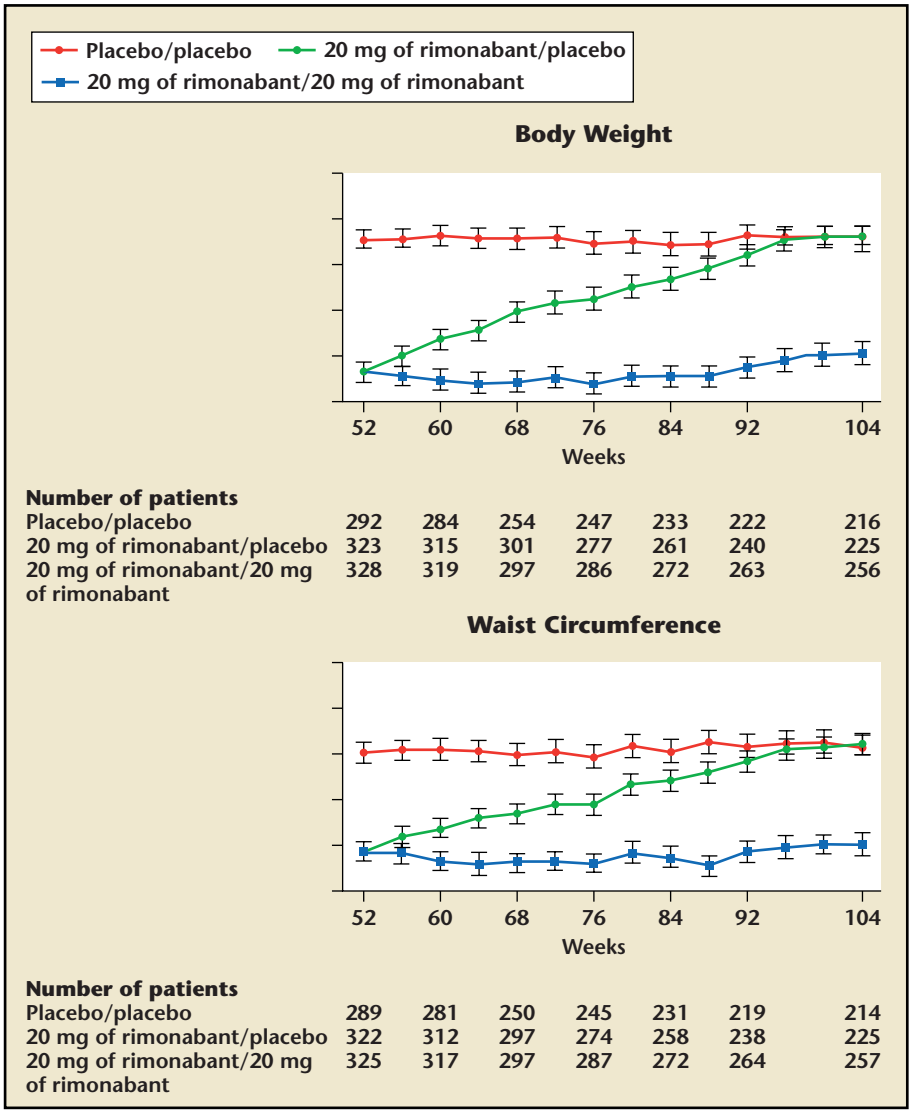

Figure 3. *Maintaining improvement in weight and waist circumference in year 2. Adapted with permission from Pi-Sunyer FX, et al.* JAMA. *2006;295:761-775.*

Atherosclerosis

The Role of C-Reactive Protein

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C-reactive protein (CRP), a serum marker, has been shown to be a valuable marker for cardiovascular disease and its clinical sequelae. This predictive value seems to be independent of the low-density lipoprotein (LDL) cholesterol level and the Framingham 10-year risk score. Despite this epidemiological evidence, the pathophysiology behind the ways CRP confers risks is not well understood. Two new studies examine how CRP promotes atherosclerosis and what determines an individual's CRP level.

