CRP、スタチン、および冠動脈リスク（Late Breaking Clinical Trial [LBCT] , Abstract # 161）

JUPITERトライアル：スタチンはコレステロールが正常だがC反応性蛋白が上昇している患者において心筋梗塞と脳卒中の発症率を低下させる

JUPITER trial: Statin reduces myocardial infarction, stroke rates in patients with normal cholesterol but elevated C-reactive protein

脂質低下薬ロスバスタチンはコレステロールが正常だが高感度C反応性蛋白（hsCRP）レベルが上昇している患者において心筋梗塞と脳卒中の発症率を低下させる、と2008年American Heart Association学会で発表された。JUPITERトライアルは、冠動脈関連の死亡および障害に関して「ロスバスタチンの明確な有益性」がスタディデータから示されたため、スケジュールより2年早く2008年3月に終了した。このLate-Breaking Clinical Trialの結果は、同時にNew England Journal of Medicineに掲載された。プラセボ治療群の患者と比較し、ロスバスタチンを投与された患者は、一次エンドポイントである初回の主要な心血管イベント－心筋梗塞、脳卒中、血行再建術、不安定狭心症による入院および心血管死の合計－が44%少なかった。ロスバスタチン群はまた、心筋梗塞が54%、脳卒中が48%、血行再建術の必要が46%少なく、総死亡率は20%低かった。特に注目すべき点は、hsCRP上昇以外にリスクファクターを有さないスタチン群の男女において、初回イベントが37%軽減できたことである。サブグループ解析の結果、性別、人種、民族およびフラミンガムリスクスコアに関わらず同じ結果が認められた。

Full Text

A lipid-lowering drug reduced myocardial infarction by 54 percent in people who had normal cholesterol but elevated levels of high sensitivity C-reactive protein (hsCRP), according to a study presented at the American Heart Association Scientific Sessions 2008. Rosuvastatin in the Prevention of Cardiovascular Events Among 17,802 Men and Women with Elevated Levels of C-Reactive Protein: the JUPITER Trial was presented as a late-breaking clinical trial. The study was simultaneously published in the New England Journal of Medicine.

"Compared to those who received placebo, patients receiving the drug rosuvastatin also had a 48 percent reduction in stroke, a 46 percent reduction in the need for interventions to reopen blocked blood vessels and a 20 percent drop in all-cause mortality," said Paul M. Ridker, M.D., lead author of the study and director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital, Boston, Mass.

Patients included in the trial were men over age 50 and women over age 60, with no history of cardiovascular disease (CVD), with LDL levels <130 mg/dL and hsCRP ≥2 mg/L. They could have other risk factors for CVD, such as high blood pressure up to 190/100, obesity, current smoking, abnormal glucose tolerance (but not frank diabetes) and/or the metabolic syndrome, and/or a family history of premature heart disease. About half had a Framingham risk score (FRS) ≤10 percent and half >10 percent (10 percent to 20 percent indicates an intermediate risk level). While they had not had any cardiovascular event, those with a FRS >10 would be considered to be at higher risk for such events than a low risk or completely healthy population. More than 89,000 patients were screened to find the 17,802 who participated. Most of those excluded had either LDL levels that were too high or hsCRP levels that were too low.

Overall, compared to placebo-treated participants in the trial, those given rosuvastatin had a 44 percent reduction in the primary endpoint of a first major cardiovascular event - a composite of myocardial infarction, stroke, revascularization, hospitalization for unstable angina and cardiovascular death. Hospitalizations for cardiac reasons were also reduced and the authors suggested that the strategy tested in JUPITER of treating elevated hsCRP patients with statin therapy could be cost-effective.

Ridker said one particularly striking finding was a 37 percent reduction in first events in men and women in the statin group who had no other risk factors except for elevated hsCRP, a sign of inflammation that can be associated with increased coronary disease risk.

The researchers found no increase in the number of patients with either muscle pain or cancer among those given rosuvastatin. As in almost all prior statin trials, they observed a small increase in reported diabetes, said Ridker, the Eugene Braunwald Professor of Medicine at Harvard Medical School.

The very low LDL levels produced by rosuvastatin (median 54 at 24 months) raise the question of whether other adverse effects might be seen over a longer time period, but they were not evident here.

JUPITER participants had average LDL levels of 108 milligrams per deciliter (mg/dL) at the study's start - well below the 160 mg/dL level at which doctors normally consider beginning treatment with statins to lower cholesterol.

The study did not provide details as to how patients with hsCRP levels >10mg/L were handled. The 2003 consensus statement by the Centers for Disease Control and Prevention and the American Heart Association suggests that many elevations at those levels are due to transient inflammation from minor infections and that patients should have the test repeated to properly determine their chronic hsCRP level.

The 17,802 participants, recruited from 1,300 clinical sites in 26 countries, were randomly assigned to 20 milligrams (mg) of rosuvastatin a day or a daily placebo. The study's independent data and safety monitoring board ended the trial in March 2008, more than two years ahead of schedule, when it determined that the study data indicated "unequivocal benefit of rosuvastatin" on coronary-related death and disability.

"Not only do we confirm that apparently healthy men and women with elevated hsCRP are at high risk of cardiovascular events, but we demonstrate that a simple therapy can reduce their risk of heart attack, stroke or cardiovascular death," Ridker said.

JUPITER included nearly 6,801 women and 5,119 members of minority groups in the randomized cohort.

"For the first time in a major statin prevention trial, we have clear evidence of benefits in women as well as men, in blacks and Hispanics as well as Caucasians, and perhaps most importantly, a substantial reduction in all-cause mortality," he said. "It appears hsCRP predicts high risk even when cholesterol is low."

However, that issue was not specifically tested in this study.

The benefits of rosuvastatin in people with elevated hsCRP extended across all subgroups evaluated, including those with low Framingham scores and those with LDL levels of less than 100mg/dL, Ridker said.

This is consistent with the earlier Heart Protection Study, a largely secondary prevention study where the benefit of a statin was similar at high and low levels of LDL cholesterol.

Diet, exercise and smoking cessation are all known to lower hsCRP levels and are first-line interventions recommended for the general population to reduce the risk of heart attack and stroke. However, until now, no large, prospective data study has shown that any pharmacologic therapy given to those without elevated cholesterol levels but with elevated hsCRP could prevent cardiovascular events.

Since statins lower both LDL cholesterol and hsCRP, the findings presented at the meeting cannot determine whether cholesterol lowering, a reduction in inflammation, or a combination of both are responsible for the reductions seen.

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