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ORIGINAL RESEARCH ARTICLE

Atorvastatin Effect on Aortic Dilatation and Valvular Calcification Progression in Bicuspid Aortic Valve (BICATOR): A Randomized Clinical Trial

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BACKGROUND: Ascending aorta dilation and aortic valve degeneration are common complications in patients with bicuspid aortic valve. Several retrospective studies have suggested the benefit of statins in reducing these complications. This study aimed to determine whether atorvastatin treatment is effective in reducing the growth of aortic diameters in bicuspid aortic valve and if it slows the progression of valve calcification.

METHODS: In a randomized clinical trial, 220 patients with bicuspid aortic valve (43 women; 46±13 years of age) were included and treated with either 20 mg of atorvastatin per day or placebo for 3 years. Inclusion criteria were ≥18 years of age, nonsevere valvular dysfunction, nonsevere valve calcification, and ascending aorta diameter ≤50 mm. Computed tomography and echocardiography studies were performed at baseline and after 3 years of treatment.

RESULTS: During follow-up, 28 patients (12.7%) discontinued medical treatment (15 on atorvastatin and 13 taking placebo). Thus, 192 patients completed the 36 months of treatment. Low-density lipoprotein cholesterol levels decreased significantly in the atorvastatin group (median [interquartile range], −30 mg/dL [−51.65 to −1.75 mg/dL] versus 6 mg/dL [−4, 22.5 mg/dL]; $P<0.001$). The maximum ascending aorta diameter increased with no differences between groups: 0.65 mm (95% CI, 0.45–0.85) in the atorvastatin group and 0.74 mm (95% CI, 0.45–1.04) in the placebo group ($P=0.613$). Similarly, no significant differences were found for the progression of the aortic valve calcium score ($P=0.167$) or valvular dysfunction.

CONCLUSIONS: Among patients with bicuspid aortic valve without severe valvular dysfunction, atorvastatin treatment was not effective in reducing the progression of ascending aorta dilation and aortic valve calcification during 3 years of treatment despite a significant reduction in low-density lipoprotein cholesterol levels.

REGISTRATION: URL: https://www.clinicaltrialsregister.eu; Unique identifier: 2015-001808-57. URL: https://www.clinicaltrials.gov; Unique identifier: NCT02679261.

Key Words: aortic valve ■ aortic valve insufficiency ■ aortic valve stenosis ■ atorvastatin ■ bicuspid aortic valve disease ■ dilatation

Bicuspid aortic valve (BAV) is the most frequent congenital cardiac malformation and is associated with an increased risk of both aortic valve degeneration and ascending aortic (AscAo) dilation. AscAo dilation is a common complication in patients with BAV.[1] The population-based incidence rate of

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Clinical Perspective

What Is New?

- Among patients with bicuspid aortic valve without severe valvular dysfunction, atorvastatin treatment was not effective in reducing the growth of ascending aorta diameters during 3 years of treatment.
- Among patients with bicuspid aortic valve without severe valvular dysfunction, atorvastatin treatment did not reduce the progression of aortic valve calcification and dysfunction during 3 years of treatment.
- The rate of aortic diameter growth in patients with bicuspid aortic valve and no severe valvular dysfunction measured by contrast-enhanced, ECG-gated computed tomography was 0.23 mm per year, which is lower than most of the previous reports.

What Are the Clinical Implications?

- Several observational studies on patients with aortic stenosis reported lower valve dysfunction progression for patients treated with statins compared with control subjects, but none of these findings were supported in randomized controlled trials.
- Whether statin therapy is effective in reducing ascending aorta growth or aortic valve calcification in relatively young patients with no aortic valve, calcium should be tested in randomized clinical trials.
- The rate of aortic diameter growth in patients with bicuspid aortic valve with no severe valvular dysfunction is low; thus, special care should be taken to quantify the impact of treatment on diameter progression in these patients.

Nonstandard Abbreviations and Acronyms

AR	aortic valve regurgitation
AS	aortic valve stenosis
AscAo	ascending aorta
BAV	bicuspid aortic valve
CT	computed tomography
LDL	low-density lipoprotein

aortic dilatation >45 mm in patients with BAV is >25% at 25 years of follow-up, with >20% of patients requiring surgery for aorta repair.[2] Timely surgical intervention is the basic treatment strategy for aortic dilatation with BAV. It is well established that statins limit the progression of abdominal aortic aneurysms by reducing matrix metalloproteinase expression.[3,4] In addition, retrospective analyses conducted in patients with thoracic aorta aneurysms have shown its potential benefits in reducing aorta enlargement and aorta adverse events.[5–7] Recent American College of Cardiology/American Heart Association guidelines indicate statin therapy as a reasonable option for patients with sporadic and degenerative aortic aneurysm and evidence of atherosclerosis.[8] Furthermore, these guidelines indicate that statin therapy might be considered for patients with thoracic aorta aneurysms and no evidence of atherosclerosis, although the level of evidence is low.[8] In the context of BAV, despite 3 retrospective studies suggesting the benefit of statin treatment to reduce the risk of aortic dilation,[9–11] no prospective studies have been carried out so far.

Progressive aortic valvular dysfunction is a common complication in patients with BAV, which will require aortic valve surgery in >65% of patients over their lifetime,[12] and it is most commonly driven by severe aortic stenosis (AS). BAV predisposes to early aortic valve calcification, which appears ≈2 decades earlier than in tricuspid valves and has been associated with several cardiovascular risk factors.[13] Three randomized clinical trials failed to demonstrate any significant benefit of lowering low-density lipoprotein (LDL) cholesterol with statins on the progression of AS, which was attributed to the advanced degree of valve calcification in participating patients.[14–16] To the best of our knowledge, no study has analyzed the impact of statins on the progression of BAV calcification in its initial stages, which can be accurately quantified by aortic valve calcium score assessed with dedicated computed tomography (CT) imaging.

