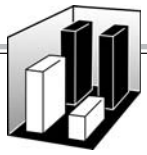
CLINICAL TRIALS REPORT



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Simvastatin–Ezetimibe and Aortic Valve Stenosis: No Benefit With Unforeseen Harm?

Rossebo AB, Pedersen TR, Boman K, et al.: **Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis.** *N Engl J Med* 2008, **359:**1343–1356.

Rating: •Of importance.

Introduction: The importance of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial (ClinicalTrials.gov no. NCT00092677) relates to the conclusion of its main outcome, aortic valve stenosis (AVS), and probably even more to the discussion it engendered about a potential unanticipated adverse event: cancer.

Aortic stenosis is the most common valvular heart disease in developed countries. Its pathogenesis and preceding abnormalities, including aortic valve sclerosis and calcification, appear to have a number of commonalities with the atherosclerotic process. Therefore, lipid-lowering therapy could be an appropriate tool for the prevention and treatment of AVS. Although preliminary data suggested the benefits of such an approach, most of the information came from retrospective and small case-control studies. In fact, one prospective randomized study did not find any effect of lipid-lowering therapy on the progression of AVS.

Aims: Therefore, the SEAS trial was designed to study the effects of long-term, intensive cholesterol lowering with daily use of simvastatin and ezetimibe on clinical and echocardiographic outcomes in patients with asymptomatic mild to moderate AVS and no other indication for lipid-lowering treatment.

Methods: This randomized double-blind trial included 1873 patients with mild to moderate asymptomatic aortic stenosis who received placebo or 40 mg of simvastatin plus 10 mg of ezetimibe daily. 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 AVS and ischemic cardiovascular events.

Results: After a follow-up of about 4.3 years, the primary outcome had been reached by about 35% of the patients in the simvastatin–ezetimibe group and 38% in the placebo group, which was far from statistically significant ($P = 0.59$). Likewise, aortic valve replacement was performed in 28% of participants in the simvastatin–ezetimibe group and in 30% of those receiving a placebo ($P = 0.97$). The only positive outcome of this study came from the significantly lower number of patients having ischemic cardiovascular events in the simvastatin–ezetimibe group than in the placebo group, resulting in an HR of 0.78 ($P = 0.02$). Conversely, cancer occurred more frequently in the simvastatin–ezetimibe group (105 vs 70; $P = 0.01$). It was this unexpected adverse event, rather than the primary outcome, that caused the study to garner attention in the press.

Discussion: Despite lowering cholesterol levels, this study clearly shows that the combination of a statin (simvastatin) and an intestinal cholesterol inhibitor (ezetimibe) did not reduce overall cardiovascular events. The unexpected increase in cancer in the simvastatin–ezetimibe group also raised serious concerns about the use of this combination.

Editor's comments

The primary mechanism by which statins lower cardiovascular disease risk is through their clinically significant reduction of circulating low-density lipoprotein (LDL) concentrations. Moreover, the sometimes greater than expected clinical benefits observed in a number of trials suggest that statins may be working through a variety of pleiotropic effects beyond their effects on lipid metabolism. Along these lines, several clinical and experimental studies have shown that statins may have anti-inflammatory properties and antithrombotic effects and reduce myocardial ischemia-reperfusion injury and endothelial dysfunction. An extensive body of literature has been growing that supports the benefits of statins on other pathologies, including osteoporosis, cancer, chronic kidney disease, Alzheimer's disease and related vascular dementia, and many others.

The major goal of the SEAS trial was to use the more comprehensive scientific evidence afforded by a prospective randomized clinical trial to conclusively answer a relevant clinical question: Should lipid-lowering therapies be used for the prevention and treatment of valvular heart disease? The trial was successful in this regard: The combination of simvastatin and ezetimibe had no impact on the progression of aortic stenosis or on cardiovascular clinical events in general, with the exception of coronary

artery bypass surgery, which was performed less frequently in the active-treatment group than in the placebo group. Although the findings were bad news for the drug combination and for patients with valvular heart disease, the really bad news came from the observed increase in cancer incidence during the study for those in the drug arm of the study.

