

ORIGINAL ARTICLE

A Randomized Trial of Intensive Lipid-Lowering Therapy in Calcific Aortic Stenosis

S. Joanna Cowell, B.M., David E. Newby, M.D., Robin J. Prescott, Ph.D., Peter Bloomfield, M.D., John Reid, M.B., Ch.B., David B. Northridge, M.D., and Nicholas A. Boon, M.D., for the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators

ABSTRACT

BACKGROUND

Calcific aortic stenosis has many characteristics in common with atherosclerosis, including hypercholesterolemia. We hypothesized that intensive lipid-lowering therapy would halt the progression of calcific aortic stenosis or induce its regression.

METHODS

In this double-blind, placebo-controlled trial, patients with calcific aortic stenosis were randomly assigned to receive either 80 mg of atorvastatin daily or a matched placebo. Aortic-valve stenosis and calcification were assessed with the use of Doppler echocardiography and helical computed tomography, respectively. The primary end points were change in aortic-jet velocity and aortic-valve calcium score.

RESULTS

Seventy-seven patients were assigned to atorvastatin and 78 to placebo, with a median follow-up of 25 months (range, 7 to 36). Serum low-density lipoprotein cholesterol concentrations remained at 130 ± 30 mg per deciliter in the placebo group and fell to 63 ± 23 mg per deciliter in the atorvastatin group ($P < 0.001$). Increases in aortic-jet velocity were 0.199 ± 0.210 m per second per year in the atorvastatin group and 0.203 ± 0.208 m per second per year in the placebo group ($P = 0.95$; adjusted mean difference, 0.002; 95 percent confidence interval, -0.066 to 0.070 m per second per year). Progression in valvular calcification was 22.3 ± 21.0 percent per year in the atorvastatin group, and 21.7 ± 19.8 percent per year in the placebo group ($P = 0.93$; ratio of post-treatment aortic-valve calcium score, 0.998; 95 percent confidence interval, 0.947 to 1.050).

CONCLUSIONS

Intensive lipid-lowering therapy does not halt the progression of calcific aortic stenosis or induce its regression. This study cannot exclude a small reduction in the rate of disease progression or a significant reduction in major clinical end points. Long-term, large-scale, randomized, controlled trials are needed to establish the role of statin therapy in patients with calcific aortic stenosis.

From the Department of Cardiology, Royal Infirmary, Edinburgh (S.J.C., D.E.N., P.B., N.A.B.); Public Health Sciences, University of Edinburgh Medical School, Edinburgh (R.J.P.); the Department of Radiology, Borders General Hospital, Melrose, Roxburghshire, United Kingdom (J.R.); and the Department of Cardiology, Western General Hospital, Edinburgh (D.B.N.). Address reprint requests to Dr. Newby at the Department of Cardiology, Royal Infirmary, Old Dalkeith Rd., Little France, Edinburgh EH16 4SU, United Kingdom, or at d.e.newby@ed.ac.uk.

N Engl J Med 2005;352:2389-97.

Copyright © 2005 Massachusetts Medical Society.

IN THE WESTERN WORLD, CALCIFIC AORTIC stenosis is the most common form of valvular heart disease, and its incidence increases with age such that 3 percent of adults over 75 years of age have aortic stenosis.¹ It is a gradually progressive disease, characterized by a long asymptomatic phase, lasting several decades, followed by a shorter symptomatic phase associated with severe narrowing of the orifice of the aortic valve. Once symptoms occur, the prognosis is poor and surgery is usually mandated. Calcific aortic stenosis is now the leading indication for valve replacement in North America and Europe. However, there are currently no effective disease-modifying treatments, and the possibility of halting the disease process would represent a therapeutic advance.

Calcific aortic stenosis is mediated by a chronic inflammatory disease process that has many similarities with atherosclerosis and includes inflammatory-cell infiltrates, lipoproteins, lipids, extracellular-bone-matrix proteins, and bone mineral.²⁻⁵ Consistent with these observations, clinical studies have revealed a strong association with coronary artery disease^{6,7} and many of its risk factors, including hypercholesterolemia.¹ Disease progression in aortic stenosis is variable and influenced by several factors, including the degree of stenosis,⁸ valvular calcification,⁹⁻¹¹ and hypercholesterolemia.^{12,13} Indeed, calcific aortic stenosis is a feature of severe homozygous familial hypercholesterolemia,¹⁴ and intensive lipid-lowering therapy with plasmapheresis can reverse valvular stenosis in patients with this disease.¹⁵

The use of hydroxymethylglutaryl-coenzyme A reductase inhibitors, or statins, is an established treatment for the primary and secondary prevention of coronary artery disease.^{16,17} Several studies have shown that these drugs can halt the progression of coronary artery disease¹⁸⁻²⁰ and reduce coronary calcification.²¹⁻²³ Given the clinical association with hypercholesterolemia and coronary artery disease, and the histologic similarities with atheroma, it has been suggested that statin therapy may halt the progression, or even induce regression, of calcific aortic stenosis. This hypothesis is supported by numerous retrospective observational studies²⁴⁻²⁹ showing that concomitant statin therapy was associated with a delay in disease progression, demonstrated by a reduction of 0.30 m per second per year in the rate of change in aortic-jet velocity, and of 30 percent per year in valvular calcification.