The aim of this double-blind randomized controlled trial was to determine whether atorvastatin is effective in reducing the progression of AscAo dilation (primary outcome), aortic root dilation, tubular AscAo dilation, aortic valve calcification, and aortic valve dysfunction (secondary outcomes) in patients with BAV without severe valvular dysfunction.

METHODS

Trial Design and Participants

BICATOR (Bicuspid Aortic Valve Atorvastatin Treatment Study) was a double-blind randomized placebo-controlled clinical trial performed at 10 centers in Spain with previous network research experience in BAV. Two hundred twenty patients with BAV were recruited, randomized, and treated with either 20 mg atorvastatin per day or placebo for 3 years. The trial started in 2017 and was successfully completed in 2021, complied with the Declaration of Helsinki, and was approved by the ethics committees of the hospitals. All patients provided written informed consent. The trial was registered in the EU Clinical Trial Registry (No. EudraCT, 2015-001808-57) and ClinicalTrials.gov (NCT02679261). This trial was reported in accordance with the Consolidated Standards of Reporting Trials guidelines.[17]

Materials and Data Availability

The data that support the findings of this study are available from the corresponding authors on reasonable request.

Patients

We included patients >18 years of age with a definitive diagnosis of BAV with less than severe valvular dysfunction (mean aortic valve gradient <30 mm Hg or aortic regurgitation [AR] vena contracta <6 mm) without severe valve calcification[18] and aortic root and tubular AscAo diameters ≤50 mm as measured by transthoracic echocardiography. Exclusion criteria were uncontrolled hypertension; ongoing statin treatment or treatment with other lipid-lowering drugs; previous adverse reaction to iodinated contrast media; desire for pregnancy during the study period; presence or antecedent of cardiac or aortic surgery; aortic dissection; aortic coarctation; transaminase >2-fold the upper normality limit according to the local laboratory, creatinine clearance <30 mL/min, or creatinine >2.5 mg/dL; myopathy or creatine kinase levels >5-fold the upper normality limit; other gastrointestinal, hematological, or endocrine diseases; or any other situation that, according to the investigators' criteria, could affect study treatment evaluation.

Randomization and Masking

Eligible patients were randomly assigned to receive either atorvastatin or placebo. A computer-generated scheme using randomly permuted blocks of 10 was used. A sealed opaque envelope containing information on the type of study medication assigned, and a random allocation number was provided for each patient by the pharmacy department. Containers and both study medications were identical in color and shape. The randomization code was not available to the investigators, thereby ensuring the masking assignment during the 3-year treatment period.

Transthoracic Echocardiography

Transthoracic echocardiography was acquired at baseline and annually thereafter by expert echocardiographers. Valvular dysfunction and AscAo diameters were quantified according to American Society of Echocardiography guidelines[19] and European Association of Cardiovascular Imaging recommendations[20] at each participating center. Peak aortic velocity and mean gradient were evaluated by continuous-wave Doppler in all cases, and vena contracta width was assessed by color Doppler when AR was present. AS was quantified as mild (mean pressure gradient of 10–19.9 mm Hg or peak aortic velocity of 2.5–2.9 m/s), moderate (mean pressure gradient of 20–39.9 mm Hg or peak aortic velocity of 3–3.9 m/s), and severe (mean pressure gradient ≥40 mm Hg or peak aortic velocity ≥4 m/s). AR was quantified as mild when the vena contracta was <3 mm, moderate at 3 to 6 mm, and severe at >6 mm. BAV morphotype was categorized as right (R) and left (L) coronary cusp fusion, right coronary and noncoronary cusp fusion, and left coronary and noncoronary cusp fusion.

Computed Tomography

All centers performed baseline (at inclusion) and follow-up (3 years later) ECG-gated thoracic CT studies consisting of a calcium score scan followed by the administration of iodinated contrast media and a CT angiography. ECG gating was set at 75% to 80% of the R-R interval, and tube voltage was set at 120 kVp. At the discretion of the attending clinician, some centers administered beta-blockade to achieve a resting heart rate of ≤65 bpm. The analysis of aortic valve calcium and aortic diameters was centralized in a core laboratory (Hospital Universitari Vall d´Hebron) and performed with CVI42 software (Circle, Calgary, Canada) by experienced personnel blinded to study drug allocation and clinical and demographic data. The Agatston score was calculated by multiplying the area of selected pixels with an attenuation >130 Hounsfield units by a correction factor, as described by Agatston et al.[21] Maximum aortic diameters were measured on CT angiography at the aortic root and in the tubular segment of the AscAo after multiplanar reconstruction (double oblique method) using inner-to-inner convention at end diastole.[20]

Outcomes

The primary outcome was the maximum progression (ie, absolute change) of the AscAo diameter measured by CT at either the aortic root or tubular segment during the 3 years of treatment. Secondary outcomes were the change in aortic diameter from baseline to follow-up at (1) the aortic root and at (2) the tubular segment of AscAo, (3) the absolute changes in the valvular calcium score determined by CT and the change in aortic valvular dysfunction assessed as (4) peak aortic velocity and (5) regurgitant jet width by transthoracic echocardiography.

Participant Monitoring

Clinical follow-up included specific inquiry into the presence of symptoms and treatment compliance. Blood test analyses for control of total, LDL, and high-density lipoprotein cholesterol levels and surveillance of creatine phosphokinase, glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, and gamma-glutamyl transferase levels to detect side effects of the treatments were performed at 6, 12, 24, and 36 months.

Role of the Funding Source

The trial was funded and sponsored entirely by the Spanish Ministry of Science and Innovation (ICI1400197) and the Spanish Society of Cardiology (SEC/PZA-INV-CLI 20/012), which had no participation in the study design, data collection and analysis, or manuscript writing.

