Inflammation, CRP and Atherosclerosis – Where Do We Currently Stand?

Sandeep Gupta

Consultant Cardiologist, Department of Cardiology, Whipps Cross and St Bartholomew's University Hospitals, Leytonstone, London E11 1NR, UK

28

INFLAMMATION AND ATHEROSCLEROSIS

Atherosclerosis is an inflammatory disease.[1] From atherogenesis, plaque progression through to acute cardiac events – the role of inflammation seems pivotal. Atherosclerosis is much more than a simple accumulation of lipids in the vessel wall – from the Framingham Heart Study, 26 year follow up data revealed that more than one third of patients with CHD had cholesterol levels less than 200mg/dl.[2] Furthermore, approximately 50% of patients who present with unstable angina or acute myocardial infarction do not have the classical risk factors.[3]

A number of "novel" risk factors might complement the current knowledge and improve risk stratification of subjects with atherosclerotic disease. Haemostatic, infectious, thrombotic and inflammatory processes and genetic factors are gaining increasing interest in the quest for such markers. [4]

C-reactive protein (CRP), the classical acute phase protein, represents a highly sensitive marker of inflammation – increasing by several hundred-fold in response to acute injury, infection or other inflammatory stimuli. Robust anti-CRP antibodies and a well-established WHO International reference standard for CRP are available so that precise sensitive clinical plasma/serum assays can be readily undertaken.

CRP AND RISK OF CHD

The Physicians Health Study examined CRP levels in apparently healthy men in whom myocardial infarction, venous thrombosis or strokes subsequently developed and in a similar number of men in whom vascular disease did not develop – over a follow up period of at least 8 years.[5] The subjects were assigned to receive placebo or aspirin at the beginning of the study. Baseline plasma CRP were higher in men who subsequently had a MI with the men in the quartile with the highest CRP having nearly three times the relative risk for MI compared with those in the lowest quartile. The increased risk remained stable at least 6 years of follow up. Such an association was similarly found in Women's Health Study by the same group of investigators – with the highest quartile of CRP levels associated with five times likelihood to suffer a cardiovascular event compared with those subjects in the lowest quartile.[6] Other studies have reproduced very similar data. In a formal meta-analysis of n=11 prospective studies with almost 2000 cases a relative risk of two-fold, for CHD was found after adjustment of various confounders in the individuals in the top third compared to the bottom third of CRP distribution. [7]

The implication of elevated CRP levels

Whilst the underlying mechanism that may trigger the low-grade inflammatory response in atherosclerosis remains unclear, CRP can be regarded as the primary surrogate marker for the inflammatory processes. C-reactive protein may behave as a pro-coagulant marker since it is known to induce expression of tissue factor in monocytes. It may exert direct vascular and endothelial effects in that CRP is found within the vessel wall even in the early stage of plaque formation. It is chemotactic for monocytes, avidly binds to human neutrophils and induces complement activation. More recently increased plasma CRP levels were shown to directly impair endothelial cell function. [8]

CRP in risk prediction

There is on-going debate whether concentrations of CRP will have a role in routine cardiovascular risk assessment. Interestingly the following properties have been noted:

- Consistency of results from several prospective population-based studies in apparently healthy subjects is quite remarkable.
- The association between CRP and future coronary events is strong – with a risk ratio 2-fold in those in the upper tertile of CRP distribution compared to those in the lower tertile. This holds true in both men and women
- The association between CRP in coronary risk has proved to be independent of a wide number of potential confounders – including cigarette smoking and social class.

