Relation of Lipid-Lowering Therapy to Need for Aortic Valve Replacement in Patients With Asymptomatic Mild to Moderate Aortic Stenosis

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In this study, we aimed to determine if pretreatment low-density lipoprotein (LDL) levels and aortic stenosis (AS) severity alter the efficacy of lipid-lowering therapy on reducing aortic valve replacement (AVR). We used 1,687 patients with asymptomatic mild-to-moderate AS, who were randomly assigned (1:1) to 40/10 mg simvastatin/ezetimibe combination versus. placebo in the simvastatin and ezetimibe in aortic stenosis (SEAS) trial. Pretreatment LDL levels (>4 mmol/L) and peak aortic jet velocity (3 m/s) were used to partition study participants into 4 groups, which were followed for a primary endpoint of AVR. Cox regression with tests for interaction was used to study the effect of randomized treatment in each subgroup. During a median follow-up of 4.3 years (IQR 4.2 to 4.7 years; total 7,396 patient-years of follow-up), 478 (28%) patients underwent AVR and 146 (9%) died. A significant risk dependency was detected between simvastatin/ezetimibe combination, LDL levels and mild versus moderate AS on rates of AVR (p = 0.01 for interaction). In stratified analyses, randomized treatment, therefore, reduced the rate of AVR in patients with LDL levels >4 mmol and mild AS at baseline (HR 0.4; 95% CI: 0.2 to 0.9). There was no detectable effect of randomized treatment on the need for AVR in the 3 other participants subgroups. We conclude, that in a secondary analysis from a prospective randomized clinical trial, treatment with simvastatin/ezetimibe combination reduced the need for AVR in a subset of patients with mild AS and high pretreatment LDL levels (Unique identifier on clinicaltrials.gov: NCT00092677). **(Am J Cardiol 2019;124:1736−1740)**

Hyperlipidemia is a risk factor for both atherosclerotic vascular and calcific aortic valve disease.[1] Lipid-lowering is key to primary and secondary prevention of vascular atherosclerosis, but do not translate to a similar benefit on slowing the progression of aortic stenosis (AS).[2] A prevailing opinion is therefore that AS is an unmodifiable disease, for which the only remedy is transcatheter or surgical aortic valve replacement (AVR). However, this longstanding notion was recently contested in a secondary analysis from the SEAS (simvastatin and ezetimibe in aortic stenosis) trial, which showed that simvastatin/ezetimibe slowed progression of peak aortic jet velocity in patients with mild AS and pretreatment low-density lipoprotein (LDL) levels >4 mmol/L.[3] Yet, it is unknown if LDL levels and AS severity also impact on the efficacy of lipid-lowering therapy to delay clinical progression of AS. The aim of this study was therefore to assess the effect of lipid-lowering on AVR in the SEAS trial, when stratified by LDL >4 mmol/L and mild versus moderate AS at baseline. We hypothesized that simvastatin/ezetimibe combination versus placebo would reduce the need for AVR in participants with mild AS and pretreatment LDL >4 mmol/L.

Methods

The SEAS trial was a multicenter, randomized, double-blind, placebo-controlled study, investigating whether intensive lipid lowering with simvastatin/ezetimibe combination versus placebo could reduce hemodynamic progression of AS, the need for AVR and cardiovascular morbidity and mortality in patients (n = 1,873), aged 45 to 85 years, with asymptomatic nonsevere AS (defined as echocardiographic aortic valve thickening accompanied by a Doppler-measured aortic peak flow velocity ≥2.5and ≤4.0 m/s) and

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1. The publication of this study was approved by the SEAS steering committee, all patients had provided written informed consent, and the protocol was approved by local ethics committees.

2. Data analysis was performed by the following authors: Greve.

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See page 1739 for disclosure information.

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normal systolic left ventricular function. The main outcome including complete study protocol, study design, organization, clinical measures, exclusion criteria (most important systolic heart failure, diabetes, and known ischemic heart disease) and baseline characteristics have been published previously.[4,5] This post hoc and not prespecified study tested the hypothesis that the efficacy of lipid lowering on reducing AVR depends on pretreatment LDL levels and AS severity. We included all SEAS participants (n = 1,687) with ascertained pretreatment LDL levels and at least 1 in-study echocardiographic examination of peak aortic jet velocity. The SEAS study complies with the Declaration of Helsinki, locally appointed ethics committee had approved the research protocol and informed consent was obtained from all subjects.