Statistical Analysis

Sample size calculation was based on the primary end point. It was performed with an online calculator (apisal.es). Group size ratio was set to 1, α risk to 0.05, and β risk to 0.2 in a 2-sided 2-independent-means test. Progressive dilatation of the aorta in patients with BAV was estimated at 0.42±0.60 mm per year[22] (1.3 mm in 3 years). The expected difference between the 2 groups was estimated to be 0.25 mm per year (0.75 mm in 3 years).[5] The sample size necessary to detect these changes with a statistical power of 80% and a type I risk of 0.05 was estimated at 91 patients per arm. Assuming losses or withdrawals of ≈15% throughout the study, the estimated necessary size would be ≈110 patients in each treatment arm.

Eligible patients were randomized in a 1:1 fashion to receive either 20 mg of atorvastatin or a placebo daily. The patients, treating physicians, and investigators were blinded to the treatment assignment.

Continuous variables are expressed as median (first–third interquartile [interquartile range]). Statistical significance was

considered at $P \leq 0.05$ (2-sided). The prespecified comparison of continuous outcomes was made by the Student *t* test. When normality was not assumed, nonparametric analyses were performed instead. Categorical variables are expressed as percentages.

Modified intention-to-treat analyses including all patients who had both basal and final imaging studies were performed for both primary and secondary outcomes. In addition, 2 sensitivity analyses for the primary outcome were performed including all randomized patients. In the first, missing data for the primary outcome were imputed as per mean outcome in each treatment arm, and a Student *t* test was performed. In the second, missing data for the final maximum aortic diameter were imputed using baseline maximum aortic diameter and mean observed change in diameter in each treatment arm, and a generalized linear mixed-effect model was used to assess the main effect of the treatment.

In addition, for nonprespecified subgroup analyses, a generalized linear mixed-effect model was used to assess the main effect, including the treatment group as a main factor and considering the interaction of the different subgroups. All statistical analyses were conducted with Stata version 15.1 (StataCorp); boxplots were built with Matlab 2022b (MathWorks).

RESULTS

Two hundred twenty patients 46±13 years of age, 43 (19.5%) of whom were women, were enrolled in the study; 110 were randomly assigned to receive atorvastatin and 110 to receive placebo. Demographic and clinical characteristics of the enrolled patients are shown in Table S1. During follow-up, 28 patients (12.7%) discontinued medical treatment and left the study. Among them, 15 had received atorvastatin and discontinued in the context of myalgia (6), tendinitis (4), surgical treatment (3), and noncompliance (2). Thirteen discontinued the placebo in the context of joint pain (5), noncompliance (3), significant hypercholesterolemia requiring treatment (3), and surgical treatment (2). Thus, 192 patients completed the 36 months of treatment (95 with atorvastatin and 97 with placebo) and could be evaluated for the primary outcome (Figure 1).

Baseline demographic, clinical, and imaging data for the 192 patients who completed the protocol treatment are shown in Table 1. Most patients (78%) had an R-L BAV, and a raphe (82%) was visible by echocardiography. Mild or moderate AS was diagnosed in 22% of patients, and mild or moderate AR was present in 49%. Notably, aortic valve calcium by CT was absent in 55% of the cohort. Baseline calcium score, aortic root diameter, and tubular AscAo diameter were similar in both treatment groups.

After 36 months of treatment, total and LDL cholesterol levels decreased significantly in the atorvastatin compared with the placebo group (median [interquartile range], −30.5 mg/dL [−53.5 to −1 mg/dL] versus 11 mg/dL [−4.25 to 22.5 mg/dL]; $P<0.001$; and −30 mg/dL [−51.65 to −1.75 mg/dL] versus 6 mg/dL [−4 to 22.5 mg/dL]; $P<0.001$, respectively; Figure 2). Conversely, no differences were found in high-density lipoprotein cholesterol (0 mg/dL [−5 to 6 mg/dL] versus 0.35 mg/dL [−3 to 6 mg/dL]; $P=0.550$) or triglyceride levels (1 mg/dL [−17.75 to 24.25 mg/dL] versus 0 mg/dL [−16.25 to 20.5 mg/dL]; $P=0.344$).

Primary Outcome

There was no difference in maximum AscAo diameter absolute increase after 36 months of atorvastatin compared with placebo treatments: 0.65 mm (0.45–0.85 mm) versus 0.74 mm (0.45–1.04 mm), respectively ($P=0.613$; Table 2). No difference in maximum AscAo diameter absolute increase after 36 months of atorvastatin compared with placebo treatments was obtained in the first (0.65 mm [0.48–0.82 mm] versus 0.74 mm [0.49–1.00 mm], respectively; $P=0.553$) and second (0.65 mm [0.43–0.88 mm] versus 0.74 mm [0.52-0.97 mm], respectively; $P=0.577$) sensitivity analyses.

Secondary Outcomes

There were no differences between atorvastatin and placebo in the absolute increase in aortic root diameters (0.45 mm [0.25–0.64 mm] versus 0.50 mm [0.33–0.68 mm]; $P=0.685$) or tubular segment AscAo diameters (0.71 mm [0.52–0.90 mm] versus 1.00 mm [0.76–1.24 mm]; $P=0.061$) during the study period (Table 2; Figure 3). Furthermore, the intervention had no impact on the aortic valve calcium score changes (278.2 Agatston units [155.0–401.3 Agatston units] versus 173.7 Agatston units [87.0–260.4 Agatston units]; $P=0.167$) or AS and AR progression as measured by peak velocity (17.2 cm/s [10.4–24.1 cm/s] versus 19.3 cm/s [12.7–25.9 cm/s]; $P=0.659$) or regurgitant vena contracta (0.19 mm [−0.01 to 0.40 mm] versus 0.27 mm [0.11–0.44 mm]; $P=0.547$) changes from baseline to follow-up. Semiquantitative severity progression of AS and AR was similar between the atorvastatin and placebo groups: 8 (8.5%) versus 9 (9.5%) and 26 (29.5%) versus 22 (23.7%; $P=0.817$ and 0.370, respectively).

