The conundrum of C-reactive protein as a risk marker for cardiovascular risk assessment: insight from EPIC-Norfolk and JUPITER

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This editorial refers to ‘Clinical implications of JUPITER in a contemporary European population: the EPIC-Norfolk prospective population study’1, by B.M. Sondermeijer et al., on page 1350

The challenge presented by the need to identify individuals with moderate cardiovascular risk who go on to undergo a clinical event remains a topic of intense debate. Subjects in this group present a SCORE of 1–5% at 10 years, and are typified by middle-aged men and women, an ever-expanding group as demographic patterns change worldwide. It is therefore of considerable relevance that criteria for risk assessment in this group in the recent Joint ESC/EAS Guideline recommendations for management of dyslipidaemia not only feature a lower target for LDL-cholesterol (LDL-C; 115 mg/dL), but also emphasize the critical need for estimation of the total cardiovascular risk profile.1 Such an approach to risk evaluation in primary prevention must now, however, integrate the concept of lifetime risk burden, which has the distinct advantage of integrating cumulative risk exposure as compared with a ‘point’ estimate at any given moment over a lifetime.2 A further dimension of risk assessment to enhance predictive power in this group concerns the potential use of circulating biomarkers of inflammation, either alone or in a multimarker panel. Use of high-sensitivity C-reactive protein, which, amongst other biomarkers, is associated with cardiovascular risk, has been prominent in such analyses.3

In this issue of the journal,4 and in continuity with their recent publications,1–8 Sondermeijer and colleagues have focused on the evaluation of both cardiovascular risk and the risk of future coronary heart disease (CHD) events in subjects at moderate risk in the large UK-based EPIC-Norfolk prospective population study, and included high-sensitivity C-reactive protein as a biomarker of systemic inflammation. Applying the inclusion criteria for the JUPITER trial (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin),9 they sought to quantify how many subjects met the JUPITER criteria and, in addition, to determine how many would then qualify for statin therapy. Some 846 (10.1%) of the subjects in EPIC-Norfolk fulfilled the JUPITER criteria of having an LDL-C <130 mg/dL plus a C-reactive protein level ≥ 2 mg. The analysis revealed that this group had a 10-person-year event rate of 14.6% compared with 7.0% for those whose LDL-C was also <130 mg/dL, but whose C-reactive protein was ≤ 2 mg (P = 0.001); this translated into an adjusted hazard ratio for future CHD of 1.70 [95% confidence interval (CI) 1.31–2.21].

This analysis of the EPIC-Norfolk cohort therefore indicates that JUPITER-eligible individuals are at an increased risk of CHD compared with those with low C-reactive protein in this European population. Importantly, of those individuals in EPIC-Norfolk who did not qualify for statin therapy based on the SCORE (n = 4652) or ATP III criteria (n = 4466), 18.1% and 18.9% of these subjects, respectively, would have qualified using the JUPITER criteria, a coherent finding given the two-fold increment in event rate in the C-reactive protein ≥ 2 subgroup.

The authors correctly highlight a number of limitations in the interpretation of this analysis, although it is highly unlikely that these limitations would have had any major impact on the interpretation of their findings. It is not likely, for example, that the results would have been very different if the EPIC-Norfolk lipid levels had been measured in fasting rather than in non-fasting samples. It is also unlikely that the absence of adjudication of the reported CHD events in EPIC-Norfolk would have had more than a minor impact on the conclusion drawn. Perhaps one of the more important limitations relates to the failure to include stroke in the composite endpoint analysis, especially as there is reasonably compelling evidence that the C-reactive protein level might be superior to LDL-C concentration as a predictor of stroke.
The relationship between C-reactive protein levels and cardiovascular risk has been the subject of much discussion and, in many cases, serious disagreement. On the one hand, there is substantial evidence that the plasma level of C-reactive protein is a cardiovascular risk predictor that is apparently independent of conventional risk factors. On the other hand, arterial inflammation, a critical component of unstable plaque, may underlie the elevated plasma C-reactive protein level, which itself may not be causal in precipitating the clinical event. This critical question is further clouded by an observation that is rarely considered in the JUPITER studies, and which, as emphasized elegantly by Wang, concerns the fact that clinical benefit in the JUPITER cohort was attenuated at baseline C-reactive protein levels $\geq 4$ mg/L.

A key question concerns the factors which drive chronic, moderately elevated systemic inflammation, and, in turn, C-reactive protein level (Figure 1). Potentially, socio-economic, environmental, lifestyle, and genetic factors contribute to an inflammatory state, of which C-reactive protein is an indicator. Thus, individuals with an increased visceral fat mass as a component of the metabolic syndrome constitute classical examples of the interaction between these multiple factors. Moreover, such individuals tend to display elevated levels of C-reactive protein, thereby suggesting that C-reactive protein reflects the presence of other factors such as insulin resistance or diabetes. Sondermeijer et al. do not make the claim that C-reactive protein is a causative factor; rather, they interpret their results in terms of the role of C-reactive protein as a marker of CHD risk in subjects at moderate risk with low levels of LDL-C. Importantly, complementary analyses in the original JUPITER cohort have revealed that it is the achieved high-sensitivity C-reactive protein concentration after or during statin therapy which appears most predictive of CHD event rates. When considered together, it was the combined reduction of LDL-C and high-sensitivity C-reactive protein ($<72$ mg/dL and $<1$ mg/L, respectively) which was the most strongly associated with event reduction.

The central issue to resolve as a consequence of this retrospective analysis concerns the question as to whether inclusion of C-reactive protein measurement may enhance identification of an original high-risk subgroup within the moderate risk individuals in the general European population, and whether new strategies for goal attainment on statin therapy should include the C-reactive protein level in addition to LDL-C in this primary prevention group. Currently, C-reactive protein measurement is not widely advocated in primary prevention across Europe. Clearly the simulation

Figure 1 Interactive factors which impact circulating levels of C-reactive protein (CRP). Potential effects on individual factors due to reverse causality and arising from elevated CRP levels cannot be excluded.
performed by Sondermeijer et al. 4 must be confirmed in an inde-
pendent prospective intervention trial. If indeed such a study con-
irms the working hypothesis that C-reactive protein assay
strengthens the efficiency of primary prevention with statins, then
such a finding would shift a sizable proportion of moderate risk
people to eligibility for statin therapy. The eventual benefits in
terms of quality of life and of long-term healthcare economics
remain indeterminate, but merit consideration relative to other
strategies for prevention of chronic diseases and their associated
morbidity-mortality.

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