The Time for Cardiovascular Inflammation Reduction Trials Has Arrived
How Low to Go for hsCRP?

Paul M Ridker

Inflammation is a major determinant of atherothrombosis, and based on more than a decade of consistent prospective epidemiological evidence, the inflammatory biomarker highsensitivity C-reactive protein (hsCRP) is in clinical use as an independent determinant of cardiovascular risk, even when levels of LDL-C are low. Guidelines for use of hsCRP as an adjunct to global risk prediction were issued by the American Heart Association in 2003, and risk algorithms incorporating hsCRP such as the Reynolds Risk Score have been developed and validated. Increased hsCRP levels not only predict future risk of myocardial infarction, stroke, and cardiovascular death, but are intimately associated with metabolic syndrome and incident diabetes. As a result of interrelationships with insulin resistance, leptin, adiponectin, cytokine function, endothelial dysfunction, and impaired fibrinolysis, CRP has been hypothesized to present a common link in pathways connecting vascular inflammation, diabetes, and premature atherosclerosis. There appears to be an underlying genetic basis for these relationships; in a genome wide association study of more than 6000 women, unsuspected genetic determinants of CRP have been found that include polymorphism in the leptin receptor gene LEPR and in 2 loci that are more commonly considered genes associated with maturity onset diabetes of the young, GCKR and HNF1.

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Despite the consistency of these data, it remains controversial as to whether lowering CRP is a relevant therapeutic goal, and if so, how low hsCRP levels should go in clinical practice. In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Arima and colleagues working within the Hisayama Study in Japan provide new information about the predictive value of very low levels of hsCRP; in a manner almost identical to that observed in studies done in Europe and North America, apparently healthy Japanese with baseline hsCRP levels in the highest quartile had an adjusted relative risk of future coronary heart disease 3 times that of individuals with hsCRP levels in the lowest quartile (95% CI 1.53 to 5.82). What makes these data intriguing, however, is that the median hsCRP level in this Japanese cohort was only 0.43 mg/L, substantially lower than median values reported in almost all European and North American studies (1.5 to 2.0 mg/L), but quite similar to levels previously reported in Japanese populations. Moreover, in terms of considering CRP as a potential target for therapy, the Hisayama data demonstrate that the relationship between hsCRP and vascular risk is continuous and graded even at levels currently considered “low” in the AHA guidelines (<1.0 mg/L). This observation for hsCRP parallels epidemiological observations made decades ago that cholesterol levels in Japan, while also much lower than in the West, nonetheless were linearly associated with risk. A similar situation exists for body mass index; in Japan, the magnitude of risk associated with overweight is similar to that in Europe and North America, yet the definition of “obesity” is typically defined as a body mass index >25 kg/m², rather than >30 kg/m².

What should constitute an “optimal” level of hsCRP? In 2004, using data from the Women’s Health Study, we noted that both very high and very low hsCRP levels had clinical utility for risk prediction and that the relationship of hsCRP to risk was linear and graded across an almost 100-fold range of basal hsCRP levels. This observation was of pathophysiologic interest at both the upper and lower ends of the hsCRP spectrum; at very high levels (>20 mg/L), the continuous relationship suggested that any source of inflammation, whether endogenous or exogenous, was translating into high cardiovascular risk. Since that time, chronically elevated levels of hsCRP have been interpreted correctly as being highly informative of vascular dysfunction. By contrast, at the lower end of the hsCRP spectrum observed within the WHS data (0.5 to 1.0 mg/L), rates of incident plaque rupture were exceptionally low, despite the presence of other risk factors and of underlying atherosclerotic disease. In this context, the Hisayama data suggest that at even lower levels of hsCRP than observed in the WHS, risk still appears both continuous and graded.

When interpreting these comparative data, it is important to note that hsCRP levels predict future clinical events, but correlate only modestly with underlying extent of atherosclerosis; what the inflammation detected by hsCRP appears to represent is a propensity for plaque rupture more than an overt acceleration of atherosclerosis. Thus, if individuals with...
extremely low levels of hsCRP live in a vasculo-protective state, might inhibiting inflammation itself be of clinical value?

