Effects of Rosuvastatin on Progression of Stenosis in Adult Patients With Congenital Aortic Stenosis (PROCAS Trial)

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Recent trials have failed to show that statin therapy halts the progression of calcific aortic stenosis (AS). We hypothesized that statin therapy in younger patients with congenital AS would be more beneficial, because the valve is less calcified. In the present double-blind, placebo-controlled trial, 63 patients with congenital AS (age 18 to 45 years) were randomly assigned to receive either 10 mg of rosuvastatin daily (n = 30) or matched placebo (n = 33). The primary end point was the progression of peak aortic valve velocity. The secondary end points were temporal changes in the left ventricular mass, ascending aortic diameter, and N-terminal pro-brain natriuretic peptide (NT-proBNP). The median follow-up was 2.4 years (interquartile range 1.9 to 3.0). The mean increase in peak velocity was 0.05 ± 0.21 m/s annually in the rosuvastatin group and 0.09 ± 0.24 m/s annually in the placebo group (p = 0.435). The annualized change in the ascending aorta diameter (0.4 ± 1.7 mm with rosuvastatin vs 0.5 ± 1.6 mm with placebo; p = 0.826) and left ventricular mass (1.1 ± 15.8 g with rosuvastatin vs −3.7 ± 30.9 g with placebo; p = 0.476) were not significantly different between the 2 groups. Within the statin group, the NT-proBNP level was 50 pg/ml (range 19 to 98) at baseline and 21 pg/ml (interquartile range 12 to 65) at follow-up (p = 0.638). NT-proBNP increased from 40 pg/ml (interquartile range 20 to 92) to 56 pg/ml (range 26 to 130) within the placebo group (p = 0.008). In conclusion, lipid-lowering therapy with rosuvastatin 10 mg did not reduce the progression of congenital AS in asymptomatic young adult patients. Interestingly, statins halted the increase in NT-proBNP, suggesting a potential positive effect of statins on cardiac function in young patients with congenital AS. **(Am J Cardiol 2011; 108:265–271)**

The Progression of Stenosis in Adult Patients With Congenital Aortic Stenosis (PROCAS) trial was designed to study the effect of long-term lipid-lowering therapy with daily use of rosuvastatin on the echocardiographic and neurohumoral outcomes in asymptomatic young adult patients with congenital aortic stenosis (AS). We hypothesized that statins prevent calcifications and halt the progression of congenital AS.

Methods

The PROCAS study was a prospective, double-blind, randomized, placebo-controlled, multicenter trial that evaluated the effect of rosuvastatin on the progression of asymptomatic congenital AS in young adult patients. The study was conducted at 6 tertiary referral centers for congenital heart disease in The Netherlands and Belgium. Enrollment occurred from December 2005 to December 2007. The intended follow-up duration was 3 years. Annually, patients underwent transthoracic echocardiography, laboratory testing, and electrocardiography. After the baseline assessment and randomization, the patients were scheduled for telephone interviews every 3 months to assess potential side effects and to emphasize the importance of compliance. For patients undergoing aortic valve replacement (AVR) during the study period, the findings from the last transthoracic echocardiogram, laboratory tests, and electrocardiogram before AVR were used in the present analysis. The medical ethics committee of each participating center approved the PROCAS study, and all patients gave written informed