Nonprespecified Subgroup Analyses

There were no differences in any end point with respect to sex and the presence or absence of raphe (Figure 4; Figures S1 and S2). Patients <45 years of age in the atorvastatin arm presented a tendency for lower tubular AscAo diameter enlargement compared with patients in the placebo arm (0.72 mm [0.42–1.02 mm] versus 1.31 mm [0.91–1.71 mm]; Figure S2; Table S2), without statistical significance for the interaction effect ($P=0.06$). Similarly, patients with a basal calcium score of 0 in the atorvastatin arm presented a tendency for lower tubular AscAo diameter enlargement compared with those in the

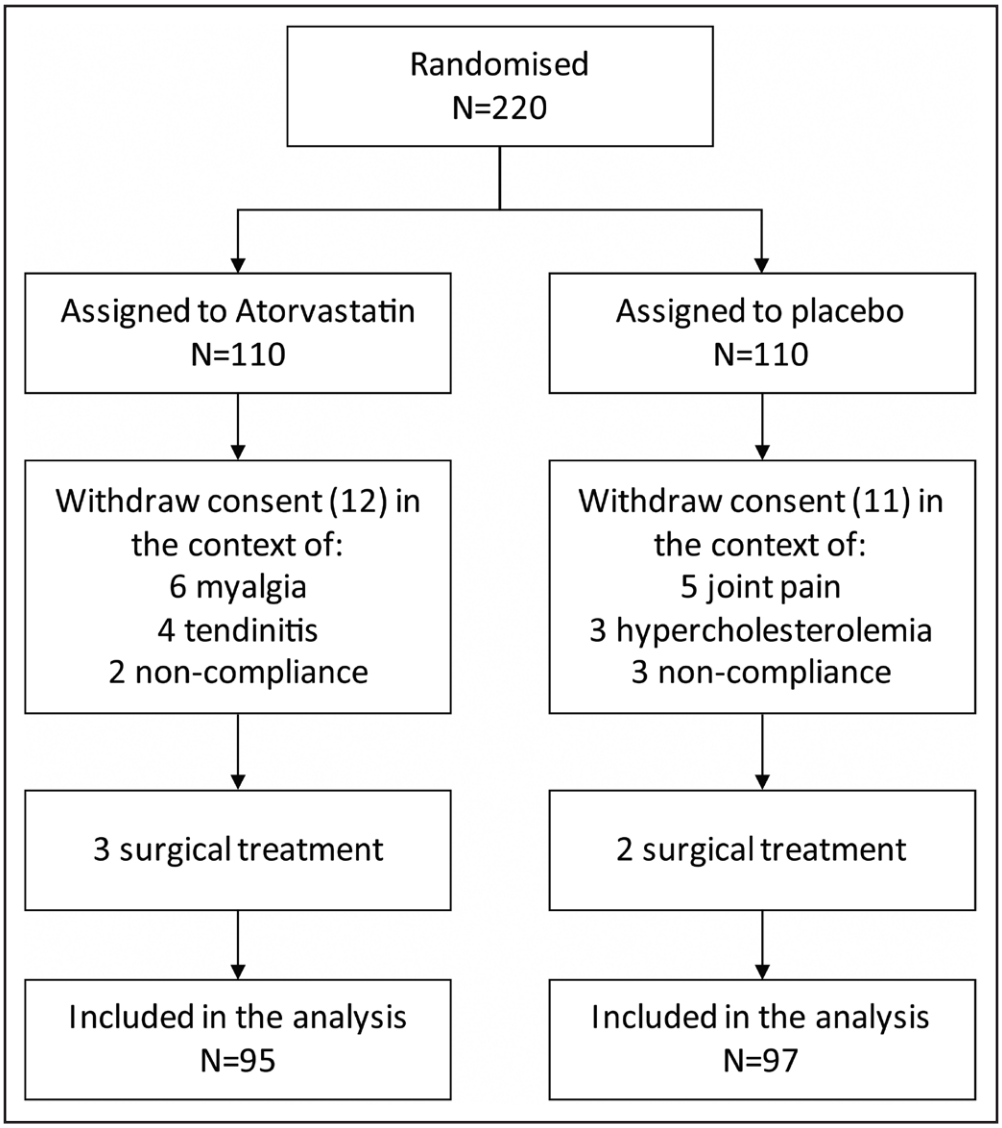

Figure 1. Flow diagram for inclusion and follow-up of patients.

placebo arm (0.66 mm [0.40–0.93 mm] versus 1.17 mm [0.83–1.51 mm]; Figure S2; Table S3), but the interaction term was not significant (P=0.09). Furthermore, patients with a baseline calcium score of 0, but not those with a baseline calcium score >0, had a tendency for smaller calcium score increase under atorvastatin treatment compared with placebo (1.2 [−0.3 to 2.6] versus 27.1 [6.7–47.4] and 610.2 [385.6–834.8] versus 409.6 [216.7–602.5], respectively: $P_{interaction}$=0.055). In particular, after 36 months of treatment, 47 patients (95.5%) in the atorvastatin group compared with 44 (80%) in the placebo group retained a calcium score of 0 (Figure 5; Table S3).

DISCUSSION

This is a double-blind randomized controlled trial comparing the effect of 20 mg of atorvastatin per day with placebo in patients with nonadvanced BAV dysfunction. Despite a significant reduction in total and LDL cholesterol levels in the atorvastatin-treated arm, no significant differences were found in the changes in AscAo diameter and aortic valve calcification during the 3-year study.

