Prognosis and Risk Factors in Patients With Asymptomatic Aortic Stenosis and Their Modulation by *Atorvastatin* (20 mg)

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The aim of the prospective, randomized, placebo-controlled Tyrolean Aortic Stenosis Study (TASS) was to characterize the natural history and risk factors and their possible modulation by new-onset atorvastatin treatment (20 mg/day vs placebo) in patients with asymptomatic calcified aortic stenosis. Forty-seven patients without previous lipid-lowering therapy or indications for it according to guidelines at study entry were randomized to atorvastatin treatment or placebo and prospectively followed for a mean study period of 2.3 ± 1.2 years. Patients' prognoses were worse than expected, with 24 (51%) experiencing major adverse clinical events, in most cases the new onset of symptoms followed by aortic valve replacement. In multivariate regression analysis, independent risk factors for worse clinical outcomes were aortic valve calcification, as assessed by multidetector computed tomography, and plasma levels of C-reactive protein. In univariate analysis, mean systolic pressure gradient or an increased N-terminal–pro-B-type natriuretic peptide plasma level allowed the prediction of major adverse clinical events as well, whereas concomitant coronary calcification, age, and the initiation of atorvastatin treatment had no significant prognostic implication. As shown in a subgroup of 35 patients (19 randomly assigned to atorvastatin and 16 to placebo), annular progression in aortic valve calcification and hemodynamic deterioration were similar in both treatment groups. In conclusion, TASS could demonstrate a poor clinical outcome in patients with asymptomatic calcified aortic stenosis which can be predicted by new risk factors such as strong AVC or increased plasma levels of CRP or NT-proBNP. The study does not support the concept that treatment with a HMG-CoA reductase inhibitor (20 mg atorvastatin once daily) halts the progression of calcified aortic stenosis. **(Am J Cardiol 2008;102:743–748)**

The aim of the Tyrolean Aortic Stenosis Study (TASS) was to further evaluate risk factors, the progression rate of the disease, and possible beneficial effects of new-onset lipid-lowering therapy with atorvastatin at a standard daily dose of 20 mg compared with placebo in patients with asymptomatic calcified aortic stenosis.

Methods

Study population: Of 120 patients consecutively referred to our echocardiography laboratory for the evaluation of asymptomatic calcified aortic stenosis, 50 were enrolled from November 2003 to November 2005 and followed until February 2008. Baseline and follow-up assessments after every 12 months included clinical examination, transthoracic echocardiography, multidetector computed tomography, and the biochemical analysis of blood. Patients aged >18 years with calcific aortic stenosis, mean systolic gradients of ≥15 mm Hg, valvular stenotic flow velocities ≥2.0 m/s, and aortic valve calcification (AVC) on echocardiography were eligible for inclusion. At study entry, no patient had evident clinical signs suggestive of aortic valve or coronary artery disease, such as angina pectoris, dyspnea, dizziness, syncope, or severe cardiac arrhythmia. Exclusion criteria were child-bearing potential, severe liver disease, concomitant mitral valve stenosis, severe mitral or aortic regurgitation, advanced left ventricular dysfunction (ejection fraction <40%), planned aortic valve replacement, intolerance of statins, or an indication for statin therapy according to guidelines at study entry.[1] Atorvastatin and placebo were provided by Pfizer Austria (Vienna, Austria), which had no other input into the study. The study was approved by the local ethics committee. All patients gave written informed consent.

Multidetector computed tomography: Multidetector computed tomography (Sensation 16; Siemens Medical Systems, Erlangen, Germany) was performed to assess AVC and coronary artery calcification at baseline and after 12 and 24 months, with the following scanning parameters: detector collimation 16 × 1.5 mm, table feed 3.8 mm/rotation, gantry rotation 0.5 seconds, 130 mAs, 120 kV, effective slice thickness 3 mm, increment 1.5 mm, medium convolution kernel B35f, and retrospective electrocardiographic gating at mid- to late diastole (60% to 80% of the

