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ORIGINAL ARTICLE

Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis

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ABSTRACT

BACKGROUND

Hyperlipidemia has been suggested as a risk factor for stenosis of the aortic valve, but lipid-lowering studies have had conflicting results.

METHODS

We conducted a randomized, double-blind trial involving 1873 patients with mild-to-moderate, asymptomatic aortic stenosis. The patients received either 40 mg of simvastatin plus 10 mg of ezetimibe or placebo 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 aortic-valve stenosis and ischemic cardiovascular events.

RESULTS

During a median follow-up of 52.2 months, the primary outcome occurred in 333 patients (35.3%) in the simvastatin–ezetimibe group and in 355 patients (38.2%) in the placebo group (hazard ratio in the simvastatin–ezetimibe group, 0.96; 95% confidence interval [CI], 0.83 to 1.12; P=0.59). Aortic-valve replacement was performed in 267 patients (28.3%) in the simvastatin–ezetimibe group and in 278 patients (29.9%) in the placebo group (hazard ratio, 1.00; 95% CI, 0.84 to 1.18; P=0.97). Fewer patients had ischemic cardiovascular events in the simvastatin–ezetimibe group (148 patients) than in the placebo group (187 patients) (hazard ratio, 0.78; 95% CI, 0.63 to 0.97; P=0.02), mainly because of the smaller number of patients who underwent coronary-artery bypass grafting. Cancer occurred more frequently in the simvastatin–ezetimibe group (105 vs. 70, P=0.01).

CONCLUSIONS

Simvastatin and ezetimibe did not reduce the composite outcome of combined aortic-valve events and ischemic events in patients with aortic stenosis. Such therapy reduced the incidence of ischemic cardiovascular events but not events related to aortic-valve stenosis. (ClinicalTrials.gov number, NCT00092677.)

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Aortic-valve stenosis is common in elderly persons, with a prevalence of 3 to 5% in the population over 75 years of age.[1,2] 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.[2-19] 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.[20-22] The standard treatment is surgical replacement when the valve becomes severely stenotic.[23,24]

Epidemiologic[2] and genetic[25,26] studies have identified risk factors for the development of aortic-valve stenosis, and experimental work has elucidated the cellular mechanisms involved in disease progression, many of which resemble atherosclerosis.[27-30] One interpretation of these findings is that lipid-lowering treatment might prevent progression of aortic-valve stenosis and thus reduce the need for aortic-valve replacement.

The effect of statin treatment on aortic-valve stenosis has been assessed in several retrospective or small case–control studies.[27,31-33] 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.[34]

The Simvastatin and Ezetimibe in Aortic Stenosis (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 aortic-valve stenosis and no other indication for lipid-lowering treatment.

METHODS

PATIENT POPULATION

The study design and baseline characteristics of the patients have been reported previously.[35] 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, were eligible for the study. 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. The study was approved by all relevant institutional ethics committees or by ethics committees in each country, and all patients provided written informed consent.

STUDY PROTOCOL

The study was initiated by the investigators and was designed by the steering committee on the basis of a protocol developed for the Simvastatin in Aortic Stenosis (SAS) study,[35] 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. The SAS study was sponsored by Merck but was otherwise managed by the SAS study steering committee.

From March 2001 through December 2002, a total of 196 patients underwent randomization. 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 in the larger SEAS trial, as suggested by the sponsor. The responsibility for the logistics of the SEAS trial was transferred to the sponsor, but the scientific responsibility remained with the independent steering committee, which included two nonvoting members of the sponsor.[35] The patients who were assigned to receive simvastatin in the SAS study remained in the active-treatment group in the SEAS trial, in which ezetimibe was added to simvastatin, and the patients in the SAS placebo group remained in the SEAS placebo group. During this process, neither the patients nor the investigators were aware of study-group assignments. After a 4-week run-in period in which all patients were given single-blind placebo tablets and were instructed to follow a lipid-lowering diet according to the recommendations of the National Cholesterol Education Program,[36] eligible patients underwent randomization in a 1:1 fashion in blocks of two to receive either simvastatin–ezetimibe or placebo (Fig. 1).

Open-label lipid-lowering therapy, which included up to 40 mg of simvastatin or an equipotent dose of another lipid-lowering drug, could be administered in addition to the study drug at the discretion of each treating physician, although patients and investigators remained unaware of study-group assignments. The numbers of patients receiving open-label therapy are shown in Figure 1.

