大動脈弁狭窄は脂質低下では改善しない

SEASスタディ：シンバスタチン／エゼチミブの併用による強力な脂質低下療法は大動脈弁狭窄の進行を抑制しない

SEAS: Intensive lipid-lowering therapy with simvastatin/ezetimibe combination does not affect the progression of aortic valve stenosis

無症候性の軽度～中等度大動脈弁狭窄患者においてシンバスタチンとエゼチミブの併用療法による強力なLDLコレステロール低下療法は大動脈弁狭窄の進行を抑制しないが心血管虚血性イベントのリスクは軽減しうる。SEAS：Simvastatin and Ezetimibe in Aortic Stenosis（大動脈弁狭窄におけるシンバスタチンとエゼチミブ）スタディの結果が2008年European Society of Cardiology学会で発表され、New England Journal of Medicineに掲載された。軽度～中等度の大動脈弁狭窄を有し脂質低下療法の適応のない患者1,873人（平均年齢67歳）を、シンバスタチン（1日40mg）とエゼチミブ（1日10mg）の併用にて強力にコレステロールを低下させる群またはプラセボ群に無作為に割り付けた。複合一次エンドポイントである主要な心血管イベント（LDL低下療法333人対プラセボ355人；ハザード比［HR］0.96；95%信頼区間［CI］0.83～1.12）または二次エンドポイントである大動脈弁疾患イベント単独（308人対326人； HR 0.97；95% CI 0.83～1.14）は二群間で有意差がなかった。この併用療法により動脈硬化イベント単独は軽減した(15.7%対20.1%、p=0.02)。治療群では癌発症率が高かった(11.1%対7.5%、p=0.01)が、これは患者数が少なかったため偶然認められたと考えられる。

Full Text

Results from the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study indicate that intensive LDL-cholesterol lowering with the combination of simvastatin and ezetimibe does not affect the progression of aortic valve stenosis, but can reduce the risk of cardiovascular ischemic events in subjects with mild-to-moderate asymptomatic aortic stenosis, when compared with placebo. The use of simvastatin and ezetimibe in such patients was generally well tolerated and safe. The results were presented at the European Society of Cardiology Congress 2008.

The SEAS study is the first large-scale randomized trial to assess the effects of lowering LDL-cholesterol in patients with aortic stenosis. The study was initiated and designed by academic researchers in Scandinavia, and carried out at 173 clinical centers in Norway, Denmark, Sweden, Finland, Germany, UK and Ireland. It included 1,873 patients with mild to moderate aortic stenosis without symptoms who were not considered to have a clear indication for treatment with cholesterol-lowering drugs. Patients were randomly assigned to receive either intensive cholesterol lowering with the combination of simvastatin (40 mg daily) and ezetimibe (10 mg daily) or matching placebo. The first patient was included in 2001. The study was completed according to the study plan when the last patient included had been followed for 4 years (March 2008). Vital status at the end of the study was established for all patients. All data have been checked for completeness and the data file for analysis was closed on 30 June 2008.

The primary endpoint of the SEAS study was "major cardiovascular events", which is the composite of events associated with aortic valve disease and with atherosclerotic disease. The secondary endpoints were the two separate components of the primary endpoint: "aortic valve disease events" (surgical valve replacement, hospitalization because of heart failure, and cardiovascular death) and "atherosclerotic disease events" (non-fatal myocardial infarction, coronary artery bypass surgery or percutaneous coronary intervention, hospitalization because of unstable angina pectoris, non-hemorrhagic stroke and cardiovascular death). Subsidiary outcomes included echocardiographic evidence of aortic stenosis progression and safety.

Compared with placebo, the combination of simvastatin and ezetimibe reduced LDL-cholesterol by an average of 61%, corresponding to a reduction of about 2 mmol/L (76 mg/dl), and this effect was sustained throughout the study. 688 patients had one or more primary endpoint events. No significant difference was observed between the treatment groups for the combined primary endpoint (333 patients with an event on LDL-lowering treatment versus 355 on placebo; hazard ratio [HR] 0.96; 95% confidence interval [CI] 0.83 to 1.12). Nor was there a significant difference for the secondary endpoint of aortic valve disease events alone (308 versus 326; HR 0.97; 95% CI 0.83 to 1.14). The combination of simvastatin and ezetimibe did, however, produce a statistically significant 22% (95% CI 3% to 37%; p=0.02) proportional reduction in the secondary endpoint of atherosclerotic events alone: 148 (15.7%) in the simvastatin plus ezetimibe group versus 187 (20.1%) in the placebo group.

The study therapy was generally well tolerated, with no significant differences between the treatment groups in the proportions of patients who stopped taking study treatment (irrespective of whether it was active or placebo). In the subsidiary safety analyses, a total of 175 patients were recorded with a serious adverse event attributed to cancer. More of these events were observed among patients assigned the combination of simvastatin and ezetimibe than among those assigned placebo (105 [11.1%] versus 70 [7.5%]; unadjusted p=0.01), this included patients with recurrent cancer and cancer prior to randomization as well as cancer diagnosed more than 2 weeks after withdrawal from the study. There were also slightly more cancer deaths (39 [4.1%] versus 23 [2.5%]; unadjusted p=0.05). These apparent differences were not related to any particular type of cancer and did not become significantly larger with more prolonged treatment.

The observed differences in cancer in the SEAS study are based on small numbers and could have occurred as a result of chance. In order to assess their relevance, the SEAS data have been provided to an independent academic group for combined analysis with data on cancer from the two other large trials of simvastatin and ezetimibe, which are still in progress. The SHARP (Study of Heart and Renal Protection) study is a randomized placebo-controlled trial of simvastatin and ezetimibe in 9400 patients with chronic kidney disease. The IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial) study is a randomized double-blind trial of simvastatin and ezetimibe compared to simvastatin alone which has recruited 12,000 of a planned 18,000 patients with acute coronary disease.

In combination, the SHARP and IMPROVE-IT studies involve about 4 times as many cancers as in the SEAS study. The analysis of SHARP and IMPROVE-IT does not support the suggestion of an increase in cancer that was raised by the subsidiary analyses of the relatively small numbers of cancers in the SEAS study. Independent analysis of these data was initiated and has been conducted and interpreted by the Clinical Trial Service Unit (CTSU) at the University of Oxford, UK. The CTSU also designed and is conducting the SHARP trial, which is funded by a research grant to the University of Oxford from MSD and Schering-Plough academic. Both the SHARP study and the analyses of cancer data have been conducted by the CTSU independently of the pharmaceutical companies.

The scientific leadership of the SEAS study was a Steering Committee consisting of 14 academic representatives of centers in each of the participating countries and two members (a statistician and a coordinator) representing the funders. The SEAS study is funded by the pharmaceutical companies Merck Sharp & Dohme (MSD) and Schering-Plough who market the drugs being tested. All clinical endpoint events were adjudicated by an independent committee that was blinded to the study treatment allocation. The study was monitored by an independent Data Safety and Monitoring Board. Data collection was performed by MSD, and the data were analyzed by statisticians at Ulleval University Hospital in Oslo, Norway, and at MSD.