The aim of the Scottish Aortic Stenosis and Lipid

Lowering Trial, Impact on Regression (SALTIRE) was to establish whether intensive lipid-lowering therapy with 80 mg of atorvastatin daily would halt the progression or induce regression of the aortic-jet velocity on Doppler echocardiography, and of the aortic-valve calcium score on computed tomography (CT), in patients with calcific aortic stenosis.

METHODS

PATIENTS

Patients older than 18 years of age with calcific aortic stenosis, an aortic-jet velocity of at least 2.5 m per second, and aortic-valve calcification on echocardiography¹¹ were eligible for inclusion. Exclusion criteria were child-bearing potential without contraception, active or chronic liver disease, a history of alcohol or drug abuse, severe mitral-valve stenosis (mitral-valve area, <1 cm²), severe mitral or aortic regurgitation,³⁰ left ventricular dysfunction (ejection fraction, <35 percent), a planned aortic-valve replacement, intolerance of statins, statin therapy or a potential benefit from statin therapy (according to the treating physician), a baseline serum total cholesterol concentration of less than 150 mg per deciliter (4.0 mmol per liter), and presence of a permanent pacemaker or cardiodefibrillator. Of the patients screened, 455 were eligible for inclusion, 173 agreed to participate, and 155 ultimately underwent randomization.

STUDY PROTOCOL

Between March 2001 and April 2002, the blinded study coordinator randomly assigned eligible patients by the minimization technique³¹ with the use of a dedicated, locked computer program (Edinburgh University) incorporating the following eight variables: age, sex, smoking habit, hypertension, diabetes mellitus, serum cholesterol concentration, aortic-jet velocity, and aortic-valve calcium score. Patients were assigned to either 80 mg of atorvastatin (Lipitor, Pfizer) or matched placebo as a single daily dose. Numbered containers were used.

Patients were assessed at baseline, two months, and six months and every six months thereafter for a minimum of two years. Clinical evaluation included assessment of functional status and adverse events, and the biochemical analysis of blood. Echocardiography and CT were performed at baseline, at each annual visit, and before withdrawal from the study. Patients who underwent randomization and who were subsequently started on open-

label statin therapy by their attending physician were immediately scanned and withdrawn from the study.

Drs. Cowell, Reid, Northridge, and Bloomfield collected the data; Drs. Newby, Northridge, and Boon designed the study and vouch for the data and the analysis; Dr. Prescott analyzed the data; and all investigators participated in writing the article. The drug and the placebo were provided by Pfizer, who had no other input into the study. The investigation conformed to the Declaration of Helsinki and was approved by all regional ethics committees. All patients gave written informed consent.

ECHOCARDIOGRAPHY

Assessment of valvular stenosis was determined by a single dedicated research ultrasonographer. Patients were studied with the use of a 3-MHz transducer for M-mode (single-dimensional) and pulsed and continuous-wave Doppler scanning. All measurements were determined online, averaged from three cardiac cycles (five cycles if the patient was in atrial fibrillation), and recorded onto super-VHS videotape and optical disk according to a standard protocol.

Peak and mean aortic-valve pressure gradients were calculated with the Bernoulli equation, and aortic-valve area was calculated with the continuity equation. The severity of aortic stenosis was determined with echocardiography according to the following standard guidelines: normal is defined by a peak velocity of 1.0 to 2.0 m per second, peak and mean gradients of 0 mm Hg, and a valve area of greater than 2.0 cm²; mild by a peak velocity of 2.1 to 3.0 m per second, a peak gradient of 16 to 35 mm Hg, a mean gradient of less than 15 mm Hg, and a valve area of 2.0 to 1.3 cm²; moderate by a peak velocity of 3.1 to 4.0 m per second, a peak gradient of 36 to 64 mm Hg, a mean gradient of 15 to 50 mm Hg, and a valve area of 1.2 to 0.8 cm²; and severe by a peak velocity of greater than 4.0 m per second, a peak gradient of greater than 64 mm Hg, a mean gradient of greater than 50 mm Hg, and a valve area of less than 0.8 cm².

COMPUTED TOMOGRAPHY

CT was performed by a single operator with the use of a double-helix scanner (Twin II Flash, Philips Medical Systems) calibrated against a standard phantom. The region of the aortic valve was scanned with a spiral CT with the use of 2.7-mm slices, a pitch of 0.7, and an increment of 1.4 mm during

inspiratory breath-holding sessions. All images were analyzed by a single operator with the use of automated computerized software (Picker Cardiac Scoring), involving a modified Agatston scoring method³² with a threshold of 90 Hounsfield units to compensate for nongated imaging.

