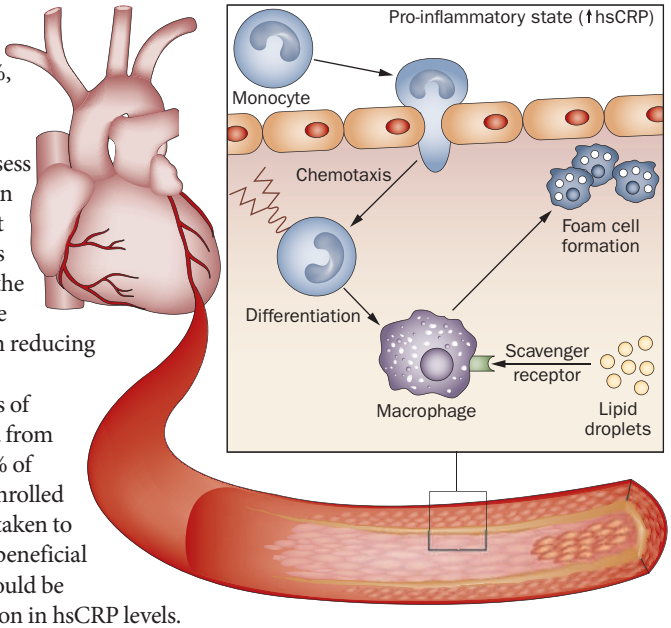
PREVENTION

# Prophylactic statin therapy in the management of cardiovascular disease

A prospective study conducted as part of the JUPITER trial suggests that preventive measures against coronary artery disease could be improved by reducing both inflammation and LDL cholesterol. A daily dose of statin reduced the risk of adverse cardiovascular events in individuals over the age of 50 years who were healthy except for elevated levels of high-sensitivity C-reactive protein (hsCRP).

LDL cholesterol has long been recognized as a key factor contributing to coronary artery disease, and lowering LDL cholesterol to levels recommended by current guidelines has been shown to reduce cardiovascular risks. Inflammation is also known to be a major underlying factor in the development of atherosclerosis. Indeed, statins—the drugs of choice for lowering LDL cholesterol—also reduce levels of hsCRP, a marker of inflammation. Elevated levels of hsCRP are associated with an increased risk of adverse cardiovascular events, whereas lowering hsCRP improves clinical outcomes. However, the extent to which hsCRP is involved in the progression of coronary atherosclerosis has been questioned and it is unclear whether reducing hsCRP in asymptomatic individuals is warranted.

The JUPITER trial was conducted to determine whether statin therapy aimed specifically at reducing hsCRP would be beneficial in preventing cardiovascular events in individuals with evidence of inflammation but normal LDL-cholesterol levels and no history of cardiovascular disease. Men and women over the age of 50 years, seemingly healthy except for hsCRP levels in excess of 2 mg/l, were recruited from 26 countries and randomly assigned to receive either rosuvastatin (20 mg daily) or placebo. Participants were assessed for the occurrence of cardiovascular events, including myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina or cardiovascular-related death. Rosuvastatin reduced hsCRP levels by 37% and LDL-cholesterol levels by 50%, compared with the placebo. The study was originally planned to assess the effects of rosuvastatin over a 5-year period, but was terminated after less than 2 years because of the overwhelmingly positive effect of the treatment in reducing cardiovascular events.




A prospective analysis of baseline and 1-year data from 15,548 participants (87% of the number originally enrolled in the study) was undertaken to determine whether the beneficial effects of rosuvastatin could be attributed to the reduction in hsCRP levels. Participants in the rosuvastatin group were subdivided according to whether or not they achieved LDL-cholesterol and hsCRP levels of less than 1.8 mmol/l (70 mg/dl) and 2 mg/l, respectively. A significant reduction in adverse events was observed when participants achieved the lower levels of either LDL cholesterol or hsCRP. However, the lowest rate of cardiovascular events was observed when both LDL-cholesterol and hsCRP levels were reduced.

The findings of the JUPITER trial are consistent with those of earlier trials showing that statin-induced reductions in the levels of both LDL cholesterol and hsCRP produce the best clinical outcomes for patients with acute coronary syndromes. However, two important features of the JUPITER design strengthen the validity of the results. First, the trial was designed to adjust for baseline clinical characteristics so that changes observed could be attributed to effects of the treatment and not to baseline variation. Second, the absence of overt disease in the participants minimizes confounding factors that might have influenced the interpretation of the results.

The results of the trial suggest that asymptomatic individuals with evidence of inflammation but who are normolipidemic according to current guidelines could benefit from statin therapy. Erin Michos and Roger Blumenthal from Johns Hopkins University estimate that this would represent an additional 6.5 million people. Given the findings of studies showing a decrease in the progression of coronary atherosclerosis in patients with LDL-cholesterol levels below 1.8 mmol/l, the cut-off point used in the JUPITER trial, an important question that emerges is whether the current guidelines should be reassessed. "The standard is so important because many more people will qualify for statin therapy and many heart attacks, strokes and episodes of deep-vein thrombosis can be delayed or prevented," said Blumenthal.

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**Original article** Ridker, P. M. *et al.* Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *Lancet* **373**, 1175–1181 (2009).