C-Reactive Protein Induces Matrix Metalloproteinase-1 and -10 in Human Endothelial Cells: Implications for Clinical and Subclinical Atherosclerosis

Montero I, Orbe J, Varo N, et al.

J Am Coll Cardiol. 2006;47:1369–1378.

Until recently, CRP was thought to be produced exclusively in the liver. However, data now suggest that it is also produced in the atheroma itself. CRP mRNA is found to be at a much higher concentration in atheroma than in normal tissue; it is synthesized and secreted by smooth muscle and endothelial cells. Why are these cells making CRP? What role does CRP play in atherogenesis and plaque instability?

The article by Montero and colleagues provides insight into several mechanisms by which CRP promotes atherosclerosis. First, CRP promoted matrix metalloproteinase (MMP) -1 and -10 mRNA expression in culture cells (human umbilical vein endothelial cells and cryopreserved human aortic endothelial cells). MMP plays a central role in the breakdown of fibrous cap, transforming atheromas into vulnerable plaques. This induction of MMP secretion can be blocked by the inhibition of the mitogen-activated protein kinase pathway. Second, after adjusting for confounding variables, both MMP-1 and MMP-10 levels were elevated in patients with CRP $>$ 3 mg/L compared to patients with lower levels. Third, the authors found CRP and MMP-10 to be co-localized in the endothelial layer and macrophage-rich areas in advanced atherosclerotic plaques.

This article complemented a series of recent works showing that CRP can have numerous pro-atherogenic and pro-thrombotic effects on the endothelial cells. The pro-atherogenic role comprises up-regulation of intercellular adhesion molecules, vascular cell adhesion molecules, and chemokines MCP-1, IL-6, and IL-8. Moreover, CRP has been shown to promote the uptake of oxidized LDL, which would be relevant to the genesis of the atherosclerotic lesion. The pro-thrombotic effects are inhibition of the endothelial isoform of nitric oxide synthase, prostacyclin, and tissue plasminogen activator, and up-regulation of plasminogen activator inhibitor-1.

Emerging evidence clearly shows that CRP plays an essential role in the pathogenesis of atherosclerosis. The unknown questions are: What are the triggers for CRP? What therapies can be targeted toward lowering CRP independently from lowering cholesterol levels? These and many other clinically interesting questions are subjects of intense research in atherosclerosis.

Contribution of Clinical Correlates and 13 C-Reactive Protein Gene Polymorphisms to Interindividual Variability in Serum C-Reactive Protein Level

Kathiresan S, Larson MG, Vasan RS, et al.

Circulation. 2006;113:1415–1423.

The serum level of C-reactive protein predicts the incidence of cardiovascular disease as well as its complications. The current literature suggests that an individual's CRP level is influenced by a variety of clinical and genetic factors. The relative contributions of these 2 groups of factors are unclear.

This study uses recent advances in genomics and the Framingham Heart Study database to examine the interindividual variability of serum CRP levels. There are about 11 million single nucleotide polymorphisms (SNPs) with a minor allele frequency of $>$ 1%. Linkage disequilibrium is a term used to describe when several of these neighboring SNPs are correlated. Thus, the authors determined the SNPs in the region of the CRP gene to see if the linkage disequilibrium correlates with the serum level of CRP.

Clinical data were available for 3301 patients, and genetic information was available for 1809 patients. Both sets of data were available for 1640 patients. Twelve clinical factors significantly correlated with the serum level of CRP: age, sex, body mass index, hormone replacement therapy, cigarette smoking, total/high-density lipoprotein cholesterol ratio, hypertension treatment, lipid-lowering therapy, prevalent cardiovascular disease, triglycerides, systolic blood pressure, and diastolic blood pressure. Body mass index alone explained about 15% of the variance. The authors studied 13 gene polymorphisms in the region of the CRP gene. One triallelic SNP was found to explain 1.4% of the total variance in CRP levels.

This study provided insights into what determined an individual's CRP level. By far the most important factor is the body mass index, which predicts the development of the metabolic syndrome and diabetes. However, genetic factors can also play a significant role in determining the serum CRP marker and, potentially, its clinical consequences.