Outcome of Patients With Low-Gradient "Severe" Aortic Stenosis and Preserved Ejection Fraction

Nikolaus Jander, MD*; Jan Minners, MD, PhD*; Ingar Holme, PhD; Eva Gerdts, MD, PhD; Kurt Boman, MD, PhD; Philippe Brudi, MD; John B. Chambers, MD; Kenneth Egstrup, MD, PhD; Y. Antero Kesäniemi, MD, PhD; William Malbecq, PhD; Christoph A. Nienaber, MD; Simon Ray, MD; Anne Rossebø, MD; Terje R. Pedersen, MD, PhD; Terje Skjærpe, MD, PhD; Ronnie Willenheimer, MD, PhD; Kristian Wachtell, MD, PhD; Franz-Josef Neumann, MD; Christa Gohlke-Bärwolf, MD

Background—Retrospective studies have suggested that patients with a low transvalvular gradient in the presence of an aortic valve area <1.0 cm^2 and normal ejection fraction may represent a subgroup with an advanced stage of aortic valve disease, reduced stroke volume, and poor prognosis requiring early surgery. We therefore evaluated the outcome of patients with low-gradient "severe" stenosis (defined as aortic valve area <1.0 cm^2 and mean gradient $\leq$40 mm Hg) in the prospective Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study.

Methods and Results—Outcome in patients with low-gradient "severe" aortic stenosis was compared with outcome in patients with moderate stenosis (aortic valve area 1.0 to 1.5 cm^2; mean gradient 25 to 40 mm Hg). The primary end point of aortic valve events included death from cardiovascular causes, aortic valve replacement, and heart failure due to aortic stenosis. Secondary end points were major cardiovascular events and cardiovascular death. In 1525 asymptomatic patients (mean age, 67$\pm$10 years; ejection fraction, $\geq$55%), baseline echocardiography revealed low-gradient severe stenosis in 435 patients (29%) and moderate stenosis in 184 (12%). Left ventricular mass was lower in patients with low-gradient severe stenosis than in those with moderate stenosis (182$\pm$64 versus 212$\pm$68 g; $P<0.01$). During 46 months of follow-up, aortic valve events occurred in 48.5% versus 44.6%, respectively ($P=0.37$; major cardiovascular events, 50.9% versus 48.5%, $P=0.58$; cardiovascular death, 7.8% versus 4.9%, $P=0.19$). Low-gradient severe stenosis patients with reduced stroke volume index ($\leq$35 mL/m^2; n=223) had aortic valve events comparable to those in patients with normal stroke volume index (46.2% versus 50.9%; $P=0.53$).

Conclusions—Patients with low-gradient "severe" aortic stenosis and normal ejection fraction have an outcome similar to that in patients with moderate stenosis. **(*Circulation*. 2011;123:887-895.)**

Key Words: aortic valve stenosis ■ echocardiography ■ outcome ■ stroke volume

In up to 30% of patients sent for echocardiographic evaluation of the severity of aortic stenosis, the clinician will be confronted with a discrepancy in echocardiographic parameters indicating severe stenosis based on aortic valve area but nonsevere stenosis based on mean pressure gradient despite a normal ejection fraction.[1] Recent retrospective studies have suggested that such a low transvalvular gradient in the presence of a calculated aortic valve area <1.0 cm^2 and preserved ejection fraction may be due to reduced stroke volume and that patients with this constellation represent a subgroup with advanced stage of severe aortic valve disease with impaired ventricular function and poor prognosis requiring early valve surgery.[2–5]

Editorial see p 838
Clinical Perspective on p 895

Evaluation and grading of aortic valve stenosis with 2-dimensional and Doppler echocardiography play key roles in the management and assessment of prognosis of patients with

Received August 17, 2010; accepted December 20, 2010.

From the Herz-Zentrum Bad Krozingen, Bad Krozingen, Germany (N.J., J.M., F.N., C.G.-B.); Oslo University Hospital, Ullevål Centre of Preventive Medicine, Oslo, Norway (I.H.); Institute of Medicine, University of Bergen, Haukeland University Hospital, Bergen, Norway (E.G.); Department of Medicine, Skellefteå, Institution of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden (K.B.); Merck/Schering-Plough Pharmaceuticals, Inc, Whitehouse Station, NJ (P.B.); Cardiothoracic Centre, Guys-St Thomas Hospital Trust, London, UK (J.B.C.); Department of Medicine, Svendborg Hospital, Svendborg, Denmark (K.E.); Department of Internal Medicine and Biocenter Oulu, University of Oulu, Finland (Y.A.K.); MSD Europe, Inc, Brussels, Belgium (W.M.); Medizinische Klinik I, Universitätsklinikum Rostock, Germany (C.A.N.); Department of Cardiology, University Hospitals of South Manchester, South Manchester, UK (S.R.); Division of Cardiology, Oslo University Hospital, Aker, Norway (A.R.); University of Oslo, Ullevål, Centre of Preventive Medicine, Oslo, Norway (T.R.P.); Section of Cardiology, St Olav's Hospital, Trondheim, Norway (T.S.); Heart Health Group and Lund University, Malmö, Sweden (R.W.); and Department of Cardiology, Rigshospitalet, Copenhagen, Denmark (K.W.).