The echocardiographic study protocol, reading procedures and reproducibility have been published.[6] Briefly, transthoracic echocardiograms were read blinded to the randomization and study visits at the SEAS echocardiographic core laboratory, located at Haukeland University Hospital in Bergen, Norway. Quantitative echocardiography was performed following the American Society of Echocardiography guidelines.[7] Patients with peak aortic jet velocities <3 m/s were classified as having mild AS and those with ≥3-4 m/s as having moderate AS.[8]

The primary endpoint in this study was AVR, which was an a priori defined endpoint in the SEAS trial.[4] The efficacy of simvastatin/ezetimibe combination versus placebo on reducing AVR was tested as the effect of randomization regardless of whether patients adhered to the treatment.

Data were analyzed using the statistical analytical software version 9.4 (SAS, Cary, NC). Continuous data are expressed as mean ± SD and categorical variables as proportions. t tests, Wilcoxon, Chi-square and Fisher's exact test was used as appropriate. Cox regression was used to examine the effect of simvastatin/ezetimibe combination versus placebo on reducing the need for AVR. Absolute probabilities of AVR by randomized treatment were calculated by Fine and Gray competing risk regression, using all-cause mortality as a competing event.[9] To identify a possible effect modification of pretreatment LDL levels and AS severity on the efficacy of randomized treatment, we tested for interactions between pretreatment LDL levels and baseline peak aortic jet velocity. For LDL, a cutoff of 4 mmol/L was applied, which has previously been demonstrated to be important for an effect of lipid-lowering therapy,[3] and for peak velocity a cutoff of 3 m/s (mild versus moderate AS) was used. Because of a significant third order interaction between treatment, pretreatment LDL and peak aortic jet velocity on AVR, the effect modification of pretreatment LDL levels on randomized treatment was investigated separately in patients with mild and moderate AS at baseline. For all hypothesis tested, a 2-tailed $p < 0.05$ was regarded as statistically significant.

Results

Of the 1,873 SEAS study participants, 1,687 (90%) subjects had ascertained pretreatment LDL levels and at least 1 in-study measurement of peak aortic jet velocity. Randomization was well-preserved in the subset of participants eligible for this study, of which 855 (50.7%) were in the active arm (Table 1). Median follow-up was 4.3 years (IQR 4.2 to 4.7 years; total 7,396 patient-years of follow-up), during which 478 (28%) patients underwent AVR and 146 (9%) died. A significant risk dependency was detected between simvastatin/ezetimibe combination, LDL and mild versus moderate AS on rates of AVR (p = 0.01 for interaction). In

Table 1
Baseline characteristics in SEAS participants with ascertained peak aortic jet velocity and low-density lipoprotein levels at baseline*

Baseline variables	Simvastatin/ezetimibe (n = 855)	Placebo (n = 832)	p value
Clinical parameters			
Age (years)	67.5 ± 9.4	67.1 ± 9.7	0.41
Men	62.0%	60.6%	0.55
Systolic blood pressure (mm Hg)	145.5 ± 20.1	143.9 ± 20.1	0.09
Diastolic blood pressure (mm Hg)	82.1 ± 10.7	82.0 ± 10.0	0.83
Body mass index (kg/m^2)	26.9 ± 4.4	27.0 ± 4.4	0.50
Peak aortic jet velocity (m/s)	3.1 ± 0.5	3.1 ± 0.5	0.75
Tricuspid aortic valve	94.9%	93.7%	0.35
Left ventricular ejection fraction (%)	65.8 ± 8.3	65.5 ± 8.3	0.96
Left ventricular mass index (g/m^2)	100.3 ± 29.1	99.3 ± 31.0	0.53
eGFR (ml/min per 1.73m^2)	68.5 ± 12.7	68.4 ± 12.0	0.84
Glucose (mmol/ml)	5.3 ± 0.8	5.3 ± 0.8	0.46
High-density lipoprotein (mmol/l)	1.5 ± 0.4	1.5 ± 0.4	0.73
High-density lipoprotein (mg/dl)	57.9 ± 15.4	57.9 ± 15.4	0.73
Low-density lipoprotein (mmol/l)	3.6 ± 0.9	3.6 ± 0.9	0.82
Low-density lipoprotein (mg/dl)	139.0 ± 34.8	139.0 ± 34.8	0.82
Medicine			
Digoxin	3.0%	2.3%	0.33
Ca2+-blocker	16.6%	17.1%	0.80
Beta-blocker	26.8%	28.5%	0.43
Renin-angiotensin inhibitor	25.4%	25.5%	0.96
Diuretics	22.0%	25.0%	0.14

* This baseline table differs from the original SEAS publication by including only participants with ascertained peak aortic jet velocity and low-density lipoprotein levels at enrollment. eGFR = estimated glomerular filtration rate.