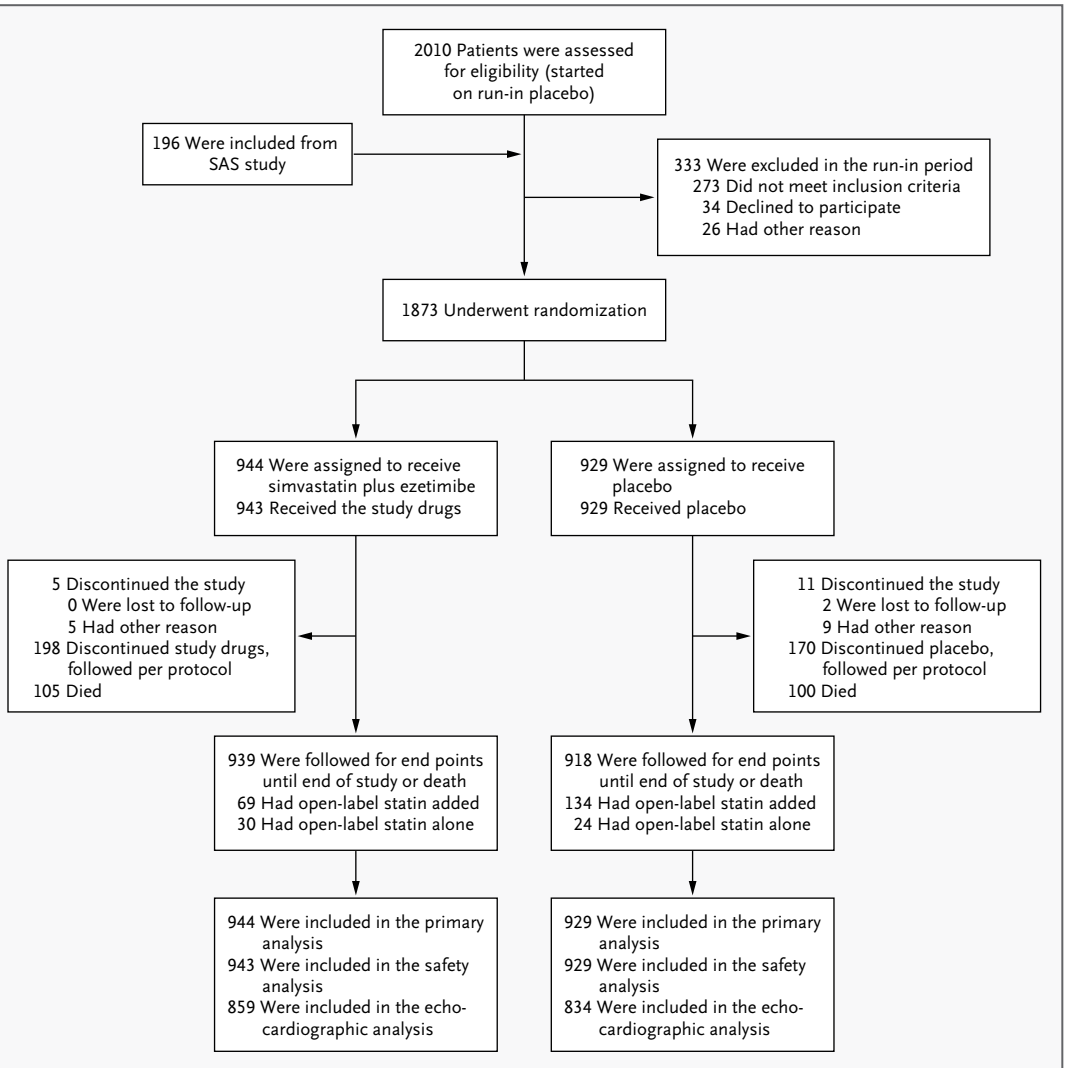

Figure 1. Enrollment and Outcomes.
SAS denotes the Simvastatin in Aortic Stenosis Study.

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.[35]

The SEAS steering committee designed the study and vouches for the accuracy and completeness of the data and the analysis. The sponsor gathered the data; the Echocardiography Core Laboratory read the locally recorded echocardiograms. The statistical analysis was performed by Merck, according to a predefined protocol. In addition, parallel statistical analysis with the use of SPSS software (version 15.0) was performed on raw data by an independent statistician, a process that generated identical results. The first draft of the manuscript was written by the lead academic author.

EFFICACY OUTCOMES

The primary outcome of the study was major cardiovascular events, a composite consisting of death from cardiovascular causes, aortic-valve replacement, congestive heart failure as a result of progression of aortic-valve stenosis, nonfatal myocardial infarction, hospitalization for unstable angina, coronary-artery bypass grafting (CABG), percutaneous coronary intervention (PCI), or nonhemor-

rhagic stroke. The primary composite outcome included aortic-valve–related clinical events and ischemic events to account for possible cardiovascular symptoms and events occurring in patients with aortic-valve stenosis.[21]

