Editorial

The JUPITER Trial Results Boost the Evidence for the Use of hsCRP as a Treatment Target and as Part of the Assessment of Vascular Risk: Time for New Guidelines?

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Inflammation characterises all phases of atherothrombosis and provides a pathophysiological link between early lesion formation and plaque rupture leading to vessel lumen occlusion (clinical event).[1,2] The inflammatory marker high sensitivity C-reactive protein (hsCRP) may represent a useful tool for vascular risk assessment in apparently healthy persons (especially when lipid levels are low).[3-5] However, the joint statement of the Centre for Disease Control (CDC) and the American Heart Association (AHA) in 2003[6] does not support generalised screening for inflammatory markers, particularly in those at low vascular risk. The CDC/AHA recommendations endorse the optional use of hsCRP to identify patients without established cardiovascular disease (CVD) who may be at higher risk than estimated using traditional risk factors.[6,7] Measurement of hsCRP may obviate the need for further evaluation (e.g. imaging or exercise testing) in these "intermediate risk" patients (10-20% 10-year CVD risk) and may help to guide drug treatment (e.g. lipid-lowering, antiplatelet or other cardioprotective agents).[6] The CDC/ AHA statement also recommends that secondary prevention measures and acute coronary syndrome (ACS) management should not depend on hsCRP levels.[6] This is because the guidelines for aggressive intervention in these cases result from evidence that does not include hsCRP measurement.[6] Moreover, according to the CDC/AHA statement, little evidence supports the use of serial hsCRP testing as a measure of disease activity or to monitor treatment.[6]

It appears that inflammatory markers such as hsCRP can be monitored cost-effectively and may influence the selection of drugs that target both established vascular risk factors and inflammation[8] in high risk patients with ACS, stable coronary heart disease (CHD) and diabetes mellitus (DM) or metabolic syndrome (MetS), non-alcoholic fatty liver disease (NAFLD), or systemic autoimmune diseases. In these high risk groups, inflammation might correlate with the extent and severity of atherosclerosis and might serve as target of therapy.[8,9]

Despite the importance of blood lipids in CVD, 50% of all myocardial infarctions (MI) occur among individuals without overt hyperlipidaemia and as many as 20% of all coronary events occur in the absence of any

of the established major vascular risk factors.[10] For example, in the Women's Health Study (28,000 healthy middle-aged US women followed up for 8 years) 77% of all CVD events occurred among those with low density lipoprotein cholesterol (LDL-C) levels <160 mg/dL (4.2 mmol/L), and 46% occurred among those with LDL-C levels <130 mg/dL (3.4 mmol/L).[10] More than 10 population studies have shown that hsCRP levels are independently associated with vascular events.[3-5,11-13] In addition, hsCRP provides prognostic information at all LDL-C levels, at all levels of the Framingham risk score and at all numbers of MetS characteristics.[14,15]

In this context, the Randomised Trial of Rosuvastatin in the Primary Prevention of Cardiovascular Events Among Individuals With Low Levels of LDL-C and Elevated Levels of CRP (JUPITER trial)[16] was designed to address some important questions about the relation between vascular risk and inflammation:

1. Does hsCRP reduction *per se* lower CVD risk?
2. Is the effect of statins on hsCRP clinically relevant, independently of LDL-C lowering?
3. Should we be treating with statins not only patients with hyperlipidaemia but also those with elevated hsCRP levels?

JUPITER enrolled healthy men over 50 and women over 60 years of age who did not qualify for statin therapy because their LDL-C levels were <130 mg/dL (3.4 mmol/L);[16] median LDL-C was very low (108 mg/dL; 2.8 mmol/L). However, enrolled subjects had high levels of hsCRP (>2 mg/L; median 4.2 mg/L), suggesting an increased vascular risk. Patients were randomly allocated to receive rosuvastatin 20 mg/day or placebo. The primary endpoint of JUPITER was the first occurrence of a major CVD event, defined as CVD death, stroke, MI, unstable angina or arterial revascularisation. Secondary endpoints included the components of the primary endpoint and all-cause mortality.[16]

A total of 89,890 subjects were screened and 17,802 were included in the study (8,901 subjects in each group).[16] This means that 1 in 5 middle-aged subjects without overt CVD appears to be at increased risk for CVD on the basis of hsCRP levels (>2 mg/L). JUPITER included 6,801 women (38.2%), whereas previous statin trials for primary prevention included either no women (West of Scotland Coronary Prevention Study)[17] or lower numbers (997 women in the Air Force/ Texas Coronary Atherosclerosis Prevention Study).[18] Furthermore, JUPITER included 2,224 (12.5%) black and 2,261 (12.7%) Hispanic participants; these ethnic minorities were also underrepresented in other statin trials. In addition, 7,375 (41.4%) participants had MetS.[16]

In JUPITER, rosuvastatin reduced LDL-C levels by 50% and hsCRP levels by 37%. The trial was stopped after a median follow-up of 1.9 years for ethical reasons.[16] The primary endpoint was reduced by 44% (hazard ratio for rosuvastatin, 0.56; 95% confidence interval [CI], 0.46-0.69; p<0.00001). The anticipated reduction in the incidence of the primary endpoint, related to the 50% reduction in LDL-C, was 25%, whereas in fact a 44% reduction was recorded. This means that a substantial reduction in low grade inflammation (as expressed by the decrease of hsCRP by 37%) *per se* lowers actual CVD risk. Moreover, the results of the JUPITER trial suggest that the effect of statins on hsCRP is clinically relevant, independently of LDL-C lowering (44% reduction in primary endpoint instead of the expected 25%).[16]

Compared with placebo, rosuvastatin reduced MI by 54% (p=0.0002), stroke by 48% (p=0.002), revascularisation or unstable angina by 47% (p<0.00001), the combined end point of MI, stroke, or death from CVD causes by 47% (p<0.00001) and all cause mortality by 20% (p=0.02). Relative hazard reductions were similar in women (46%) and men (42%), and were observed in all subgroups evaluated (according to age, race, ethnic group, region of origin, number of traditional risk factors and Framingham risk score).

Conclusions

The JUPITER trial[16] has important implications for the primary prevention of CVD. Subjects with hsCRP levels >2 mg/L, regardless of their LDL-C levels, are at increased risk for CVD and this risk is substantially reduced (44% vs. placebo) by rosuvastatin.[16] The benefit is evident in men and women, subjects with MetS, Caucasians, blacks, and Hispanics. These findings provide a rationale for including hsCRP assessment in guidelines, both for risk stratification and as a treatment target. In the broader context, the JUPITER results suggest that drugs that markedly lower hsCRP levels, in addition to being effective in their primary role (e.g. reducing the blood pressure or LDL-C levels), may be the preferred choice in the treatment of vascular disease.

Considering hsCRP levels might lead to an intensification of lifestyle modifications or the administration of statins. One remaining problem is related with technical issues about hsCRP assessment (implementing standardised, reproducible and cost effective assays), which need to be resolved. Time for revised guidelines?

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