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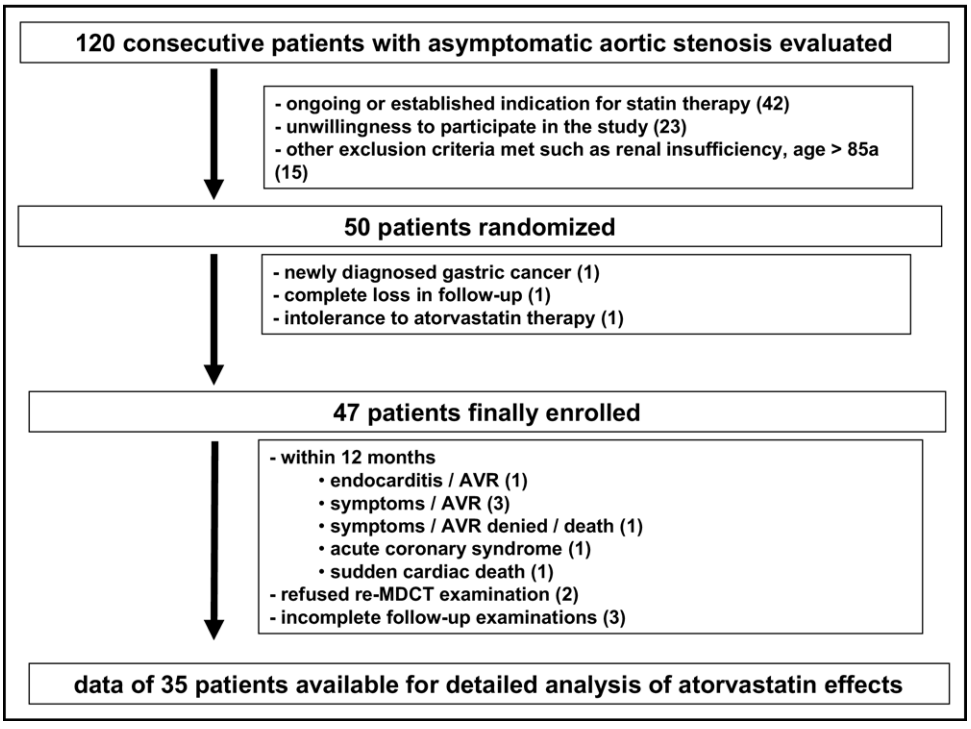

Figure 1. Patient disposition. AVR = aortic valve replacement; MDCT = multidetector computed tomographic.

RR interval) or late systole (30% to 40% of the RR interval), depending on heart rate. AVC and coronary artery calcification were quantified by using dedicated software (Calcium Score; Siemens Medical Systems) to calculate the Agatston score on an off-line computer workstation (Leonardo; Siemens Medical Systems).

Transthoracic echocardiography: Measurements were performed using a standard ultrasound system (Acuson Sequoia 256; Siemens Medical Systems) equipped with a 3.5- or 1.75-MHz transducer by experienced class III observers (S.M., W.D., and H.F.A.). Mean and maximal transvalvular pressure gradients were measured in all patients using continuous-wave Doppler.

Laboratory parameters: Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, N-terminal–pro-B-type natriuretic peptide (NT-proBNP), and C-reactive protein (CRP) plasma levels were determined in all patients.

Statistical analysis: Predefined major adverse clinical events (MACEs) included cardiovascular death, the onset of symptoms (such as heart failure, syncope, and/or angina pectoris) related to aortic stenosis (usually followed by aortic valve replacement), acute coronary syndromes, and endocarditis. To evaluate associations of MACEs with established and possible risk factors, we used a stepwise multiple regression model. AVC and CRP plasma levels were logarithmically transformed so that parametric analytic techniques could be used. Concerning analyses of atorvastatin effects, predefined end points were the progression of AVC, as measured by multidetector computed tomography, and the progression of hemodynamic parameters (increases in mean and peak pressure gradients as assessed by Doppler echocardiography). Values are expressed as mean ± SD, except for triglycerides, CRP, and NT-proBNP, which are expressed as median ± SD. For paired samples, a paired Student's *t* test was used for normally distributed data, and Wilcoxon's signed rank test was used for nonparametric variables. For unpaired samples, Student's *t* test and the Mann-Whitney U test were used as appropriate. Dichotomous variables were compared using the chi-square test. Two-sided p values <0.05 were considered to be statistically significant. Analyses were performed using SPSS version 15.0 (SPSS, Inc., Chicago, Illinois).