*Drs Jander and Minners contributed equally to this work.

Correspondence to Nikolaus Jander, MD, Herz-Zentrum Bad Krozingen, Suedring 15, 79189 Bad Krozingen, Germany. nikolaus.jander@herzzentrum.de

Circulation **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.110.983510**

aortic stenosis.[6–11] Precise echocardiographic grading is of particular importance in patients presenting with dyspnea suffering from comorbidities such as chronic obstructive pulmonary disease, hypertension, or obesity, in which the relation between aortic stenosis and symptoms remains unclear. Current American and European guidelines both recommend an aortic valve area partition value of <1.0 cm^2 or, indexed by body surface area, <0.6 cm^2/m^2 for severe aortic stenosis.[10,12] Corresponding values for peak transvalvular flow velocity are 4 m/s and for mean pressure gradient >40 mm Hg in the presence of a "normal" cardiac output.[12] Moderate stenosis is characterized by an aortic valve area between 1.0 and 1.5 cm^2 and a mean pressure gradient between 25 and 40 mm Hg.

In the present study, we investigated the prognostic impact and progression rate of low-gradient "severe" aortic valve stenosis in the prospective, randomized, multicenter Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial.[13,14]

Patients and Methods

Patients

The SEAS study enrolled 1873 patients with asymptomatic aortic stenosis, defined by echocardiography at local study centers as aortic valve thickening and peak transaortic Doppler velocity ≥ 2.5 and ≤ 4.0 m/s. Patients were randomized from January 2001 to February 2004 to at least 4-year placebo-controlled combined treatment with ezetimibe 10 mg/d and simvastatin 40 mg/d. Patients with coronary heart disease, heart failure, diabetes mellitus, history of stroke or peripheral vascular disease, clinically significant mitral valve disease, severe or predominant aortic regurgitation, rheumatic valvular disease, aortic valve prosthesis, or renal insufficiency and patients already on lipid-lowering therapy or having an indication for lipid lowering according to guidelines were excluded. The SEAS study was approved by regional ethics committees in all participating countries, and all patients gave written informed consent. In the individual patient, the decision to proceed to valve replacement was made by the treating physician according to the recommendations in current guidelines. Design of and results from the SEAS study have been published recently,[13,14] showing no difference in major cardiovascular events between the treatment and placebo groups but a significant reduction in ischemic events in patients treated with ezetimibe/simvastatin.

Echocardiography

Baseline echocardiograms were obtained with the use of echocardiographs with second harmonic imaging and following a standardized protocol in all participating hospitals.[13] All echocardiograms were sent for central interpretation at the SEAS echocardiography core laboratory at Haukeland University Hospital, Bergen, Norway. Subaortic and transaortic blood flow velocities and gradients were derived from velocity time integrals, measured by pulsed-wave Doppler in the left ventricular outflow tract (LVOT) near the aortic valve and by continuous-wave Doppler from different (including right parasternal and suprasternal) windows by imaging and nonimaging transducers, respectively. The highest transaortic velocity was used for tracing of the time-velocity integral. Aortic valve annulus was measured at end-diastole in the 2-dimensional parasternal long-axis view by an inner-edge-to-inner-edge method.[15] The effective aortic valve area was calculated with the continuity equation.[11] Stroke volume was calculated as the product of velocity time integral of subvalvular flow velocity and aortic annulus area. A detailed description of the echocardiographic protocol has been published previously.[16]

Definition of Severity of Aortic Valve Stenosis

Adhering to the partition values shown in current American guidelines,[12] we defined 2 types of aortic stenosis: low-gradient "severe" aortic stenosis characterized by a discrepancy in echocardiographic parameters indicating severe stenosis based on aortic valve area but nonsevere stenosis based on mean pressure gradient (aortic valve area <1.0 cm^2; mean pressure gradient ≤ 40 mm Hg)[1] and moderate aortic valve stenosis fulfilling both criteria for moderate stenosis (aortic valve area 1.0 to 1.5 cm^2; mean pressure gradient 25 to 40 mm Hg).