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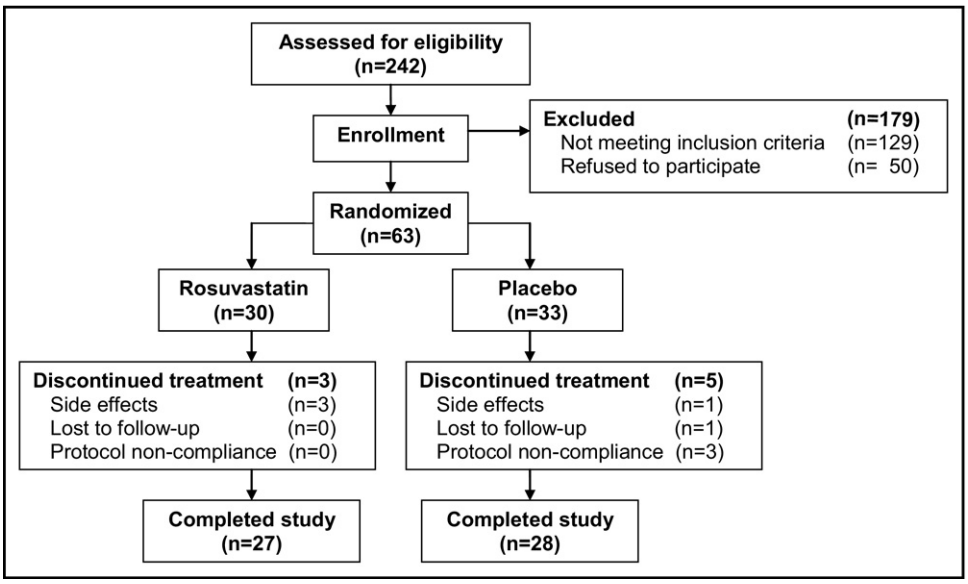

Figure 1. Enrollment and randomization of patients in PROCAS trial.

consent. The clinical trial registration number was ISRCTN56552248 (available at: *www.controlled-trials.com/*).

Eligible patients were selected from the CONgenital CORvitia (CONCOR) database,[1] the Dutch registry for adult patients with congenital heart disease, and from the Leuven local congenital heart disease database. We included men and women 18 to 45 years old with native valvular congenital AS, with a peak aortic valve velocity >2.5 m/s. The patients who already used statins or had contraindications for the use of statins, such as known muscle disease, active liver disease, creatine kinase >600 U/L, or severe kidney dysfunction (creatinine >200 μmol/L) were excluded. Other exclusion criteria were previous AVR, a history of acute rheumatic fever, mitral valve stenosis or regurgitation, and severe aortic regurgitation. For young women, the wish to become pregnant within the next 5 years was also a contraindication. Eligible patients were randomized in a 1:1 fashion in blocks of 4 to receive either rosuvastatin 10 mg daily or a matching placebo. The randomization schedule was centralized and generated by a computer program at the Erasmus Medical University Center pharmacology department, which had no access to the rest of the data. When a center was ready to randomize a patient, the pharmacology department sent a randomization number to the site coordinator and the study medication to the patient. The patients, treating physicians, and investigators were all unaware of the treatment assignment.

Annually, a complete Doppler transthoracic echocardiogram was performed by trained echocardiographers. Randomly selected studies were reviewed to ensure that the studies and measurements were performed in accordance with the protocol. The recommended parameters for the clinical evaluation of AS severity are the peak velocity, mean gradient, and aortic valve area.[2] We used the peak aortic velocity as the primary end point, because it is the most reproducible measurement of the severity of AS and left ventricular (LV) function was normal in all patients.[2] The ascending aorta diameter was measured at 4 levels: the annulus, sinus of Valsalva, sinotubular junction, and proximal ascending aorta. We considered the aorta dilated if the value was 2 standard deviations greater than the normal value, according to gender, in the guidelines.[3] The LV mass was calculated using the Devereux-modified formula.[4] LV hypertrophy was defined by a body surface area-indexed threshold of >134 g/m^2 for men and >110 g/m^2 for women.[5] We defined the aortic valve as calcified if thickening was present combined with increased echogenicity of the leaflets in the parasternal long- or short-axis views. Annual laboratory tests included high-sensitivity C-reactive protein, N-terminal pro-brain natriuretic peptide (NT-proBNP), lipid profile, creatine kinase, and creatinine. After a patient had rested for 30 minutes, venous blood samples were collected and stored at −80°C until the end of the study. Kits to determine the NT-proBNP levels were offered by Roche Diagnostics (Basel, Switzerland), with a cutoff value for elevation of 125 pg/ml.[6] Creatine kinase was considered elevated at >200 U/L in men and 170 U/L in women.