Key secondary outcomes were aortic-valve events (which were defined as aortic-valve replacement surgery, congestive heart failure due to aortic stenosis, or death from cardiovascular causes) and ischemic events (which were defined as death from cardiovascular causes, nonfatal myocardial infarction, hospitalization for unstable angina, CABG, PCI, or nonhemorrhagic stroke). Other secondary objectives were progression of aortic stenosis, as seen on echocardiography, and the safety of the study drugs.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Placebo (N=929)	Simvastatin–Ezetimibe (N=944)	P Value†
Age — yr	67.4±9.7	67.7±9.4	0.46
Female sex — no. (%)	360 (38.8)	363 (38.5)	0.92
White race — no. (%)‡	928 (99.9)	940 (99.6)	NA
Blood pressure — mm Hg			
Systolic	144.0±20.0	145.6±20.4	0.08
Diastolic	82.0±10.0	82.0±10.6	0.98
Hypertension — no. (%)	476 (51.2)	489 (51.8)	0.82
Smoking status — no. (%)			0.59
Current	171 (18.4)	189 (20.0)	
Former	344 (37.0)	333 (35.3)	
Never	414 (44.6)	422 (44.7)	
Body-mass index	26.8±4.3	26.9±4.3	0.58
Atrial fibrillation — no. (%)§	90 (9.7)	87 (9.2)	0.75
Atrioventricular block — no. (%)	23 (2.5)	21 (2.2)	0.76
Benign prostatic hyperplasia — no. of men (%)	63 (11.1)	74 (12.7)	0.47
Neoplasm (benign, malignant, or unspecified) — no. (%)	103 (11.1)	79 (8.4)	0.05
Drug therapy — no. (%)			
Angiotensin-converting–enzyme inhibitor	149 (16.0)	139 (14.7)	0.44
Angiotensin-receptor blocker	98 (10.5)	95 (10.1)	0.76
Calcium antagonist	160 (17.2)	157 (16.6)	0.76
Beta-blocker	268 (28.8)	242 (25.6)	0.12
Aspirin or other platelet inhibitor	260 (28.0)	236 (25.0)	0.16
Anticoagulant agent	49 (5.3)	58 (6.1)	0.43
Diuretic (including spironolactone)	229 (24.7)	209 (22.1)	0.21
Digitalis glycoside	22 (2.4)	28 (3.0)	0.47
Laboratory values			
Glucose — mg/dl	96.2±15.5	96.3±14.7	0.95
Creatinine — mg/dl	1.06±0.17	1.06±0.18	0.82
Estimated glomerular filtration rate — ml/min per 1.73 m^2¶	68.2±12.0	68.5±12.6	0.54
High-sensitivity C-reactive protein — mg/liter			0.76
Median	2.20	2.10	
Interquartile range	0.90–4.90	0.90–4.10	

Table 1. (Continued.)

Characteristic	Placebo (N=929)	Simvastatin–Ezetimibe (N=944)	P Value†
Lipids			
Cholesterol			
Total — mg/dl	221±38	223±40	0.41
LDL — mg/dl	139±35	140±36	0.42
HDL — mg/dl	58±17	58±17	0.87
Ratio of total cholesterol to HDL cholesterol	4.13±1.39	4.12±1.22	0.81
Non-HDL cholesterol — mg/dl	164±38	165±39	0.46
Triglycerides — mg/dl	126±60	126±63	0.93
Apolipoprotein B — mg/dl	130±28	132±28	0.37
Echocardiographic measures			
Peak aortic-jet velocity — m/sec	3.10±0.54	3.09±0.55	0.67
Transaortic pressure gradient — mm Hg			
Peak	39.6±13.8	39.3±13.9	0.70
Mean	23.0±8.7	22.7±8.8	0.42
Aortic valve			
Area — cm^2	1.27±0.46	1.29±0.48	0.29
Area index — cm^2/m^2	0.67±0.23	0.68±0.24	0.35
Bicuspid valve — no. (%)	47 (6.3)	38 (5.0)	0.32
Left ventricular mass — g	194.5±69.4	194.1±66.8	0.92
Left ventricular ejection fraction — %	66±7	67±6	0.56

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert values for glucose to millimoles per liter, multiply by 0.05551. To convert values for creatinine to micromoles per liter, multiply by 88.4. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and NA not applicable.
† P values for baseline comparisons were not included in the statistical analysis plan.
‡ Race was determined by the investigators.
§ Atrial fibrillation included past events and those that were intermittent, constant, or present at the baseline visit, as well as atrial flutter.
¶ The glomerular filtration rate was calculated with the formula used in the Modification of Diet in Renal Disease Study, which accounts for age, sex, race, and calibration of the serum creatinine level.

All outcomes were classified by an independent end-point classification committee whose members were unaware of study-group assignments. The data and safety monitoring board performed four preplanned interim analyses of efficacy and safety,[35] as well as two extra analyses of safety.

Echocardiography was performed at baseline and then annually and before valve surgery, according to a standardized echocardiographic protocol.[37] All images were recorded on Video Home System videotape or digitally in Digital Imaging and Communications in Medicine format on compact disk or magneto-optical disk and were forwarded to the SEAS Echocardiography Core Laboratory at Haukeland University Hospital in Bergen, Norway. All readings were performed according to the American Society of Echocardiography guidelines[38] with the use of an off-line digital computerized review system on workstations with Image Arena software (TomTec Imaging Systems). The readers were unaware of the sequence and site in order to minimize bias.