Accumulating evidence suggests that AscAo dilation in patients with BAV is related to hemodynamic, genetic, and clinical factors.[1] In this sense, aortic enlargement has been associated with age, sex, hypertension, aortic valve morphotype, valvular dysfunction severity, and AscAo wall shear stress.[23–26] From a mechanistic point of view, intrinsic aortic media abnormalities, including accelerated smooth muscle cell apoptosis, elastic fiber degeneration, increased stiffness, and increased matrix metalloproteinase expression, have been reported in the dilated aorta of patients with BAV.[23,27]

To the best of our knowledge, this is the first prospective randomized study analyzing the benefit of

Table 1. Baseline Characteristics of Randomized Patients Who Completed the Follow-Up According to Treatment Group

	Atorvastatin	Placebo	Total
n	95	97	192
Age, y	45 (39–55)	46 (37–55)	46 (38–55)
Men, n (%)	77 (81.1)	76 (78.4)	153 (79.7)
Height, cm	173 (166–180)	174 (165–178)	173 (166–178)
Weight (kg)	75 (67–85)	78 (71–84)	76 (69–85)
BSA, m^2	1.9 (1.8–2.0)	1.9 (1.8–2.0)	1.9 (1.8–2.0)
Smoking, n (%)	13 (13.7)	9 (9.3)	22(11.5)
Hypertension, n (%)	20 (21.1)	27 (27.8)	47 (24.5)
Atherosclerosis, n (%)	6 (6.3)	2 (2.1)	8 (4.2)
Total cholesterol, mg/dL	190 (171–210)	189 (171–207)	189 (171–208)
LDL, mg/dL	117 (99–134)	117 (98–136)	117 (99–135)
HDL, mg/dL	54 (46–62)	52 (45–62)	53 (45–62)
Triglycerides, mg/dL	83 (59–107)	78 (62–119)	79 (60–112)
Echocardiography			
BAV morphotype, n (%)			
BAV R-L	72 (75.8)	79 (81.4)	151 (78.6)
BAV R-N	21 (22.1)	15 (15.5)	36 (18.8)
BAV L-N	2 (2.1)	2 (2.1)	4 (2.1)
Raphe	78 (82.1)	79 (81.4)	157 (81.8)
AS, n (%)			
None	70 (73.7)	77 (79.4)	147 (76.6)
Mild	19 (17.9)	17 (17.5)	36 (17.7)
Moderate	6 (6.3)	3 (3.1)	9 (4.7)
Vmax, cm/s	174 (135–216)	160 (135–200)	166 (135–210)
AR			
None	47 (49.5)	51 (52.6)	98 (51.0)
Mild	34 (35.8)	33 (34.0)	67 (34.9)
Moderate	14 (14.7)	13 (13.4)	27 (14.1)
Vena contracta, mm	2 (0–3)	2 (0–3)	2 (0–3)
Computed tomography			
AscAo size, mm			
Max AscAo diameter	40 (37–44)	41 (37–44)	41 (37–44)
Root diameter	38 (36–41)	38 (36–41)	38 (36–41)
Tubular AscAo diameter	39 (36–43)	39 (34–43)	39 (35–43)
Valve calcium score, AU	0 (0–328)	0 (0–328)	0 (0–328)
Calcium score=0, n (%)	50 (52.6)	55 (56.7)	105 (54.7)
Calcium score >0, n (%)	45 (47.4)	42 (43.3)	87 (45.3)

Values are number (percentage) for dichotomic variables and median (interquartile range) for continuous variables.

AR indicates aortic regurgitation; AS, aortic stenosis; AscAo, ascending aorta; AU, Agatston unit; BAV, bicuspid aortic valve; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and Max AscAo, maximum diameter including root and tubular segments.

atorvastatin in patients with BAV. Statin treatment is known to limit the growth rate of abdominal aneurysms, lowering the risk of aneurysm rupture and dissection.[3] This benefit was thought to reflect the pleiotropic effect of statins, which may modify the inflammatory milieu of aneurysmal tissue by reducing the production of matrix metalloproteinases, rather than any direct effect of lowering lipid levels.[4] Other observational studies reported the benefits of statin treatment[5–7] in the reduction of aorta enlargement and adverse events in thoracic aortic aneurysms.[9,10] Angeloni et al,[5] in a large propensity score–matched cohort study on AscAo aneurysm,

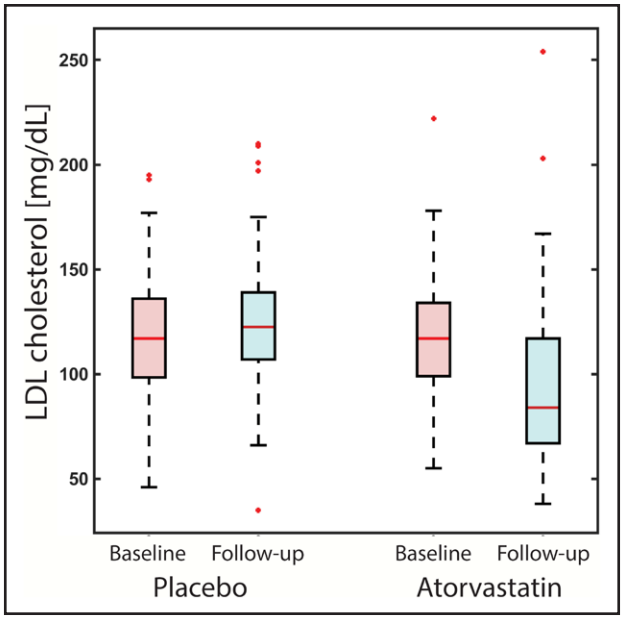

Figure 2. Changes in LDL cholesterol levels after 3 years of treatment.
LDL indicates low-density lipoprotein.

showed a significantly smaller AscAo dilation rate in statin users compared with nonusers, which resulted in improved complication-free survival. In that study, statin therapy was escalated to reach a therapeutic goal of <100 mg/dL LDL cholesterol during a period of 3 years. In terms of AscAo dilation in patients with BAV, very limited data are available. Two studies retrospectively analyzed the impact of atorvastatin treatment on AscAo size in patients with BAV, showing an association between statin use and lower aortic diameter[9,11] but no differences in growth rates.[9] In all of these retrospective studies,[5–11] indications for statin therapy and dose were not reported. Therefore, considering the low cardiovascular risk expected from inclusion and exclusion criteria, a relatively low-dose statin was indicated in the treatment arm.