For the statistical analyses, the Statistical Package for Social Sciences, version 15.0 (SPSS, Chicago, Illinois) and R (version 2.11.1, available at: *www.r-project.org*) were used. All statistical tests were 2-sided; $p < 0.05$ was considered statistically significant. The primary end point was the annual peak aortic valve velocity progression. The secondary end points were progression of the LV mass, ascending aorta diameter, and NT-proBNP. The data were analyzed according to an intention-to-treat analysis. To account for different follow-up durations, the annualized changes were calculated by dividing the change by the follow-up duration. On the basis of a standard deviation of 0.15 m/s annually, we calculated that a sample size of 90 patients in each treatment group would give the study 80% power at a 5% significance level to detect a difference in the primary end point of 0.06 m/s annually in the peak velocity. Group differences were assessed using the 2-sample *t* test, chi-square test, or Mann-Whitney *U* test. Normally distributed continuous variables were summarized using the mean

Table 1
Baseline characteristics of PROCAS trial

Variable	Rosuvastatin (n = 30)	Placebo (n = 33)
Age (years)	33 ± 9	32 ± 10
Men	21 (70%)	24 (73%)
Body mass index (kg/m^2)	25 ± 3	25 ± 4
Blood pressure (mm Hg)		
Systolic	129 ± 16	131 ± 16
Diastolic	76 ± 10	78 ± 9
Smoker		
Current	7 (23%)	10 (30%)
Former	1 (3%)	1 (3%)
Never	22 (73%)	22 (67%)
Previous intervention (surgical valvulotomy or balloon valvuloplasty)	22 (73%)	26 (79%)
Bicuspid valve	28 (93%)	29 (88%)
Aortic regurgitation		
Non/grade 1	21 (70%)	18 (55%)
Grade 2	6 (20%)	10 (30%)
Grade 3	3 (10%)	5 (15%)
Aortic valve calcium	12 (40%)	12 (36%)
Measurements of aortic stenosis		
Peak aortic valve velocity (m/s)	3.4 ± 0.7	3.6 ± 0.9
Peak aortic gradient (mmHg)	48 ± 18	56 ± 28
Mean aortic gradient (mmHg)	27 ± 10	32 ± 17
Aortic valve area (cm^2)	1.3 ± 0.4	1.3 ± 0.5
Aortic diameter at 4 levels (mm)		
Annulus	24 ± 5	25 ± 5
Sinus of Valsalva	32 ± 6	32 ± 6
Sinotubular junction	27 ± 6	28 ± 6
Proximal ascending aorta	36 ± 6	37 ± 8
Fractional shortening (%)	39 ± 8	39 ± 7
Left ventricular mass (g)	214 ± 59	212 ± 77
Left ventricular hypertrophy	6 (20.0%)	11 (33.3%)
Lipid concentrations		
Total cholesterol (mg/dl)	177 ± 36	176 ± 39
Total cholesterol (mmol/L)	4.6 ± 0.9	4.6 ± 1.0
Low-density lipoprotein cholesterol (mg/dl)	106 ± 31	104 ± 35
Low-density lipoprotein cholesterol (mmol/L)	2.8 ± 0.8	2.7 ± 0.9
High-density lipoprotein cholesterol (mg/dl)	46 ± 13	48 ± 15
High-density lipoprotein cholesterol (mmol/L)	1.2 ± 0.3	1.3 ± 0.4
Triglycerides (mg/dl)	49 ± 28	52 ± 29
Triglycerides (mmol/L)	1.3 ± 0.7	1.3 ± 0.7
High-sensitivity C-reactive protein (mg/L)	1.4 (0.8–5.3)	1.3 (0.5–2.9)
N-terminal pro-brain natriuretic peptide (pg/ml)	50 (19–98)	40 (20–92)
Creatinine (μmol/L)	69 ± 15	73 ± 11
Creatine kinase (U/L)	96 (65–110)	92 (68–124)

Data are presented as mean ± SD when normally distributed, as median (interquartile range) when non-Gaussian distributed, and as n (%) when frequencies.