STATISTICAL ANALYSIS

The study outcomes were analyzed according to the intention-to-treat principle. The study had a power of 90% to detect a reduction of 22% in the relative risk of the primary outcome. For all time-

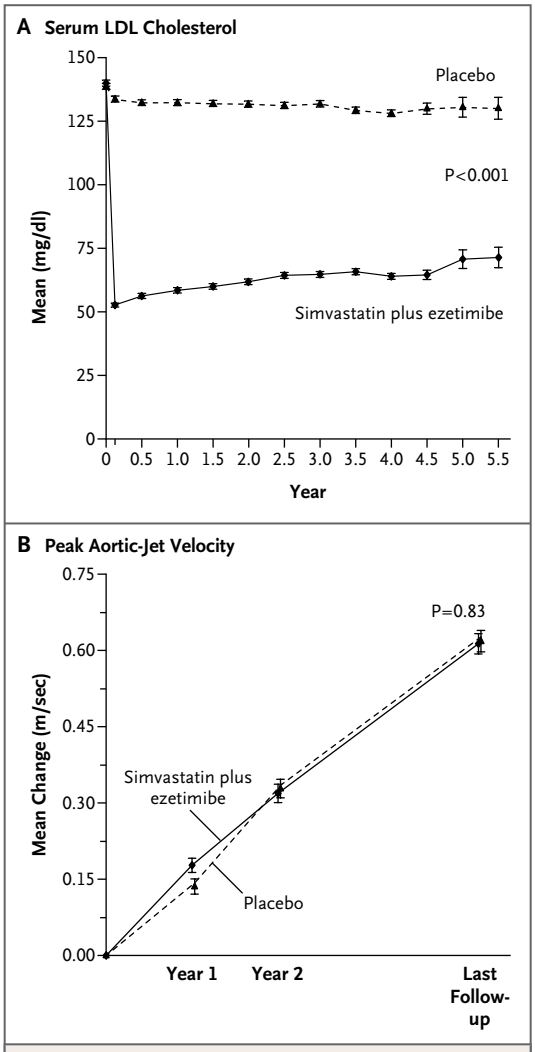

Figure 2. Serum Low-Density Lipoprotein (LDL) Cholesterol Levels (Panel A) and the Change from Baseline in Peak Aortic-Jet Velocity (Panel B).

The I bars represent standard errors. In Panel A, the first data points correspond to results at the 8-week visit.

to-event outcomes, survival analytic methods were used, with analyses based on a Cox proportional-hazards model.

Analyses were performed with the use of SAS software, version 8.2. For aortic-stenosis progression, the analysis included data from all patients with at least one baseline and one follow-up measurement. For analyses of adverse events, confidence intervals for differences in proportions of patients were computed with the method of Miettinen and Nurminen and with Fisher's exact test, when appropriate. Tests were generally performed at a two-sided significance level of 0.05, except that for the primary outcome, which was performed at a significance level of 0.0490 to account for interim analyses.

Data on adverse events were collected from all patients who underwent follow-up and analysis, with the exception of nonfatal events that did not require hospitalization and that occurred at least 15 days after the discontinuation of study drug or placebo, according to the protocol.

RESULTS

PATIENTS

A total of 1873 patients underwent randomization at 173 study sites in seven European countries.[35] Of these patients, 944 were assigned to receive 40 mg of simvastatin and 10 mg of ezetimibe daily, and 929 were assigned to receive placebo. Baseline demographic, laboratory, and echocardiographic data for the two study groups are shown in Table 1. The median follow-up period was 52.2 months.

LIPIDS

The mean serum level of low-density lipoprotein (LDL) cholesterol remained unchanged in the placebo group and decreased by 61.3%, to a mean (±SD) level of 53±23 mg per deciliter (1.36±0.60 mmol per liter) 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 (Fig. 2A).

OUTCOME MEASURES

The primary composite outcome occurred in 333 patients (35.3%) in the simvastatin–ezetimibe group and in 355 patients (38.2%) in the placebo group (hazard ratio in the simvastatin–ezetimibe group, 0.96; 95% confidence interval [CI], 0.83 to 1.12; P=0.59) (Table 2 and Fig. 3A).

There was no significant difference between the two study groups in the secondary outcome of aortic-valve–related events, including aortic-valve replacement, death from cardiovascular causes, and hospitalization for heart failure as a consequence of progression of aortic stenosis (hazard ratio, 0.97; 95% CI, 0.83 to 1.14; P=0.73) (Fig. 3B). The principal component of this secondary composite outcome was aortic-valve replacement, which occurred in 267 patients (28.3%) in the simva-