End Points

The primary end point of the present study was aortic valve events (defined as aortic valve replacement, congestive heart failure due to aortic stenosis, or death from cardiovascular causes). Secondary end points included major cardiovascular events (a composite of death from cardiovascular causes, aortic valve replacement, congestive heart failure as a result of progression of aortic valve stenosis, nonfatal myocardial infarction, hospitalization for unstable angina, coronary artery bypass grafting, percutaneous coronary intervention, or nonhemorrhagic stroke) and ischemic events (defined as death from cardiovascular causes, nonfatal myocardial infarction, hospitalization for unstable angina, coronary artery bypass grafting, percutaneous coronary intervention, or nonhemorrhagic stroke). Finally, rates of cardiovascular death were analyzed separately. All end points were adjudicated with a predefined end point protocol by an end point committee blinded for the original study conduct and results.

Outcome

Outcome over the entire follow-up as indicated by the primary and secondary end points was compared between patients with low-gradient "severe" aortic stenosis and patients with moderate stenosis on baseline echocardiography. We also analyzed outcome at the end of the first year of follow-up separately because the assignment of a given stenosis to a particular category (low-gradient "severe" aortic stenosis versus moderate stenosis versus severe stenosis) may change over time because of the progressive nature of the disease, and yearly echocardiographic assessment is recommended in current guidelines.[12] Because low stroke volume has been proposed to represent an important reason for a low transvalvular gradient in the presence of a normal ejection fraction, and low stroke volume index has indicated a worse prognosis in a recent study,[3] we also evaluated outcome in patients with low-gradient "severe" aortic stenosis according to stroke volume index. A reduced stroke volume index was defined as ≤ 35 mL/m^2 and a normal stroke volume index as >35 mL/m^2. Finally, outcome was compared between patients with and without valve replacement because a negative impact of low-gradient "severe" aortic stenosis could have been masked by the inclusion of valve replacements in the primary end point.

Statistical Analysis

Data are presented as mean±SD or as counts or proportions (%). Categorical data were compared with the use of Fisher exact test when expected cell values were <5. The Yates correction factor was applied to comparisons of groups with small numbers. Continuous data were compared with Student *t* test, irrespective of multiple testing procedures. To account for different follow-up lengths, annualized rates were calculated by dividing the total event rates by length of follow-up. The Kaplan-Meier method was used to assess event-free survival with differences checked by means of the log-rank test. Cox proportional hazards models including the variables age, gender, smoking status, heart rate, and hypertension were calculated for estimating hazard ratio (HR) for event-free survival. Although aortic valve events, major cardiovascular events, and cardiovascular death were found not to be different in the treatment versus the placebo group in the main SEAS study, the variable randomized treatment was entered into the model as a forced variable. Statistical significance was accepted for a 2-sided $P<0.05$.

Results

The present study population comprises 1525 (81.4%) of the 1873 patients recruited in the SEAS trial[14] with an ejection

Table 1. Baseline Characteristics

	Aortic Valve Stenosis		
	Low-Gradient "Severe" (AVA <1.0 cm^2; MPG ≤40 mm Hg) (n=435)	Moderate (AVA 1.5–1.0 cm^2; MPG 25–40 mm Hg) (n=184)	*P*
Age, y	69.8±9.2	66.8±9.2	<0.01
Female gender, n (%)	240 (55.2)	50 (27.2)	<0.01
Height, cm	167.2±8.8	173.2±8.7	<0.01
Weight, kg	74.4±13.6	80.2±13.1	<0.01
Body surface area, m^2	1.83±0.2	1.94±0.2	<0.01
Body mass index, kg/m^2	26.6±4.3	26.7±3.9	0.69
Whites, n (%)	432 (99.2)	184 (100)	0.53
Heart rate, bpm	68.2±10.2	68.0±11.0	0.81
Blood pressure, mm Hg			
Systolic	145.8±21.1	142.2±20.4	0.05
Diastolic	82.1±10.7	81.5±9.3	0.52
Hypertension, n (%)	213 (49.0)	93 (50.5)	0.72
Smoking, n (%)			<0.01
Current	73 (16.8)	40 (21.7)	
Former	144 (33.1)	77 (41.8)	
Never	218 (50.1)	67 (36.4)	
Glucose, mg/dL	95.8±16,4	94.2±11.7	0.29
Creatinine, mg/dL	1.03±0.17	1.09±0.19	<0.01
Cholesterol, mg/dL			
Total	225.8±37.9	219.6±37.9	0.06
Low-density lipoprotein	140.8±33.3	136.1±37.1	0.15

Clinical characteristics of 619 patients included in the SEAS trial[14] according to baseline echocardiographic assessment of aortic valve stenosis as either low-gradient "severe" stenosis (aortic valve area [AVA] <1.0 cm^2 and mean pressure gradient [MPG] ≤40 mm Hg) or moderate stenosis (aortic valve area 1.5–1.0 cm^2 and mean pressure gradient 25–40 mm Hg).

fraction ≥55% in whom a detailed echocardiographic assessment by the core laboratory at baseline was available. Low-gradient "severe" aortic stenosis was present in 435 (29%) of the study population and moderate stenosis in 184 (12%). Severe stenosis (mean pressure gradient >40 mm Hg and aortic valve area <1.0 cm^2) was observed in a limited number of patients (n=35; 2%) because of reassessment of locally obtained echocardiographic data at the core laboratory after randomization. Twenty-one patients (1%) had a mean pressure gradient >40 mm Hg with an aortic valve area >1.0 cm^2, and the remainder (n=850; 56%) had mild stenosis (mean pressure gradient <25 mm Hg and/or aortic valve area >1.5 cm^2).