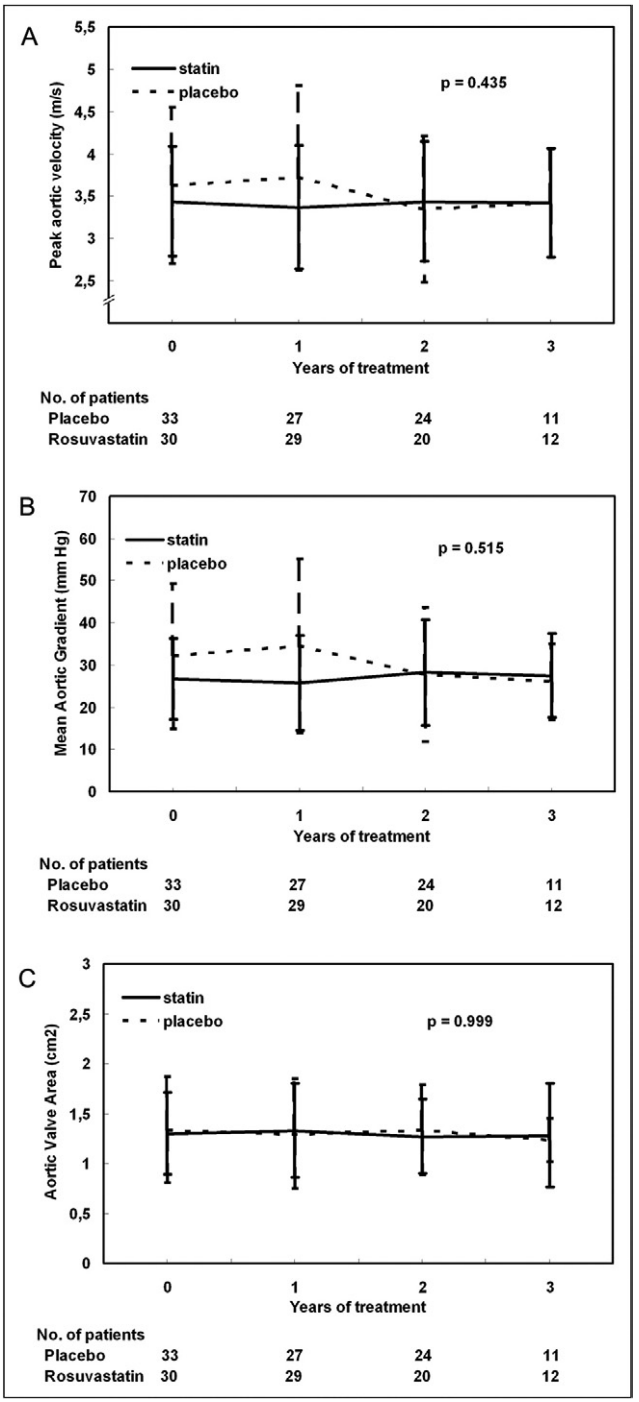

Figure 2. Progression of congenital aortic stenosis in rosuvastatin and placebo group in peak aortic velocity *(A)*, mean aortic gradient *(B)*, and aortic valve area *(C)*.

