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## My Patient has an elevated hs-CRP. What does this mean? What should I do now?

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### Why is this trial important?

Hyperlipidaemia is an established risk factor for cardiovascular and cerebrovascular disease. A standard investigation to assess a person's hyperlipidaemia is the lipid profile. This measures total cholesterol, high density lipoproteins (HDL), low density lipoproteins (LDL) and triglycerides. LDL has been implicated most as the culprit behind these vascular events. However, new research has shown that a raised high sensitivity C - reactive protein (hs-CRP), a biomarker for inflammation, is a predictor for systemic vascular endothelial inflammation and future vascular event independent of a person's LDL level.

Statins, the wonder drug for high LDL and cholesterol, have been in use for vascular protection for long. They have an

established benefit for cardioprotection and stroke risk reduction in people with high cholesterol. However, if statins offer any benefit in people with low to normal Cholesterol and raised hs-CRP was not known.

The JUPITER trial was undertaken with the objective of assessing the benefits of statins in reducing the risk of future vascular events in asymptomatic patients with cholesterol already in the desirable range but elevated hs-CRP.

### Who were the participants?

A total of 17,802 individuals from 26 countries were enrolled for the trial. There was representation of Caucasians, Blacks and Hispanics from North and South America, Africa and Europe.

Men aged  $\geq 50$  years and women aged  $\geq 60$  years with no vascular co-morbidities and LDL level  $<130$  mg/dL and hs-CRP level  $\geq 2.0$  mg/dL were eligible.

The study population had a mean age of 66 years with slight male preponderance. Study participants matched in terms of their co-morbidity status.

### What was the intervention?

JUPITER was a double-blind, placebo-controlled trial. The study subjects were randomly allocated to two groups. The intervention group was administered 20 mg Rosuvastatin daily. The control group received a placebo pill. The two groups were followed for a median duration of 1.9 years and their lipid levels and hs-CRP were assessed both at baseline and yearly thereafter for as long as they were part of the study. The primary end-point of interest was fatal and non-fatal stroke.

### What was the outcome?

At the end of the study period, the incidence rate for stroke in the Rosuvastatin group was 0.18 compared with 0.34 in the placebo group ( $p=0.002$ ) translating to a 48% risk reduction. Although Rosuvastatin reduced the risk of ischemic stroke compared to a placebo ( $p=0.004$ ), it was similar to placebo in preventing haemorrhagic stroke (0.44) and transient ischaemic attack ( $p=0.79$ ). No excess risk of haemorrhagic strokes was observed with statin therapy.

The benefits of therapy extended beyond the high risk group. People who were categorized as low risk based on body mass index  $<25$  kg/m<sup>2</sup>, without the metabolic syndrome, with a Framingham risk score  $<10$ , with low levels of LDL-C ( $<100$  mg/dL), with normal levels of HDL-C), and with normal triglyceride levels ( $<150$  mg/dL) also had similar benefits from therapy.

Twelve months of daily 20 mg Rosuvastatin was able to bring down the LDL and Cholesterol levels by 50% and the hs-CRP levels by 37%. The greatest stroke risk reduction with Rosuvastatin was seen in participants who achieved LDL  $<70$  mg/dL and hs-CRP  $< 2$  mg/L.

The adverse effect profile was similar in both groups except a slightly high incidence of Diabetes in the Rosuvastatin group ( $p=0.01$ ).

### What were the conclusions?

The investigators concluded that use of prophylactic cholesterol-lowering therapy is justified in people with normal-range LDL and cholesterol but raised hs-CRP. Daily use of 20mg Rosuvastatin was associated with a 39% relative reduction in ischaemic stroke risk for each 1mmol/L reduction in LDL level.

Other trials, namely, WOSCOPS, MEGA, AFCAPS-TextCAPS; have proven the advantage of statin therapy on stroke risk reduction in people with high LDL levels and JUPITER proves it in people with desirable LDL and raised hs-CRP levels.

### What implications does this study have for the Pakistani medical practitioners?

Daily Rosuvastatin promises reduction in the risk of stroke by 48% in people with normal-range cholesterol who are nonetheless at risk for vascular events due to elevated hs-CRP levels. This is a new vascular intervention point to consider in asymptomatic patients with LDL $<130$  but raised High Sensitivity C reactive protein levels above 2.

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### Recommended Reading

1. Everett BM, Glynn RJ, MacFadyen JG, Ridker PM. Rosuvastatin in the prevention of stroke among men and women with elevated levels of C-reactive protein: justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). *Circulation* 2010; 121: 143-50.
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