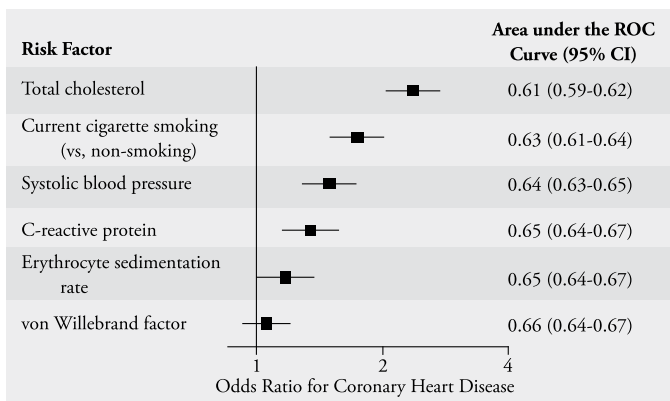

Fig. 1: CRP and other risk factors as predictors for coronary heart disease in the prospective Rekyjavic study (Ref 12)

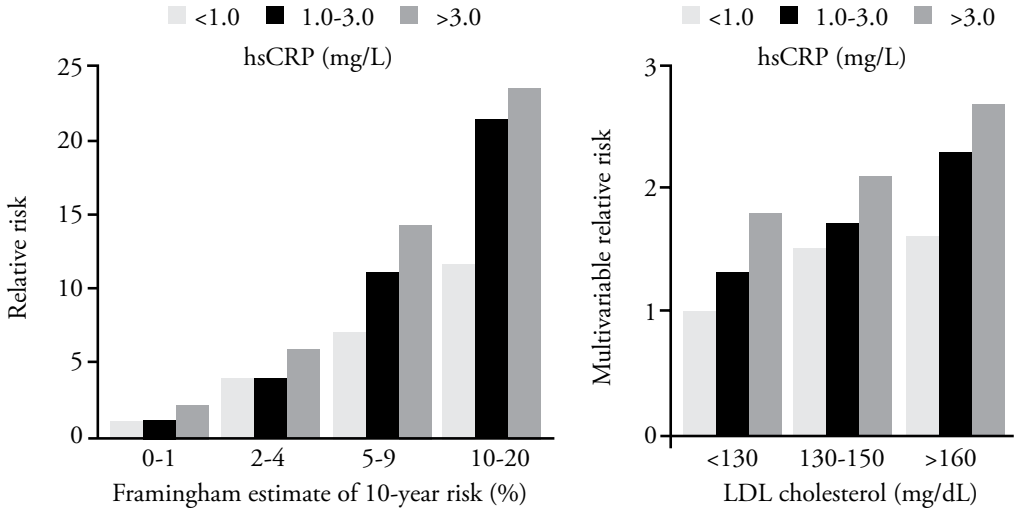

Fig. 2: CRP adds prognostic information at all levels of LDL cholesterol and at all levels of the Framingham Risk Score (Ref 16)

- Other studies seem to demonstrate that the addition of CRP determination to that of total cholesterol dramatically enhances risk prediction. [9]
- CRP is relatively stable – measured in plasma or serum and the measurement procedure is standardising. Automated high sensitivity CRP assays have low intra and interassay variability. [10]

There are several issues, which require confirmation and clarification before a full clinical role could be established. The causal relevance of CRP in atherothrombosis remains uncertain. Quartiles, tertiles and quintiles are sample- and population-dependent therefore not universally applicable. The lowering of CRP by various intervention strategies (e.g. statins/aspirin) has shown promising results but further studies are required.[11] A recent, large prospective study from Scandinavia has shown that, after controlling for confounding factors, the actual incremental predictive risk for coronary heart disease associated with CRP may not be as great as the original studies had shown – adding caution to the significance of such a marker when compared with traditional factors such as smoking, hyperlipidaemia and hypertension (Fig. 1).[12]

CRP and other risk factors

Whilst local inflammatory processes are linked with the elevation of CRP in atherothrombosis, it may also be that inflammation elsewhere is relevant. *Chlamydia pneumoniae* and *Helicobacter pylori* infections have been linked with CHD.[13,14] Whether the CRP levels are a reflection of chronic infection is debatable. Higher levels of CRP have also been strongly associated with increased body mass index and more specifically with many features of the insulin resistance/metabolic syndrome (including frank diabetes mellitus). Interestingly the oral contraceptive and hormone replacement therapy are also associated with significantly raised baseline CRP concentrations.[15] It is intriguing to note how a raised CRP adds prognostic power to both the Framingham score for CV risk and the risk associated with increasing levels of LDL-cholesterol (Fig. 2). [16]

