Clinical Chemistry 56:7
1186–1187 (2010)

Citation Classic

Establishing a Clinical Basis for hsCRP in the Prevention and Treatment of Cardiovascular Disease

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Featured Articles: Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973–9.[1]

Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000;342:836–43.[2]

In the early 1990s, the concept that inflammation was an integral component of atherothrombosis was highly controversial and based almost entirely on bench observations *(1)*. However, pioneering translational studies by Attilio Maseri, Brad Berk, Lewis Kuller, and others found that among smokers or those with acute or chronic ischemia, inflammatory biomarkers including C-reactive protein (CRP)[3] were indicative of high vascular risk. Because concentrations of CRP and other acute-phase reactants increase after ischemia and are directly related to smoking, however, studies in these populations could not exclude the likelihood that increases in CRP were a result rather than a precedent for disease.

The 2 articles highlighted here both dealt with the ability of inflammatory biomarkers in general, and high-sensitivity CRP (hsCRP) in particular, to predict vascular risk in otherwise healthy asymptomatic men and women—a relevant clinical issue, as half of all heart attacks and strokes occur among those with average or even low concentrations of cholesterol. The first paper derived from a large NIH-funded primary prevention trial comparing low-dose aspirin to placebo that was being conducted among 22 000 initially healthy American men by my epidemiologic mentor, Charles Hennekens. Working with Russ Tracy and Mary Cushman, we measured hsCRP concentrations in stored samples obtained at baseline in this cohort and found that increasing concentrations were an independent predictor of future heart attack and stroke in all participants (including nonsmokers), and that the risks associated with inflammation were stable over long periods of time. Because all study participants were healthy at the time of blood sampling, we could exclude the notion that the enhanced inflammatory response was in any way due to ongoing ischemia. Further, we found that the benefits on cardiovascular events associated with random allocation to aspirin diminished significantly with decreasing concentrations of hsCRP. This finding was crucial to us, as aspirin, in addition to being an antiplatelet agent, also has antiinflammatory effects; thus these data raised for us the possibility that inflammation could be modified for clinical benefit. We were exceptionally honored that Attilio Maseri wrote the editorial for our 1997 paper, entitling it "Inflammation, atherosclerosis, and ischemic events—exploring the hidden side of the moon."

The second paper derived from another NIH-funded cohort of more than 28 000 women established by my longstanding research colleague Julie Buring. In that study, we evaluated a panel of 12 vascular biomarkers that included lipid fractions and apolipoproteins, homocysteine, lipoprotein(a), and 4 inflammatory biomarkers [hsCRP, soluble intercellular adhesion molecule 1 (sICAM-1), interleukin (IL)-6, and serum amyloid A (SAA)] as potential determinants of future vascular events among otherwise healthy American women. To our surprise, of the 12 markers measured at study entry, hsCRP was the strongest univariate predictor of risk, was effective in predicting vascular events even when LDL cholesterol concentrations were low, and was the only novel biomarker that added prognostic information to traditional risk factors as well as the total-to-HDL cholesterol ratio. Nader Rifai, who would over the years become an invaluable scientific collaborator, performed the laboratory work for this project. Our group used the hsCRP and cholesterol data from these 2 cohorts to develop a global risk prediction algorithm known as the "Reynolds risk score" that incorporates family history and inflammation along with traditional risk factors (www.reynoldsriskscore.org). In addition, Nancy Cook, the biostatistician for this endeavor, used

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Received January 29, 2010; accepted February 22, 2010.
Previously published online at DOI: 10.1373/clinchem.2009.142240
[1] This paper has been cited more than 2835 times since publication.
[2] This paper has been cited more than 2170 times since publication.
[3] Nonstandard abbreviations: CRP, C-reactive protein; hsCRP, high-sensitivity CRP; sICAM-1, soluble intercellular adhesion molecule 1; IL, interleukin; SAA, serum amyloid A; AFCAPS/TexCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; JUPITER, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin.

these data to establish the conceptual basis for "reclassification analysis," an epidemiologic technique now widely used along with discrimination and calibration to gauge the clinical utility of risk-prediction models.

By the time the second paper was published, we had established with Marc Pfeffer, Frank Sacks, and Eugene Braunwald that statin agents lowered hsCRP independent of LDL cholesterol. That work, along with hypothesis-generating data on the ability of hsCRP to target statin therapy in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), would eventually lead to the multinational Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial in which rosuvastatin was found to reduce myocardial infarction and stroke by half among men and women with CRP ≥2 mg/L who would not otherwise qualify for statin therapy because they had LDL cholesterol concentrations <130 mg/dL *(2)*. We had a superb Steering Committee for JUPITER that included Bob Glynn, Tony Gotto, John Kastelein, Wolfgang Koenig, Alberto Lorenzatti, Jacques Genest, Jim Shepherd, Francisco Fonseca, Borge Nordestgaard, Jim Willerson, and Peter Libby, all of whom have also made major contributions to the inflammation story over the years.

Whereas these 2 papers have each been cited more than 2000 times, what has been most gratifying has been to watch these findings translate into clinical practice. In a 2010 Cambridge-based metaanalysis of 54 prospective cohort studies, hsCRP was recognized as an independent risk marker for cardiovascular disease, with a magnitude of effect at least as large as that of cholesterol or blood pressure *(3)*, and in a comprehensive review of emerging risk markers conducted in 2009 by the National Academy of Clinical Biochemistry, "only hsCRP met all of the stated criteria required for acceptance as a biomarker for risk assessment in primary prevention" *(4)*. Finally, in the past 3 months, the US Food and Drug Administration gave approval for the use of rosuvastatin to prevent heart attack and stroke among those with increased hsCRP, and national guidelines for the detection and treatment of heart disease have been issued in several countries endorsing this approach for the primary prevention of cardiovascular disease *(5)*. What remains uncertain is whether reducing inflammation directly can reduce vascular events. Moving forward, our group hopes to conduct a series of cardiovascular inflammation reduction trials addressing this issue *(6)*.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures of Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:*

Employment or Leadership: None declared.
Consultant or Advisory Role: R.M Ridker, AstraZeneca, Merck Schering Plough, Siemens, Novartis, ISIS, and Vascular Biogenics.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: R.M Ridker, AstraZeneca, Merck, Novartis, and SanofiAventis.
Expert Testimony: None declared.
Other Remuneration: R.M Ridker is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease that have been licensed to Siemens and AstraZeneca.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

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