorvastatin 80 mg regimen with a moderate LDL-lowering pravastatin 40 mg regimen, improved cardiovascular outcomes for aggressive statin therapy were demonstrated.[5] The Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial, using the same statin regimen, identified a reduced rate of progression of atherosclerosis with the intensive lipid-lowering atorvastatin regimen.[6] Both studies revealed significant reductions in CRP levels with aggressive statin therapy.[3,7]

Citation

Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005;352:20-8.

Methods

This study by Ridker et al was a substudy of PROVE IT – TIMI 22. It consisted of 3,745 participants representing 90% of the original study cohort. PROVE IT – TIMI 22 was a randomized trial between November 2000 and February 2004 which compared the effect of intensive statin therapy (atorvastatin 80 mg daily) with moderate statin therapy (pravastatin 40 mg daily) and of gatifloxacin and placebo on the risk of recurrent coronary events after acute coronary syndromes.[5] Members of the substudy population were alive and free of recurrent events 30 days after the study's end. Each participant had plasma measurements of both LDL cholesterol and hs-CRP at baseline randomization, 30 days, four months, and at the end of the study. The achieved levels of these two measures was defined as those obtained at the 30-day follow-up visit. The study population was divided into quartiles based on the levels of achieved LDL cholesterol and achieved CRP. The population was further divided on the basis of the approximate median achieved LDL cholesterol level (70 mg/dL) and the approximate median achieved CRP level (2 mg/L). These values served as target levels for the study. Researchers evaluated whether the rates of events differed between patients with values above the median and those below the median.

Results

The levels of both LDL cholesterol and CRP were reduced by the statin therapy at the end of 30 days. Intensive atorvastatin therapy reduced LDL cholesterol levels to below 70 mg/dL and CRP levels to below 2 mg/L more effectively than moderate pravastatin therapy. There was little evidence that either agent led to better clinical outcomes once target LDL cholesterol and CRP levels were achieved. Achieving both of these target levels was of greater importance for event-

More. . .

free survival than was the type of statin therapy. The correlation (r) between achieved LDL cholesterol levels and achieved CRP levels was small (r = 0.16, P = 0.001). Less than 3% of the variance in achieved CRP levels was explained by the variance in achieved LDL cholesterol. Recurrent myocardial infarctions or deaths in the study population were expressed as age-adjusted events per 100 patient years. These results are expressed below.

LDL/CRP Level*	**Event Rate**	**P Value****
LDL ≥ 70	4.0	0.008
LDL < 70	2.7	
CRP ≥ 2	3.9	0.006
CRP < 2	2.8	
LDL ≥ 70 & CRP ≥ 2	4.6	<0.001
LDL < 70 & CRP ≥ 2	3.1	
LDL ≥ 70 & CRP< 2	3.2	
LDL ≤ 70 & CRP< 2	2.4	
CRP ≥ 1	3.8	<0.001
CRP < 1	2.1	
LDL ≥ 70 & CRP ≥ 1	4.5	<0.001
LDL < 70 & CRP ≥ 1	3.1	
LDL ≥ 70 & CRP< 1	2.3	
LDL ≤ 70 & CRP< 1	1.9	

*LDL units = mg/dL, CPR units = mg/L

**P values for comparison between two or among four groups

Author Conclusions

Despite resultant levels of LDL cholesterol, patients who had low CRP levels after statin therapy had better clinical coronary outcomes than those with higher CRP levels. Monitoring CRP and LDL cholesterol should be used in lowering cardiovascular risks with statin therapy.

Commentary

This substudy of PROVE IT – TIMI 22 offers the first evidence suggesting that CRP is an independent factor useful in monitoring and adjusting statin therapy. Event rates were similar for LDL < 70 mg/dL and CRP ≥ 2 mg/L compared with LDL ≥ 70 mg/dL and CRP < 2 mg/L at 3.1 vs. 3.2 events per 100 patient-years, respectively. Furthermore, event rates for LDL < 70 mg/dl and CRP ≥ 1 mg/L were reported to be 3.1. Whereas, event rates for LDL ≥ 70 mg/dL and CRP < 1 mg/L were 2.3. When LDL ≤ 70 mg/dL and CRP < 1 mg/L, event rates were the lowest reported in the study.[8]

In a 502 patient substudy of the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study[7], the extent of both LDL cholesterol lowering and CRP lowering using the same statins and doses as in PROVE IT – TIMI 22 were associated with reduced progression of atheroma volume. Intensive atorvastatin therapy (80 mg per day) reduced the atheroma progression rate more than did moderate pravastatin therapy (40 mg per day). With reductions in LDL cholesterol and CRP both greater than their respective median percent changes, total atheroma volume showed the greatest reduction (-1.98 mm^3). As in the study by Ridker et al,[8] correlation between reductions in LDL cholesterol and reductions in CRP were weak (r = 0.13, P = 0.005). These data indicate that statin reductions in CRP are independent from statin reductions in LDL cholesterol. These authors conclude that their findings suggest that the level of CRP may be an important therapeutic target. They do not believe that their data is sufficient to recommend routine measurements of CRP alone for statin therapy modification.

The substudy data of the PROVE IT – TIMI 22 trial supports the aggressive use of statins to achieve target levels of both LDL cholesterol and CRP for reduction of coronary events in post acute coronary syndrome patients [Evidence level A; high-quality RCT].[8]

Guidelines currently do not recommend routine use of CRP as a screening test for the general population. Rather, it is recommended for detecting enhanced absolute risk in those where multiple risk factor scoring projects a ten year coronary heart disease risk in the range of 10% to 20%.[9] The American Heart Association (AHA) in their 2004 Scientific Statement on Preventing Cancer, Cardiovascular Disease, and Diabetes identify hs-CRP as an additional factor that may help in the prognostification of risk.[10]

More. . .

Further studies will be needed to answer the question whether CRP alone will be useful for initiation and modulation of statin therapy.

Users of this document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and Internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

References

1. Kehoe WA. C-reactive protein and heart disease. *Pharmacist's Letter/Prescriber's Letter* 2003;19(1):190105.
2. Kushner JM. When to use C-reactive protein in cardiovascular disease. *Pharmacist's Letter/Prescriber's Letter* 2003;19(3):190301.
3. Topol EJ. Intensive statin therapy – a sea change in cardiovascular prevention. *N Engl J Med* 2004;350:1562-4.
4. Almog Y, Shefer A, Novack V, et al. Prior statin therapy is associated with a decreased rate of severe sepsis. *Circulation* 2004;110:880-5.
5. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495-504.
6. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA* 2004;291:1071-80.
7. Nissen, SE, Tuzcu, EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med* 2005;352:29-38.
8. Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005;352:20-8.
9. Pearson TA, Mensah, GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Center for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499-511.
10. Eyre H, Kahn R, Robertson RM. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. *Circulation* 2004;109:3244-55.

Cite this Detail-Document as follows: C-reactive protein and statin benefits. Pharmacist's Letter/Prescriber's Letter 2005;21(2):210208.

PHARMACIST'S LETTER

The most practical knowledge in the least time…

PRESCRIBER'S LETTER

3120 West March Lane, P.O. Box 8190, Stockton, CA 95208 ~ TEL (209) 472-2240 ~ FAX (209) 472-2249