Table 1
Baseline characteristics of patients

Characteristic	Placebo (n = 24)	Atorvastatin (n = 23)	Pearson's Correlation Coefficient
Age (yrs)	69.7 ± 10.6	64.2 ± 12.0	0.23
Male gender	13 (54%)	15 (65%)	0.44
Coronary artery calcification	4 (17%)	9 (39%)	0.09
Arterial hypertension	14 (58%)	9 (39%)	0.15
Current smoking	1 (4%)	4 (17%)	0.16
Renal insufficiency	2 (8%)	3 (13%)	0.48
Atrial fibrillation	3 (13%)	2 (9%)	0.52
Diabetes mellitus	5 (21%)	1 (4%)	0.10
Acetylsalicylate	14 (58%)	7 (30%)	0.06
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	11 (46%)	6 (26%)	0.16
Calcium antagonist	2 (8%)	1 (4%)	0.58
β blocker	5 (21%)	3 (13%)	0.48
Vitamin K antagonist	3 (13%)	2 (9%)	0.67

Data are expressed as mean ± SD or as number (percentage).

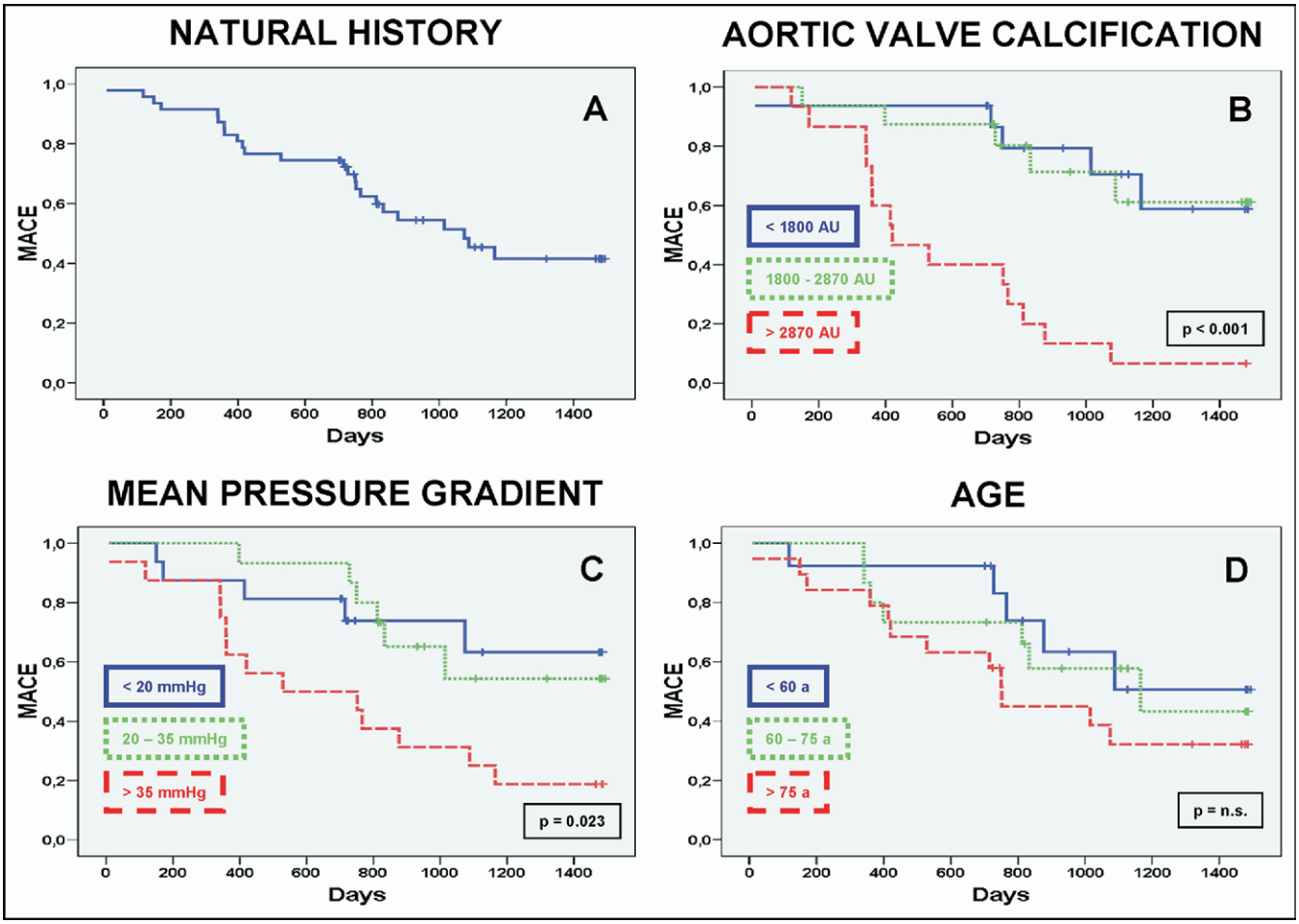

Figure 2. Kaplan-Meier curves showing overall MACE-free survival *(A)* and MACE-free survival stratified to tertiles of AVC *(B)*, mean systolic pressure gradients *(C)*, and age *(D)*.

Results

Patients: Of 120 patients screened, 50 were randomized, and 47 were ultimately enrolled in the study (Figure 1). Three patients were excluded from the study (1 patient in the placebo group was diagnosed with gastric cancer 3 months after randomization, 1 patient randomized to placebo was lost during follow-up, and 1 patient stopped medication with atorvastatin because of intolerance without any increase in creatinine kinase or hepatic enzyme levels). Baseline characteristics are listed in Table 1. No significant difference between treatment groups was found for any of the baseline characteristics. Follow-up examinations were performed after 12 and 24 months. Within the first 12 months, 5 patients developed clinical