C-Reactive Protein, Inflammation, and Cardiovascular Disease

Clinical Update

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Two-and-a-half years ago, we presented C-reactive protein (CRP) data from the Women's Health Study, a large prospective study of 30,000 healthy middle-aged women followed over 10 years for the occurrence of first-ever cardiovascular events (the final results of the Women's Health Study regarding the effects of aspirin and of vitamin E randomization have just been published [*N Engl J Med* 2005;352:1293-304 and *JAMA* 2005;294:56-65]). We showed that high-sensitivity CRP is a very good predictor of vascular events in this population. Moreover, CRP provides prognostic information beyond low-density lipids (LDL). We identified a unique population—low-LDL, high-CRP individuals—that otherwise might have been missed. This was the impetus for the JUPITER trial, which I'll mention later.

At all levels of LDL, at all levels of metabolic syndrome, and at all levels of Framingham risk, CRP provides additive information on vascular risk. In conjunction with Peter Wilson and Scott Grundy, we are developing a CRP-modified Framingham Risk Score. There are now 34 large-scale prospective studies that have all come to the same conclusion: CRP is one of the most consistent risk stratifiers that we have. But it is important to think beyond CRP as a simple marker for high risk of disease. It also tells us something about the underlying biology.

Metabolic Syndrome and CRP

There is a component of the metabolic syndrome that's proinflammatory and hypofibrolytic, which conveys additional risk. Two years ago, we were able to show that CRP provided further discriminatory value to the presence or absence of metabolic syndrome. Patients without metabolic syndrome and with low CRP have very low risk; patients with metabolic syndrome and high CRP have very high risk. Clearly, when the inflammatory mechanisms are engaged, metabolic syndrome patients do much worse. There is tremendous enthusiasm among endocrine investigators for tying together the endocrine dysfunction of metabolic syndrome and the development of both diabetes and vascular events. It might even be possible to redefine metabolic syndrome to include this added risk. One way to do this would be to leave the obesity component alone, and to change the triglyceride and HDL components to one (since they are so often linked): triglycerides greater than 150 or an HDL less than 40. Keep the blood pressure and glucose components, but add a new qualifier: a CRP greater than 3. This modified definition seems to predict both diabetes and vascular events better than the old one does, at least in our cohorts, where we've tested it.

Unfortunately, the big picture is a little more complicated. For high sensitivity assays of CRP or "hsCRP," we say that less than 1 mg/L is low risk, 1 to 3 mg/L is moderate risk, and greater than 3 mg/L is high risk—that's simple enough. But the continuum extends beyond that. The patients with the very highest levels of hsCRP—5 to 10, 10 to 20, or even greater than 20 mg/L—are, in fact, at the very highest risk. These are not false positives. These data help to explain why those with periodontal disease, arthritis, and other systemic inflammatory disorders all have higher vascular risk. Perhaps inflammation from any cause has an adverse effect on the vascular endothelium.

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Lowering CRP with Exercise

What about lowering CRP? Does that reduce risk? There's no doubt that the very best way to lower CRP is through exercise, weight loss, and dietary control; of course, those are all proven already to lower vascular risk. There is a paper that came out in February comparing the Atkins diet, the Zone diet, the Weight Watchers diet, and the Ornish diet. All these diets did basically the same thing: they got weight down a little bit, the lipid ratios came down, the CRPs came down, and insulin levels came down. These processes are all intimately interrelated. Dieting works. Even gastric bypass surgery works. CRP, interleukin-6 (IL-6), and tumor necrosis factor (TNF) all come down in gastric surgery patients. But just removing the fat isn't good enough. Our patients have to do the hard work. As published in the *New England Journal of Medicine* last year, liposuction does not alter insulin sensitivity; does not reduce CRP, IL-6, or TNF; and does not affect other risk factors for coronary heart disease.

I believe that the true impact of exercise has been underestimated in the general community. There are over 50 papers about the impact of exercise on inflammatory markers and event reduction. Here is an example: Milani and coworkers noted that cardiac rehab did a nice job of lowering CRPs, regardless of whether the patients were or were not on statins. Moreover, CRPs fell whether or not the patients actually lost weight. The exercise benefit was independent of weight loss.

Recent Data Pertaining to Statins

Do we as cardiologists need to think about monitoring CRP in secondary prevention? These are already high-risk patients; is there incremental benefit to measuring CRP? In January of this year, 2 new papers came out that have really added important new perspective to this question.