Reproducibility of echocardiography and CT assessments was determined in two subsets of 20 patients, as described elsewhere.³³ Coefficients of reproducibility³⁴ for aortic-jet velocity and aortic-valve calcium score were 0.32 m per second and 0.07 log arbitrary units (AU), respectively.³³

STATISTICAL ANALYSIS

The two primary end points were progression of stenosis, determined according to changes in aortic-jet velocity on Doppler echocardiography, and progression of valvular calcification, as measured by CT. Secondary end points were a composite of clinical end points (death from cardiovascular causes, aortic-valve replacement, or hospitalization attributable to severe aortic stenosis), aortic-valve replacement, death from any cause, hospitalization for any cause, and hospitalization for cardiovascular causes. On the basis of standard deviations of 0.32 m per second per year^{8,29,35} and 1100 AU per year,³² we calculated that the planned sample size of 75 patients per group would give the study a power of 80 percent at a 5 percent significance level to detect a difference in the primary end points of 0.15 m per second per year in aortic-jet velocity and 500 AU per year in aortic-valve calcium score. These differences are equivalent to a reduction of more than 30 percent in the rate of progression of aortic stenosis. This would exclude a clinically significant effect in the majority of older patients with established disease, although a smaller effect may be clinically relevant in younger patients with mild aortic stenosis.

The data-monitoring committee conducted two interim assessments of safety and an interim assessment of efficacy one year after enrollment began. The trial was to be terminated early in the event of a negative effect of treatment (i.e., $P < 0.05$) or a strong benefit of treatment (i.e., $P < 0.001$). On the recommendation of the data-monitoring committee, the trial continued until the study was completed.

Analyses were performed using SPSS software, version 12.0, and SAS software, version 8e. Intention-to-treat analyses were used for all clinical outcome variables. Disease progression was deter-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Atorvastatin (N=77)	Placebo (N=78)
Age — yr	68±11	68±10
Male sex — %	68	72
Hypertension — no.	48	54
Hyperlipidemia — no.	8	5
Diabetes mellitus — no.	3	4
Current smoker — no.	21	22
Coronary heart disease — no.	18	21
Cerebrovascular disease — no.	9	11
Peripheral vascular disease — no.	5	13
Drug history — no.		
Aspirin	43	40
ACE inhibitor	12	14
Beta-blocker	21	27
Warfarin	8	12
Height — cm	168±9	169±8
Weight — kg	79±15	80±15
Heart rate — bpm	68±11	66±12
Systolic blood pressure — mm Hg	144±18	144±21
Diastolic blood pressure — mm Hg	82±10	81±12
Biochemistry†		
Total cholesterol — mg/dl	220±38	217±34
LDL cholesterol — mg/dl	137±34	133±30
Cholesterol:HDL ratio	4.1±1.1	4.1±1.4
Urea — mg/dl	38±13	43±13
Creatinine — mg/dl	1.07±0.25	1.08±0.26
Glucose — mg/dl	91±19	95±21
Sinus rhythm — %	94	92
Atrial fibrillation — %	6	8
Romhilt–Estes score — median (interquartile range)	1 (0–3)	2 (1–4)
Tricuspid aortic valve — %	96	97
Bicuspid aortic valve — %	4	3
Aortic-jet velocity — m/sec	3.39±0.62	3.45±0.67
Peak gradient — mm Hg	47.8±17.4	49.5±19.5
Aortic-valve area — cm ²	1.03±0.4	1.02±0.41
Aortic-valve calcium score — median AU (interquartile range)	5424 (2750–9689)	6221 (3037–9575)
Log aortic-valve calcium score — log AU	3.7±0.5	3.7±0.6

* Plus-minus values are means ±SD. ACE denotes angiotensin-converting enzyme, LDL low-density lipoprotein, HDL high-density lipoprotein, and AU arbitrary units.

† To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for urea to millimoles per liter, multiply by 0.357. To convert values for creatinine to micromoles per liter, multiply by 88.4. To convert values for glucose to millimoles per liter, multiply by 0.05551.

mined primarily by dividing the change between the baseline and final scans by the duration of follow-up. Treatment comparisons for the continuous outcome variables were based on an analysis of covariance, with the prerandomization level of a variable used as a covariate. In a confirmatory analysis of the primary end points, random-coefficient models were fitted to incorporate all observations.³⁶ In the subgroup analyses, interaction terms between treatment and subgroup have been added to a model incorporating prerandomization level, treatment, and subgroup to identify factors that were associated with a differential treatment effect within subgroups. Categorical variables have been analyzed using Fisher's exact test. Two-tailed tests were used throughout. Two-sided P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

Seventy-seven patients were assigned to atorvastatin and 78 to placebo, with a median follow-up of 25 months (range, 7 to 36). As a consequence of minimization, baseline characteristics were well matched (Table 1). Mean aortic-jet velocity was 3.43±0.64 m per second (range, 2.5 to 5.0), and the median aortic-valve calcium score was 5920 AU (interquartile range, 2485 to 14,231). Of the 155 patients, 119 had mild-to-moderate aortic stenosis (aortic-jet velocity, 2.5 to 3.9 m per second), and 36 had severe stenosis (aortic-jet velocity, ≥4.0 m per second).