Low-Gradient "Severe" Aortic Stenosis Versus Moderate Stenosis

Patients with low-gradient "severe" aortic stenosis were older, smaller, and more often female and had higher systolic blood pressure than patients with moderate stenosis. Body mass index was comparable (Table 1). Echocardiographic parameters for patients with low-gradient "severe" aortic stenosis and moderate stenosis are shown in Table 2. Patients with low-gradient "severe" aortic stenosis had a lower mean pressure gradient and a smaller aortic valve area than patients with moderate stenosis. Left ventricular end-diastolic diameter, mass, outflow tract diameter, and stroke volume index were significantly lower in patients with low-gradient "severe" aortic stenosis than in patients with moderate stenosis, whereas ejection fraction was comparable between groups.

At the end of the first year of follow-up, there were few aortic valve events (3.2% versus 3.8%; *P*=0.71) both for patients with low-gradient "severe" aortic stenosis and for patients with moderate aortic stenosis. Similarly, there were no significant differences between groups with respect to major cardiovascular events (4.8% versus 4.3%; *P*=0.80) and cardiovascular death (1.1% versus 0.5%; *P*=0.49). Outcome over the entire follow-up (mean of 45.8±14.1 months) is summarized in Table 3. There was no significant difference between patients with low-gradient "severe" aortic stenosis and moderate stenosis with respect to all predefined end points. Kaplan-Meier curves for event-free survival from aortic valve events, major cardiovascular events, and cardiovascular death are depicted in Figure 1A through 1C.

Similarly, annualized rates of aortic valve events (13.8±1.0% versus 12.7±1.4%; *P*=0.43), major cardiovascular events (14.8±1.0% versus 14.1±1.5%; *P*=0.59), and cardiovascular death (1.8±0.3% versus 1.1±0.4%; *P*=0.18) showed no significant difference between patients with low-gradient severe aortic stenosis and those with moderate stenosis.

Table 2. Baseline Echocardiographic Parameters

	Aortic Valve Stenosis		
	Low-Gradient "Severe" (AVA <1.0 cm^2; MPG ≤40 mm Hg) (n=435)	Moderate (AVA 1.5–1.0 cm^2; MPG 25–40 mm Hg) (n=184)	*P*
Aortic valve			
Peak aortic jet velocity, m/s	3.3±0.5	3.6±0.3	<0.01
Transaortic peak pressure gradient, mm Hg	44.8±11.9	53.0±7.4	<0.01
Transaortic mean pressure gradient, mm Hg	26.2±7.3	31.2±4.1	<0.01
Aortic valve area, cm^2	0.82±0.13	1.19±0.13	<0.01
Aortic valve area index, cm^2/m^2	0.46±0.08	0.63±0.09	<0.01
Velocity time integral aortic valve, cm	78.0±13.0	82.0±10.0	<0.01
Dimensionless velocity index	0.26±0.06	0.30±0.06	<0.01
Stroke volume			
LV outflow tract diameter, mm	20.2±0.2	22.8±0.2	<0.01
Velocity time integral LV outflow tract, cm	20.1±4.1	24.2±4.9	<0.01
Stoke volume, mL	63.8±13.1	97.5±13.9	<0.01
Stoke volume index, mL/m^2	35.1±7.3	50.7±8.5	<0.01
Cardiac output, L/min	4.3±1.0	6.6±1.2	<0.01
Cardiac index, L/min	2.4±0.56	3.4±0.71	<0.01
LV			
LV ejection fraction, %	66.9±5.7	66.7±5.8	0.68
LV end-diastolic diameter, mm	49.0±6.1	50.7±5.6	<0.01
LV end-diastolic diameter index, mm/m^2	26.9±3.4	26.3±3.2	0.04
LV end-diastolic volume, mL	115.3±32.7	124.4±31.1	<0.01
LV end-diastolic volume index, mL/m^2	63.0±16.5	64.3±15.6	0.36
LV end-systolic diameter, mm	31.0±5.1	31.6±5.0	0.18
LV end-systolic diameter index, mm/m^2	17.0±2.7	16.4±2.7	<0.01
Fractional shortening, %	36.8±5.6	37.8±6.0	0.05
LV end-diastolic septum thickness, mm	11.4±2.8	12.3±2.9	<0.01
LV end-diastolic posterior wall thickness, mm	8.8±1.9	9.4±1.9	<0.01
LV mass, g	182.3±63.6	211.6±67.5	<0.01
LV mass index, g/m^2	98.9±30.6	108.9±33.3	<0.01
Relative wall thickness, %	36.5±9.5	37.3±8.9	0.30

Baseline echocardiographic measures in 619 patients included in the SEAS trial[14] according to assessment of aortic valve stenosis as either low-gradient "severe" or moderate stenosis. AVA indicates aortic valve area; MPG, mean pressure gradient; and LV, left ventricular.

