血管手術におけるフルバスタチンの心保護作用

DECREASE IIIスタディ：フルバスタチンは待機的大血管手術の周術期の循環器系予後を改善する

DECREASE III: Fluvasatatin improves perioperative cardiac outcomes after elective major vascular surgery

DECREASE IIIスタディ：Dutch Echographic Cardiac Risk Evaluation Applying Stress Echo III（オランダにおけるストレスエコーを用いた心臓リスク評価 III）スタディの結果、フルバスタチン徐放製剤をベータ遮断薬に併用することにより、待機的大血管手術を施行されスタチンを初回投与されたハイリスク患者の周術期の循環器系予後が有意に改善する、と2008年European Society of Cardiology学会で報告された。患者（年齢中央値65.7歳、男性75%、冠動脈疾患の既往39%、脳卒中の既往29%、糖尿病20%）は、徐放性フルバスタチン（1日80mg；250人）またはマッチさせたプラセボ（247人）を術前30日より開始し術後30日以上継続する群に無作為に割り付けられた。フルバスタチン投与によりベースラインの総コレステロールおよびLDLコレステロールがそれぞれ20%と21%減少したのに対し、プラセボではそれぞれ4%および3%の減少であった（両方ともp<0.001）。同様にフルバスタチンは炎症マーカーである高感度C反応性蛋白およびインターロイキン-6をそれぞれ21%および33%減少させたのに対し、プラセボ群では＋3%および-4%の変化であった（両方ともp<0.001）。一次エンドポイントである初回血管手術後30日以内の心筋虚血性イベントに達したのは、フルバスタチンを投与された患者において有意に少なかった（心筋虚血と診断されたのはフルバスタチン群で10.9%であったのに対し、プラセボ群では18.9%であった；p=0.016）。

Full Text

Annually, approximately 40 million people undergo noncardiac surgery in the European Union. Of these patients approximately 400,000 (1%) will suffer a perioperative myocardial infarction (PMI) while approximately 133,000 (0.3%) die because of cardiac complications. In particular in patients undergoing noncardiac vascular surgery the incidence of perioperative cardiac complications is high with cardiac mortality rates exceeding 2%. Indeed perioperative cardiac events are the major cause of adverse outcome in vascular surgery patients.

The pathophysiology of a PMI is complex. While cardiac oxygen demand / supply mismatch in patients with coronary artery disease might be counteracted by appropriate beta-blocker use or coronary revascularization in these patients, coronary plaque instability leading to plaque rupture and thrombosis remains a significant problem. Recent retrospective studies suggested a potential beneficial role of statins in the prevention of PMI, in particular by "stabilizing" coronary plaques due to their pleiotropic, anti-inflammatory effects. Therefore the aim of the randomized, double blind, Dutch Echographic Cardiac Risk Evaluation Applying Stress Echo (DECREASE) III trial was to assess the cardioprotective effect of fluvastatin XL on top of beta-blocker therapy in vascular surgery patients.

Between June 2004 and April 2008 497 statin-naive patients (median age 65.7 years, 75% men, 39% prior coronary artery disease, 29% prior stroke, 20% diabetic) scheduled for vascular surgery were included in the trial at Erasmus MC Rotterdam, the Netherlands. Patients were randomized to receive either placebo or fluvastatin extended at a dose of 80 mg once daily. Treatment was started at the outpatient clinic on the day of randomization, median 37 days prior to the surgical procedure and was continued at least during the first 30 days after surgery. Inflammatory markers at baseline, including hs-CRP and IL-6 were assessed in patients allocated to fluvastatin or placebo. At hospital admission levels of hs-CRP and IL-6 were significantly lower in patients on fluvastatin (respectively 6.00 mg/L vs 4.66 mg/L, p=0.030 and 8.45 pg/ml vs 5.75 pg/ml, p=0.024). The primary analysis was intention-to-treat and involved all patients who were randomly assigned to either fluvastatin or placebo. Directly after surgery, study treatment was temporarily discontinued in 115 (23%) patients for a median duration of 2 days because of the inability to take the study drug orally. A total of 34 patients discontinued study medication because of laboratory abnormalities; 16 (3.2%) because of ALAT exceeding 3x upper limit of normal, 13 (2.6%) because of CK exceeding 10x upper limit of normal, and 5 (1.0%) because of a combination of elevated ALAT and CK.

Myocardial ischemia was detected in 74 (14.9%) patients within 30 days of the initial vascular surgical procedure. A total of 27/250 (10.9%) patients allocated to fluvastatin reached the primary endpoint compared to 47/247 (18.9%) patients allocated to placebo treatment (OR 0.53; 95% CI 0.32-0.88). Hence, the number needed to treat (NNT) to prevent one patient experiencing myocardial ischemia was 12.5 patients.

A total of 18 (3.6%) patients died within 30 days after surgery of which 12 (2.4%) were attributable to cardiovascular causes. 25 (5.0%) patients experienced a nonfatal myocardial infarction during that same period. The combined endpoint of cardiovascular death and nonfatal myocardial infarction was reached in 37/497 (7.4%) patients. A total of 12/250 (4.8%) patients allocated to fluvastatin therapy reached the combined endpoint, compared to 25/247 (10.1%) allocated to placebo. Hence, fluvastatin therapy was associated with a 52% relative reduction in the incidence of cardiovascular death or MI (OR 0.48; 95% CI 0.24-0.95). The NNT for the composite endpoint of cardiovascular death or nonfatal MI is 18.9 patients.

The proportion of patients experiencing any adverse event was similar between the fluvastatin and placebo groups. The proportion of patients experiencing a CK rise > 10x the upper limit of normal was 4.1% in the fluvastatin group and 3.0% in the placebo group. The median peak CK level was 141 U/Lin patients on fluvastatin and 113 U/L in patients on placebo (p=0.24). The proportion of patients with significant increase in ALAT levels, ie > 3x times upper limit of normal, was 3.1% in the fluvastatin group and 5.2% in the placebo group. The median peak ALAT level was 23 U/L in patients on fluvastatin and 24U/L in patients on placebo.
The study authors conclude that fluvastatin XL therapy was associated with improved postoperative cardiac outcome in high-risk patients undergoing elective vascular surgery.

Conference News