The recent evolution in concepts for pathogenesis and treatment of atherosclerotic cardiovascular disease offers the intrigue and allure of a best-selling novel. Indeed, recent pathological, physiological, angiographic, and intravascular ultrasound evaluations are remarkably concordant in identifying the multicentric vascular inflammatory process integral to the pathogenesis of atherothrombotic events. A complex interplay between proinflammatory stimuli and endogenous heritable-genetic vascular reparative processes has been proposed as a determinant of vascular disease activity. The validity of this premise is supported by the presence and prospective predictive value of cytokine and cellular “markers” of inflammation, including interleukins 6 and 18 and C-reactive protein (CRP). Furthermore, the fact that physiologically occurring concentrations of CRP exert proinflammatory, proatherogenic, and prothrombotic effects provides impetus to define antiinflammatory treatments capable of suppressing this incestuous marker-mediator cycle. To date, data in support of inflammation (CRP) targeted and/or guided therapy to improve clinical outcomes have been intuitive, inferential, and hypothesis-generating, but they remain unproven. Although high sensitivity (hs) CRP screening is readily available and relatively inexpensive, more widespread implementation has been hampered by the lack of a well-defined and accepted algorithm for treatment. The prevalence of elevation in CRP levels depends on the clinical syndrome present (Figure). As only about half of patients with coronary heart disease have hypercholesterolemia, only half of all patients who experience an acute myocardial infarction in the absence of an unstable angina prodrome will have an elevation in CRP. Similarly, approximately 35% of patients who present with unstable angina will have a “normal” CRP level. These observations underscore the multifactorial pathogenesis of coronary heart disease and the complementarity of multiple factors for prediction of risk or as targets for therapeutic intervention. The opinions and data provided by Ridker1 and Yeh and Willerson2 in the current issue of Circulation are compelling for illustrating the role of inflammation in the pathogenesis and acuity of the atherothrombotic vascular disease process, as well as the potential utility of inflammatory markers in describing prognosis and response to therapy. These thought leaders have provided an algorithm for response to measurements of CRP and the conceptual framework required for using CRP in
current clinical practice. What is missing are prospectively acquired, controlled data about specific therapies demonstrated to suppress CRP (detailed by Ridker\(^1\)) that will provide clinically relevant benefit in the form of reduction in vascular ischemic events or objective measures of disease severity. The time has come! The hypothesis is generated and remains untested. The list of potential adjunctive therapies with demonstrable anti-inflammatory activity is growing rapidly and includes aspirin, statins, angiotensin converting enzyme inhibitors, clopidogrel, fibrates, thiazolidinedione (peroxisome proliferator-activated receptor) agents, low molecular weight heparins (especially enoxaparin and tinzaparin), platelet glycoprotein IIb/IIIa receptor antagonists (especially abciximab), and cyclooxygenase-2 inhibitors. At the very least, further insight into this important arena will be gleaned by the inclusion of inflammatory markers into ongoing randomized trials, whereby the level of inflammatory activity and its response to therapy (or lack thereof) may be correlated with clinical outcomes.

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