In multivariate Cox regression analysis controlling for the effects of age, gender, smoking, heart rate, hypertension, and, as a forced entry, treatment allocation (ezetimibe/simvastatin versus placebo), low-gradient "severe" aortic stenosis was not an independent predictor for aortic valve events (HR, 1.01 [confidence interval, 0.94 to 1.23]; *P*=0.29; Table 4), major cardiovascular events (HR, 1.06 [confidence interval, 0.92 to 1.20]; *P*=0.41), or cardiovascular death (HR, 1.15 [confidence interval, 0.79 to 1.67]; *P*=0.48).

Stroke Volume Index

In patients with low-gradient severe stenosis, a reduced stroke volume index of ≤35 mL/m^2 was diagnosed in 223 individuals (51%) (mean, 29±4 mL/m^2). Mean pressure gradient (24±7 versus 29±7 mm Hg; *P*<0.01) was lower and aortic valve area (0.77±0.1 versus 0.88±0.1 cm^2; *P*<0.01) was smaller than in patients with a normal stroke volume index (>35 mL/m^2; mean, 41±5 mL/m^2). Ejection fraction (66.7±5.8% versus 67.2±5.6%; *P*=0.45) was comparable between groups. Patients with a reduced stroke volume index suffered an aortic valve event during follow-up in 46.2%, which was not significantly different from patients with a normal stroke volume index (50.9%; *P*=0.53; Figure 2; major cardiovascular events, 49.8% versus 51.9%; *P*=0.94). Similarly, cardiovascular death was comparable in both groups (8.1% versus 7.5%; *P*=0.77).

Outcome With and Without Valve Replacement

In a separate analysis restricted to patients who did not undergo valve replacement (252 patients with low-gradient "severe" aortic stenosis and 108 with moderate stenosis), no significant difference was found in major cardiovascular events (15.1% versus 12.0%; *P*=0.45) or cardiovascular death (9.1% versus 5.6%; *P*=0.25). Furthermore, in the group of patients with low-gradient severe stenosis, cardiovascular death rates were

Table 3. Primary and Secondary Outcomes

	Aortic Valve Stenosis	
	Low-Gradient "Severe" (AVA <1.0 cm^2; MPG ≤40 mm Hg) (n=435)	Moderate (AVA 1.5–1.0 cm^2; MPG 25–40 mm Hg) (n=184)
Aortic valve events, n (%)	211 (48.5)	82 (44.6)
Aortic valve replacement	183 (42,1)	76 (41.3)
Congestive heart failure due to aortic stenosis	17 (3.9)	4 (2.2)
Death from cardiovascular cause	34 (7.8)	9 (4.9)
Major cardiovascular events, n (%)	221 (50.9)	89 (48.4)
Death from cardiovascular cause, n (%)	34 (7.8)	9 (4.9)
Related to cardiac surgery	6 (1.4)	2 (1.1)
Heart failure	2 (0.5)	2 (1.1)
Myocardial infarction	5 (1.1)	1 (0.5)
Stroke	6 (1.4)	0 (0)
Sudden death	12 (2.8)	2 (1.1)
Other cardiovascular death	3 (0.7)	2 (1.1)
Overall death	56 (12.9)	19 (10.3)
Ischemic events, n (%)	102 (23.4)	40 (21.7)
Nonfatal myocardial infarction	12 (2.8)	2 (1.1)
Coronary artery bypass grafting	53 (12.2)	22 (12.0)
Percutaneous coronary intervention	7 (1.6)	1 (0.5)
Hospitalization for unstable angina	2 (0.5)	0 (0)
Nonhemorrhagic stroke	21 (4.8)	8 (4.3)
Death from cardiovascular cause	34 (7.8)	9 (4.9)

Aortic valve events, major cardiovascular events, death from cardiovascular causes, ischemic events, and their components according to the assessment of aortic valve stenosis at baseline as either low-gradient "severe" or moderate stenosis. AVA indicates aortic valve area; MPG, mean pressure gradient.