symptoms; 4 of them underwent aortic valve replacement (1 patient additionally had aortic valve endocarditis); 1 patient was not accepted for surgery and died soon afterward. In the placebo group, 1 patient developed unstable angina and successfully underwent percutaneous coronary intervention (along with the initiation of statin therapy), and 1 patient with moderate to severe aortic stenosis died from sudden cardiac death 9 days after study entry. Follow-up data were incomplete in 5 patients (2 patients refused repeated multidetector computed tomography, and 3 patients missed follow-up examinations at the precise intervals). Therefore, data from 47 patients were analyzed regarding natural history, risk factor evaluation, and the occurrence of MACEs. Detailed investigations of atorvastatin effects on hemodynamic parameters, valvular calcification, and laboratory measurements were available from 35 patients.

Table 2
Multivariate regression analysis predicting major adverse clinical events

Variable	Hazard Ratio (95% Confidence Interval)	p Value
Age (per yr)	1.01 (0.96–1.08)	0.644
Gender (male)	0.52 (0.18–1.55)	0.242
Atorvastatin treatment	0.78 (0.32–1.87)	0.569
Elevated NT-proBNP	1.57 (0.41–6.04)	0.509
Mean pressure gradient (per mm Hg)	1.02 (0.96–1.08)	0.551
CRP (per log mg/dl)	1.62 (1.01–2.61)	0.046
AVC (per log Agatston unit)	3.61 (1.11–11.77)	0.033

Risk factor stratification and natural history: Within a mean study period of 2.3 ± 1.2 years, 24 of 47 patients (51%) had MACEs (Figure 2). In multiple regression analysis (Table 2), AVC and CRP plasma levels were independent risk factors for adverse outcomes. As shown by Kaplan-Meier curves, tertiles of AVC (Figure 2), tertiles of