In contrast to previous echocardiographic studies, ECG-gated CT angiograms, the most accurate method to identify changes in aortic diameters, were used in the present study. No differences in aortic root or tubular AscAo growth rates between groups were identified. However, in subgroups analyses, we identified a potential reduction of the tubular AscAo diameter growth rate in younger patients (<45 years of age) and in patients with a valve calcium score of 0 treated with atorvastatin compared with placebo. Given the nonprespecified nature of subgroup analyses and considering that the *P* values for the interaction did not met the statistical significance threshold, these results should be considered hypothesis generating and should be confirmed in new prospective studies.

Progressive aortic valve calcification is a common complication of BAV. Calcific valve changes can develop early in life. Hope et al[28] demonstrated that aortic valvular calcification may be present 14 years earlier in patients with BAV than in those with a tricuspid aortic valve. Histologically, calcified regions of aortic valves have features such as the presence of lipids, inflammatory cells, and neoangiogenesis.[29] Furthermore, patients with dyslipidemia are at increased risk of developing BAV stenosis.[13] In addition to lowering LDL cholesterol, statins have a powerful anti-inflammatory action, which may limit the extent of aortic valve calcification, critical to the development of BAV stenosis. Several observational studies in patients with AS reported lower valve dysfunction progression in patients treated with statins compared with control subjects.[30,31] However, none of these findings were supported in randomized controlled trials.[14–16] The PROCAS trial (Effects of Rosuvastatin on Progression of Stenosis in Adult Patients With Congenital Aortic Stenosis) did not find any benefits of rosuvastatin in moderate to severe congenital AS.[32] These findings were in line with those of the BAV patient subgroup of the ASTRONOMER trial (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin).[16] Furthermore, a secondary analysis of the SEAS trial (Simvastatin and Ezetimibe in Aortic Stenosis) correlated treatment with slower disease progression only in patients with a mildly calcified valve in AS and high pretreatment LDL cholesterol levels (LDL >150 mg/dL).[33] In our study, up to 56% of patients had no valve calcification (ie, Agatston score of 0), and up to 32% had a calcium score of <800 Agatston units.

Table 2. Change in Aortic Diameters and Aortic Valve Calcification During Follow-Up

	Atorvastatin (n=95)	Placebo (n=97)	Differences atorvastatin vs placebo	*P* value
Max AscAo diameter change, mm	0.45, 0.65 (0.45 to 0.85)	0.59, 0.74 (0.45 to 1.04)	−0.09 (−0.45 to 0.26)	0.613
Root diameter change, mm	0.42, 0.45 (0.25 to 0.64)	0.40, 0.50 (0.33 to 0.68)	−0.05 (−0.31 to 0.21)	0.685
Tubular AscAo diameter change, mm	0.51, 0.71 (0.52 to 0.90)	0.77, 1.00 (0.76 to 1.24)	−0.29 (−0.59 to 0.15)	0.061
Valve calcium score change, AU	0.0, 278.2 (155.0 to 401.3)	0.0, 173.7 (87.0 to 260.4)	104.4 (−44.1 to 253.0)	0.167
Peak AscAo velocity change, cm/s	8.0, 17.2 (10.4 to 24.1)	10.0, 19.3 (12.7 to 25.9)	−2.1 (−11.6 to7.3)	0.659
Regurgitant vena contracta change, mm	0.00, 0.19 (−0.01 to 0.40)	0.00, 0.27 (0.11 to 0.44)	0.08 (−0.34 to 0.18)	0.547

Values are median, mean (CI=95% of the mean). Each outcome is presented as a line; columns show the median, mean, and 95% CI of the mean for each treatment arm and their differences.
AscAo indicates ascending aorta; AU, Agatston unit; and Max AscAo, maximum diameter including root and tubular segments.

