BIOMARKERS

Is CRP level useful to guide statin therapy? Lack of evidence from HPS fuels the debate

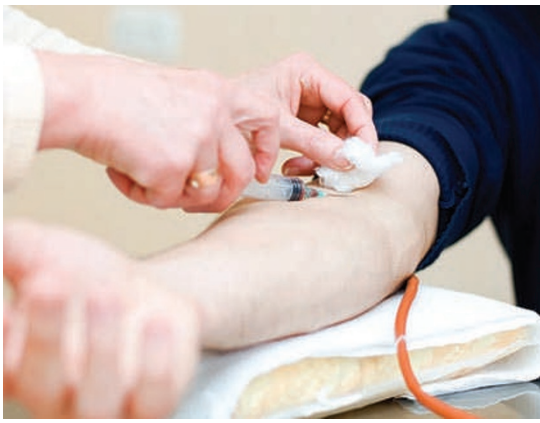
Whether the concentrations of C-reactive protein (CRP) in blood can predict a patient's response to statin therapy has been hotly debated. A new analysis by the Heart Protection Study (HPS) Collaborative Group, published in the *Lancet*, shows no correlation between baseline levels of CRP and the benefits of statin therapy in patients at high vascular risk.

CRP level is a well-known biomarker of inflammation. Raised CRP level has been associated with increased risk of vascular disease and mortality. Whether this association is causal or indirect—a result of the positive correlation between inflammation and standard vascular risk factors—is not entirely clear. Statins, which are the most common therapeutic agents used to reduce LDL-cholesterol levels, have been shown to protect against vascular events in primary and secondary prevention trials. These beneficial effects were shown to depend mainly on the reduction in LDL-cholesterol levels, but statins could have additional, nonlipid effects, such as acting against inflammation. If this hypothesis were true, statin therapy could potentially be more effective in people with raised levels of circulating inflammatory markers, such as CRP. By contrast, people with low CRP levels might benefit little from statin therapy. Baseline CRP measurements could, therefore, be useful to select patients for whom statin therapy is appropriate.

Evidence from several trials has indeed suggested that baseline CRP level influences the magnitude of the protective effects of statins. The large JUPITER trial, in which 17,802 individuals with no apparent vascular disease were randomly assigned to receive rosuvastatin or placebo, has lent substantial weight to this hypothesis. In JUPITER, the reduction in the incidence of vascular events observed in patients receiving rosuvastatin was greater than that expected solely from the reduction in LDL-cholesterol levels, and was proposed to be due to the observed concomitant reduction in the level of CRP.

The new HPS analysis contradicts this hypothesis. In HPS, 20,536 patients at high risk of vascular events were randomly assigned to receive placebo or 40 mg simvastatin daily. CRP level was measured by a high-sensitivity assay and patients were classified into one of six groups according to their baseline CRP levels. At the end of follow-up, which took place over a mean period of 5 years, a 24% significant proportional reduction in the incidence of major vascular events (coronary-related death, myocardial infarction, stroke, or revascularization) was observed in the simvastatin group when compared with the placebo group. As expected, simvastatin therapy was also associated with a reduction in the mean level of LDL cholesterol from baseline. Although the mean level of CRP was also reduced in patients receiving simvastatin, the reductions in the incidence of composite or individual vascular end points achieved with therapy did not differ significantly between the six groups of patients with different baseline CRP levels. Furthermore, no significant association was found between baseline CRP level and changes in LDL-cholesterol level during follow-up, nor between baseline LDL-cholesterol level and later changes in CRP level. These results indicate that baseline CRP level is not useful to predict the response to statin therapy in patients at high vascular risk, neither in terms of reduction in the incidence of vascular events nor in the degree of change in LDL-cholesterol level.

In addition to CRP, the baseline blood concentrations of other inflammatory markers, such as lipoprotein-associated phospholipase A_2 or albumin, were also not associated with the proportional reduction in the incidence of vascular events seen with simvastatin therapy in HPS. The study investigators conclude that their analysis



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"does not lend support to the suggestion from hypothesis-generating studies that the beneficial effects of statin therapy are affected by ... inflammation status".

The HPS investigators explain the discrepancy between the results of their analysis and earlier trials by the small number of vascular events recorded in other studies, which could have rendered the analyses underpowered. As for JUPITER, the HPS researchers suggest that the early termination of the trial (owing to clear evidence of benefit of rosuvastatin) could have overestimated the size of the real effects of treatment.

Do these findings herald the end of CPR measurements to guide statin therapy? The HPS researchers believe that the results of their study could be applicable to both primary and secondary prevention and to therapy with other statins. However, these are points of controversy that are likely to raise debate and potentially lead to further studies on the usefulness of this marker in assessment of vascular risk.

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Original article Heart Protection Study Collaborative Group. C-reactive protein concentration and the vascular benefits of statin therapy: an analysis of 20,536 patients in the Heart Protection Study. *Lancet* doi:10.1016/S0140-6736(10)62174-5