SERUM CHOLESTEROL CONCENTRATIONS

The mean serum low-density lipoprotein (LDL) cholesterol concentration remained at 130±30 mg per deciliter (3.4±0.8 mmol per liter) in the placebo group and decreased by 53 percent to 63±23 mg per deciliter (1.7±0.6 mmol per liter) in the atorvastatin group (P<0.001) (Fig. 1C). Serum total cholesterol was 209±35 mg per deciliter (5.5±0.9 mmol per liter) and 132±27 mg per deciliter (3.5±0.7 mmol per liter) in the placebo and atorvastatin groups, respectively (P<0.001), and is in keeping with 97 percent adherence to the study treatment in both groups, which was confirmed by a pill count.

EFFECT OF ATORVASTATIN ON DISEASE PROGRESSION

Intensive lipid-lowering therapy with 80 mg of atorvastatin daily had no effect on the rate of change in

Figure 1. Progression in Aortic-Valve Stenosis and Serum LDL Cholesterol Concentrations in Patients Treated with Intensive Atorvastatin Therapy or Matched Placebo.

Patients received 80 mg of atorvastatin daily or matched placebo. LDL denotes low-density lipoprotein, CT computed tomography, and AU arbitrary units. I bars indicate SDs.

aortic-jet velocity or valvular calcification (Table 2). Progression in valvular calcification was 22.3 ± 21.0 percent per year in the atorvastatin group, and 21.7 ± 19.8 percent per year in the placebo group ($P=0.93$; ratio of post-treatment aortic-valve calcium score, 0.998; 95 percent confidence interval, 0.947 to 1.050). We also performed a longitudinal analysis of the rate of change over time for the two treatment groups with the use of a mixed-effects linear model.³⁶ This showed no difference in the rate of disease progression, with point estimates and 95 percent confidence intervals for the treatment difference that were similar to those shown in Table 2 (mean difference in the rate of change of aortic-jet velocity [the change in the atorvastatin group minus that in the placebo group], 0.008 m per second per year [-0.058 to 0.075]; mean difference in rate of change of aortic-valve calcium score, 71 AU per year [-524 to 666]). Serum LDL cholesterol concentrations did not correlate with disease progression demonstrated on echocardiography ($r=0.021$, $P=0.81$) or CT ($r=-0.109$, $P=0.21$). The proportion of patients reaching secondary clinical end points seemed to be less in the atorvastatin group, but none of the comparisons achieved statistical significance (Table 3).

SUBGROUP ANALYSES

Prespecified subgroup analysis of the primary end-point data was conducted in patients with mild-to-moderate aortic stenosis (aortic-jet velocity, <4.0 m per second) and severe aortic stenosis (aortic-jet velocity, ≥ 4.0 m per second) at baseline. As anticipated from earlier studies, patients with severe stenosis at baseline progressed more rapidly ($P=0.04$), but the study findings were consistent regardless of the severity of stenosis at baseline (Table 4).

Likewise, the length of follow-up did not influence outcome. In those followed for more than 24

