Creating controversy where none exists: the important role of C-reactive protein in the CARE, AFCAPS/TexCAPS, PROVE IT, REVERSAL, A to Z, JUPITER, HEART PROTECTION, and ASCOT trials

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This editorial refers to ‘Evaluation of C-reactive protein prior to and on-treatment as a predictor of benefit from atorvastatin: observations from the Anglo-Scandinavian Cardiac Outcomes Trial†, by P.S. Sever et al., on page 486

Based on substantial laboratory evidence that inflammation plays a major role in atherothrombosis, clinical investigators showed in the mid-1990s that inflammatory biomarkers, such as C-reactive protein, serum amyloid A, and fibrinogen were associated with increased risk of first as well as recurrent cardiovascular events.1,2 It has since become clear from a meta-analysis of >50 prospective cohort studies involving >160 000 subjects that the magnitude of risk associated with C-reactive protein (and other inflammatory markers) is as large as that of total cholesterol and of blood pressure.3 The addition of C-reactive protein and family history to the usual Framingham risk factors, as in the Reynolds Risk Score, has been shown to improve significantly the ability to estimate 10-year cardiovascular risk.4 The ability of C-reactive protein to assess risk, especially in the reclassification of persons at intermediate risk, has been demonstrated in a number of populations, including those from the MONICA5 and Framingham6 studies. Given the consistency of these data and the pathophysiological importance of inflammation in vascular disease, it is not surprising that C-reactive protein evaluation has become a part of prevention guidelines in the USA and Canada, particularly for those at intermediate risk.

Beyond use as an effective tool for the prediction of vascular risk, the level of C-reactive protein measured in patients receiving statins also has clinical relevance as a method to define patients who will benefit from this therapy, even when LDL-cholesterol (LDL-c) levels are low. In 1998, we reported in the Cholesterol and Recurrent Events (CARE) trial, a secondary prevention trial in post-infarct patients without elevated LDL-c, that statins reduce C-reactive protein independently of LDL-c in individual patients,7 an observation that has subsequently been confirmed. Subsequently, investigators in the AFCAPS/TexCAPS study, a trial of primary prevention, reported in a post-hoc analysis that individuals with low levels of LDL-c, but elevated levels of C-reactive protein at baseline benefited markedly from lovastatin, whereas those with low levels of both LDL-c and C-reactive protein did not.8 In 2005, we showed in the PROVE IT-TIMI 22 trial in patients post-acute coronary syndrome that achieving low levels of C-reactive protein after initiating statin therapy was associated with a better outcome.9,10 Also in 2005, investigators in the REVERSAL trial of statin therapy in patients with chronic ischaemic heart disease reported that regression of vascular disease, as assessed by intravascular ultrasound, occurred only among patients who achieved low levels of both C-reactive protein and of LDL-c,11 findings similar to those in PROVE IT-TIMI 22. In 2006, in our analysis of the A to Z trial, we confirmed that the clinical benefits of simvastatin occurred most frequently in patients post-acute coronary syndrome who had low on-treatment levels of both LDL-c and C-reactive protein.12

However, it was not until 2008 with the publication of the results of the JUPITER trial that, in the opinion of this editorialist, the clinical impact of C-reactive protein as a means of improving public health became more widely appreciated. In JUPITER, 17 802 apparently healthy men and women who had no indication for statin therapy based on LDL-c levels were screened for elevated levels of C-reactive protein (≥2.0 μg/dL) and then were...
randomly allocated to either rosuvastatin 20 mg or to placebo. The trial was stopped early due to overwhelming evidence of efficacy, including highly significant reductions in myocardial infarction, ischaemic stroke, the need for coronary bypass surgery or angioplasty, venous thrombosis, and all-cause mortality. Virtually identical results were observed in all subgroups, including those with Framingham scores well below 10% and among those with baseline (pre-treatment) LDL-c levels < 70 mg/dL, as well as in subgroups with mild, moderate, and marked elevation of baseline C-reactive protein. Moreover, in pre-specified analyses, and with full adjustment for baseline characteristics, on-treatment levels of C-reactive protein were again found to be of similar importance to on-treatment levels of LDL-c in their association with vascular risk.