To date, most studies of hsCRP reduction have been performed within statin-based lipid lowering trials. As demonstrated in the CARE, PRINCE, AFCAPS/TexCAPS, PROVE IT–TIMI 22, and A to Z trials, not only do statins lower hsCRP levels in a manner largely independent of LDL-C reduction, but the clinical benefit of statin therapy appears greater in the presence of inflammation than in its absence. In both the PROVE IT–TIMI 22 and A to Z trials, the best clinical outcomes occurred not only when LDL-C levels dropped below 70 mg/dL, but when hsCRP levels also dropped below 2 mg/L. The apparent benefit of achieving these “dual goals” for statin therapy is further supported by the observation in both trials that even lower achieved levels of hsCRP (<1 mg/L) were associated with even better outcomes. It is also of interest given controversial results of the ENHANCE trial that ezetimibe significantly reduces LDL-C but has minimal effect on hsCRP.17

Though enticing, epidemiological evidence suggesting that very low levels of hsCRP associate with very low levels of risk does not prove causality. Fundamentally, a direct test of the inflammatory hypothesis of atherothrombosis requires an agent that (1) inhibits inflammation without having major impact on other components of the atherothrombotic process including lipids, and (2) is known to have an acceptable safety profile for evaluation in a large-scale randomized trial. Despite the importance of this question, no end point trial addressing this issue has been initiated either by industry or a federal agency. For example, the ongoing JUPITER trial will determine whether rosuvastatin can reduce vascular event rates among primary prevention patients with elevated levels of hsCRP in the absence of hyperlipidemia, an important public health issue with broad consequences for preventive cardiology.18 However, because JUPITER is testing an agent that markedly lowers LDL-C as well as hsCRP, this trial cannot directly address whether lowering inflammation alone lowers vascular risk. Nonetheless, if JUPITER is successful, an immediate and substantial clinical need will arise for trial evidence addressing whether adjunctive antiinflammatory therapies beyond statins can be effective at lowering vascular risk, particularly among postinfarction patients with persistently elevated hsCRP levels.

A variety of agents can be considered for such a trial. Pepys and colleagues have developed a 1,6-bis(phosphocholine)-hexanethiol that in rat models appears to reduce infarct size associated with CRP preinfusion.19 Antisense inhibitors directly targeting CRP translation are also in development. However, as the appropriate target for therapy might prove to be inflammation in general rather than CRP in particular, broader agents that either target interleukin (IL)-6 (tocilizumab) or tumor necrosis factor (TNF) (enterecept, infliximab, adalimumab) additionally need consideration. For each of these potential antiinflammatory vascular interventions, issues of toxicity, delivery, and cost need clarification before substantive trials can move forward.

An alternative and highly attractive agent that could be used to immediately test the inflammatory hypothesis of atherothrombosis is low dose methotrexate (LDM). LDM (10 to 15 mg/wk) has been in wide use for almost 2 decades among patients with rheumatoid arthritis, and guidelines from the American College of Rheumatology already exist regarding dosing regimens, drug monitoring, and the identification of high-risk patient subgroups.20 As such, off target toxicity associated with LDM is likely to be low. Moreover, LDM has previously been shown to reduce several inflammatory biomarkers including hsCRP, IL-6, and TNF-α among those with rheumatoid arthritis and psoriasis, patient groups at elevated vascular risk on an inflammatory basis.21–22 Finally, among both rheumatoid arthritis and psoriasis patients, available observational data consistently suggest that exposure to LDM is associated with reductions in cardiovascular morbidity and mortality, despite the fact that those receiving LDM have worse vascular risk factor profiles, data strongly mitigating against indication bias.23 Unfortunately, as LDM is a generic product, industry support for such a study is unlikely.

That inflammation plays a fundamental role in atherothrombosis and that hsCRP is a clinically effective predictor of risk is no longer controversial. If anything, from an epidemiological perspective, the attributable risk of coronary heart disease associated with inflammation is as large as that associated with hyperlipidemia. It would thus appear that the time for randomized trials directly testing the inflammatory hypothesis of atherothrombosis has arrived.

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References


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