Table 2
Annualized changes in primary and secondary end points

Variable	All Patients (n = 59)	Rosuvastatin (n = 27)	Placebo (n = 32)	p Value
Aortic stenosis progression				
Peak aortic velocity (m/s)	0.07 ± 0.23	0.05 ± 0.21	0.09 ± 0.24	0.435
Peak aortic gradient (mm Hg)	3.0 ± 7.7	2.5 ± 5.7	3.5 ± 9.2	0.638
Mean aortic gradient (mm Hg	1.6 ± 4.2	1.2 ± 3.3	1.9 ± 4.8	0.515
Aortic valve area (cm^2)	−0.03 ± 0.15	−0.03 ± 0.11	−0.03 ± 0.18	0.999
Aortic diameter progression				
Annulus (mm)	0.4 ± 2.2	0.1 ± 1.9	0.7 ± 2.5	0.330
Sinus of Valsalva (mm)	0.2 ± 1.6	0.2 ± 1.2	0.1 ± 1.7	0.802
Sinotubular junction (mm)*	0.2 ± 2.1	−0.1 ± 1.4	0.5 ± 2.5	0.332
Proximal ascending aorta (mm)*	0.4 ± 1.6	0.4 ± 1.7	0.5 ± 1.6	0.826
Left ventricular mass (gram)	−1.6 ± 25.2	1.1 ± 15.8	−3.7 ± 30.9	0.476
N-terminal pro-brain natriuretic peptide (pg/ml)†	0.4 (−8.0–8.7)	−0.9 (−8.0–6.3)	4.1 (−6.9–13.4)	0.187

Data are presented as mean ± SD when normally distributed and as median (interquartile range) when non-Gaussian distributed.
* Rosuvastatin group, n = 26; placebo group, n = 31, total, n = 57.
† Rosuvastatin group, n = 24; placebo group, n = 24; total, n = 48.

Table 3
Changes in echocardiographic characteristics

Characteristics	Rosuvastatin (n = 30)			Placebo (n = 32)		
	Baseline	Follow-up	p-value	Baseline	Follow-up	p-value
Peak aortic valve velocity (m/s)	3.4 ± 0.6	3.5 ± 0.7	0.410	3.6 ± 0.9	3.7 ± 1.1	0.046
Peak aortic gradient (mmHg)	46 ± 16	51 ± 18	0.042	55 ± 28	60 ± 35	0.034
Mean aortic gradient (mmHg)	26 ± 8	29 ± 11	0.082	31 ± 17	35 ± 22	0.038
Aortic valve area (cm^2)	1.3 ± 0.4	1.3 ± 0.5	0.251	1.3 ± 0.5	1.3 ± 0.5	0.260
Annulus (mm)	24 ± 5	24 ± 4	0.904	25 ± 5	26 ± 6	0.294
Sinus of Valsalva (mm)	31 ± 5	32 ± 5	0.441	32 ± 6	32 ± 6	0.948
Sinotubular junction (mm)*	27 ± 6	27 ± 5	0.665	28 ± 5	29 ± 6	0.508
Proximal ascending aorta (mm)*	35 ± 6	36 ± 6	0.229	37 ± 8	38 ± 8	0.110
Left ventricular mass (gram)	212 ± 56	212 ± 75	0.947	209 ± 77	203 ± 77	0.456

Values are shown as mean ± standard deviation when normally distributed and as median (interquantile range) when non-Gaussian distributed.
* Rosuvastatin group n = 26, placebo group n = 31, total n = 57.

Table 4
Changes in cholesterol and high-sensitivity C-reactive protein levels

Characteristic	Rosuvastatin (n = 27)			Placebo (n = 32)		
	Baseline	Follow-up	p-value	Baseline	Follow-up	p-value
Total cholesterol (mg/dl)	177 ± 36	120 ± 30	<0.001	176 ± 39	178 ± 36	0.362
Total cholesterol (mmol/l)	4.6 ± 0.9	3.1 ± 0.8	<0.001	4.6 ± 1.0	4.6 ± 0.9	0.362
Low-density lipoprotein cholesterol (mg/dl)	106 ± 30	61 ± 22	<0.001	104 ± 35	97 ± 32	0.170
Low-density lipoprotein cholesterol (mmol/l)	2.8 ± 0.8	1.6 ± 0.6	<0.001	2.7 ± 0.9	2.5 ± 0.8	0.170
High-density lipoprotein cholesterol (mg/dl)	46 ± 13	46 ± 13	0.273	48 ± 16	47 ± 24	0.713
High-density lipoprotein cholesterol (mmol/l)	1.2 ± 0.3	1.2 ± 0.3	0.273	1.3 ± 0.4	1.2 ± 0.6	0.713
High sensitivity C-reactive protein (mg/l)	1.4 (0.8–5.3)	1.2 (0.6–3.0)	0.019	1.3 (0.5–2.9)	1.6 (0.8–2.5)	0.158