Table 2. Prespecified Primary and Secondary Composite Outcomes and Death.*

Outcome	Placebo (N=929)	Simvastatin plus Ezetimibe (N=944)	Hazard Ratio (95% CI)†	P Value
	number (percent)			
Primary outcome				
Patients with any event‡	355 (38.2)	333 (35.3)	0.96 (0.83–1.12)	0.59
Death from cardiovascular causes	56 (6.0)	47 (5.0)	0.83 (0.56–1.22)	0.34
Aortic-valve replacement surgery	278 (29.9)	267 (28.3)	1.00 (0.84–1.18)	0.97
Congestive heart failure as a result of progression of aortic stenosis	23 (2.5)	25 (2.6)	1.09 (0.62–1.92)	0.77
Nonfatal myocardial infarction	26 (2.8)	17 (1.8)	0.64 (0.35–1.17)	0.15
Coronary-artery bypass grafting	100 (10.8)	69 (7.3)	0.68 (0.50–0.93)	0.02
Percutaneous coronary intervention	17 (1.8)	8 (0.8)	0.46 (0.20–1.06)	NA
Hospitalization for unstable angina	8 (0.9)	5 (0.5)	0.61 (0.20–1.86)	NA
Nonhemorrhagic stroke	29 (3.1)	33 (3.5)	1.12 (0.68–1.85)	0.65
Secondary outcomes				
Aortic-valve events	326 (35.1)	308 (32.6)	0.97 (0.83–1.14)	0.73
Aortic-valve replacement surgery	278 (29.9)	267 (28.3)	1.00 (0.84–1.18)	0.97
Congestive heart failure as a result of progression of aortic stenosis	23 (2.5)	25 (2.6)	1.09 (0.62–1.92)	0.77
Death from cardiovascular causes§	56 (6.0)	47 (5.0)	0.83 (0.56–1.22)	0.34
Ischemic events	187 (20.1)	148 (15.7)	0.78 (0.63– 0.97)	0.02
Nonfatal myocardial infarction	26 (2.8)	17 (1.8)	0.64 (0.35–1.17)	0.15
Coronary-artery bypass grafting	100 (10.8)	69 (7.3)	0.68 (0.50– 0.93)	0.02
Percutaneous coronary intervention	17 (1.8)	8 (0.8)	0.46 (0.20–1.06)	NA
Hospitalization for unstable angina	8 (0.9)	5 (0.5)	0.61 (0.20–1.86)	NA
Nonhemorrhagic stroke	29 (3.1)	33 (3.5)	1.12 (0.68–1.85)	0.65
Death from cardiovascular causes§	56 (6.0)	47 (5.0)	0.83 (0.56–1.22)	0.34
Death				
From any cause	100 (10.8)	105 (11.1)	1.04 (0.79–1.36)	0.80
From cardiovascular causes	56 (6.0)	47 (5.0)	0.83 (0.56–1.22)	0.34
Myocardial infarction	10 (1.1)	5 (0.5)	0.49 (0.17–1.42)	
Stroke	6 (0.6)	5 (0.5)	0.82 (0.25–2.70)	
Sudden death	20 (2.2)	20 (2.1)	0.99 (0.53–1.83)	
Related to cardiac surgery (perioperative)	7 (0.8)	7 (0.7)	0.99 (0.35–2.83)	
Heart failure	5 (0.5)	6 (0.6)	1.21 (0.37–3.95)	
Other	8 (0.9)	4 (0.4)	0.49 (0.15–1.63)	
From noncardiovascular causes	44 (4.7)	56 (5.9)	1.26 (0.85–1.86)	0.26
Cancer¶	23 (2.5)	39 (4.1)	1.67 (1.00–2.79)	0.05
Infection	14 (1.5)	7 (0.7)	0.50 (0.20–1.23)	
Violence or accident	1 (0.1)	3 (0.3)	2.95 (0.31–28.4)	
Other	6 (0.6)	7 (0.7)	1.15 (0.39–3.42)	
Could not be classified	0	2 (0.2)		

* NA denotes not applicable because of the small number of events.
† The hazard ratio is for the simvastatin–ezetimibe group versus the placebo group.
‡ Patients could have more than one event.
§ All deaths from cardiovascular causes were included in both secondary outcomes.
¶ Numbers include recurrent cancers in three patients in the placebo group and one patient in the simvastatin–ezetimibe group. One patient in the simvastatin–ezetimibe group died from cancer that was diagnosed in the SAS study before randomization in the SEAS study.