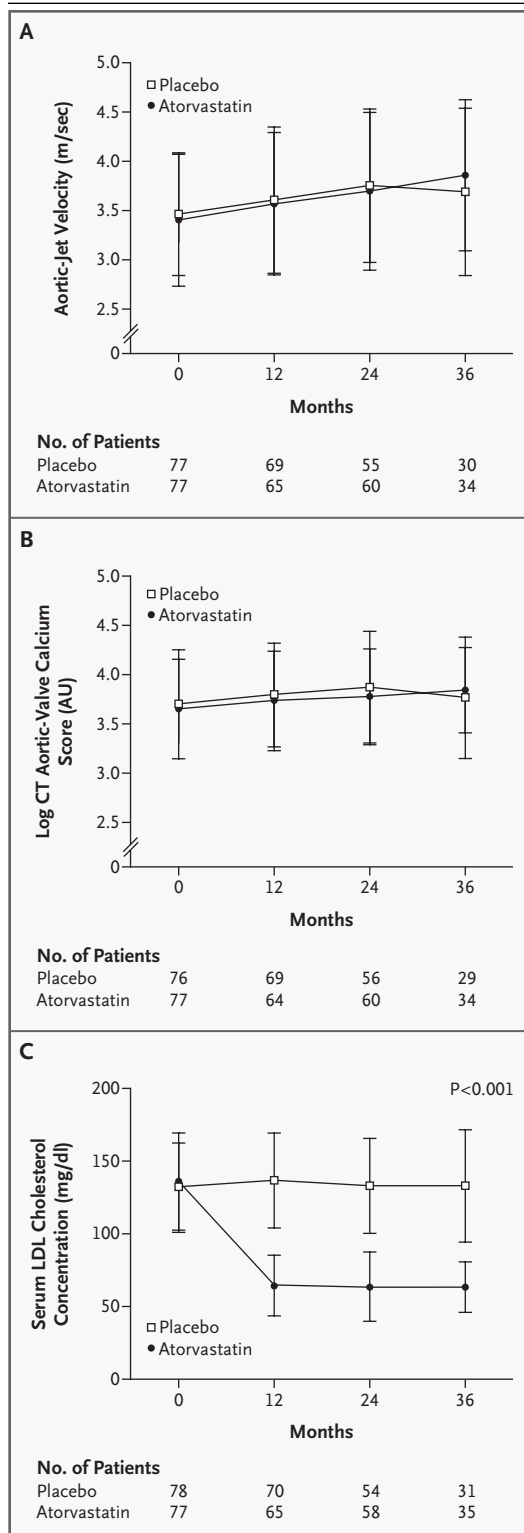


Table 2. Progression from Baseline of Aortic-Valve Stenosis on Echocardiography and Computed Tomography.*

Variable	All Patients	Atorvastatin	Placebo	Adjusted Difference: Atorvastatin–Placebo (95% CI)	P Value
Echocardiography					
No. of patients	134	65	69		
Change in aortic-jet velocity (m/sec/yr)	0.201±0.208	0.199±0.210	0.203±0.208	0.002 (–0.066 to 0.070)	0.95
Increase in peak gradient (mm Hg/yr)	6.52±7.24	6.48±7.43	6.56±7.10	0.21 (–2.02 to 2.45)	0.85
Change in aortic-valve area (cm ² /yr)	–0.081±0.107	–0.079±0.107	–0.083±0.107	0.007 (–0.026 to 0.040)	0.68
Computed tomography					
No. of patients	133	64	69		
Absolute change in aortic-valve calcium score (AU/yr)	1608±1865	1564±1956	1648±1790	85 (–554 to 723)	0.80
Change in log aortic-valve calcium score (per yr)	0.20±0.16	0.20±0.16	0.20±0.15	0.00 (–0.05 to 0.05)	0.93

* Plus–minus values are means ±SD. CI denotes confidence interval, and AU arbitrary units.

Table 3. Number of Patients Reaching Secondary End Points.

Secondary End Point	Atorvastatin (N=77)	Placebo (N=78)	P Value (Fisher's Exact Test)
Composite*	13	21	0.19
Death from cardiovascular causes	3	3	1.00
Aortic-valve replacement	11	19	0.17
Hospitalization for severe aortic stenosis	3	5	0.73
Death from any cause	3	5	0.73
Hospitalization for any cause	10	12	0.84

* The composite end point was death from cardiovascular causes, aortic-valve replacement, or hospitalization for severe aortic stenosis.

months (median, 33), the increase in aortic-jet velocity was 0.21±0.20 m per second per year in the atorvastatin group and 0.17±0.14 m per second per year in the placebo group (Table 4). In those followed for 24 months or less (median, 23), the increase in aortic-jet velocity was 0.19±0.22 m per second per year in the atorvastatin group and 0.23±0.25 m per second per year in the placebo group.

ADVERSE EVENTS

There were similar rates of adverse events in the two treatment groups. Four patients (5 percent) in the placebo group and seven patients (9 percent) in the atorvastatin group discontinued the study drug (P=0.52 by Fisher's exact test), predominantly as a result of gastrointestinal symptoms. Three patients in the atorvastatin group had an increase in

the creatine kinase level to more than five times the upper limit of the normal range, without symptoms of myositis; one of these patients was withdrawn at the request of the data-monitoring committee. There were no cases of rhabdomyolysis and no serious adverse events.

DISCUSSION

In this randomized, double-blind, placebo-controlled, parallel-group trial of lipid-lowering therapy in patients with calcific aortic stenosis, a single coordinating center used a consistent and reproducible approach to assess the severity of aortic stenosis.³³ We have clearly shown that high-dose atorvastatin reduces serum LDL cholesterol concentrations by more than a factor of two, as anticipated,³⁷ but it does not halt the progression or induce regression of the valvular disease process. This was shown with the use of two distinct measures of disease severity — aortic-jet velocity assessed with Doppler echocardiography and valvular calcification assessed with helical CT. Moreover, there was no relationship between serum LDL cholesterol concentrations and the progression of aortic stenosis, nor did high-dose atorvastatin have a demonstrable effect on clinical end points. Thus, regardless of the method of assessing disease progression, we have consistently shown that aortic stenosis progresses despite intensive reductions in serum cholesterol concentrations.

