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THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

A Test in Context

High-Sensitivity C-Reactive Protein

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JACC JOURNAL CME

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CME Objective for This Article: After reading this article, the reader should be able to: 1) discuss the role of high-sensitivity C-reactive protein (hsCRP) as a tool for risk prediction in both primary and secondary prevention of atherosclerotic events; 2) communicate to colleagues where hsCRP testing is appropriate and where hsCRP testing is not warranted; 3) recognize that "residual inflammatory risk" poses as large a clinical problem for atherosclerosis patients as does "residual cholesterol risk"; and 4) describe to both colleagues and patients the rationale for ongoing clinical trials that target vascular inflammation but have no effects on LDL cholesterol.

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Medium of Participation: Print (article only); online (article and quiz).

CME Term of Approval

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Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

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A Test in Context

High-Sensitivity C-Reactive Protein

ABSTRACT

The inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) adds prognostic information on cardiovascular risk comparable to blood pressure or cholesterol. Values <1, 1 to 3, and >3 mg/l indicate lower, average, or higher relative cardiovascular risk, respectively. Global risk algorithms that include hsCRP outperform those solely using Framingham covariates. Although diet, exercise, and smoking cessation are first steps for patients with a proinflammatory response, JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial data demonstrate that statins reduce by 47% the rate of first myocardial infarction, stroke, or confirmed cardiovascular death when given to patients with low-density lipoprotein-C levels of <130 mg/dl and hsCRP of >2 mg/l (hazard ratio: 0.53; 95% confidence interval: 0.40 to 0.69; $p < 0.00001$). In current U.S. guidelines, hsCRP carries a class IIb assessment and is most appropriate in primary prevention when clinical decisions to initiate statin therapy are uncertain. Ongoing multinational trials are pursuing whether reducing inflammation will decrease vascular event rates. (J Am Coll Cardiol 2016;67:712–23) © 2016 by the American College of Cardiology Foundation.

Inflammation is ubiquitous in the atherothrombotic process and interplay between adhesion molecules, cytokines, circulating mononuclear cells, oxidized low-density lipoprotein cholesterol (LDL-C), and the vascular endothelium contribute to the lifelong risk of heart attack and stroke (1). These insights led to the recognition that a substantial proportion of unexplained vascular disease relates to inflammatory mechanisms. The clinical expression of this discovery has been use of the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) to detect elevated vascular risk in both primary and secondary prevention settings. In current U.S. guidelines, hsCRP carries a Class IIb recommendation and is most appropriate in primary prevention when clinical decisions related to the initiation of statin therapy are uncertain.

This review describes the relationships of hsCRP with incident vascular disease and diabetes, a suggested approach to interpretation of hsCRP results, settings where hsCRP testing is appropriate, and the interaction between inflammation and lipid-lowering therapy. Areas of controversy are then discussed, including whether C-reactive protein (CRP) is only a biomarker of disease or if it plays a causal role in atherothrombosis. Finally, ongoing cardiovascular inflammation reduction trials—the ultimate test of the inflammatory hypothesis of atherosclerosis—are described.

THE RELATIONSHIP OF hsCRP LEVELS TO FUTURE VASCULAR RISK

Initially described as a critical component of the acute phase response in the 1930s, CRP gained attention among cardiovascular researchers following reports in the mid-1990s that increased levels are associated with unstable angina and acute coronary ischemia (2,3). Whether this was a result or a cause of ischemia, however, could not be addressed in cross-sectional studies or among those in the midst of an ischemic event. In 1997, data from the prospective Physicians' Health Study, in which elevated hsCRP levels were described in healthy subjects many years in advance of first-ever vascular events, resolved this critical issue (4). That study additionally showed that low-grade systemic inflammation, as defined by hsCRP, is stable across long periods of time and that the anti-inflammatory agent aspirin significantly modified the effects of hsCRP on vascular risk. This latter observation would usher in attempts to decrease inflammation as a target for atherothrombotic protection.

The core findings made in male participants in the Physicians' Health Study would soon be confirmed in women (5) and, later, in more than 50 epidemiological studies worldwide. In a 2010 meta-analysis (6), encompassing more than 160,000 subjects with 1.3 million person-years of follow-up and nearly 28,000 incident vascular events, each standard deviation increase in log-normalized hsCRP was associated with a multivariate-adjusted relative increase in risk of 1.37 for coronary heart disease (95% confidence interval: 1.27 to 1.48) and 1.55 (95% confidence interval: 1.37 to 1.76) for cardiovascular mortality. The magnitude of these effects was at least as large as those reported in the same study participants for total cholesterol, high-density lipoprotein cholesterol (HDL-C), and blood pressure (**Figure 1**).