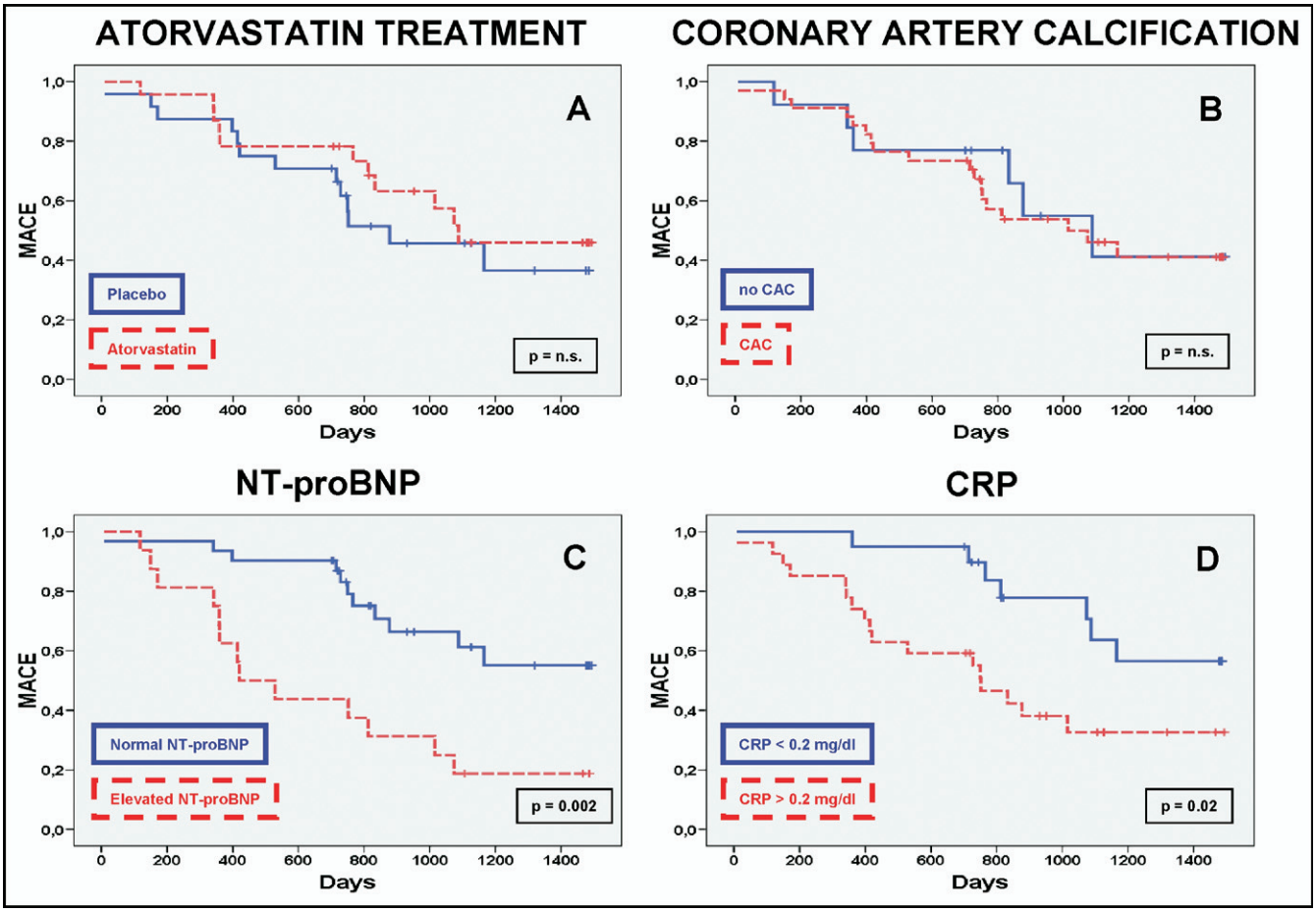

Figure 3. Kaplan-Meier curves showing MACE-free survival stratified to the initiation of atorvastatin treatment *(A)*, the presence of coronary artery calcification (CAC) *(B)*, and increased NT-proBNP *(C)* and CRP *(D)* plasma levels.

