

Hi Lipidaholics: It is early February and dreary in the Northeast, so it's time to talk about some heat: INFLAMMATION. Everyone seems to be all fired up about C-reactive protein so what is my take. I just received the following e-mail from a clinician:

I have a 60 year old woman who is in good health. BP is 125/85. Thyroid studies normal. Glucose = 121 mg/dL. I checked a LipoScience recently and found the following:

Original NMR LipoProfile

LDL -P 2103 umol/L (perfect < 1000)  
Small LDL-P = 1456 (desirable < 700)  
DL size 19.8 (small is <M 20.6)  
large HDL 20 mg/dL (desirable > 30 in drug naive pt)  
large VLDL 55 (desirable < 7)  
She was started on Pravachol 40 mg and ASA 81 mg day and ASA 81 mg

LDL-P 1013 umol/L (perfect < 1000)  
Small LDL- P = 605 (desirable < 700)  
LDL size is small at 20.5 nm  
Large HDL is decreased at 14 mg/dL  
Large VLDL is increased at 63 mg/dL (desirable < 7)

These lipoprotein numbers seem to me to be decent. She probably has the metabolic syndrome, but her lipids seem controlled. Her CRP is 7, however. She takes no other medicine and is not obese. "I can't really figure out what to make of CRP. Should she have TriCor in spite of the good LDL numbers? What does it mean?"

#### **DAYSRING DISCUSSION:**

What in is CRP? Is there anything not associated with an elevated CRP. Seems like every time I pick up a journal it is related to something new.

CRP is a hepatically produced pentraxin that plays a key role in the inflammatory response. Certainly several studies have shown it to be an independent predictor of CVD events in men and women. There are many articles demonstrating that CRP is not only a marker of plaque but also a mediator of atherosclerosis. In the THROMBO (AJC May 2003) study elevated CRP in post-infarction patients was associated with von Willebrand factor, D-dimer and fibrinogen. Of increasing importance is also the knowledge that CRP is a strong and independent predictor of type 2 diabetes, where inflammation is very much involved (Diabetes 53:693-700, 2004). Interestingly the association between CRP and insulin resistance is independent of obesity (Circulation. 2002;106:2908-2912.).

In a very powerful editorial Paul Ridker, Peter Wilson (Framingham) and Scott Gfrundy (NCEP Chairman) stated: "Given the consistency of prognostic data for hsCRP and the practicality of its use in outpatient clinical settings, we believe the time has come for a careful consideration of adding hsCRP as a clinical criterion for metabolic syndrome and for the creation of an hsCRP-modified coronary risk score useful for global risk prediction in both men and women. Toward this end, we believe experts in the fields of epidemiology, prevention, vascular biology, and clinical cardiology should be convened to begin discussing the merits of this proposal. (Circulation. 2004;109:2818-2825.)

CRP should be reported as mg/L. Less than 1 mg/L is low risk, 1-3 mg/L is moderate risk, 3-11 mg/L is high risk and anything greater is likely and acute phase reaction.

For the most spectacular reviews of inflammation and atherosclerosis (with many fantastic color sketches) see Peter Libby's review published in Nature 420:868 December 2002 and Scientific American May 2002

Two years ago the AHA in conjunction with the CDC issued guidelines on how CRP is best utilized in clinical practice. (Circulation. 2003;107:499-511.) They state:

On the basis of the available evidence, the Writing Group recommends against screening of the entire adult population for hs-CRP as a public health measure. The Writing Group does conclude that it is reasonable to measure hs-CRP as an adjunct to the major risk factors to further assess absolute risk for coronary disease primary prevention.

At the discretion of the physician, the measurement is considered optional, based on the moderate level of evidence. In this role, hs-CRP measurement appears to be best employed to detect enhanced absolute risk in persons in whom multiple risk factor scoring projects a 10-year CHD risk in the range of 10% to 20%.

The finding of a high relative risk level of hs-CRP > 3.0 mg) may allow for intensification of medical therapy to further reduce risk and to motivate some patients to improve their lifestyle or comply with medications prescribed to reduce their risk.

Individuals at low risk (>10% per 10 years) will be unlikely to have a high risk (>20%) identified through hs-CRP testing.

