INFLAMMATION AND ATHEROSCLEROSIS
Atherosclerosis is an inflammatory disease. 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. Furthermore, approximately 50% of patients who present with unstable angina or acute myocardial infarction do not have the classical risk factors.

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.

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. 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. 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.

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 procoagulant 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.

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.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Area under the ROC Curve (95% CI)</th>
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<tr>
<td>Total cholesterol</td>
<td>0.61 (0.59-0.62)</td>
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<tr>
<td>Current cigarette smoking (vs. non-smoking)</td>
<td>0.63 (0.61-0.64)</td>
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<tr>
<td>Systolic blood pressure</td>
<td>0.64 (0.63-0.65)</td>
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<tr>
<td>C-reactive protein</td>
<td>0.65 (0.64-0.67)</td>
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<tr>
<td>Erythrocyte sedimentation rate</td>
<td>0.65 (0.64-0.67)</td>
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<tr>
<td>von Willebrand factor</td>
<td>0.66 (0.64-0.67)</td>
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Fig. 1: CRP and other risk factors as predictors for coronary heart disease in the prospective Reykjavic study (Ref 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