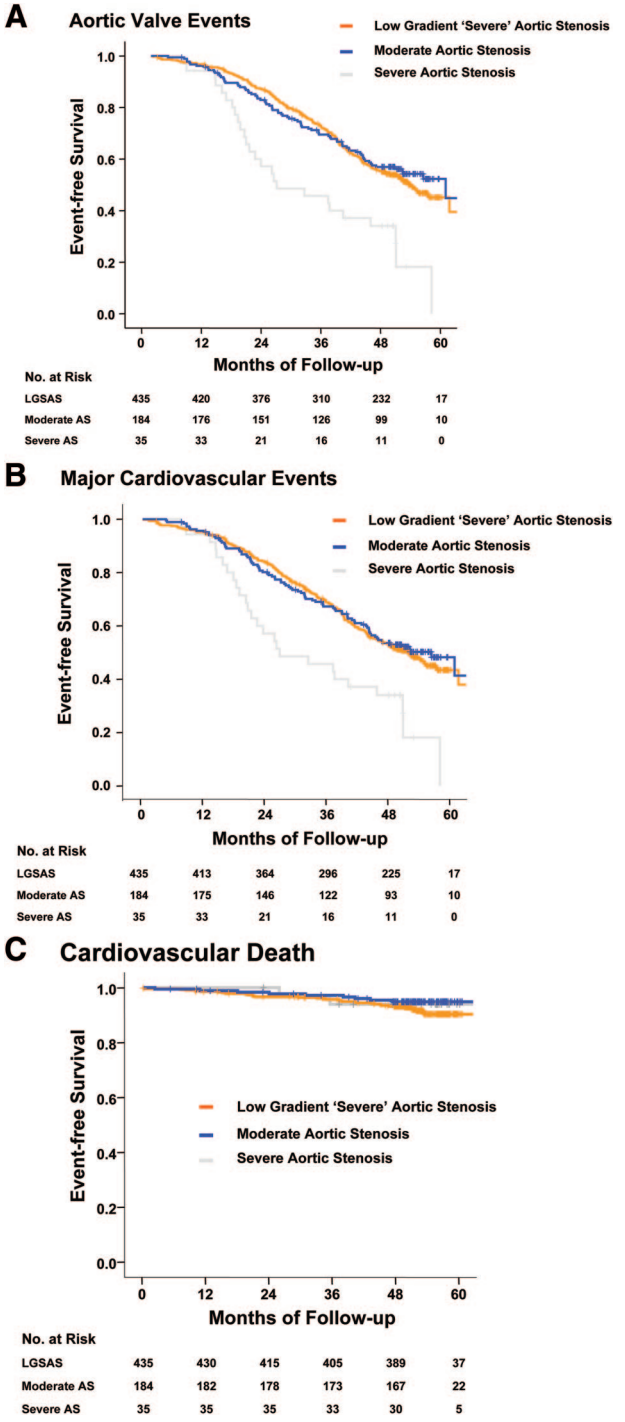

Figure 1. Kaplan-Meier plots for freedom from aortic valve events, major cardiovascular events, and cardiovascular death (A, B, and C, respectively) in patients with low-gradient "severe" aortic stenosis (LGSAS) (aortic valve area <1.0 cm^2; mean pressure gradient ≤40 mm Hg) and moderate aortic stenosis (AS) (aortic valve area 1.5 to 1.0 cm^2; mean pressure gradient 25 to 40 mm Hg). There was no statistically significant difference by means of the log-rank test between low-gradient severe and moderate stenosis (aortic valve events, P=0.48; major cardiovascular events, P=0.64; cardiovascular death, P=0.19). For comparison, event rates of a small group of patients (n=35) with severe stenosis (aortic valve area <1.0.cm^2, mean pressure gradient >40 mm Hg) are shown in gray.

comparable between those patients who underwent valve replacement (11/183; 6.0%) and those who were followed conservatively (23/252; 9.1%; P=0.23).

Low-Gradient "Severe" Aortic Stenosis Versus Severe Aortic Stenosis

Thirty-five patients randomized for the SEAS study fulfilled both criteria for severe stenosis (mean pressure gradient >40 mm Hg and aortic valve area <1.0 cm^2). Patients with severe stenosis experienced an aortic valve event in 74.3% (low-gradient "severe" aortic stenosis, 48.5%; P<0.01; Figure 1) and a major cardiovascular event also in 74.3% (low-gradient "severe" aortic stenosis, 50.9%; P<0.01) because all major cardiovascular events were due to aortic valve events. Rates of cardiovascular death were similar in both groups (7.8% versus 5.7%; P=0.65).

