Book Review

C-Reactive Protein and Cardiovascular Disease

Few biomarkers of disease have generated as much interest, promise, and debate as C-reactive protein (CRP). CRP, a heptatically derived pentraxin, was discovered in 1930 by Rockefeller University investigators William Tillett and Thomas Francis' in patients with pneumococcal infection. Later described as an “acute phase reactant” present in the serum of patients in a variety of inflammatory states, its first relationship to atherosclerosis was appreciated in 1943 when Gunnar Lofstrom demonstrated elevated levels of high-sensitivity CRP (hsCRP) after acute myocardial infarction.

Although many subsequent studies documented high levels of hsCRP in patients with acute atherothrombotic states, a confirmation of its central role in predicting future myocardial infarction and stroke awaited a prospective study of the biomarker in the Physicians’ Health Study. In 1997, Ridker and colleagues published data confirming the importance of hsCRP in predicting future events in initially healthy men, as well as its role in influencing the beneficial effects of aspirin. This landmark report sparked further studies of nearly unequivocal scope and intensity, and the measurement hsCRP was included in virtually every subsequent clinical study of vascular disease. Though now widely accepted as an important biomarker of atherosclerosis and its sequelae, the role of hsCRP in atherogenesis remains an unclear but attractive proposition.

Ridker and Rifai have assembled an outstanding review of the history, development, and clinical application of hsCRP. Consisting of 24 chapters organized into 7 topic areas and written by 37 authors, the book contains contributions from luminaries in the field (Eugene Braunwald, Peter Libby, Christy Ballantyne, Attilio Maseri, and Geoffrey Ginsburg), as well as a phalanx of research fellows and junior faculty, the workers who generated much of the knowledge contained in the book. It should be noted that much of the information in the book has been published previously in scientific literature, reflected in the exceptionally useful bibliographies after each chapter which include over 1300 citations.

The book begins with an informative forward by Eugene Braunwald in which he traces the history of our understanding of atherosclerosis and coronary artery disease. In his discussion of biomarkers, he presents a brief overview of C-reactive protein, the current state of our knowledge, and the possibility of its role in the causation of atherosclerosis and subsequent complications. Chapter 1 by Ridker and Rifai lays an excellent foundation for the more detailed chapters to follow. Reviewing the role of C-reactive protein in the primary prevention of myocardial infarction and stroke, they present a concise review of the adequacy of other biomarkers and the degree to which hsCRP fulfills the criteria for highly predictive plasma-based biomarkers, as well as an excellent summary of the evidence that hsCRP augments “global risk assessment” in detecting and preventing myocardial infarction and stroke. This chapter is the book’s most valuable, as it brings together the essential data placing hsCRP in clinical perspective.

Clinician and investigator alike will find valuable information in this book. Topic areas of particular interest to the clinician include “Inflammation and Atherogenesis,” which contains a chapter on atherosclerosis and inflammation by Peter Libby, and the conclusions of which are based upon the fundamental data on which the role of hsCRP is based. A chapter on plaque rupture, co-authored by Attilio Maseri, defines serious gaps in our understanding of this commonly cited event. Equally interesting is a chapter by Verma and Szmitko, which explores the proposition that CRP plays a causal role in atherogenesis. The data cited are compelling, although the authors call for appropriate in vivo animal models for further study. It remains unclear whether CRP is a modifiable risk factor for atherogenesis or an extremely valuable biomarker.

Both clinician and investigator will find interest in the topic area, “Clinical Role of C-Reactive Protein in Cardiovascular Disorders,” which discusses acute coronary syndromes, arrhythmias, peripheral vascular disease, and heart failure. Although levels of hsCRP are valuable markers for outcome prediction and severity estimates in patients with acute coronary syndromes, it is interesting to note that only 10% to 70% of such patients have an elevated hsCRP. The data supporting a relationship of CRP to arrhythmias, peripheral vascular disease, and heart failure are intriguing and, although relatively early in development, potentially very fruitful areas of future investigation.

In the topic areas on “C-Reactive Protein in Disorders Associated With Premature Atherosclerosis” and “Environmental and Genetic Determinants of C-Reactive Protein,” the authors present data from various studies that appear to support an integrated framework linking inflammation and CRP with multiple conditions known to be risk factors for atherosclerosis. Insulin resistance, type 2 diabetes mellitus, hypertension, and advanced renal disease share common elements of inflammation. Further data supporting a possible integrated framework are presented in chapters on lifestyle, diet, and body weight. The concluding chapter in this topic area presents current information on the genetics of CRP. Well written in language appreciated by clinicians, the book explores the complexity of attributing baseline hsCRP levels to a genetic component. The authors conclude that this is an evolving field requiring further study for clarity.

In addition to Chapter 1, many clinicians will find the topic area on the “Effects of Pharmacological Agents on C-Reactive Protein” the most useful section of the book. Ridker has authored a comprehensive chapter on CRP and statin therapy, followed by a similarly excellent chapter involving nonstatin lipid-lowering therapy by Nambi and Ballantyne. Ridker summarizes the major lipid-lowering trials that used statins and discusses in detail the antiinflammatory and non–lipid-lowering pleiotropic effects of the statins. This is information that should be known to all clinicians using statins in the management of vascular disease. Nambi and Ballantyne discuss the array of nonstatin lipid-lowering agents, some of which have antiinflammatory properties. They emphasize the value of combination therapy and point to new drugs with lipid-lowering potential on the horizon.

The final topic area “Laboratory Evaluation of C-Reactive Protein” contains a heterogeneous set of chapters that are of primary interest to investigators. The chapter entitled “CRP and Risk Factors for Coronary Heart Disease in Children and Adolescents,” however, is of special interest, as the beginnings of atherosclerosis can be traced to early life. Extensive international studies of hsCRP levels in children and adolescents have thus far failed to produce results that are consistent with those in adults.
The role of hsCRP measurement for risk assessment in children and adolescents has not been established at this time.

The construction of the book deserves special mention. Each chapter begins with an introduction to the topic and ends with an informative conclusion, both of which are valuable to those wishing to rapidly peruse the contents. The typography is well chosen for easy reading and the writing style is unusually consistent from chapter to chapter for a volume produced by so many authors. Numerous tables, graphs, and illustrations are presented with occasional limitations due to the black and white format. Perhaps most valuable is the book’s index, an exceptional asset affording access to virtually the entire literature on CRP.

In producing their book, Ridker and Rifai have made an outstanding contribution. Although many questions concerning the role of CRP in atherosclerosis remain unanswered, they have compiled the most complete discussion on the topic currently available. For the reader who is already studying CRP, the book offers relatively little new information. However, for the majority of readers, who want a single source of authoritative information about CRP, this book can be highly recommended.

**Disclosures**

Dr Messer has served as a technical advisor for the National Quality Forum.

**References**


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Circulation. 2006;114:e253-e254
doi: 10.1161/CIRCULATIONAHA.106.633909
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/114/7/e253

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