The minimization technique helped ensure that there were no baseline inequalities between the

Table 4. Subgroup Analyses of Disease Progression According to Aortic-Jet Velocity.*

Characteristic	Atorvastatin				Placebo			
	No.	Baseline Value <i>m/sec</i>	No.	Rate of Change <i>m/sec/yr</i>	No.	Baseline Value <i>m/sec</i>	No.	Rate of Change <i>m/sec/yr</i>
Baseline severity of stenosis†								
Mild to moderate	58	3.12±0.43	49	0.17±0.21	61	3.18±0.44	55	0.19±0.20
Severe	19	4.24±0.21	16	0.27±0.21	17	4.45±0.26	14	0.27±0.23
Duration of follow-up								
≤24 Mo‡	30	3.49±0.69	30	0.19±0.22	37	3.64±0.67	37	0.23±0.25
>24 Mo§	35	3.31±0.55	35	0.21±0.20	32	3.28±0.61	32	0.17±0.14

* Plus–minus values are means ±SD. P=0.57 for the interaction of treatment and the baseline severity of stenosis, and P=0.41 for the interaction of treatment and the duration of follow-up.

† Patients with mild-to-moderate aortic stenosis had an aortic-jet velocity of less than 4.0 m per second, and those with severe stenosis an aortic-jet velocity of at least 4.0 m per second.

‡ The median follow-up was 23 months.

§ The median follow-up was 33 months.

treatment groups. Several factors may have influenced our ability to detect an effect of statin therapy on the progression of aortic stenosis in this trial. First, as a consequence of our inclusion criteria, we recruited some patients with severe disease and an aortic-jet velocity of at least 4 m per second, and it could be argued that lipid-lowering therapy is unlikely to influence disease progression at such an advanced stage. We therefore conducted a prespecified subgroup analysis excluding patients with a baseline aortic-jet velocity of 4 m per second or more. Our findings were consistent regardless of the severity of stenosis at baseline — atorvastatin had no effect on disease progression, even in the majority of patients with mild-to-moderate stenosis. We excluded patients with an aortic-jet velocity of less than 2.5 m per second, and we acknowledge that intervening at this earlier stage of the disease process may have been more beneficial. However, such patients do not commonly present to routine clinical practice, and their identification would potentially require population screening.

Second, two years of treatment may not have been sufficient to influence the natural history of the disease. We assessed this possibility by determining if patients with a longer follow-up showed a treatment benefit. In patients who underwent nearly three years of treatment with intensive statin therapy, no trend toward a beneficial effect of atorvastatin was apparent. Therefore, we do not believe that the lack of an effect was due to an inadequate treatment period.

Finally, our study was designed to detect a substantial delay in disease progression and was not powered to assess meaningful effects on clinical end points, such as valve replacement and cardiovascular death. Although we can exclude a treatment benefit of the magnitude previously reported in retrospective observational studies (a reduction in the aortic-jet velocity of 0.30 m per second per year²⁹ and valvular calcification of 30 percent per year^{24,26}), the 95 percent confidence intervals indicate that we may have missed a modest treatment benefit (a delay in disease progression of <0.07 m per second per year for aortic-jet velocity and <5 percent per year for valvular calcification). Although such modest reductions are unlikely to be meaningful in the majority of older patients, a small decrease in disease progression may be clinically important in younger patients with mild disease that may progress over many years.

Given the strength of the data linking aortic stenosis with atherosclerosis and hypercholesterolemia, why have we failed to halt the progression of calcific aortic stenosis? One potential explanation is that, although these features may drive the initiation of aortic stenosis, disease progression may depend on other factors. The aortic valve is subject to continuous dynamic mechanical stress, and the plasticity and structure of the leaflets can have an overriding influence, as is the case with a bicuspid valve. Moreover, in contrast to atherosclerosis, aortic stenosis is associated with a virtual absence of smooth-muscle-cell proliferation and lipid-laden

macrophages² and is dominated by earlier and more extensive mineralization. Decreasing the lipid pool and strengthening the fibrous cap may be less relevant to the progression of aortic stenosis than they are for the reduction in atherosclerotic-plaque rupture with statin therapy in patients with coronary heart disease.

Because of the association between aortic stenosis and coronary artery disease, statin therapy in patients with aortic stenosis may confer secondary preventive benefits that are independent of its effects on the valvular disease process. The current study was not powered to assess the benefits of lipid-lowering therapy on cardiovascular end points such as nonfatal and fatal myocardial infarction. It remains a possibility that aortic stenosis and sclerosis³⁸ may be important markers of occult vascular disease and may identify patients who would gain from the preventive benefits of statin therapy.