Values are shown as mean ± standard deviation when normally distributed and as median (interquantile range) when non-Gaussian distributed.

± SD. Non-normally distributed continuous variables were summarized using the median and interquantile range. The categorical variables were summarized using the frequency and percentage. The treatment groups were compared through the use of the 2-sample *t* test or Mann-Whitney *U* test. A subgroup analysis was performed in patients with less severe AS (peak aortic velocity <3.0 m/s) and in patients without aortic valve calcifications. To compare the changes in cholesterol and high-sensitivity C-reactive protein levels within the groups over time, the repeated measurements analysis of variance test and Friedman test were used for comparison. Intervention-free survival analysis to detect differences between the treatment groups was performed using the Kaplan-Meier survival analysis. Cox regression analysis was used to evaluate the prognostic significance of variables that potentially could predict intervention-free survival. A correlation analysis of the NT-proBNP level with age and AS severity parameters was performed using the Pearson correlation test or Spearman correlation test.

Results

From December 2005 to December 2007, 242 patients were assessed for eligibility to participate in the PROCAS trial (Figure 1). The main reason for refusal was the burden of taking medication for 3 years. The main reasons for not meeting the inclusion criteria were young women considering pregnancy, previous AVR, and severe aortic regurgitation. The median follow-up was 2.4 years (interquartile range 1.9 to 3.0). The baseline characteristics of the 2 treatment groups were well balanced (Table 1), without significant differences between the treatment groups at baseline.

No significant differences were found between the rosuvastatin and placebo group in the annual change in the primary and secondary end points (Table 2). The subgroup analyses did not show interaction effects for the annual progression of peak aortic velocity in patients with less severe AS (p = 0.864) or in patients without baseline aortic valve calcification (p = 0.316). Figure 2 shows the comparison data for AS progression at 0, 1, 2, and 3 years of treatment. The numerical values for the echocardiographic parameters at baseline and at the end of the study are listed in Table 3. The median NT-proBNP in the rosuvastatin group at baseline was 50 pg/ml (interquartile range 19 to 98) and 21 pg/ml (interquartile range 12 to 65) at the end of the follow-up period (p = 0.638). The median NT-proBNP in the placebo group at baseline was 40 pg/ml (interquartile range 20 to 92) and increased with time to 56 pg/ml (interquartile range 26 to 153; p = 0.008). The NT-proBNP level showed weak correlations with the peak velocity (r = 0.311; p = 0.020), peak gradient (r = 0.291; p = 0.029), mean gradient (r = 0.297; p = 0.026), aortic valve area (r = −0.338; p = 0.011), and age (r = 0.320; p = 0.016). The prevalence of aortic root dilation was high: 33% at the annulus level, 27% at the sinus of Valsalva level, 79% at the sinotubular junction level, and 78% at the proximal ascending aorta level. Dilation of the ascending aorta at any of the 4 levels occurred in 84% of the patients.