Individuals at high risk (>20% risk over 10 years) or with established arteriosclerotic disease generally should be treated intensively regardless of their hs-CRP levels, so the utility of hs-CRP in secondary prevention appears to be more limited. In patients with stable coronary disease or acute coronary syndromes, hs-CRP measurement may be useful as an independent marker for assessing likelihood of recurrent events, including death, myocardial infarction, or revascularization after percutaneous coronary intervention.

Secondary preventive interventions with proven efficacy should not be dependent on hs-CRP levels.

Further, **serial testing of hs-CRP should not be used to monitor effects of treatment.**

*Briefly put, high risk patients already qualify for the most aggressive treatment so CRP would not be of help in treatment decisions.*

Very recently the AHA published findings of a workshop and consensus panel: (Circulation. 2004;110:e550–e553.) Here are the conclusions:

#### Recommendations for Clinical Practice

1. High-sensitivity C-reactive protein (hsCRP) is an independent marker of risk that may be used at the discretion of the physician in patients judged by global risk assessment to be at intermediate risk (10% to 20% risk of coronary heart disease [CHD] per 10 years) for cardiovascular disease (CVD). hsCRP may help direct further evaluation and therapy in the primary prevention of CVD. The benefits of such therapy based on this strategy remain uncertain.

2. hsCRP is an independent marker of risk and may be used at the discretion of the physician as part of a global coronary risk assessment in adults without known CVD. The benefits of this strategy remain uncertain. hsCRP levels may be useful in motivating patients to improve their lifestyle behaviors.

4. Patients with persistently unexplained marked elevation of hsCRP ( $\geq 10$  mg/L) after repeated testing should be evaluated for noncardiovascular causes.
5. Inflammatory markers (cytokines, other acute-phase reactants) other than hsCRP should not be measured for the determination of coronary risk.
6. hsCRP measurement in patients with stable coronary disease or acute coronary syndromes (ACS) may be useful as an independent marker of prognosis for recurrent events, including death, myocardial infarction, and restenosis after percutaneous coronary intervention (PCI).
7. Application of secondary prevention measures should not depend on hsCRP determination.
8. Application of management guidelines for ACS should not depend on hsCRP levels.
9. Serial testing of hsCRP should not be used to monitor the effects of treatment.

Confounding all of the above is the recent data from PROVE IT and REVERSAL studies where both reduction in clinical outcomes and reduction of coronary plaque itself seemed to correlate with both LDL-C and CRP reduction. The patients who did best were those who normalized both LDL-C and CRP. Based on these two new bits of information some are now advising achieving CRP goal with across the board use of gorilla statins (high dose). The folks who now spout this throw around the term evidence based medicine! This is the same crowd that was using Lipitor for 5 years before it had any outcome evidence instead of Pravachol or Lipitor that had plenty of outcome evidence. Isn't it amusing how docs saying you need evidence only say that when it justifies what they are doing.

Here is my opinion: The best way to reduce arterial wall inflammation and CRP is to keep sterols (mostly cholesterol out of the artery wall). If you stop pouring gas on a fire, the fire goes out. How does one prevent sterols from entering an artery wall: normalize apoB (the particles that carry cholesterol). Most of my readers know that in our insulin resistant patients (TG/HDL axis disorders) there is little correlation between LDL-C and LDL-P. So I find it misleading to say that you must lower CRP and LDL-C. We need data from those above trials that show CRP is independent from LDL-P.

To normalize LDL-P we are going to have to use combinations of statins, ezetimibe, fibrates, niacin and resins. As monotherapy statins, fibrates both lower CRP with statistical significance. Niacin and Zetia do not. Other drugs that can lower CRP are Plavix, TZDs and ASA in some studies but not others. However when you add niacin or Zetia to a statin there is significant additional CRP lowering. So if you believe you need to get to a CRP goal (not even hinted at in any guidelines) why would not you use a statin with Zetia, TriCor or Niaspan. All of those combinations are great at keeping cholesterol out of the artery wall (through different mechanisms) and all should lower CRP beyond what the statin does. Combo therapy with the above combos will lower apoB particles much better than statin monotherapy.

In case you think statins are the only drugs with magical, mystery pleiotropic (non lipid effects) think again. In the VA-IT trial almost half of the benefit of fibrate had nothing to do with lipoproteins changes induced by the fibrate. The reduction in outcomes was related to pleiotropic benefits of the fibrate. Much if not all of the statin pleiotropy is due to the inhibition of mevalonic acid synthesis. This results in less farnesyl and geranylgeranylPP. These will affect rho, ras, PPAR's and ultimately nuclear factor kappa B a regulator of vascular wall inflammation. So again, in effect the statin pleiotropy may be solely related to decreasing mevalonic acid synthesis.

