

# The Final Common Pathway Leading to Atherosclerosis



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Every day, we see in our offices patients who have hypertension, diabetes, obesity and dyslipidemia. We watch as these conditions, alone or in combination, alter the lives of our patients, reducing their quality of life, longevity and earning potential. Hospitalized for the sequelae of atherosclerosis (e.g., stroke, MI, etc.) we deal with the psychosocial impact this inflammatory condition has on the families we see. In an attempt to prevent these complications, we utilize biomarkers such as total cholesterol and LDL-C not only to define our high-risk population to initiate treatment, but as a therapeutic target for future risk reduction and as a goal for ongoing treatment titration. However, our biomarkers have been crude, occasionally missing patients. Framingham's 26-year follow-up defined that 50% of coronary heart disease occurred in people with below-average total cholesterol. As outlined in this issue's first article, research has defined additional biomarkers to prevent these patients from slipping through the cracks.

In a recent needs analysis, family physicians have ranked biomarkers, such as hs-CRP and the concept of endothelial dysfunction, as one of the top areas of interest.

C-reactive protein structurally looks like a five-sided martial arts throwing star. As this analogy has a sinister nature, so does this protein. Being not only a biomarker, CRP is a now thought to be a modifiable risk factor. Where LDL-C is able to define the calcified old lesions, hs-CRP is able to identify the new acutely high-risk plaques. Originally thought to be made by the liver, CRP has recently been shown to be made by adipose tissue. In the average patient, 30% of CRP is thought to be made by fat cells, but this amount increases as the patient becomes more obese. This finding can be seen early in the pediatric age group, where obese 10.5-year-old children were found to have increased CRP.

Dr. Roussin has stated that patients with inflammatory arthritis, such as rheumatoid arthritis, who are known to have very high CRPs have a 3.5-fold increase in risk of cardiovascular events.

Diabetics have elevated CRP. Poor glycemic control increases CRP and, in conjunction with elevated CRP, increases the rate of apoptosis (programmed cell death) in endothelial cells.

CRP has been shown to mediate its effect like angiotensin by working through the AT1 receptor. By mediating the negative effects on the smooth muscle

cells of the vessel wall and on macrophages, CRP is able to drive the atherosclerotic process. Hyperlipidemia has been shown by Nickenig to increase the number of AT1 receptors, potentially allowing CRP to have more sites to act. This upregulation of the AT1 receptor, he showed in his 1999 *Circulation* article, could be down-regulated with the use of a statin.

As outlined in the first article in this issue, several therapeutic agents are able to modulate vascular inflammation. Nitric-oxide production is increased (improved) with ACE inhibitors, CCBs, statins and several other medications. HMG CoA-reductase inhibitors have effects that go beyond LDL-C lowering. These pleiotropic effects are thought to result in acute and long-term benefits on vascular function through the reduction of vascular inflammation. Numerous studies with statins have shown CRP reduction (e.g., with atorvastatin by 14% to 47%, simvastatin by 11.8% to 28.7%, simvastatin and ezetimibe by 27% to 40%, pravastatin by 13% to 20%, lovastatin by 15%, fluvastatin by 0%, rosuvastatin by 34% to 39.8%). Though primary mortality endpoints for hs-CRP are not yet available, surrogate markers, such as the halting of atherogenic progression, have been shown in the REVERSAL study.

Currently, with the results of the Physicians and Women's Health Studies, the best biomarker as a predictor of risk is thought to be a sum of hs-CRP and non-HDL cholesterol. Though this may become the new guideline in the future, it is not yet ready for prime-time, as outlined in the article by Dr. Greenberg.

For years, we have focused on small areas of occlusion as being the main culprit lesion, losing sight of the fact that, in a relative value system, this represents a small area of 0.0002 square meters of a total human body vascular bed equal to 1,000 square metres. This diffuse vascular inflammation that we call atherosclerosis requires systemic medical management that we employ every day in our office. By using ASA, ACE inhibitors, CCBs, statins, lifestyle modification, etc., we alter not only surrogate markers, but primary endpoints such as death. This issue attempts to give understanding to the process and is not intended as a promotion for using new and evolving biomarkers on a regular basis. By putting the pathophysiologic and pharmacologic pieces together, we hope to give you an understanding of how the interventions we use on a daily basis evoke their benefit through modulation of the final common pathway referred to as vascular inflammation. ☺

Yours,

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