Role of hs-CRP In Risk Prediction

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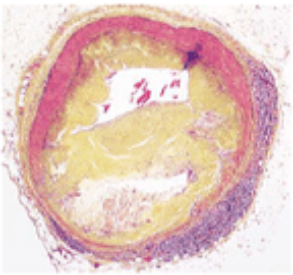
Coronary artery disease is a major cause of death in the western world. Inflammation plays an important role in the initiation and progression of atherothrombosis and in the pathogenesis of acute cardiovascular disease (CVD) events. Dr Paul M Ridker (Brigham and Women's Hospital, Boston) estimates that 25 million to 30 million healthy, middle aged adults in the US, who have "normal" cholesterol and LDL-C levels but above average inflammation levels, are at high-risk for CVD events.

Figure 1. Coronary Artery Inflammation



High-sensitivity or cardiac C-reactive protein (hs-CRP) is a sensitive marker of chronic inflammation that is not affected by ischemic injury. It is an inexpensive, easily measured assay that is widely available and reliable. This *Heartbeat* will cover the utility of a high hs-CRP as a marker and predictor of future cardiovascular events to assist us with global risk reduction. New data will be covered which indicate that hs-CRP is a stronger marker for risk than LDL-C, and that both should be considered markers for risk. Clinical implications of this new information and a plan of how this can be used as a guide to aggressive therapy for the prevention and treatment of CVD will be outlined.

Global Risk Reduction

"If prevention is your goal, don't focus on the hole, focus on the donut." …Unknown

We now know that aggressive preventative action will significantly reduce CV events in high-risk patients. Global risk reduction (with attention to the vascular wall and endothelial dysfunction—including inflammation) to prevent initial and/or recurrent CV events may be more important than interventional treatment. Initiating smoking cessation, exercise and diet programs, control of diabetes and hypertension and appropriate medical therapy with aspirin, ACE-inhibitors, beta-blockers and statins would all be part of the global risk-reduction package.

Risk stratification is important because information about the probability of a CV event in the future can help target therapy and resources to those who will benefit most. Current guidelines (NCEP- ATP III) recommend global risk reduction and goal LDL-C of < 100mg/dL for all with known CVD and those with coronary heart disease (CHD) equivalent disease [diabetes mellitus (DM) and those with > 20% 10 year risk of developing CHD-based on the Framingham Risk Score[1]].

New Use for an Old Test … Predictor?

"Prediction is very difficult, especially about the future."…Niels Bohr

The recent results of the Heart Protection Study[2] showed that patients with very low LDL-C levels at baseline could still benefit from LDL-C reduction with statins. This is good reason for

physicians to be more aggressive than present guidelines suggest and treat all patients with disease regardless of LDL-C levels. In another survey only half of patients with CHD had hypercholesterolemia.[3] This information emphasizes the need to identify new markers to enable us to optimally target risk other than LDL-C.

Evidence has accumulated in recent years that show hs-CRP is a marker of inflammation that plays a central role in the origins and complications of atherothrombosis. *The data clearly suggest that higher levels of hs-CRP serve as predictors of CV risk.* In the most recent study, Ridker et al. add to the growing body of evidence that hs-CRP is an independent predictor of CVD.[4] In this 8-year study of nearly 28,000 women, C-reactive protein (CRP) levels were found to predict the risk of subsequent cardiovascular events independently of other known coronary risk factors. CRP and low-density lipoprotein cholesterol levels were found to be complementary in the prediction of future CV events and appeared to identify different groups at risk. The two markers appeared to be independent of each other, to the point of delineating different high-risk groups, Ridker said. "So cholesterol is important, but inflammation is also important, and they're different patients, so when you combine the two things, you actually get a very powerful way to predict cardiac risk."

Most of the events were occurring at LDL-C levels, not just below the guideline levels for initiating drug therapy, but also below the target for treatment, thus providing further implication for the detection and prevention of CVD.

As you would anticipate, survival curves demonstrated that patients with both high LDL-C and high hs-CRP were at high risk, and those with low levels of both markers were at low risk. The critically *important point is that patients with low LDL-C/high hs-CRP (not usually targeted for treatment) have significantly higher risk of a cardiac event than those with high LDL-C/ low hs-CRP (usually targeted for treatment).*

Further analysis showed that hs-CRP measurement added to the prognostic information gained using the Framingham Risk Score. Increasing levels of hs-CRP were associated with increased risk of CV events at all levels of estimated 10-year risk.

Major Dilemma

What to do with all of the new information on hs-CRP is a major issue. Questions include: How should hs-CRP be used to identify additional people who may benefit from care? Is there a role for CRP in primary prevention or acute coronary syndrome? Does CRP have a direct role in the process of atherothrombosis—making it a risk factor in addition to a marker? Should CRP be used for global risk assessment at this time?