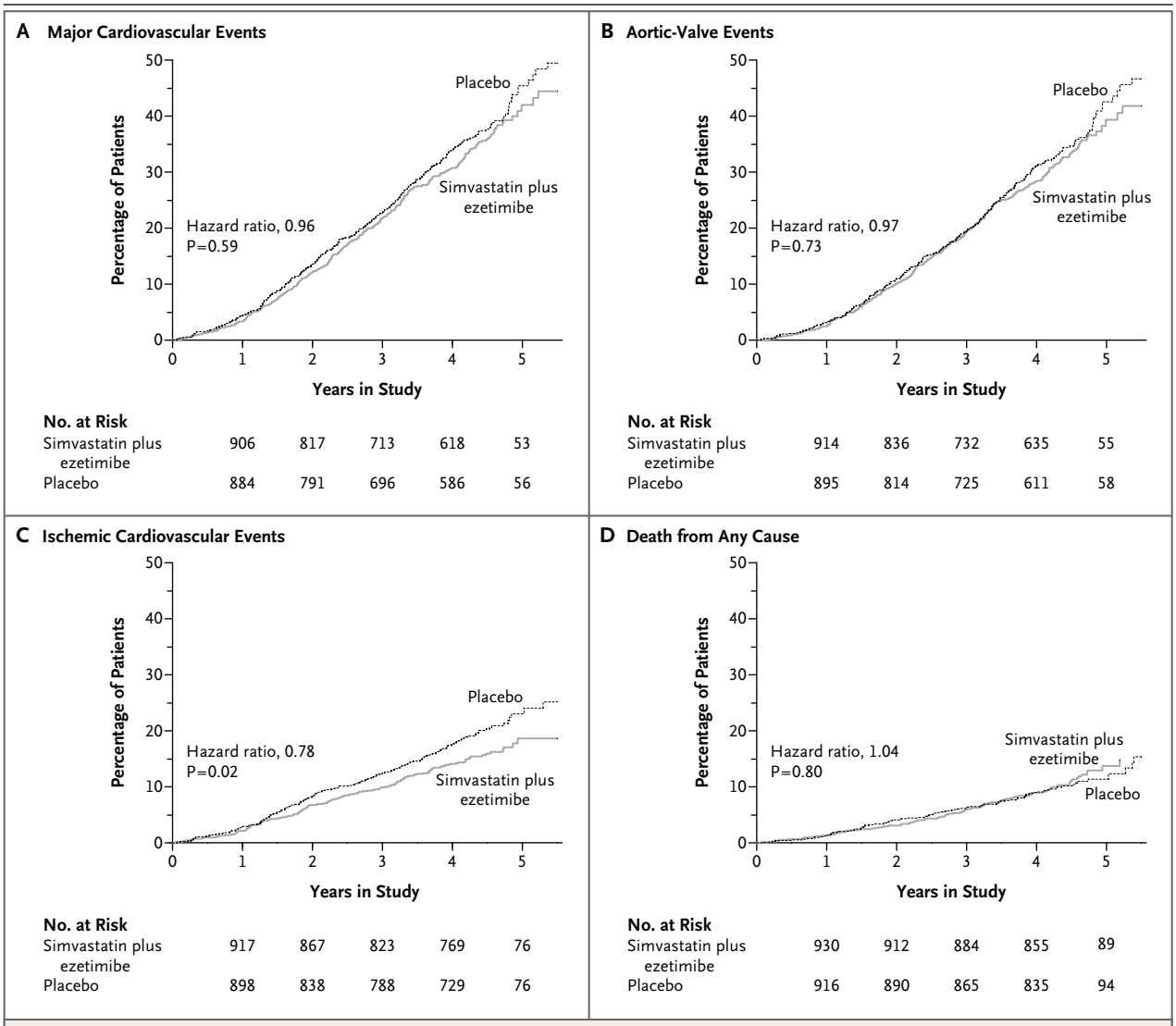

Figure 3. Kaplan–Meier Curves for Primary and Secondary Outcomes and Death.

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 (Panel A). Secondary outcomes were events related to aortic-valve stenosis (Panel B) and ischemic cardiovascular events (Panel C). There was no difference between the study groups in overall mortality (Panel D).

statin–ezetimibe group and in 278 patients (29.9%) in the placebo group (hazard ratio, 1.00; 95% CI, 0.84 to 1.18; P=0.97).

There were fewer patients with the secondary composite outcome of ischemic cardiovascular events in the simvastatin–ezetimibe group (148 patients, or 15.7%) than in the placebo group (187 patients, or 20.1%) (hazard ratio, 0.78; 95% CI, 0.63 to 0.97; P=0.02) (Table 2 and Fig. 3C). The treatment effect was dominated by a significant reduction in the need for CABG, with 69 patients (7.3%) in the simvastatin–ezetimibe group, as compared with 100 patients (10.8%) in the placebo group, undergoing the procedure (hazard ratio, 0.68; 95% CI, 0.50 to 0.93; P=0.02). All but one of the CABG procedures were performed together with aortic-valve replacement.

EFFECT ON PROGRESSION

In the placebo group, the mean (±SD) 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 (95% CI, −0.06 to 0.05; P=0.83) (Fig. 2B). This was the predefined key echocardiographic measure for the evaluation of progression of aortic stenosis. 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. Annualized changes in the mean (±SE) peak aortic-jet velocity were 0.15±0.01 m per second per year in the simvastatin–ezetimibe group and 0.16±0.01 m per second per year in the placebo group. The mean transaortic pressure gradient increased by 2.7±0.1 mm Hg per year in the simvastatin–ezetimibe group and by 2.8±0.1 mm Hg per year in the placebo group. There was an annualized reduction in the aortic-valve area of 0.03±0.01 cm^2 per year in each of the two groups.

MORTALITY

There was no significant difference between the study groups in overall mortality (Table 2 and Fig. 3D). The composite outcome of death from cardiovascular causes and the components of this composite outcome also did not differ significantly between the two groups.

Deaths from noncardiovascular causes occurred in 56 patients (5.9%) in the simvastatin–ezetimibe group and in 44 patients (4.7%) in the placebo group (hazard ratio in the simvastatin–ezetimibe group, 1.26; 95% CI, 0.85 to 1.86; P=0.26). The numbers of fatal cancers were 39 (4.1%) in the simvastatin–ezetimibe group and 23 (2.5%) in the placebo group (hazard ratio, 1.67; 95% CI, 1.00 to 2.79; P=0.05 according to the prespecified data-analysis plan; P=0.06 with Yates' continuity correction) (Table 2). Of these patients, one in the simvastatin–ezetimibe group and three in the placebo group died from recurrent cancers, plus one patient in the simvastatin–ezetimibe group died from cancer that was diagnosed in the SAS trial, before entry into the SEAS trial.