Other drugs that might be used for reasons other than lipid control that can help CRP: are Plavix and TZDs and omega-3 FA.

To really throw a monkey wrench into this whole CRP things is a just published paper (Arch Intern Med. 2005;165:221-226) which just demonstrated that repeated CRP measurements jump all over the place: Here are the findings:

Results: C-reactive protein values in individual patients fluctuated considerably when examined in the following ranges: less than 1 mg/L, 1 to 3 mg/L, and greater than 3 mg/L, proposed to indicate low, average, and high risk. Sixty-four patients (40.3%) changed risk category between the first and the second measurement. Within patient variances of CRP and IL-6 levels were 1.79 mg/L (95% confidence interval, 1.60-2.00) and 2.69 pg/mL (95% confidence interval, 2.29-3.18), respectively. The variability of CRP was consistent over different times and across clinical groups, and independent of body mass index, smoking status, medication, and clinical events.

Conclusions: Relatively important fluctuations in CRP levels in patients with stable ischemic heart disease may be problematic for risk stratification and treatment monitoring.

A similar IL-6 variability suggests that these patients have a dynamic inflammatory status whose kinetics may modulate acute coronary risk.

We need to wait for the following: The ongoing Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) was designed to assess the effect of statin therapy on cardiovascular events in individuals who have high CRP levels ( $\geq 2$  mg/L) but do not have elevated LDL cholesterol (entry criterion  $< 130$  mg/dL) [55•]. Projected enrollment is approximately 15,000 men (aged  $\geq 55$  years) and women (aged  $\geq 65$  years) without a prior cardiovascular event or CHD risk equivalent as defined in the US National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) guidelines.

DAYSRING ADVICE: Use CRP as an emerging risk factor to help ascertain risk and then get lipoproteins to goal using available lipid medications. Be aggressive with combination therapies. In insulin resistant patients statin/Zetia/TriCor would solve the overwhelming majority of lipoprotein abnormalities seen in most patients.

## REFERENCES OF THE WEEK

- 1) Utility of Statin Therapy Using Highsensitivity C-Reactive Protein As an Indicator of Coronary Heart Disease Risk Vijay Nambi, MD, and Christie M. Ballantyne, MD Current Atherosclerosis Reports 2005, 7:22–28. This is a great follow up to this case discussion.
- 2) Should Age and Time Be Eliminated From Cardiovascular Risk Prediction Models? Rationale for the Creation of a New National Risk Detection Program Paul M Ridker, MD, MPH; Nancy Cook, ScD. A great discussion on maybe we are paying too much attention to age in risk assessment. (Circulation. 2005;111:657-658.)
- 3) National Study of Physician Awareness and Adherence to Cardiovascular Disease Prevention Guidelines Circulation. 2005;111:499-510.) This is a special report to physicians from the AHA. It is very depressing showing how underutilized guidelines are and therefore how poorly and aggressively high risk patients are being treated. BOTTOM LINE: DO NOT NE A WOMEN IN AMERICA AND EXPECT COMPETENT PREVENTICE CARDIOVASCULAR CARE

## DAYSRING TRAVELS

Columbus and Cincinnati, OH  
Burlington, NC  
Atlanta, GA  
Phoenix, AZ  
Louisville and Lexington, KY  
Providence, RI  
Gary, IN  
Chicago, IL  
San Diego, CA

For my GYN friends: I will be doing a series of CME programs in person and through webcasts throughout the US discussing estrogens, progestins, CHD in women, etc. Look for me in March in San Diego, Minneapolis, Chicago, Philadelphia, Detroit

Join National Lipid Association [www.lipid.org](http://www.lipid.org)  
Join the North American Menopause Society [www.menopause.org](http://www.menopause.org)

Great meeting this summer: An International Symposium in Manhattan  
All of the worlds experts will be here July 14-17th  
Triglycerides and HDL-C: Role in CVD and Metabolic Syndrome  
Visit [www.lorenzinfoundation.org](http://www.lorenzinfoundation.org)

As always thoughts for our troops. I again all of you to visit the following Website to appreciate our heroes: You will not be disappointed.

<http://www.clermontyellow.accountsupport.com/flash/UntilThen.swf>

Happy Lipiding and watch those lipids on Valentines day.

Tom

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