Table 4. Multivariate Analysis

	Aortic Valve Events		Major Cardiovascular Events		Cardiovascular Death	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Low-gradient "severe" aortic stenosis	1.01 (0.94–1.23)	0.29	1.06 (0.92–1.20)	0.41	1.15 (0.79–1.67)	0.48
Gender, female	0.76 (0.59–0.98)	0.03	0.73 (0.57–0.93)	0.01	0.57 (0.30–1.10)	0.09
Heart rate	1.01 (1.00–1.03)	0.02	1.01 (1.00–1.02)	0.02	1.04 (1.01–1.07)	<0.01
Age	1.01 (0.99–1.02)	0.25	1.01 (1.00–1.02)	0.20	1.16 (1.10–1.22)	<0.01
Smoking, former	1.14 (0.81–1.59)	0.45	1.17 (0.84–1.63)	0.36	0.45 (0.19–1.04)	0.06
Smoking, never	0.96 (0.69–1.35)	0.83	1.06 (0.76–1.48)	0.72	0.41 (0.17–0.96)	0.04
Blood pressure, systolic	1.00 (0.99–1.01)	0.82	1.00 (0.99–1.01)	0.99	1.01 (0.99–1.02)	0.41
Treatment allocation	0.94 (0.75–1.19)	0.61	0.92 (0.73–1.15)	0.46	1.01 (0.55–1.85)	0.99

CI indicates confidence interval. Multivariate analysis including patients with low-gradient "severe" and moderate stenosis (n=619), indicating that the echocardiographic constellation of low-gradient "severe" aortic stenosis (aortic valve area <1.0 cm^2; and mean pressure gradient ≤40 mm Hg) was not an independent predictor of aortic valve events, major cardiovascular events, or cardiovascular death. Male gender and an increased heart rate were predictive of aortic valve and major cardiovascular events. An increased age and heart rate and smoking status were predictive of cardiovascular death. Treatment allocation specifies treatment with ezetimibe/simvastatin vs placebo in the original SEAS trial.[14]

Progression and Outcome According to the Last Available Echocardiogram

Data from the last echocardiogram before an end point (or before the termination of the study in patients who did not reach an end point) showed that of the 1326 patients with complete echocardiographic data, 319 (24%) had reached the stage of severe stenosis, 275 (21%) had low-gradient "severe" aortic stenosis, and 216 (16%) had moderate stenosis. Progression to severe stenosis was observed in 62 of 163 patients (38%) with moderate stenosis and in 154 of 374 (41%) with low-gradient "severe" aortic stenosis at baseline ($P=0.50$). Aortic valve events and major cardiovascular events were comparable between patients with low-gradient "severe" aortic stenosis and moderate stenosis (aortic valve events, 26.2% versus 24.5%; major cardiovascular events, 29.5% versus 26.4%; both P=NS). In contrast, patients with severe stenosis had experienced more aortic valve events (53.9%) and major cardiovascular events (56.4%) than patients with low-gradient severe aortic stenosis or patients with moderate stenosis (both $P<0.01$). No difference between groups was noted with respect to cardiovascular deaths (low-gradient "severe" aortic stenosis, 2.5%; moderate stenosis, 1.9%; and severe stenosis, 4.7%; P=NS).

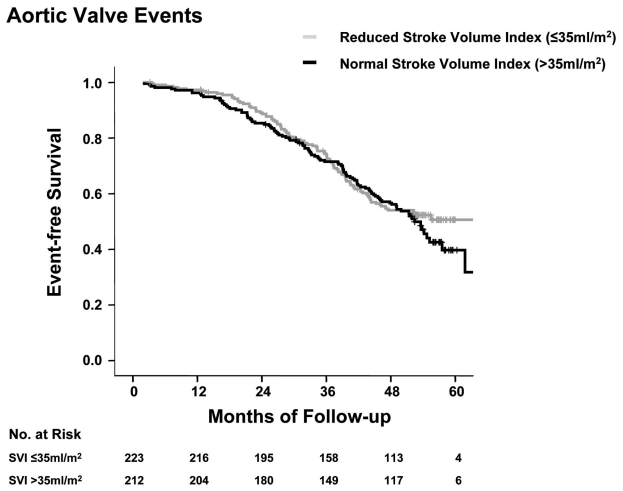

Figure 2. Kaplan-Meier plots for freedom from aortic valve events in patients with low-gradient "severe" aortic valve stenosis (n=435) stratified according to reduced stroke volume index (SVI) (≤35 mL/m^2; n=223) and normal stroke volume index (>35 mL/m^2; n=212). There was no statistically significant difference in event-free survival after a mean follow-up of 46 months between the 2 groups (53.8% versus 49.1%, respectively; P=0.53).

Discussion

The present study, based on the largest prospective trial in aortic stenosis to date, demonstrates that low-gradient "severe" aortic stenosis (aortic valve area <1.0 cm^2; mean pressure gradient ≤40 mm Hg) is a frequent echocardiographic constellation in asymptomatic patients with preserved left ventricular function (ejection fraction ≥55%). The associated echocardiographic characteristics denote no more than moderate aortic valve disease. Outcome and progression rate in patients with low-gradient "severe" aortic stenosis are similar to those in patients with moderate stenosis with a markedly better outcome than reported previously. Consistent results were observed in both medically and surgically treated patients. Low-gradient "severe" aortic valve stenosis was associated with a decreased stroke volume index in 51% of cases, with no difference in outcome between patients with reduced and normal flow. Therefore, low-gradient "severe" aortic stenosis, in general, does not indicate severe aortic valve disease, and patients can be followed safely with serial clinical and echocardiographic evaluations.