ADVERSE EVENTS

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 (Table 3). There were no differences in clinical, organ-related adverse events, except for significantly higher incident cancers in the simvastatin–ezetimibe group (Table 3).

CANCER

In the simvastatin–ezetimibe group, incident cancer was diagnosed in 105 patients (11.1%), as compared with 70 patients (7.5%) in the placebo group (P=0.01). Cancers that had been diagnosed before randomization recurred in eight of these patients (three in the simvastatin–ezetimibe group and five in the placebo group), and one patient had a cancer that developed during the SAS trial, before enrollment in the SEAS trial. The excess cancers in the simvastatin–ezetimibe group were not clustered at any particular site (Table 4). In addition, the risk of incident cancer was not associated with the degree of LDL-cholesterol lowering. Figure 4 shows Kaplan–Meier curves for cancer-related mortality in the two study groups.

DISCUSSION

The combination of simvastatin and ezetimibe resulted in an average reduction in LDL cholesterol of at least 50%, as compared with placebo. Despite this favorable effect over a minimum period of 4 years, there was no overall effect on aortic-valve stenosis and no significant overall effect on the composite primary outcome. The lack of any effect on the progression of aortic stenosis as seen on echocardiography supports the conclusion that the lack of effect on clinical valve-related events was real and not due to a lack of statistical power. The finding of increased numbers of incident and fatal cancers in the simvastatin–ezetimibe group, as compared with the placebo group, was unexpected and requires further exploration in trials of simvastatin and ezetimibe.

The lack of effect on aortic-valve stenosis is in agreement with the findings of the smaller Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) study, in which atorvastatin was used.[34] The results of the Rosuvastatin Affecting Aortic Valve Endothelium (RAAVE) study (ClinicalTrials.gov number, NCT00114491) indicated a favorable effect on aortic stenosis, but the study had a nonrandomized and open-label design, with comparisons of various categories of patients with aortic stenosis.[39]

Our study population did not represent all pa-

Table 3. Adverse Events (Safety Population).*

Event	Placebo (N=929)	Simvastatin plus Ezetimibe (N=943)	P Value†
	no./total no. (%)		
Clinical			
Any event	852 (91.7)	854 (90.6)	
Any serious event‡	463 (49.8)	468 (49.6)	
Incident cancer§	70 (7.5)	105 (11.1)	0.01
Recurrent cancer	5 (0.5)	3 (0.3)	
New cancer	65 (7.0)	102 (10.8)¶	0.01
New cancer after ezetimibe	65 (7.0)	101 (10.7)	0.01
Event attributed to study treatment‖			
Any	110 (11.8)	134 (14.2)	
Serious	3 (0.3)	5 (0.5)	
Event resulting in permanent discontinuation of study treatment			
Any	122 (13.1)	144 (15.3)	
Attributed to treatment	29 (3.1)	46 (4.9)	
Serious event resulting in permanent discontinuation of study treatment			
Any	79 (8.5)	77 (8.2)	
Attributed to treatment	1 (0.1)	2 (0.2)	
Musculoskeletal condition	181 (19.5)	165 (17.5)	0.28
Hepatitis	6 (0.6)	5 (0.5)	0.77
Gastrointestinal condition	281 (30.2)	308 (32.7)	0.27
Gallbladder-related condition	11 (1.2)	10 (1.1)	0.83
Allergic reaction or rash	102 (11.0)	104 (11.0)	1.00
Laboratory findings			
Creatine kinase			
>10 times ULN without muscle-related symptoms	2/915 (0.2)	2/925 (0.2)	1.00
>10 times ULN with muscle-related symptoms	0	0	NA
>10 times ULN with muscle-related symptoms and drug relationship	0	0	NA
Liver enzymes			
Alanine aminotransferase or aspartate aminotransferase ≥3 times ULN (consecutive)**	5/915 (0.5)	16/925 (1.7)	0.03

* Listed are the numbers of patients who had at least one event (or elevated value) during the study period, with each event counted only once within a category. Patients could have more than one event in different categories. The denominators are the numbers of patients who received at least one dose of study drug or placebo. One patient who underwent randomization was not included in the safety analyses because he did not receive study drug or placebo. NA denotes not applicable, and ULN upper limit of the normal range.

† P values were not calculated for comparisons between small numbers and for those for which there was no a priori hypothesis, with the exception of cancer.

‡ Serious adverse events included fatal or life-threatening conditions, those resulting in hospitalization or persistent disability, cancer, and any drug overdose.

§ This category includes 11 patients whose fatal cancers were diagnosed after the discontinuation of study drug or placebo and were therefore not reported as serious adverse events, according to the study protocol.

¶ This number includes one patient who had a newly diagnosed cancer before randomization in the SEAS study.

‖ Events attributed to study treatment were those that were determined by the investigator to be associated with study drug or placebo.

** This category includes patients with values that were three or more times the ULN at two or more consecutive visits, the single last visit, or at least one visit, with a subsequent value that was less than three times the ULN when measured more than 2 days after the last dose of study drug or placebo.

Table 4. Incident Cancer (Safety Population).

