

Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis

Nora TOMA, Specialist in Cardiology, Researcher in Cardiology
Cardiology Department, Emergency University Hospital, Bucharest, Romania

Aortic-valve stenosis is common in elderly persons, with a prevalence of 3 to 5% in the population over 75 years of age. The condition has been shown to be an inflammatory process associated with cardiovascular risk factors, with histopathological changes in the valve leaflets that are similar to those in other atherosclerotic diseases.

Changes in the aortic valve are associated with an increased risk of death from cardiovascular causes and myocardial infarction, even in the absence of hemodynamic obstruction and signs of coronary disease. Hyperlipidemia has been suggested as a risk factor for stenosis of the aortic valve, but lipid-lowering studies have had conflicting results.

Most studies have suggested a beneficial effect of statins, whereas one prospective, randomized study did not find any effect of lipid-lowering therapy on the progression of aortic-valve stenosis.

This study was designed by the steering committee on the basis of a protocol developed for the Simvastatin in Aortic Stenosis (SAS) study, which evaluated the effect of lipid-lowering therapy with simvastatin (at a dose of 40 to 80 mg) as compared with placebo on clinical and echocardiographic outcomes in patients with aortic stenosis. A total of 1873 patients underwent randomization, men and women between the ages of 45 and 85 years who had

asymptomatic, mild-to-moderate aortic-valve stenosis, as assessed on echocardiography, with a peak aortic-jet velocity of 2.5 to 4 m per second. Patients were excluded if they had received a diagnosis or had symptoms of coronary artery disease, peripheral arterial disease, cerebrovascular disease, or diabetes mellitus or if they had any other condition requiring lipid-lowering therapy.

To improve the lipid-lowering effect while decreasing the risk of myopathy, the steering committee decided to add ezetimibe (at a dose of 10 mg daily) to 40 mg of simvastatin. Echocardiography was performed at baseline and then annually and before valve surgery, according to a standardized echocardiographic protocol.

The study was completed according to the protocol when all patients had been followed for a minimum of 4 years after randomization, at which point the primary outcome had occurred in at least 464 patients.

Results

The mean serum level of low-density lipoprotein (LDL) cholesterol remained unchanged in the placebo group and decreased by 61.3%, at 8 weeks, in the simvastatin-ezetimibe group.

During the entire follow-up period, the mean percent reduction in LDL cholesterol was 53.8% in the simvastatin-ezetimibe group and

3.8% in the placebo group. In the placebo group, the mean peak aortic-jet velocity was 3.71 ± 0.76 m per second at the end of the study, an increase of 0.62 ± 0.61 m per second. This change was similar to that in the simvastatin–ezetimibe group, in which the velocity was 3.69 ± 0.78 m per second at the end of the study, an increase of 0.61 ± 0.59 m per second.

In the placebo group, the mean pressure gradient was 22.5 ± 8.5 mm Hg at baseline and increased to 34.4 ± 14.9 mm Hg at the end of the study, as compared with a value of 22.2 ± 8.5 mm Hg at baseline with an increase to 34.0 ± 15.1 mm Hg in the simvastatin – ezetimibe group. Neither the difference between the two groups at either time point nor the difference in the change from baseline in the aortic-valve area was significant.

The primary outcome was a composite of major cardiovascular events, including death from cardiovascular causes, aortic-valve replacement, nonfatal myocardial infarction, hospitalization for unstable angina pectoris, heart failure, coronary-artery bypass grafting,

percutaneous coronary intervention, and nonhemorrhagic stroke.

Secondary outcomes were events related to aortic-valve stenosis and ischemic cardiovascular events. There was no difference between the study groups in overall mortality. There was a significant increase in the number of patients with elevated liver enzyme levels in the simvastatin–ezetimibe group, as compared with the placebo group, during the study period. There were no differences in clinical, organ-related adverse events, except for significantly higher incident cancers in the simvastatin–ezetimibe group (11.1% vs 7.5%).

Conclusion

In patients with mild-to-moderate, asymptomatic aortic-valve stenosis and no traditional indications for lipid-lowering therapy at baseline, long-term, intensive lipid-lowering therapy with simvastatin and ezetimibe had no overall effect on the course of aortic-valve stenosis. However, lipid-lowering therapy reduced the risk of ischemic cardiovascular events, especially the need for CABG.

Comment on the paper:

Anne B. Rossebo, Terje R. Pedersen, Kurt Boman, et al for the SEAS Investigators – Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis. *New England Journal of Medicine*, September 2008; 359(25):1343-1356