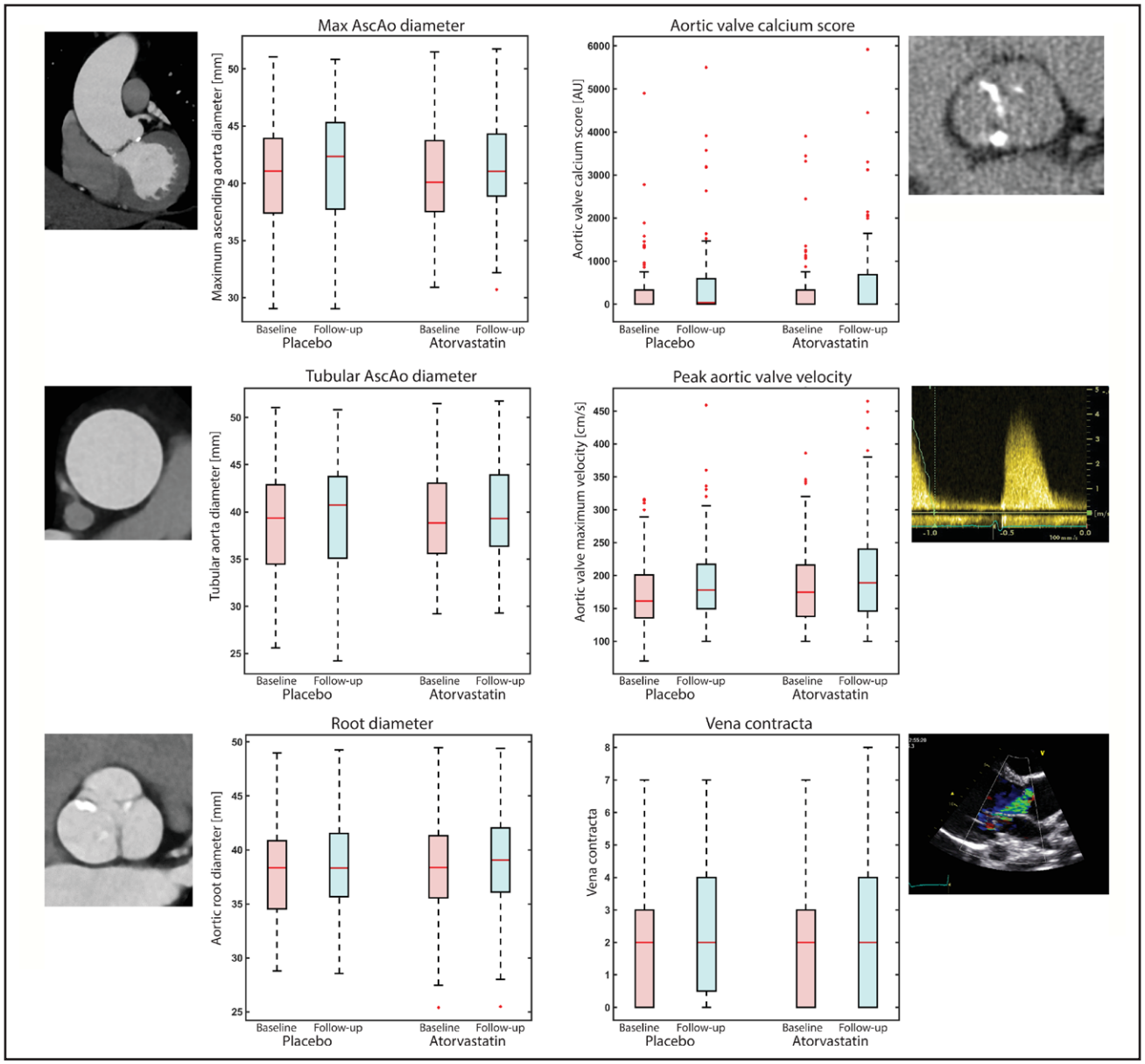

Figure 3. Progression of maximum ascending aorta, aortic root and tubular segment diameters, calcification of aortic valve, and valvular dysfunction after 3 years of atorvastatin vs placebo treatments.
AU indicates Agatston units.

Despite that, atorvastatin treatment did not significantly reduce progressive valve calcification. However, when we analyzed only the subgroup of patients with a baseline valve calcium score of 0, atorvastatin-treated patients showed a tendency for lower calcium score at the final study compared with those treated with placebo. This resulted in 95% of atorvastatin-treated patients retaining a calcium score of 0 after 3 years of treatment compared with 80% of patients treated with placebo. Furthermore, in patients with a basal score >0, there were no differences in valve calcium score increase between groups. Given the nonprespecified nature of subgroup analyses and the nonsignificant $P_{interaction}$ value (P=0.055), further studies are required to support these results. In this sense, several studies have suggested that statin-mediated atheroma calcification may enhance plaque stability,[34,35] and it is unknown whether statins may exhibit a procalcific effect on the valvular structures. The results of this study showed only a trend of increasing the valve calcium score in the atorvastatin. Therefore, the results may support the hypothesis that the efficacy of statins in BAV might depend on the stage of aortic valve calcification.

Limitations

This study has several limitations that deserve consideration. First, 3 years of treatment may have been

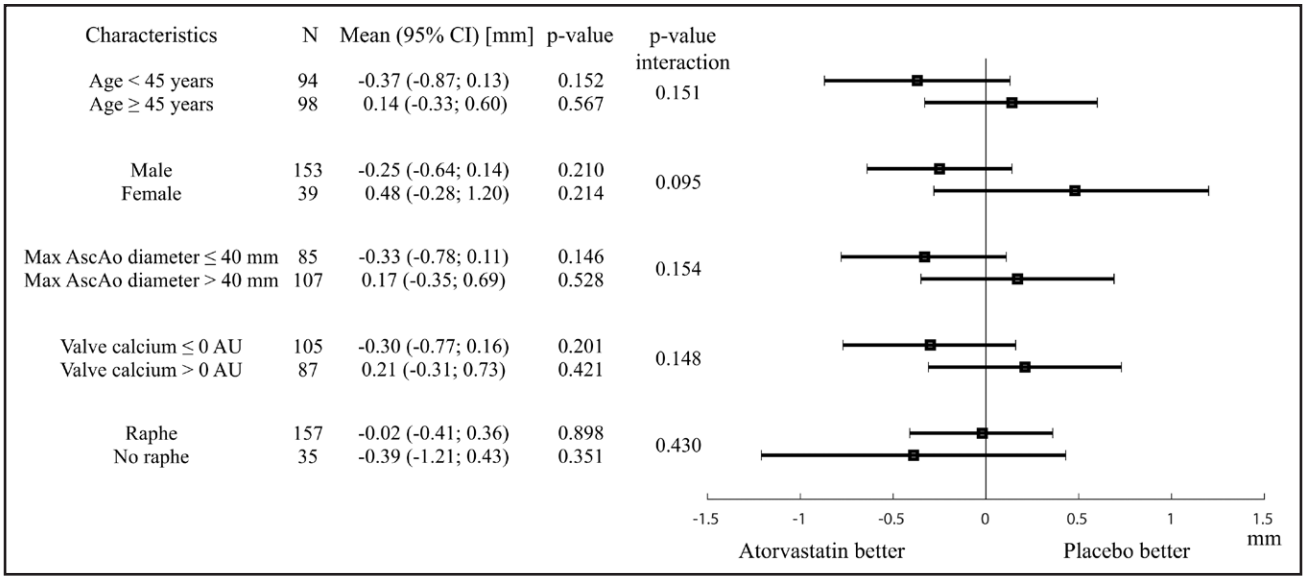

Figure 4. Effect of atorvastatin on the differences in maximum AscAO diameter growth (in millimeters) during follow-up in subgroups of patients with BAV.
Right, Mean differences (in millimeters) after 3 years of treatment are indicated by solid squares; horizontal lines represent 95% CIs. AscAO indicates ascending aorta; and AU, Agatston units.

