Limited Benefit for Aggressive Lipid Lowering with Simvastatin/Ezetimibe in Patients with Aortic Stenosis; Possible Increased Risk of Cancer

Rossebo AB, Pedersen TR, Boman K, et al; SEAS Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008;359:1343–56.

Study Overview

Objective. To determine if aggressive lipid lowering with simvastatin and ezetimibe can improve outcomes in patients with mild to moderate aortic valve stenosis.

Design. Randomized controlled trial.

Setting and participants. 1873 patients aged 45 to 85 years with mild to moderate, asymptomatic aortic stenosis, as defined by a peak aortic jet velocity of 2.5 to 4 m/sec on echocardiography. Patients were excluded if they had a preexisting indication for treatment with lipid-lowering therapy or had coronary artery disease (CAD) or a CAD equivalent (ie, diabetes mellitus, peripheral arterial disease, cerebrovascular disease). Enrollment occurred in 7 European countries and 173 study sites. Eligible patients were randomized to either simvastatin 40 mg plus ezetimibe 10 mg or placebo daily.

Main outcome measures. The primary endpoint 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 resulting from a progression of aortic stenosis, coronary artery bypass grafting (CABG), percutaneous coronary intervention, and nonhemorrhagic stroke. Secondary endpoints included outcomes related to aortic valve stenosis and ischemic cardiovascular events, measures of safety, and echocardiographic progression of aortic stenosis.

Main results. After a mean of 52.2 months of follow-up, no difference in the primary endpoint emerged between patients treated with simvastatin plus ezetimibe versus placebo despite a 50% reduction in low-density lipoprotein (LDL) cholesterol in the treatment group. 35% of patients in the treatment group and 38% in the control group experienced the primary endpoint (hazard ratio, 0.96 [95% confidence interval {CI}, 0.83–1.12]; $P = 0.59$). There was no difference between groups for endpoints related to aortic valve stenosis. A moderate reduction in ischemic cardiovascular events for the treatment group was found (hazard ratio, 0.78 for treatment vs. placebo [95% CI, 0.63–0.97]; $P = 0.02$), resulting from a reduced need for CABG at the time of aortic valve replacement. Cancer occurred more frequently in the simvastatin plus ezetimibe group ($P = 0.01$).

Conclusion. Aggressive lipid lowering with simvastatin plus ezetimibe has limited benefit in patients with asymptomatic aortic valve stenosis.

Commentary

This trial by Rossebo et al, the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial, provides further evidence of the limitations of simvastatin plus ezetimibe. The addition of ezetimibe to a statin medication effectively lowers LDL cholesterol compared with statin monotherapy, but this LDL reduction thus far has not resulted in clinical benefits [1]. In the ENHANCE trial that involved 720 patients with familial hypercholesterolemia, no difference in carotid artery intima-media thickness was found for patients treated with simvastatin 80 mg plus ezetimibe 10 mg versus simvastatin 80 mg plus placebo after 2 years. The null finding resulted despite significant additional lowering of LDL cholesterol, triglycerides, and C-reactive protein in the simvastatin plus ezetimibe group.

The theoretical underpinning of the SEAS trial emerged because of the increased risk of cardiovascular death in patients with aortic stenosis as well as histopathologic data showing that changes in the aortic valve in patients with stenosis are similar to atherosclerotic changes in patients with CAD [2–4]. Since lipid lowering has been successful in reducing cardiovascular events in patients with CAD, speculation has arisen that lipid lowering might also reduce the progression of aortic stenosis as well as events related to progression. Only 1 prospective randomized trial has been published assessing lipid lowering in aortic stenosis, and it showed no difference in progression of calcific aortic stenosis with treatment with 80 mg of simvastatin versus placebo [5].

Similiarly, no difference between groups was found in the primary endpoint (ie, composite of major cardiovascular events) in the SEAS trial. The only benefit that emerged in

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the simvastatin plus ezetimibe group was a reduction in ischemic events (a secondary outcome), and even this finding was limited. The overall reduction in ischemic events was primarily composed of a reduced need for CABG surgery at the time of aortic valve surgery in the treatment group.

The trial design is mostly robust, as it was double-blind, had a limited number of patients who withdrew from the trial (11 in the placebo group and 5 in the intervention group), and used an intent-to-treat analysis protocol. Some limitations should be noted. Open-label treatment with a lipid-lowering drug was allowed at the discretion of treating physicians; the placebo group had double the number of patients receiving open-label treatment compared with the treatment group, thereby biasing any possible result to the null. Furthermore, the design of the trial was a bit unusual in that 196 of the participants in the SEAS trial were carried over from a preexisting trial designed to evaluate the effect of treatment with differing doses of simvastatin in patients with aortic stenosis. Based on the authors' descriptions, it appears that this initial trial was discontinued on the advice of the sponsor (Merck, the manufacturer of simvastatin and ezetimibe), and its subjects were thus incorporated into the SEAS trial (also sponsored by Merck).

The most press-worthy finding of this study was the increased cancer incidence among those in the simvastatin plus ezetimibe group. Cancer incidence was rare in both groups (101 cases in the treatment group and 65 in the placebo group), but the difference was significant in the data analysis. Because this was an unexpected finding, researchers commenced an analysis of data from 2 ongoing trials using simvastatin plus ezetimibe, the Study of Heart and Renal Protection (SHARP) involving 9264 patients with chronic kidney disease (simvastatin 20 mg plus ezetimibe 10 mg vs. placebo) and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) involving 11,353 patients with acute coronary syndrome (simvastatin 40 mg plus ezetimibe 10 mg vs. simvastatin 40 mg) [6]. In SHARP and IMPROVE-IT, no increased incidence of cancer was found in patients treated with simvastatin plus ezetimibe over a mean follow-up of 2.7 years and 1 year, respectively. There was an increased risk of cancer-related mortality; however, this finding was not significant (total deaths, 97 in treatment groups vs. 72 in placebo groups; $P = 0.07$). Follow-up in both studies was substantially shorter than in the SEAS trial, but the number of patients in this analysis was 10 times larger than in the SEAS trial. The authors concluded that simvastatin plus ezetimibe do not increase the risk of cancer and that the finding of SEAS was likely random.

Applications for Clinical Practice

Although ezetimibe has been shown to have an additive effect on LDL lowering when combined with statin therapy, documentation of improved outcomes related to this addition remain elusive. Based on the results of this trial and others, there is no evidence to support the use of lipid-lowering therapy in patients with aortic stenosis without another clear indication for lipid-lowering therapy, and the use of ezetimibe for any indication is difficult to recommend. The possible harms of ezetimibe are still under examination, and the final results of ongoing trials as well as an ongoing analysis by the U.S. Food and Drug Administration will provide more definitive answers on this matter.

—Review by Jason P. Block, MD, MPH

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