CRP and risk – a current viewpoint

Accumulating data suggest that CRP is a useful predictor of short and long-term outcome in previously unrecognised cardiac disease and established acute coronary syndromes. In daily clinical practice the choice of cut-off levels for appropriate differentiation of lowering high-risk patients remains problematic. As patients with different clinical presentations have been studied using different assays the data and literature may not fully comparable. It is proposed that levels greater than 3mg/l are associated with high risk of events, as per recent guidelines set by AHA/CDC.[17] Emerging and consistent data suggest that statins reduce CRP levels – indicative of the pleotrophic properties of such agents – with those decreasing the levels of LDL-cholesterol the most, achieving the greater reduction in CRP.[18]

The use of biochemical markers such as CRP in the setting of both primary and secondary prevention risk assessment is steadily creeping into clinical practice. Defining the causal relationship, the degree of detrimental risk and the effects of interventions still require further research. Exciting times lie ahead

REFERENCES

1. Ross R. Atherosclerosis – an inflammatory disease. *N Engl J Med* 1999;340:115-26.
2. Castelli W. Lipids, risk factors and ischaemic heart disease. *Atherosclerosis* 1996;124 (Suppl):S1-S9.
3. Braunwald E. [The Shattuck Lecture]. Cardiovascular medicine at the turn of the millennium: triumph, concerns and opportunities. *N Engl J Med* 1997;337:1360-9.
4. Libby P, Ridker P. Novel inflammatory markers of coronary risk. Theory versus practice. *Circulation* 1999;100:1148-50.
5. Ridker P, Cushman M, Stampfer M, et al. Inflammation, aspirin and risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997;336:973-9.
6. Ridker P, Buring J, Shih J, et al. Prospective study of C-reactive protein and risk of future cardiovascular events among apparently healthy women. *Circulation* 1998;98:836-43.
7. Danesh J, Whincup P, Walker M, et al. Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ* 2000;321:194-204.
8. Koenig W. C-reactive protein: risk assessment in the primary prevention of atherosclerotic disease. Has the time come for including it in the risk profile? Ital *Heart J* 2001;2:157-163.
9. Ridker P, Glynn R, Hennekens C. C-reactive protein adds to the predictive value of total and HDL cholesterol in determining risk of myocardial infarction. *Circulation* 1998;97:2001-11.
10. Rifai N, Tracy R, Ridker P. Clinical efficacy of an automated high-sensitivity C-reactive protein assay. *Clin Chem* 1999;45:2136-41.
11. Ridker P, Rifai N, Pfeffer M, et al. Long-term effects of pravastatin on plasma concentration of C-reactive protein. *Circulation* 1999;100:230-5.
12. Danesh J, Wheeler J, Hirschfield G, et al. C-reactive protein and other circulation markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 2004;350:1387–1397.

13. Gupta S, Kaski J. *Chlamydia* causes coronary heart disease: an inflammatory idea? *Acute Coronary Syndromes* 1999;2:42-8.
14. Gupta S. Chronic infection in the aetiology of atherosclerosis - focus on *Chlamydia pneumoniae*. [The John French Memorial Lecture] *Atherosclerosis* 1999;143:1-6.
15. Ridker P, Hennekens C, Rifai N, et al. Horrmone replacement therapy and increased plasma concentration of C-reactive protein. *Circulation* 1999;100:713-6.
16. Ridker P, Rifai N, Rose L, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;347:1557–1565.
17. Pearson T, Mensah G, Alexander R, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice. A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499–511.
18. Gupta S. Does aggressive statin therapy offer improved cholesterol-independent benefits compared to conventional statin treatment? *Int J Cardiol* 2004;96:131-9.