Table 3
Effects of atorvastatin treatment (n = 19) versus placebo (n = 16)

	Placebo			Atorvastatin		
	Baseline	12 Months	24 Months	Baseline	12 Months	24 Months
AVC (AU)	2,197 ± 1,178	2,576 ± 1,579	2,749 ± 1,376	2,421 ± 1,326	2,782 ± 1,607	2,979 ± 1,228
Coronary artery calcification (AU)	412 ± 529	481 ± 609	665 ± 756	277 ± 702	333 ± 824	405 ± 924
Mean systolic pressure gradient (mm Hg)	25.6 ± 9.3	29.9 ± 15.9	29.9 ± 14.8	29.2 ± 9.1	33.2 ± 17.2	31.3 ± 12.3
Peak systolic pressure gradient (mm Hg)	41.1 ± 15.0	46.6 ± 20.0	47.0 ± 21.2	46.5 ± 13.1	50.3 ± 21.5	50.7 ± 19.0
Total cholesterol (mg/dl)	225 ± 51	214 ± 41	225 ± 48	208 ± 42	160 ± 35*	160 ± 35*
LDL cholesterol (mg/dl)	144 ± 39	130 ± 28	132 ± 38	135 ± 39	86 ± 32*	89 ± 36*
HDL cholesterol (mg/dl)	66 ± 21	65 ± 23	69 ± 23	59 ± 15	64 ± 14	63 ± 15
Triglycerides (mg/dl)	147 ± 127	165 ± 196	201 ± 284	120 ± 48	112 ± 67	96 ± 43
CRP (mg/dl)	0.26 ± 0.29	0.33 ± 1.39	0.20 ± 0.13	0.21 ± 0.86	0.14 ± 0.66†	0.13 ± 0.28
NT-proBNP (ng/L)	148 ± 531	243 ± 844	244 ± 145	157 ± 809	259 ± 758	182 ± 2,054

* $p < 0.01$; † $p < 0.05$.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

mean systolic pressure gradient (Figure 2), elevated NT-proBNP (Figure 3), and increased CRP plasma levels >0.2 mg/dl (Figure 3) predicted MACEs, whereas there were no prognostic implications regarding tertiles of age (Figure 2), the initiation of atorvastatin treatment (Figure 3), or the presence of coronary artery calcification (Figure 3).

Effect of atorvastatin on lipid concentrations, CRP, and NT-proBNP plasma levels: As listed in Table 3 and shown in Figure 4, atorvastatin significantly decreased mean plasma cholesterol ($p < 0.01$) and low-density lipoprotein cholesterol ($p < 0.01$) after 12 and 24 months, but there was no effect on high-density lipoprotein cholesterol

