SCIENTIFIC EDITORIAL

C-reactive protein and vascular risk: From March to Jupiter

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Inflammation has been proposed to be a crucial component in the pathogenesis of atherothrombosis [1]. Evidence has accumulated over the past two decades suggesting that inflammation plays a major role in all stages of the atherothrombotic process, including the sudden rupture of apparently stable plaque [2]. The interaction of lipid accumulation and immune function appears to both promote premature atherosclerosis and accelerate plaque fissuring, a process that exposes the underlying matrix to circulating thrombogenic factors and ultimately leads to platelet adhesion, vessel occlusion and downstream hypoxia [3]. Clinical studies [4,5] have also supported a link between chronic inflammation and coronary heart disease (CHD), and inflammatory markers have received much attention as emerging factors that could account for some of the unexplained variability in CHD risk. C-reactive protein (CRP), an acute phase plasma protein synthesised by the liver, is a sensitive, non-specific marker of inflammation and has been extensively studied over the past two decades [1]. Much uncertainty remains, however, about whether circulating levels of CRP are a causal risk factor for vascular disease or are mainly correlated to conventional cardiovascular risk factors or markers of subclinical disease, or some combination of these possibilities.

A literature-based meta-analysis published in 2004 involving 22 prospective studies reported an odds ratio for CHD, adjusted for several conventional risk factors, of 1.6 (95% confidence interval [CI] 1.5–1.7) in a comparison of people with baseline CRP concentrations in the top third to those in the bottom third of the population distribution (corresponding to values of about 2.4 mg/L vs 1 mg/L) [6]. This odds ratio was similar in magnitude to those reported for some established causative risk factors (e.g., low-density lipoprotein cholesterol or systolic blood pressure), as well as to those for some other non-specific circulating markers of inflammation [7,8]. By contrast, an odds ratio of 2.0 (95% CI 1.6–2.5) for CHD was reported in an earlier review of the 11 initial prospective studies of CRP [9] and even more extreme odds ratios have been reported in some earlier individual studies. More recently, the Emerging Risk Factors Collaboration (ERFC) [10] reviewed the associations between CRP concentrations,
established cardiovascular risk factors and vascular risk in a collaborative analysis of individual data from 54 prospective studies. In contrast with literature-based reviews (which have access to only published or limited aggregated data), this large pooled analysis involving primary data was able to reliably characterize the magnitude and the shape of any dose-response relationships (under a range of various circumstances), provide a consistent approach to adjustment for possible confounding factors, correct for within-person variability in concentrations of CRP and of possible confounding factors, and investigate any potential sources of heterogeneity. In a total of 160,309 individuals without a history of CHD or stroke, comprising 27,769 participants that experienced a first-ever non-fatal or fatal event, CRP concentration was associated with a variety of different conditions, each of which was broadly similar in magnitude, including CHD, ischaemic stroke and deaths due to several common cancers and other non-vascular causes. Furthermore, the strength of association of CRP concentration with ischaemic vascular disease reduced considerably after adjustment for several conventional risk factors and other markers of inflammation (such as fibrinogen).

Even analyses in the ERFC (as in all observational analyses), however, are limited in their ability to judge causality [11], particularly as they are susceptible to bias by reverse association and by confounding. Although such distortion was minimized, but not eliminated, in the ERFC by studying initially disease-free individuals and by appropriately adjusting for potential known confounders, statistical adjustment is potentially limited because not all relevant confounders have been (or can be) measured in observational studies. In the absence of large-scale randomized controlled trials of suitable interventions, studies that employ genetic variants that are associated with specific changes in circulating CRP concentration can help to provide an alternative approach to assess the causal relevance of CRP to disease risk (i.e., "Mendelian randomization" analyses) [12]. A number of studies have identified several single-nucleotide polymorphisms (SNPs) within the CRP gene that influence the circulating concentration of the protein [13,14], but they are not materially associated with any established or emerging cardiovascular risk markers, suggesting that these SNPs can serve as unbiased proxy for CRP and are useful as tools for use in Mendelian randomization analyses. Such studies (including a recent meta-analysis involving 28,000 CHD patients and 100,000 controls [15]) have reported essentially null associations between CRP-related genotypes and CHD risk [16,17], reducing the likelihood of a major causal role for CRP in CHD, but even more powerful studies are needed to confirm or exclude any modest, but potentially still important, causative effect of CRP concentration on CHD.

The Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial randomized 17,802 people (62% men, 16% smokers) with no evidence of cardiovascular disease, elevated (>2 mg/L; median, 4.3 mg/L; interquartile range, 2.8–7.1 mg/L) CRP concentrations and low-density lipoprotein concentrations of <3.4 mmol/L (<130 mg/dL) (median, 2.8 mmol/L [108 mg/dL]) to rosuvastatin or placebo [18]. Following a 44% relative-risk reduction in the primary endpoint of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina or death from cardiovascular causes, the Independent Data Safety Monitoring Board halted the trial earlier than planned. When the trial was terminated, only 1076 participants had 4 years of follow-up, and 2705 had 3 years of follow-up (median follow-up, 1.9 years; maximum, 5.0 years). Each individual component of the JUPITER primary endpoint was significantly reduced: 54% reduction in myocardial infarction, 46% reduction in arterial revascularization and 48% reduction in fatal and non-fatal stroke, with a 51% reduction in the rate of ischemic stroke and no difference in the rates of haemorrhagic stroke [19]. But, as statins potentially affect low-density lipoprotein cholesterol concentrations, this trial was not able to provide specific causal inferences about CRP. Separate analyses from the JUPITER trial have reported associations between the degree of CRP-lowering achieved and risk of cardiovascular disease [20]. Compared to participants receiving placebo, a 65% reduction in vascular events was observed in subjects allocated to rosuvastatin who achieved both low-density lipoprotein cholesterol <1.8 mmol/L and CRP < 2 mg/L versus a 33% reduction in those who achieved one or neither target. A 79% reduction in vascular events was also found in subjects who achieved a low-density lipoprotein cholesterol concentration < 1.8 mmol/L and CRP < 1 mg/L [20]. As acknowledged in this report, however, these analyses may have been liable to bias because they have not been based on the trials’ randomized treatment allocations. Although this trial cannot directly address whether lowering inflammation alone lowers vascular risk, the JUPITER findings are important because they extend the evidence-base for statins to individuals who are at lower risk than those targeted by current cardiovascular risk thresholds and because they confirm that low-density lipoprotein cholesterol lowering is effective in cardiovascular prevention, even at low starting low-density lipoprotein cholesterol concentrations.

In aggregate, therefore, the available evidence does not currently support CRP itself as a direct causal mediator in the development of CHD, but its role in vascular disease is not fully resolved, and it remains unknown whether inhibiting inflammation in general will decrease the rate of vascular events. Further research is also required to address other clinically relevant questions concerning CRP, such as evaluation of the incremental value of CRP measurement beyond established risk factors for cardiovascular risk assessment [21]. Several individual prospective studies have reported on the potential utility of CRP measurements for cardiovascular disease risk prediction and a recent analysis tried to assess the predictive performance of CRP in two prospective cohort studies supplemented by a systematic review of relevant data from 31 published prospective studies [22]. This review suggested that although elevated CRP concentrations were associated consistently with increased CHD risk, measurement of CRP concentrations provides little improvement in CHD risk prediction when assessed using several metrics of predictive value [22]. Relevant investigations in the ERFC should, however, provide a more reliable and robust assessment about whether measurement of circulating CRP concentration can help to better identify individuals at increased risk of CHD than measurement of conventional risk factors alone.
Conflict of interest statement

Nothing declared.

References