During the trial, 9 patients (14%) underwent surgical AVR after a median follow-up of 1.7 years (range 0.8 to 2.0). No significant difference was found in the occurrence of AVR between the rosuvastatin and placebo groups (log-rank, 0.978; p = 0.323; Figure 3). No deaths or other aortic valve-related complications (i.e., endocarditis, aortic dissection) occurred during the follow-up period. Two factors associated with a shorter interval to AVR were identified: a greater peak aortic velocity at baseline (hazard ratio 1.8, 95% confidence interval 1.2 to 2.6) and aortic valve calcification (hazard ratio 1.7, 95% confidence interval 1.0 to 2.9). The peak aortic velocity at baseline in patients who underwent AVR was greater than that in patients who did not undergo AVR (4.5 ± 0.7 vs 3.4 ± 0.7 m/s; p <0.001). The AVR patients more often had valve calcifications at baseline (78% vs 32%; p = 0.021). The annual AS progression rate (0.41 ± 0.28 vs 0.02 ± 0.17 m/s; p <0.001) and LV mass at baseline (266 ± 32 vs 203 ± 69 g; p = 0.010) were greater in those requiring AVR, as was the median NT-proBNP (108 pg/ml, interquartile range 27 to 446, vs 42 pg/ml, interquartile range 18 to 74; p = 0.061).

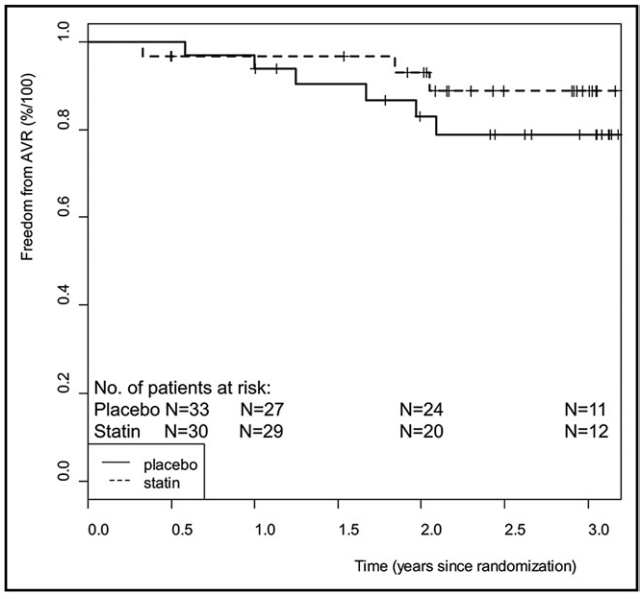

Figure 3. Kaplan-Meier curves for freedom from AVR for rosuvastatin and placebo group (log-rank, 0.978; p = 0.323).

Compliance with the study medication was judged satisfactory, according to the cholesterol and high-sensitivity C-reactive protein levels (Table 4). No difference was seen in the frequency of adverse events between the 2 groups. The incidence of muscular pain, leading to discontinuation of the study drug, was similar in the rosuvastatin and placebo group (10% vs 3%, p = 0.340). Furthermore, the incidence of elevated creatine kinase levels was comparable between the rosuvastatin and placebo group (17% vs 12%, respectively, p = 0.725). No cases of rhabdomyolysis, kidney failure, severe creatine kinase elevation, or cancer were observed.

Discussion

The present small, prospective, double-blind, randomized, placebo-controlled multicenter PROCAS trial could

not detect a significant effect of rosuvastatin on the progression of congenital AS in asymptomatic adult patients aged 18 to 45 years. Also, rosuvastatin did not have a significant effect on the progression of ascending aorta diameter, LV mass, or AVR-free survival. The results of the PROCAS trial have confirmed and extended the findings of the Scottisch Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE), Tyrolean Aortic Stenosis Study (TASS), Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) and Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) trials.[7–10] The largest difference between these trials and the PROCAS trial was the approximately 30-year younger average age of the PROCAS patients. The PROCAS trial only included patients with congenital AS, and the other trials included populations with predominantly degenerative, calcified AS in elderly patients. The PROCAS trial confirmed the findings of the subgroup analysis in the patients with a bicuspid valve in the ASTRONOMER trial.[10] The PROCAS trial showed that 38% of included young adults already had aortic valve calcification. The subgroup analysis of patients with less severe AS or without valve calcifications showed the same nonsignificant results.