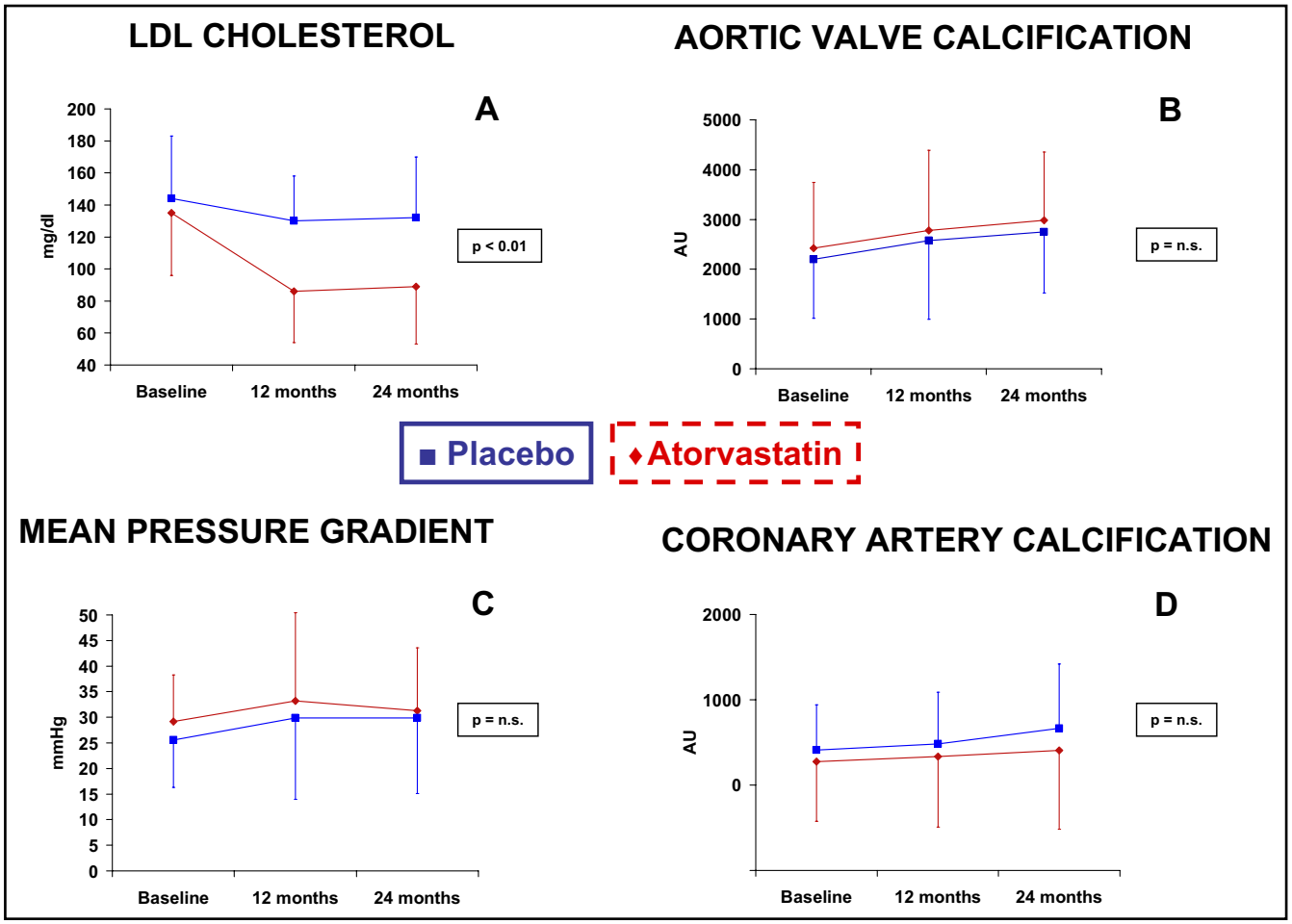

Figure 4. Changes in low-density lipoprotein (LDL) cholesterol plasma levels *(A)* as well as progression in AVC *(B)*, mean pressure gradients *(C)*, and coronary artery calcification *(D)* in patients treated with atorvastatin therapy or placebo. *Bars* indicate SDs.

or triglycerides. Atorvastatin treatment significantly decreased plasma levels of CRP after 12 but not 24 months and had no effect on plasma levels of NT-proBNP.

Effect of atorvastatin on AVC and stenosis progression: As listed in Table 3 and shown in Figure 4, annular progression in AVC and hemodynamic deterioration were similar in the 2 treatment groups. On the basis of the observed data with a sample size of 16 (placebo) versus 19 (atorvastatin), the statistical power to detect a difference of 700 arbitrary units (AU) in the annular progression of AVC and of 5.7 mm Hg in the annular progression of mean systolic pressure gradient was 80%.

Adverse events: There were no serious adverse events, such as rhabdomyolysis or liver failure; 1 patient had an increase in creatinine kinase level to 260 U/L, and 1 patient had an increase in γ–glutamyl transferase level to 40 U/L, both 24 months after the initiation of statin treatment.

Discussion

The main findings of TASS are as follows: (1) The natural histories of patients with asymptomatic aortic stenosis were poor. (2) In addition to established hemodynamic risk factors, the degree of AVC, systemic inflammation (mirrored by increased plasma CRP levels), and elevated NT-proBNP levels predicted MACEs (the latter only in univariate analysis). (3) Age or the presence of concomitant coronary artery calcium did not significantly influence prognosis. (4) Although limited by small sample size, the study does not support the concept that treatment with a statin (atorvastatin 20 mg/day) halts the progression of AVC or hemodynamic deterioration.