We conclude that intensive lipid-lowering therapy with 80 mg of atorvastatin daily does not halt the progression of calcific aortic stenosis or induce its regression. Nevertheless, this trial does not rule out a small but potentially relevant reduction in the rate of disease progression or a significant reduction in major clinical end points. Our study reinforces the need for a long-term, large-scale, randomized, controlled trial of intensive lipid-lowering therapy in patients with calcific aortic stenosis, particularly in those with early, mild disease. In the meantime, we do not recommend statin therapy for patients with calcific aortic stenosis in the absence of coexisting vascular disease.

Supported by a grant from the British Heart Foundation (PG/2000/044), by an educational award from Pfizer, and by the Wellcome Trust Clinical Research Facility, Edinburgh.

Drs. Newby, Bloomfield, and Boon report having received unrestricted educational grant support from Pfizer, and Drs. Newby, Northridge, and Boon report having received consulting fees from and having served on advisory boards for Pfizer.

APPENDIX

The following participated in the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE): **Research team:** L. Anderson, C. Bell, M. Bland, J. Burton, S. Cameron, N. Cruden, J. Cunningham, H. Cuthbertson, L. Flint, M. Henderson, D. Lyle, M. O'Donnell, F. Paterson, K. Paterson, S. Robinson, H. Spence, J. Tickner, A. White. **Collaborating centers (all in the United Kingdom):** *Borders General Hospital, Melrose* — P. Broadhurst, C. Norris, P. Leslie, J. Gaddie; *Eastern General Hospital, Edinburgh* — A. Elder; *Royal Infirmary, Edinburgh* — K. Fox, N. Grubb, A. Flapan, H. Miller, N. Uren; *Falkirk and District Royal Infirmary, Falkirk* — A. Hargreaves, P. McSorely; *Queen Margaret Hospital, Dunfermline* — D. MacLeod; *Roodland's Hospital, Haddington* — A. Flapan; *St. John's Hospital, Livingston* — J. Irving, A. Jacob; *Royal Infirmary, Stirling* — A. Bridges, S. Glen; *Wellcome Trust Clinical Research Facility, Edinburgh*; *Western General Hospital, Edinburgh* — M. Denvir, T. Shaw, I. Starkey. **Pharmacy:** *Royal Infirmary, Edinburgh* — B. Booth; *Freeman Hospital, Newcastle-upon-Tyne, United Kingdom* — A. Heed. **Medical Statistics:** *University of Edinburgh, Edinburgh* — T. Forster.

REFERENCES

1. Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease: Cardiovascular Health Study. *J Am Coll Cardiol* 1997;29:630-4.
2. Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis: histological and immunohistochemical studies. *Circulation* 1994;90:844-53.
3. Olsson M, Dalsgaard C, Haegerstrand A, Rosenqvist M, Rydén L, Nilsson J. Accumulation of T lymphocytes and expression of interleukin-2 receptors in nonrheumatic stenotic aortic valves. *J Am Coll Cardiol* 1994;23:1162-70.
4. O'Brien KD, Reichenbach DD, Marcovina SM, Kuusisto J, Alpers CE, Otto CM. Apolipoproteins B, (a), and E accumulate in the morphologically early lesion of 'degenerative' valvular aortic stenosis. *Arterioscler Thromb Vasc Biol* 1996;16:523-32.
5. Olsson M, Thyberg J, Nilsson J. Presence of oxidized low density lipoprotein in nonrheumatic stenotic aortic valves. *Arterioscler Thromb Vasc Biol* 1999;19:1218-22.
6. Mautner GC, Roberts WC. Reported frequency of coronary arterial narrowing by angiogram in patients with valvular aortic stenosis. *Am J Cardiol* 1992;70:539-40.
7. Peltier M, Trojette F, Sarano ME, Grigioni F, Slama MA, Tribouilloy CM. Relation between cardiovascular risk factors and non-rheumatic severe calcific aortic stenosis among patients with a three-cuspid aortic valve. *Am J Cardiol* 2003;91:97-9.
8. Otto CM, Burwash IG, Legget ME, et al. Prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic, and exercise predictors of outcome. *Circulation* 1997;95:2262-70.
9. Davies SW, Gershlick AH, Balcon R. Progression of valvular aortic stenosis: a long-term retrospective study. *Eur Heart J* 1991;12:10-4.
10. Bahler RC, Desser DR, Finkelhor RS, Brenner SJ, Youssefi M. Factors leading to progression of valvular aortic stenosis. *Am J Cardiol* 1999;84:1044-8.
11. Rosenhek R, Binder T, Parenta G, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med* 2000;343:611-7.
12. Palta S, Pai AM, Gill KS, Pai RG. New insights into the progression of aortic stenosis: implications for secondary prevention. *Circulation* 2000;101:2497-502.
13. Nassimiha D, Aronow WS, Ahn C, Goldman ME. Association of coronary risk factors with progression of valvular aortic stenosis in older persons. *Am J Cardiol* 2001;87:1313-4.
14. Rallidis L, Naoumova RP, Thompson GR, Nihoyannopoulos P. Extent and severity of atherosclerotic involvement of the aortic valve and root in familial hypercholesterolaemia. *Heart* 1998;80:583-90.
15. Keller C, Schmitz H, Theisen K, Zollner N. Regression of valvular aortic stenosis due to homozygous familial hypercholesterolemia following plasmapheresis. *Klin Wochenschr* 1986;64:338-41.
16. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-7.
17. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
18. Zhao XQ, Brown BG, Hillger L, et al. Ef-

