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High sensitivity CRP (hsCRP) and Cardiovascular Disease

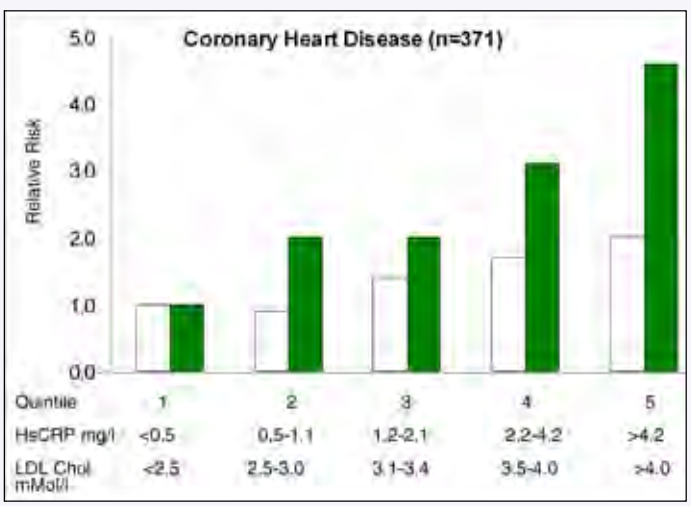
hsCRP has recently featured prominently in the medical and lay press as a novel predictor of cardiovascular disease, in particular the news that *rosuvastatin* (Crestor™) therapy conclusively lowered cardiovascular mortality in patients with normal lipids but elevated hsCRP (the Jupiter study, see below for details).

Mechanism of hsCRP elevation

Traditional risk factors do not fully explain the occurrence of cardiovascular disease; for example, a significant number of patients with normal lipids are affected by ischaemic heart disease (IHD). Other factors must be operative, and background chronic inflammation in the vascular tree, measurable using hsCRP, is now considered to be one of these. Inflammation is thought to be a key mechanism whereby stable atheromatous plaques lose their smooth endothelial surfaces, develop fissures and subsequent adherent thrombi; thus becoming the unstable plaques that give rise to the spectrum of acute coronary syndromes.

Recent important studies

Preliminary work in the *Physicians' Health Study* and *Women's Health Study* has now been backed up with data from over 28,000 healthy women in the WHS who had hsCRP levels and LDL cholesterol measured and were followed up for 8 years. The hsCRP levels were a better predictor of cardiovascular disease than was LDL cholesterol (the best lipid predictor) as shown in Figure 1 below[1].



■ *White bars show age adjusted relative risk by LDL cholesterol quintile, green bars by hsCRP quintile.*

An analysis of hsCRP levels in samples from the Busselton study confirmed levels are predictive of coronary heart disease in a local population[2]. In other studies, hsCRP levels have also been shown to correlate with central adiposity and insulin resistance.

Statins are known to have anti-inflammatory activity and reduce hsCRP levels. The just-published and much discussed Jupiter study[3] has shown that in normolipidaemic (LDL cholesterol < 3.4mmol/L) individuals with elevated hsCRP (>2mg/L), rosuvastatin reduces the risk of vascular events (myocardial infarct, stroke, revascularisation, unstable angina and cardiovascular related death) by 44%. This study of 18,000 subjects was stopped after only 1.9 years of its proposed 4 years of follow-up, as the difference between subjects receiving rosuvastatin and controls was so marked.

Clinical implications

Does this mean that widespread screening using hsCRP should be advocated with a view to starting rosuvastatin therapy if elevated? This is still contentious as although the relative risk reduction with rosuvastatin is impressive (44%) the absolute risk reduction of vascular events was low (1.8% of controls to 0.9% in the rosuvastatin group); there was a significant increase in diabetes with rosuvastatin and the drug is relatively expensive. In addition genetic variation of hsCRP levels, which is not associated with increased vascular risk, may confound results in individual patients, and minor or subclinical illness may temporarily elevate hsCRP levels. hsCRP measurement probably is, however, indicated in patients with intermediate risk (as defined by other risk factors) where the decision to start statin therapy may be influenced[4].

CRP or hsCRP: which do I request?

The standard CRP assay (normal range 0-5 mg/L) has now been used for years in ill patients to diagnose acute inflammation or monitor overt chronic inflammation.

In contrast hsCRP is used in well patients to assess baseline inflammation (usually in the range of 0-5mg/L) which is now accepted as representing inflammation present in atheromatous lesions.

Levels of <1mg/L are associated with low risk, 1-3 mg/L with average risk, and >3 mg/L with high risk, however, other risk factors (eg hyperlipidaemia etc) must also be considered to obtain a reliable overall risk estimate. Measurement of hsCRP should be done twice, optimally two weeks apart, in metabolically stable patients, and the results averaged. If the hsCRP level is >10 mg/L, the patient should be examined for sources of infection or inflammation and the test repeated when the patient is clinically better.

References

1. Ridker et al, Comparison of C Reactive Protein and LDLCholesterol levels in the Prediction of First Cardiovascular Events;NEJM 2002; 347:1557-65

2. Hung et al, C-Reactive Protein and Interleukin-18 Levels in Relation to Coronary Heart Disease: Prospective Cohort Study from Busselton Western Australia

3. Ridker et al, Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein NEJM 2008; 359:2195-207

4. Hlatky, Expanding the Orbit of Primary Prevention – Moving beyond Jupiter NEJM 2008; 359:2280-2282.