Late in the summer of 2008, the following headlines could be seen in the popular press: "Taking Statins May Increase Cancer Risk"; "Cholesterol Pill Warning: Scientists Raise Fears of Cancer Link to Statin Used by Thousands." They are in stark contrast to the promising news that filled the headlines during the first few days of 2008: "Statin Drugs May Cut Cancer Risk"; "Could Statins Prevent Cancer?" What led to such diametric positions?

The rosy view came from a review of records from patients with high blood pressure who enrolled in the Veterans Affairs New England Healthcare System between 1997 and 2005 [1]. Cancer developed in 9.4% of the 37,248 patients taking statins and in 13.2% of the 25,594 patients who were not taking statins; this difference was statistically significant. The study design was not solid, but it instigated researchers to pay more attention to this potential added benefit of statins. The darker view began to emerge in July 2007 after the publication of a meta-analysis of 13 trials involving more than 41,000 patients that detected higher rates of cancer among the patients whose use of statins achieved the lowest levels of LDL cholesterol [2]. Opinion leaders cast serious doubts on these findings, and the same authors reversed their interpretation in a second report published in September 2008 [3]. Although they originally reported an inverse association between on-treatment LDL cholesterol and incident cancer, their second report concluded that although statins produced marked reductions in LDL cholesterol, they were not associated with an increased risk of cancer [3]. Despite this clarification, doubts were already deeply rooted in the minds of physicians and the public. It therefore was not surprising that when the results of SEAS were made public, the attention focused more on the cancer results than on the main CVD outcome. Moreover, in this trial a new factor was under consideration: the combination of simvastatin and ezetimibe. Immediate damage control was needed. Publication of the main trial was accompanied by a rigorous meta-analysis of three trials testing the hypothesis that adding ezetimibe to statin therapy to produce larger LDL cholesterol reductions might increase the incidence of cancer [4]. The analysis of the combined data did not provide credible evidence of any adverse effect of ezetimibe on rates of cancer.

How do we interpret the findings from SEAS? Were they the product of an unfortunate luck of the draw or, alternatively, the product of some unknown factor related to specific environmental or genetic factors particular to the population enrolled in the study? The overall data and the lack of a convincing mechanistic interpretation suggest that the SEAS findings may be the product of chance alone. However, physicians and patients unfortunately are left with uncertainty about the efficacy and safety of the drug [5]. Until it becomes possible to use pharmacogenomics tools to explain and reconcile these controversial findings and until more targeted studies are carried out, no evidence should be dismissed [6]. Careful follow-up of the patients in these trials is essential, and other existing data on ezetimibe-treated patients should be analyzed for cancer end points to put the uncertainty to rest.

Disclosure

No potential conflict of interest relative to this article was reported.

References

1. Farwell WR, Scranton RE, Lawler EV, et al.: **The association between statins and cancer incidence in a veterans population.** *J Natl Cancer Inst* 2008, **100:**134–139.
2. Alsheikh-Ali AA, Maddukuri PV, Han H, Karas RH: **Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer: insights from large randomized statin trials.** *J Am Coll Cardiol* 2007, **50:**409–418.
3. Alsheikh-Ali AA, Trikalinos TA, Kent DM, Karas RH: **Statins, low-density lipoprotein cholesterol, and risk of cancer.** *J Am Coll Cardiol* 2008, **52:**1141–1147.
4. Peto R, Emberson J, Landray M, et al.: **Analyses of cancer data from three ezetimibe trials.** *N Engl J Med* 2008, **359:**1357–1366.
5. Drazen JM, D'Agostino RB, Ware JH, et al.: **Ezetimibe and cancer--an uncertain association.** *N Engl J Med* 2008, **359:**1398–1399.
6. Fleming TR: **Identifying and addressing safety signals in clinical trials.** *N Engl J Med* 2008, **359:**1400–1402.