"The implications of this new information are enormous," says Dr Ridker. "It means we have an entire other way of treating, targeting, and preventing heart disease that was essentially missed because of our focus on cholesterol." The problem is that trials that show that treatments with therapies such as statins will result in improved outcomes are not yet available.

Preliminary data would suggest statins are beneficial. According to a retrospective analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study, patients who lack overt hyperlipidemia but have elevated hs-CRP levels are at similar risk of a first coronary event and obtain the same benefit from treatment with statins.[5] This supports the belief that atherothrombosis is in part an inflammatory disorder and that statins have an anti-inflammatory effect. A more recent study found that statins not only act on cholesterol levels, but also significantly lower hs-CRP levels in two weeks, leading the investigators to conclude that statins work through multiple mechanisms to help protect the body from heart disease. It also concluded that, regardless of their effect on lowering LDL-C, the drugs prevent against first and recurrent heart attacks by lowering hs-CRP levels.[6]

Another recent study showed aggressive statin therapy reduces CRP more than moderate treatment.[7] In this 2-year randomized, double-blind study in 325 patients hs-CRP values were reduced by 40% with atorvastatin 80mg vs. 20% with simvastatin 40mg and patients with the largest hs-CRP reductions exhibited a 2-fold greater reduction in mean carotid artery intima media thickness. This study takes on particular relevance in light of Ridker's large study identifying CRP as an independent predictor of risk.

Other recent studies have revealed an association between high levels of CRP and metabolic syndrome (possibly predicting future diabetes), physical inactivity and the presence of coronary artery calcification and prediction of risk. Lifestyle modifications (diet, exercise and tobacco cessation) can help decrease cholesterol levels, reduce inflammatory processes, and decelerate atherothrombosis progression in these situations.

Looking to Jupiter for the Answers…

A new 15,000 patient trial (**Jupiter**) will randomize men and women with high CRP and low LDL-C (<130mg/dL) to treatment with rosuvastatin 20mg. There is no conclusive evidence that statins are beneficial in these patients who don't usually qualify for treatment with statins.

Consensus

There is compelling evidence that hs-CRP links inflammation, an important component of the atherothrombotic process to the future risk of heart disease. It is very difficult to argue not to add hs-CRP measurements to our patient global risk assessment and Framingham CHD risk scores especially in those with two risk factors or strong family history. Patients with high CRP/LDL are in the highest risk category and should be treated, including statins. Those with high CRP/low LDL are currently categorized as low risk and are presently not treated because of low LDL-C. With the new information regarding CRP, however aggressive lifestyle changes and other risk factor modification should be recommended. *High hs-CRP should be used to motivate patients who are identified as high-risk to make lifestyle changes that have been proven to be beneficial.* Unless patients have known CVD or equivalent disease further medical therapy (statins) cannot be recommended until good, prospective, randomized trials are completed.

Modifying the risk factors that have already been proved to affect CV risk is mandatory. It seems apparent that hs-CRP predictive powers should play an important part in CHD global risk assessment, determining prognosis and tailoring therapy to improve outcomes. It may act as a *tiebreaker* in deciding how aggressively to treat a patient without either CHD or DM with statins.

Recommendations to come

A joint report from the American Heart Association and the Centers for Disease Control and Prevention will be released within the first quarter of 2003 that will include recommendations on CRP screening and "what to do in the office Monday morning."

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mailto:maiese@dnamail.com
Heartbeats can be found @ www.sjhg.salu.net under Patient Education—From Your Physician

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[1] Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults. NCEP-ATP III (CHD Risk Calculator). *JAMA* May 16 2001; 285: 2486-97. (Computer and paper versions of the Framingham Risk Score are on our website-above.)

[2] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo controlled trial. *Lancet* July 6 2002; 360: 7-22.

[3] EUROASPIRE: a European Society of Cardiology survey of secondary prevention of coronary artery disease: principal results. *Eur Heart J* 1997; 18: 1569-82.

[4] Ridker PM et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* November 14 2002; 347: 1557-65.

[5] Ridker PM et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001; 344: 1959-65.

[6] Plenge JK et al. Simvastatin lowers C reactive protein within 14 days (an effect independent of low-density lipoprotein cholesterol reduction. *Circulation* September 17 2002; 106: 1447-1452.

[7] van Wissen S et al. Differential hs-CRP reduction in patients with familial hypercholesterolemia treated with aggressive or conventional statin therapy. *Atherosclerosis* December 2002; 165: 361-66.