- fects of intensive lipid-lowering therapy on the coronary arteries of asymptomatic subjects with elevated apolipoprotein B. *Circulation* 1993;88:2744-53.
19. Pitt B, Mancini GB, Ellis SG, Rosman HS, Park JS, McGovern ME. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. *J Am Coll Cardiol* 1995;26:1133-9.
 20. Jukema JW, Bruschke AV, van Boven AJ, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels: the Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 1995; 91:2528-40.
 21. Callister TQ, Raggi P, Cooil B, Lippolis NJ, Russo DJ. Effect of HMG-CoA reductase inhibitors on coronary artery disease as assessed by electron-beam computed tomography. *N Engl J Med* 1998;339:1972-8.
 22. Budoff MJ, Lane KL, Bakhsheshi H, et al. Rates of progression of coronary calcium by electron beam tomography. *Am J Cardiol* 2000;86:8-11.
 23. Achenbach S, Ropers D, Pohle K, et al. Influence of lipid-lowering therapy on the progression of coronary artery calcification: a prospective evaluation. *Circulation* 2002; 106:1077-82.
 24. Pohle K, Maffert R, Ropers D, et al. Progression of aortic valve calcification: association with coronary atherosclerosis and cardiovascular risk factors. *Circulation* 2001; 104:1927-32.
 25. Novaro GM, Tjong IY, Pearce GL, Lauer MS, Sprecher DL, Griffin BP. Effect of hydroxymethylglutaryl coenzyme A reductase inhibitors on the progression of calcific aortic stenosis. *Circulation* 2001;104:2205-9.
 26. Shavelle DM, Takasu J, Budoff MJ, Mao S, Zhao XQ, O'Brien KD. HMG CoA reductase inhibitor (statin) and aortic valve calcium. *Lancet* 2002;359:1125-6.
 27. Aronow WS, Ahn C, Kronzon I, Goldman ME. Association of coronary risk factors and the use of statins with progression of mild valvular aortic stenosis in older persons. *Am J Cardiol* 2001;88:693-5.
 28. Bellamy MF, Pellikka PA, Klarich KW, Tajik AJ, Enriquez-Sarano M. Association of cholesterol levels, hydroxymethylglutaryl coenzyme-A reductase inhibitor treatment, and progression of aortic stenosis in the community. *J Am Coll Cardiol* 2002;40: 1723-30.
 29. Rosenhek R, Rader F, Loho N, et al. Statins but not angiotensin-converting enzyme inhibitors delay progression of aortic stenosis. *Circulation* 2004;110:1291-5.
 30. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003; 16:777-802.
 31. Treasure T, MacRae KD. Minimisation: the platinum standard for trials? Randomisation doesn't guarantee similarity of groups: minimisation does. *BMJ* 1998;317: 362-3.
 32. Shemesh J, Apter S, Rozenman J, et al. Calcification of coronary arteries: detection and quantification with double-helix CT. *Radiology* 1995;197:779-83.
 33. Cowell SJ, Newby DE, Burton J, et al. Aortic valve calcification on computed tomography predicts the severity of aortic stenosis. *Clin Radiol* 2003;58:712-6.
 34. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307-10.
 35. Faggiano P, Ghizzoni G, Sorgato A, et al. Rate of progression of valvular aortic stenosis in adults. *Am J Cardiol* 1992;70:229-33.
 36. Brown H, Prescott RJ. Applied mixed models in medicine. Chichester, England: John Wiley, 1999:239-41.
 37. Jones P, Kafonek S, Laurora I, Hunninghake D. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study). *Am J Cardiol* 1998;81:582-7. [Erratum, *Am J Cardiol* 1998;82:128.]
 38. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med* 1999; 341:142-7.

Copyright © 2005 Massachusetts Medical Society.

CLINICAL TRIAL REGISTRATION

The *Journal* encourages investigators to register their clinical trials in a public trials registry. The members of the International Committee of Medical Journal Editors plan to consider clinical trials for publication only if they have been registered (see *N Engl J Med* 2004;351:1250-1). The National Library of Medicine's www.clinicaltrials.gov is a free registry, open to all investigators, that meets the committee's requirements.