Our prospective study confirmed recently published retrospective trials[2–6] showing poor natural histories in patients with asymptomatic aortic stenosis; thus, close clinical follow-up examinations are mandatory. Because AVC quantified by multidetector computed tomography and increased CRP as well as NT-proBNP plasma levels were risk factors for the development of MACEs, these parameters should be assessed in addition to history, clinical status, and echocardiographic results. In contrast to a retrospective study by Rosenhek et al[4] analyzing an Austrian population with asymptomatic aortic stenosis, age or the presence of coronary artery disease had no significant impact on prognosis. In patients with severe aortic stenosis but low perioperative risk, elective surgery might be an option in the presence of advanced AVC, increased systemic inflammatory parameters, and/or natriuretic peptides, even in the

absence of overt clinical symptoms. The delay of aortic valve replacement because of a lack of symptom recognition may result in a dismal outcome, whereas unselected premature aortic valve replacement cannot be recommended in view of the risks associated with the implantation of a prosthetic valve.

In accordance with previous studies including subjects mainly with severe aortic stenosis, CRP and NT-proBNP plasma levels predicted clinical outcomes in TASS.[7,8] However, data recently published from the much larger Cardiovascular Health Study (CHS) could not detect a correlation between CRP and the progression of aortic sclerosis to some form of stenosis.[9] Therefore, although inflammation is apparent in patients with advanced aortic stenosis, it does not necessarily play a major role in the initiation and early phase of calcified aortic valve disease.

Although TASS was not powered to definitely assess atorvastatin effects on disease progression, the described lack of a major therapeutic effect is supported by the only large prospective randomized trial published so far, the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE),[10] which consisted of a similar design in terms of inclusion and exclusion criteria, study period (median time of treatment 25 months), and primary end points. However, SALTIRE recruited patients with more advanced disease in terms of higher baseline peak gradients (47.8 ± 17.4 and 49.5 ± 19.5 mm Hg) and higher AVC (5,424 [range 2,750 to 9,689] and 6,221 [range 3,037 to 9,575] AU) in the atorvastatin and placebo groups, respectively. Furthermore, patients were randomized to intensive lipid lowering with atorvastatin 80 mg, which reduced low-density lipoprotein cholesterol levels to 63 ± 23 mg/dl (whereas atorvastatin 20 mg reduced low-density lipoprotein cholesterol levels to 86 ± 32 mg/dl after 12 months in TASS). SALTIRE detected a progression in AVC of 1,648 ± 1,790 AU (21.7 ± 19.8%/yr) in the placebo group and of 1,564 ± 1,956 AU (22.3 ± 21.0%/yr) in the atorvastatin group. In TASS, annular progression of AVC was slower (276 AU [12.6%] in the placebo group and 279 AU [11.5%] in the atorvastatin group) but could not be influenced by atorvastatin treatment either. A slower progression of AVC in absolute terms was also detected in a study by Mohler et al,[11] who reported an annular AVC increase of 275 ± 650 AU in the non-statin-treated group and 250 ± 458 AU in the statin-treated group. Differences in method and patient characteristics may contribute to these large differences in absolute terms of AVC.

The results of retrospective studies[12–15] and 1 open-label prospective trial, the Rosuvastatin Affecting Aortic Valve Endothelium (RAAVE) study,[16] suggest that statin treatment reduces the rate of change in aortic stenosis flow velocity in patients with hypercholesterolemia with calcified aortic stenosis. In contrast to these studies, TASS and SALTIRE (randomizing patients without indication for statin treatment according to guidelines) could not detect any delaying effect of atorvastatin treatment on hemodynamic progression. Therefore, statins may influence the natural history of the disease primarily in patients with hyperlipidemia, after prolonged use, initiated in an early phase of valvular leaflet thickening (aortic sclerosis). Notably, the patients in the retrospective trials were already receiving therapy at the time of inclusion in the studies, and many of them had started therapy long before study entry. Excluding patients in whom statins were indicated for hyperlipidemia probably negated some of the potential nonvalvular benefits of lipid lowering in SALTIRE and TASS.

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