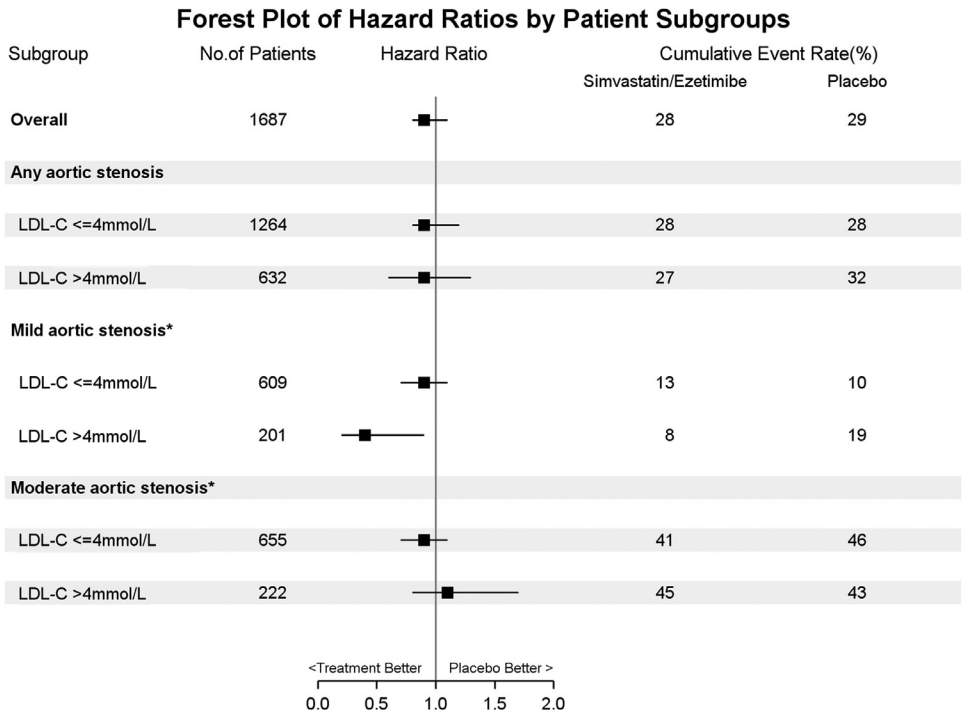

Figure 1. Simvastatin/ezetimibe combination reduced the need for aortic valve replacement in SEAS trial participants with mild aortic stenosis and high lipoproteins at baseline. Forest plot of hazard ratios for aortic valve replacement by subgroups of patients with mild versus moderate aortic stenosis (peak jet velocity >3 m/s), and high low-density lipoprotein cholesterol (LDL >4 mmol/L) at enrollment (p = 0.01 for third order interaction between treatment, peak jet velocity, and LDL, p = 0.02 for second-order interaction between treatment and high LDL and p = 0.03 for second-order interaction between treatment and mild versus moderate aortic stenosis when including the significant third order interaction term).

adjusted analyses, randomized treatment, therefore, reduced the rate of AVR in a subgroup of patients with LDL >4 mmol and mild AS at baseline (HR 0.4; 95% CI: 0.2 to 0.9, Figure 1). These findings were consistent with results from competing risk regression, using death as a competing event, where active arm participants with LDL >4 mmol/L and mild AS, had a significant lower probability of AVR (event rates 2% vs. 4% per year, respectively, Figure 2). There was no detectable impact of simvastatin/ezetimibe combination versus placebo on AVR in the 3 other subgroups (Figure 1).