In the PROCAS study, the mean age of the patients was 33 years. The vast majority of these young patients with congenital AS (84%) already had dilation of the ascending aorta, especially at the level of the sinotubular junction and the proximal ascending aorta. Statins did not have an effect on the progression of aortic dilation, which, on average, was 0.3 mm/year. In patients with Marfan syndrome, promising evidence has shown that angiotensin II blockade slows the rate of progressive aortic root dilation.[11] Because aortic dilation in bicuspid valve disease shows similarities with Marfan syndrome with regard to abnormalities in fibrillin-1 and matrix metalloproteinases, the effect of angiotensin II blockade on the progression of aortic dilation should be further investigated.[12]

The PROCAS trial showed that NT-proBNP increased over time in patients with congenital AS, and statins were able to halt this increase. It is possible that lipid-lowering therapy improves cardiac function in patients with congenital AS. A recent study of patients with heart failure showed that statin therapy reduced the NT-proBNP levels and improved cardiac function.[13] Statins also decreased the NT-proBNP levels and improved cardiac function in patients with dilated cardiomyopathy.[14] The exact mechanism and clinical implications for patients with congenital AS remain to be elucidated, and additional research of larger study populations of those with congenital AS is necessary to confirm these findings. Although many studies have been reported about the diagnostic and prognostic value of NT-proBNP in degenerative AS, no data are available on this matter in young adult patients with congenital AS. Therefore, we did not only focus on the effect of rosuvastatin on NT-proBNP, but also explored the correlation among the congenital AS severity, AVR, and NT-proBNP. The PROCAS trial prospectively showed that the NT-proBNP levels correlated positively with congenital AS severity. This is in line with degenerative AS studies of elderly patients, which also showed a similar NT-proBNP correlation with AS severity.[15] It has also been shown that the level of NT-proBNP predicts symptom development and the postoperative outcome after AVR.[16] The NT-proBNP level decreases after successful surgical therapy but increases in conservatively treated patients.[17] In our study, the NT-proBNP levels at baseline were much greater in the subgroup of patients who underwent AVR during follow-up, suggesting a correlation between a high NT-proBNP level and the need for AVR. Future research is needed to determine and confirm the diagnostic and prognostic value of NT-proBNP in congenital AS.

Observer variability and suboptimal imaging windows in transthoracic echocardiography can affect reproducibility. We limited this by trained echocardiographers using standardized protocols. Transthoracic echocardiography might not be precise enough to detect small changes, especially in the LV mass and aortic diameters. Cardiac magnetic resonance might be more suitable for those measurements in future trials.

Although a total of 242 patients were assessed for eligibility to enter the PROCAS trial, the inclusion proved very difficult. At the time of inclusion, many negative publications regarding statins had appeared in the Dutch press; consequently, young asymptomatic patients were reluctant to take statin medication. This resulted in inclusion of only 63 patients, although 180 had been anticipated. However, even if the desired number of enrolled patients had been achieved in the PROCAS trial, the follow-up time might not have been sufficient to detect an effect. According to the low-density lipoprotein density-radius theory, a longer period is required to reduce AS progression.[18] Because of the size of the radius, vascular occlusion will respond more quickly to statin therapy than will valve stenosis.[18] However, our institutions' ethical committee limited the follow-up duration to only 3 years. Statin therapy might be more beneficial in patients with mild AS and hypercholesterolemia, as was previously showed in an open-label, prospective study of calcific AS.[19] We were not able to check this hypothesis, because only 5 patients in the PROCAS trial had elevated low-density lipoprotein levels >130 mg/dl. A larger prospective, randomized, controlled trial, including more patients with hypercholesterolemia and mild AS, is necessary to draw firm conclusions about the effect of statin therapy on AS progression in young adult patients with asymptomatic congenital AS. Currently, no evidence is available to support the prescription of statins to prevent the progression of congenital AS.

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