insufficient to influence the natural history of the disease to ascertain whether atorvastatin has a beneficial effect on dilation and aortic valve calcification in patients with BAV. Nevertheless, we used CT, which is the gold standard method with excellent reproducibility, for measuring aortic valve calcification and AscAo diameter, particularly in the tubular segment of the AscAo,[36] and core laboratory analysis. The second shortcoming of the study is that it might lack statistical power to definitively rule out the potential benefit of atorvastatin in the reduction of AscAo enlargement in patients with BAV. From information from previous studies obtained

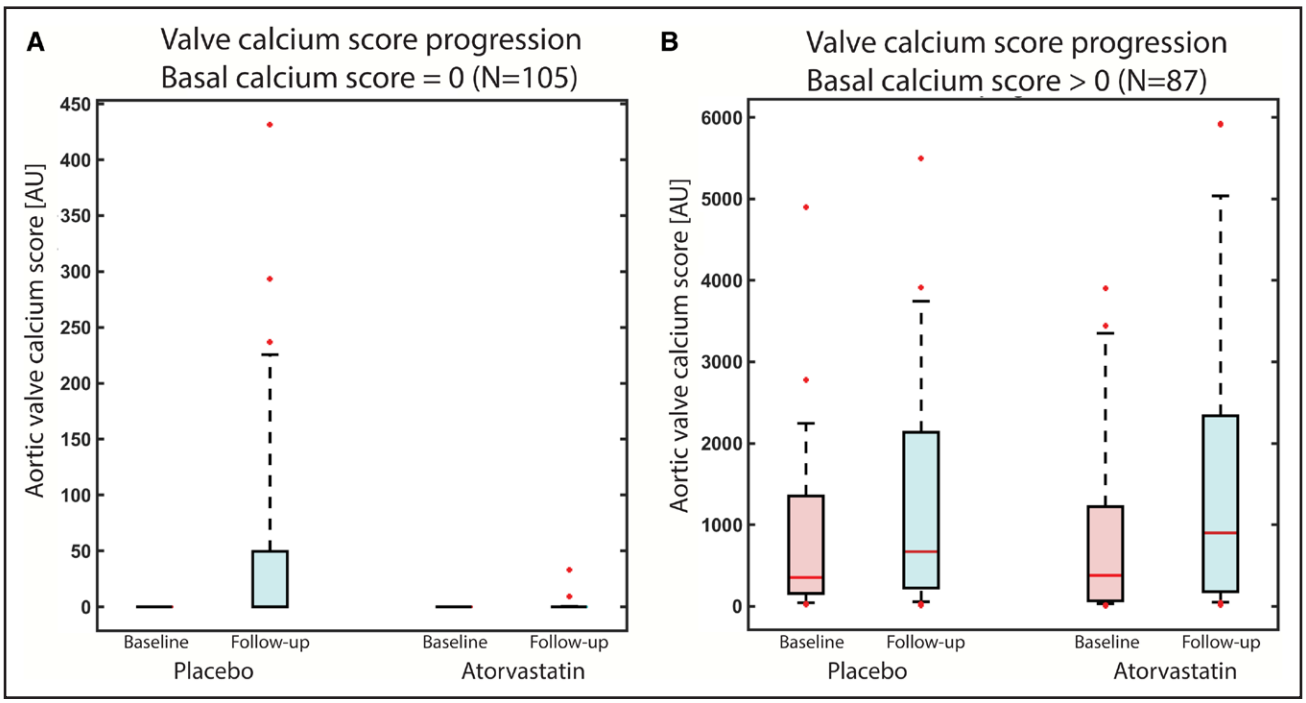

Figure 5. Changes in valve calcium score according to treatment groups in patients with a BAV with a baseline calcium score of 0 (A) and >0 (B).
Note that box limits are located at the 10th and 90th percentiles of the distribution; whisker limits are at the 5th and 95th percentiles of the distribution. AU indicates Agatston units.

by 2-dimensional echocardiography, AscAo diameter enlargement was considered to be 0.42 mm per year, whereas the actual growth rate in our trial was only 0.23 mm per year. Several recent studies using CT or magnetic resonance imaging reported significantly different annual growth rates of AscAo diameters, ranging from 0.24 mm per year[26,37] to 2 mm per year.[38] These discrepancies could be related to basal aortic diameters and the presence of other risk factors such as age, hypertension, and degree of valvular disease.[1] In any case, the absence of significant effects after 3 years of treatment in nearly 100 patients may question the real impact of statin treatment in patients with BAV with mild to moderate disease progression. The third limitation is the relatively low dose of atorvastatin (20 mg/d). However, several studies did not find any different results associated with statin doses.[39] We assessed valve calcium score progression by CT to analyze the atorvastatin benefit in aortic valve calcification in addition to valvular dysfunction severity by Doppler echocardiography. New parameters such as valve fibrosis may improve the assessment of valvular degeneration. Recent study data provide further evidence of the contribution of higher lipoprotein(a) levels to the degree of aortic valve calcification and the development of AS,[40] which may lead to new treatment strategy evaluation.[41] Furthermore, the analysis of progression of AS and regurgitation by echocardiography was not centralized in a core laboratory analysis, whereas the limited prevalence of atherosclerosis impedes an analysis of possible modulation. Finally, patients with severe valvular dysfunction and calcification were excluded from this trial. Therefore, the effect of atorvastatin on this initial stage of valvular degeneration should not be extrapolated to more advanced stages.

Conclusions

For patients with BAV with no significant valvular dysfunction, atorvastatin treatment is ineffective in reducing the progression of AscAo dilation during 3 years of treatment, despite significant reductions in LDL cholesterol levels. Moreover, no effect on aortic valve calcification or valvular dysfunction was observed. This study reinforces the need for a long-term, large-scale, randomized controlled trial of lipid-lowering therapy for patients with BAV, particularly for those with early, mild disease.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3

Figures S1 and S2

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