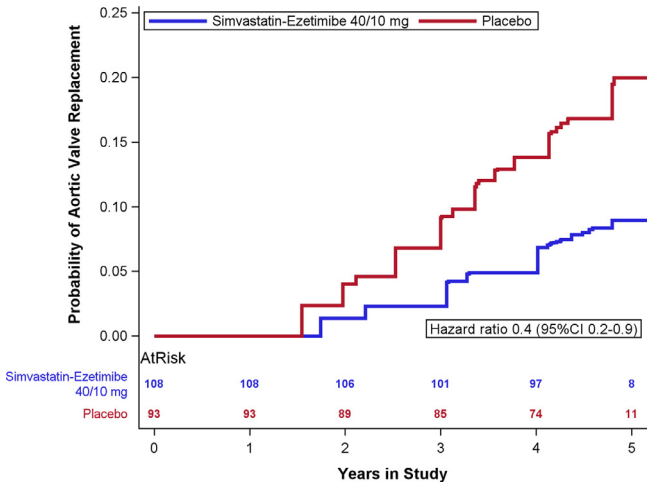

Figure 2. Cumulative incidence of aortic valve replacement in SEAS participants with mild aortic stenosis and LDL >4mmol/L at baseline. Cumulative incidence of aortic valve replacement according to treatment in patients with mild aortic stenosis (peak jet velocity >3 m/s) and LDL >4mmol/L, during a median follow-up of 4.3 years in the SEAS trial. Fine and Gray competing risk regression, using all-cause mortality as a competing event, was used to calculate the absolute probabilities.

Discussion

This is the first study to show that lipid-lowering may reduce the need for AVR. This is an important extension of our previous report on lipid-lowering and slower progression in peak aortic jet velocity per se.[3] Taken together, these findings support the notion that lowering high LDL levels mitigates adverse endpoints related to hemodynamic and clinical progression of AS.

A large body of evidence supports that transcatheter or surgical AVR ameliorates the prognosis of patients with symptomatic, severe AS.[10–12] Conversely, the optimal surgical and/or medical management of patients with asymptomatic mild-to-moderate AS remains conjecture.[8] The dearth of studies on medical therapies for patients with asymptomatic mild-to-moderate AS is partly explained by the frequent commodities, such as coronary artery disease, which precludes placebo-controlled randomized clinical trials. Current research has therefore turned to genetic epidemiology, which can be used to emulate a placebo-controlled randomized clinical trial by mendelian randomization.[13] Importantly, such genetic studies have demonstrated a causal role of high LDL and lipoprotein(a) for calcific aortic valve disease and incident clinical AS.[14,15] Of note, the level of lipoprotein(a) is, due to similar biochemical structures, included in LDL levels on routine laboratory assays.

Thus, the genetic data corroborate a causal link between high LDL and/or lipoprotein(a) on incident AS, and have already been used a template for clinical trials.[16] Importantly, there is also evidence from nongenetic research, which used orthogonal methodologies to demonstrate that high lipoprotein(a) acts as a driver for the progression of AS.[17] Furthermore, our results also agree with a report from the ASTRONOMER (Effects of Rosuvastatin on Aortic Stenosis Progression) trial, which found that the rate of hemodynamic progression in patients with AS related linearly to lipoprotein(a) level.[18] Thus, it is prudent to suspect that the negative trials on randomized in patients with AS, were caused by the inclusion of too few patients with high concentrations of LDL and/or lipoprotein(a).

There are strengths and limitations to this study. The primary strength is the prospective, randomized, placebo-controlled, clinical trial design. As such, this is the only study that is powered to explore possible effect modifications of LDL and mild versus moderate AS on the efficacy of lipid-lowering therapy. Moreover, a study like the SEAS trial, is unlikely ever to be repeated because new lipid guidelines preclude the assignment of patients to placebo. Limitations include that we did not measure lipoprotein(a) and experiment wise type 1 error rate, which is compounded by the lack of a detectable impact on the overall effect of lipid-lowering therapy in the SEAS study.

In conclusion, in patients with mild asymptomatic AS and LDL greater than 4mmol/L, randomized treatment with simvastatin/ezetimibe combination versus placebo reduced the need for AVR. Further studies aimed at determining the effect of lipid-lowering in asymptomatic patients with early AS are therefore warranted. Lipid-lowering is likely to be particularly beneficial in those with early AS and high levels of LDL and/or lipoprotein(a).

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