Site	Placebo (N=929)	Simvastatin plus Ezetimibe (N=943)	P Value*
	number (percent)		
Any cancer†	70 (7.5)	105 (11.1)	0.01
Any cancer excluding recurrent cancer	65 (7.0)	102 (10.8)‡	0.01
Lip, mouth, pharynx, or esophagus	1 (0.1)	1 (0.1)	1.0
Stomach	1 (0.1)	5 (0.5)	0.23
Large bowel or intestine	8 (0.9)	9 (1.0)	1.0
Pancreas	1 (0.1)	4 (0.4)	0.38
Liver, gallbladder, or bile ducts	3 (0.3)	2 (0.2)	1.0
Lung	10 (1.1)	7 (0.7)	0.60
Other respiratory organ	0	1 (0.1)	1.0
Skin	8 (0.9)	18 (1.9)	0.08
Breast	5 (0.5)	8 (0.8)	0.60
Prostate	13 (1.4)	21 (2.2)	0.24
Kidney	2 (0.2)	2 (0.2)	1.0
Bladder	7 (0.8)	7 (0.7)	1.0
Genital	4 (0.4)	4 (0.4)	1.0
Hematologic	5 (0.5)	7 (0.7)	0.79
Other known sites	1 (0.1)	3 (0.3)	0.63
Unspecified	6 (0.6)	9 (1.0)	0.63

* All P values were calculated with Yates' continuity correction because of small numbers.
† The numbers of patients include those with any cancers including recurrent cancer. One patient who underwent randomization was not included in the safety analyses because he did not receive study drug or placebo. Some patients had more than one site of cancer. The numbers per anatomical site exclude recurrent cancers.
‡ This number includes one patient whose cancer was diagnosed after entry in the SAS study but before randomization in the SEAS study.

tients with aortic-valve stenosis, since high-risk patients with severe hyperlipidemia requiring active lipid-lowering treatment, known atherosclerotic disease, or diabetes mellitus were not included in order to allow for placebo treatment. This factor may explain the relatively low rate of progression of aortic-valve stenosis in our study, as compared with that in other studies.[34,40] Otherwise, the patients in our study had characteristics that are typical of patients with aortic stenosis. It is possible that treatment in our study was initiated too late in the course of the disease to affect further progression, but it is also possible that high levels of LDL cholesterol are just a marker for progression of stenosis.

Therapy with simvastatin and ezetimibe resulted in a significant reduction in the risk of ischemic cardiovascular events, mainly through fewer CABG procedures. Since nearly all coronary surgery was performed as a combined procedure with aortic-valve replacement, the study-drug regimen may have had a substantial effect on atherosclerosis, as shown on coronary angiography. However, the reduction in the risk of other components of the secondary ischemic outcome was smaller than expected on the basis of the large reduction in LDL cholesterol levels.[41] There was a weaker relationship between baseline LDL cholesterol levels and any ischemic event in the placebo group than was seen in studies in high-risk populations, suggesting less potential for risk reduction with lipid-lowering therapy.

Long-term statin therapy has not been associated with an increased risk of cancer. Analysis of data from 14 statin trials involving approximately 90,000 patients showed no evidence of an increased incidence of or death from cancer.[41] However, ezetimibe has been studied less extensively than statins, and the finding of a significant difference between the two study groups in the num-

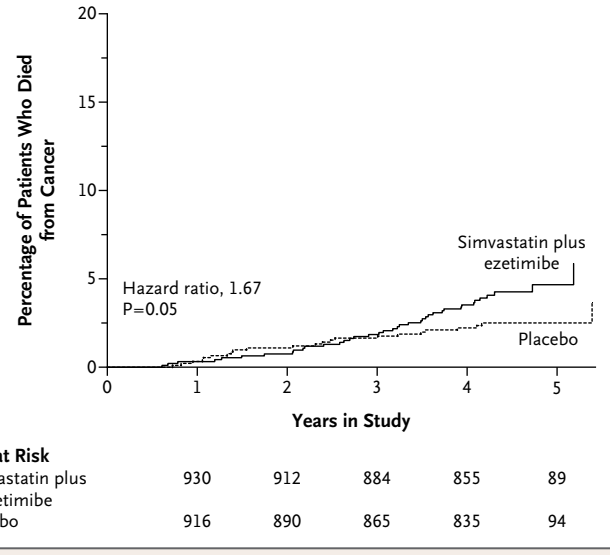

Figure 4. Kaplan–Meier Curves for Cancer-Related Mortality.
P=0.06 as calculated with log-rank continuity correction.

bers of patients with new and fatal cancers is a concern. In this issue of the *Journal*, Peto et al.[42] describe the results of an independent analysis of preliminary data on cancer from two large, ongoing studies, the Study of Heart and Renal Protection (SHARP) (NCT00125593) and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) (NCT00202878).[42] Both trials tested the same study-drug combination that we used in our study, though in other patient populations and with a combined study population of nearly 20,000 patients. Cancer was one of a very large number of safety indicators analyzed in the SEAS trial, and the observed difference in cancer rates in the study may have been the result of chance, but this possibility requires further study.

We conclude that 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. The higher incidence of cancer in the simvastatin–ezetimibe group requires further exploration in ongoing and future trials.

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