We performed a prespecified analysis in PROVE IT/TIMI 22 to determine how much of the benefit of statin therapy was attributable to LDL reduction and how much was attributable to CRP reduction. We examined the achieved LDL and the achieved CRP at 30 days, to allow resolution of the acute-phase CRP and provide time for the statins to have a stabilizing effect on LDL. From 30 days onward, how well did we predict events? Those who got their LDLs below 70 mg/dL, and about 50% of the patients did, had a lower event rate. But there is another side to the story. Fifty percent of the patients got their CRPs below 2 mg/L and 50% were above 2 mg/L at 30 days, and those levels were equally predictive of subsequent events. Are these the same patients or are they different patients? We were pretty confident that they were going to be different patients, because in all the prior work, there was virtually no relationship between LDL and CRP, and no relationship in the change in LDL and the change in CRP. That's exactly what we found. Only 3% of the variance in your patients' CRP can be predicted on the basis of their LDL. So what happens if CRP comes down, but LDL doesn't? What we found was about a 50% reduction in events in this population. What if the LDL does come down? Does lowering the CRP more provide more benefit? The simple answer to that question is yes. Roughly 25% not only got the LDL below 70 mg/dL, they also got the CRP below 2 mg/L, and as a group these patients did substantially better in terms of long-term event-free survival. Moreover, if the CRP went down even further, to less than 1 mg/L, the event rates were lower still.

The predictive value of hsCRP stands up even after adjusting for age, sex, smoking status, diabetes, hypertension, obesity, peak creatine kinase, Killip class, early revascularization, and HDL; nothing changes. Even with these adjustments, CRP remains a strong predictor of outcome. But a major question remains. Is it the drug, or is it the levels? The more potent a statin, on average, the greater the CRP reduction; but for the individual patient, this is a highly variable response.

In PROVE IT/TIMI 22, what is particularly interesting is that if the LDL was below 70 mg/dL and the CRP was below 2 mg/L, the survival was the same regardless of the drug used. The same was true for people with an LDL below 70 and high CRPs, and in people with LDLs above 70 and either high or low CRPs. In other words, what mattered was not so much the drug; what mattered was whether or not the patients achieved the "dual goals" of both LDL and CRP reduction. Achieving these dual goals appears to be more important than how you get there. When we adjusted for only these 2 factors—the LDL and the CRP that were achieved—and re-examined the overall benefit in the PROVE IT trial of atorvastatin 80 mg versus pravastatin 40 mg, the odds ratio went to 1.00; there was no difference.

The REVERSAL data appeared simultaneously; the same drugs were used, in the same doses, in stable patients, looking at intravascular ultrasound measurements of plaque volume. Those results also showed no relationship between the change in LDL and the change in CRP, either with pravastatin or atorvastatin. As LDL comes down, we look for a slowing of the progression of the disease. As the CRP comes down, there is also a slowing of the progression with a little twist—namely that when the CRPs come down a lot, the atheroma volume actually starts to fall below the zero line. The REVERSAL investigators did a similar stratified analysis, like the one we did in PROVE IT/TIMI 22, looking at whether patients ended up above or below the median LDL and CRP levels. When the LDL and the CRP did not come below their medians,

there was an 8-mm^3 progression. When only the LDL came down below median, there was less progression. When only the CRP came down, there was some regression. And when they both came down, there was more regression.

What we've learned from these 2 studies is that patients on statin therapy who achieve low levels of CRP have better clinical outcomes at all levels of achieved LDL. The best clinical outcomes are obtained among statin-treated patients who achieve the dual goals of an LDL below 70 mg/dL and a CRP below 2 mg/L. This is true for statin-treated patients; we don't know if this is true for patients on other classes of drugs. The relationship between achieved LDL and achieved CRP is highly variable for individual patients and cannot be predicted on a clinical basis. Therefore, strategies to optimally and effectively prescribe statins to reduce risk may need to measure and monitor CRP in exactly the same way we measure and monitor LDL.

The JUPITER trial goes farther, to look at primary prevention patients who don't normally qualify for statins: apparently healthy people with LDLs of less than 130 and CRPs above 2. We're randomizing these patients to either rosuvastatin or placebo and looking at hard clinical endpoints at 3 to 4 years in 15,000 patients.

Genetics

I want to say a few final words about genetics. A number of polymorphisms in the CRP gene have been identified by our group, as well as by other investigators around the world. Led by David Miller and David Kwiatkowski, we did a sequencing project across 3 different large populations—the Women's Health Study, our PRINCE cohort, and the Physicians' Health Study—and showed consistent effects across all 3 cohorts. We also would suggest that about half of the population variance in CRP is attributable to lifestyle: smoking, diet, exercise—all things that are modifiable. Because the other half is primarily inherited, the question arises: Can we identify any pharmacogenetic issues that will help us to design future trials to figure out what patients to target for this inflammatory response? We hope to have the opportunity to answer that question in the not-too-distant future.