Despite the concordance of pre-clinical, laboratory, and clinical data, there has been reluctance in some quarters to embrace the biology of vascular inflammation, and, occasionally in the C-reactive protein literature, controversy has been created when little truly exists. Sever and colleagues have now presented new analyses of baseline and on-treatment C-reactive protein levels in a case–control evaluation of the lipid-lowering arm of the ASCOT trial that was originally published in 2003. These analyses were based on 155 patients in whom both on-treatment LDL-c and C-reactive protein were measured. A relatively large proportion (79 of the 235 patients) were excluded; some analyses were based on 88 patients and some on 65. Some comparisons with JUPITER are based on subgroups comprising only 3–5 cases in ASCOT. Although presented as a ‘negative CRP study’, the ASCOT results, albeit quite limited in size, are in fact remarkably similar to those of the CARE, AFCAPS, REVERSAL, A to Z, and JUPITER trials (Figure 1), especially in light of the fact that the dose of atorvastatin was only 10 mg, while some of the other trials used considerably larger equivalent doses of statins.

First, in confirmation of prior studies, in ASCOT the baseline levels of C-reactive protein and LDL-c were comparable in identifying subsets at risk of future vascular events, with odds ratios of 1.19 and 1.31, respectively. Secondly, in ASCOT, as in almost all prior cohorts, including recent analyses from the MONICA and Framingham populations, the addition of C-reactive protein to traditional Framingham risk factors improved risk reclassification. Although Sever et al. describe the magnitude of this increase as being only ‘modest’, curiously, they do not compare it with risk reclassification improvement by LDL-c or total cholesterol.

Thirdly, in ASCOT there were no interactions between baseline values of either C-reactive protein or LDL-c and the relative effect of the statin on cardiovascular events. This observation is also consistent with the Heart Protection Study and, in the case of C-reactive protein, with both PROSPER and JUPITER.

Fourthly, the point estimates of effect in ASCOT are entirely consistent with the hypothesis that sequentially lower levels of on-treatment C-reactive protein following statin therapy predict greater subsequent relative risk reductions. In this analysis, a 14% reduction in vascular events was observed in patients treated with atorvastatin who achieved a less than median reduction in C-reactive protein, while a 39% reduction was observed among those who achieved a greater than median C-reactive protein reduction. Hence, in ASCOT there was a 25% greater relative risk reduction among those with lower levels of the on-treatment C-reactive protein, a finding remarkably similar to that previously reported in the CARE, PROVE IT, REVERSAL, A to Z, and JUPITER trials.

Figure 1 Top: hazard ratios (± 95% CI) for cardiovascular events in JUPITER according to achieved reductions of high-sensitivity C-reactive (hsCRP) (fully adjusted). From Ridker et al.14 Bottom: odds ratios (± 95% CI) for cardiovascular events in ASCOT according to achieved hsCRP above and below the median value (1.83 mg/L); cases/controls. From Sever et al.15 table 4, Model 1.
Despite these results in ASCOT which, as we have seen, are highly consistent with and confirm previous data, Sever et al. dismiss this evidence as the test for trend across on-treatment C-reactive protein subgroup was not formally significant, an issue that suggests inadequate power, given the small number of cases, rather than any actual difference between studies. In contrast, Sever et al. emphasize that a significant trend across on-treatment levels of LDL-c was observed in ASCOT. However, the statistical significance of this latter trend is driven, not by a benefit of LDL-c reduction as hypothesized, but rather by the highly improbable subgroup observation of a net hazard among those allocated to atorvastatin, who achieved a smaller than median reduction in LDL-c (hazard ratio 1.10, table 4, fully adjusted model). Thus, to accept the subgroup conclusions of Sever et al., based on a small number of events, that LDL-c reduction is clinically meaningful but that C-reactive protein reduction is not requires readers both to ignore the actual point estimates of effect for C-reactive protein (which indicate an effect fully consistent with prior work) and to accept the highly unlikely premise that atorvastatin is ‘hazardous’ for half of the ASCOT population treated. Interestingly, no actual test for a difference between the C-reactive protein and LDL-c effects was reported.

Thus, overall, I consider this case–control analysis of ASCOT to be more good news for the inflammatory hypothesis of atherosclerosis. Although the clinical use of the inflammatory marker C-reactive protein is helping to bring the concepts of vascular inflammation to the bedside, what still remains uncertain is whether or not reducing inflammation per se, without an effect on LDL-c, will reduce vascular risk. Two clinical trials are being launched that will directly test the inflammatory hypothesis of atherothrombosis, one using low-dose methotrexate and the other using the novel interleukin-1β inhibitor canakinumab. Other trials that will target alternative components of the innate and acquired immune systems, including approaches to ‘vaccinate’ against atherosclerosis, are likely to follow. The cardiology community should support these and other novel initiatives since, in the final analysis, it will require well-designed, adequately sized, prospective clinical trials to provide the crucial answers that will enhance clinical care.

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References