These prospectively collected results are in contrast to recent retrospective studies,[2–5] which have suggested that patients with low-gradient "severe" aortic stenosis may represent a subgroup with an advanced stage of severe aortic stenosis with reduced stroke volume due to impaired ventricular function despite preserved ejection fraction and resultant poor prognosis, particularly when early valve replacement is withheld.

A number of characteristics of the previous retrospective studies may explain the divergent results to the present analysis. First, previous studies included patients with an ejection fraction as low as 50%, which in the presence of concentric left ventricular remodeling cannot be considered normal. An adverse outcome in patients with reduced stroke volume may be explained by the overrepresentation of patients with reduced

ejection fraction in the low-flow group. Second, patients in previous studies were selected consecutively according to a single echocardiographic study irrespective of comorbidities. Therefore, the group of "medically treated" patients may include a certain number of individuals with poor functional status and prognosis. Some of these patients may be unable to undergo surgery because of reasons other than aortic stenosis. Third, aortic valve replacement and death were the only events recorded during follow-up. No information is available about clinical course and cause of death. Fourth, there was a high prevalence of coronary artery disease, with outcome in these patients markedly influenced by ischemic events. An improved survival in surgically treated patients may therefore be due in part to concomitant bypass surgery. In contrast, we included only patients with an ejection fraction ≥55%. All patients in the SEAS study were carefully monitored prospectively for an extended period of time (mean, 46 months) with scheduled clinical visits, regular echocardiographic assessment, timely surgery according to guidelines, and systematic assessment of cause of death. Patients with coronary heart disease and other overt comorbidities at baseline, including diabetes mellitus, renal insufficiency, history of stroke or peripheral vascular disease, or the indication for lipid-lowering therapy, were excluded. Therefore, the present analysis allows for the assessment of outcome predominantly determined by aortic stenosis.

An additional difference is the fact that retrospective studies did not report on symptom status.[3,4] However, the presence of symptoms has an important impact on outcome and clinical management in patients with aortic stenosis. Because patients in the previous studies had been included consecutively, it is likely that both symptomatic and asymptomatic patients had been recruited with unknown distribution to different subgroups. Therefore, conclusions about clinical management and the need and timing of valve replacement should be interpreted with caution. In contrast, the present analysis was restricted to asymptomatic patients at baseline, showing that low-gradient "severe" aortic stenosis is a frequent finding in these patients and is associated with a markedly better outcome than previously reported when patients are followed carefully. Fifty percent of patients remain event free and do not require surgery over 46 months despite the progressive nature of aortic valve disease, indicating that low-gradient severe stenosis per se does not represent an advanced stage of aortic valve disease.

Mechanisms of Low-Gradient "Severe" Aortic Stenosis

Several unrelated mechanisms may account for a low pressure gradient in combination with a severely stenotic aortic valve area in the presence of a preserved ejection fraction. First, low pressure gradient in the presence of a severe aortic stenosis may be the result of reduced stroke volume despite preserved ejection fraction due to decreased ventricular size and/or impaired myocardial function.[3,16] However, a low stroke volume index was found in only one half of patients with low-gradient "severe" aortic stenosis in the present study, confirming previous findings that low stroke volume may only partly explain this constellation.[1] Second, low-gradient "severe" aortic stenosis in the presence of a normal stroke volume may be due to inconsistencies in current guidelines regarding the partition value for severe stenosis. We and others have recently shown that low-gradient "severe" aortic stenosis can be observed in the presence of normal stroke volume even when catheter-based calculations are used,[17–19] indicating that a valve area of 1.0 cm^2 usually does not correlate with a mean pressure gradient of 40 mm Hg. Third, patients with small body size and left ventricular dimensions may exhibit a lower transvalvular pressure gradient because of a lower albeit normal stroke volume. Indeed, our data show that patients with low-gradient "severe" aortic stenosis had smaller body size and left ventricular dimensions compared with patients with moderate stenosis. Fourth, difficulties in proper calculation of aortic valve area may be a reason for the observation of low-gradient "severe" aortic stenosis. Echocardiography tends to underestimate the LVOT diameter partially owing to its elliptic rather than circular anatomy.[20–22] Because the square of the radius is used in the continuity equation, small errors in the measurement of the LVOT diameter will result in a substantial error in aortic valve area. To minimize the error in calculating LVOT area, we measured aortic annulus diameter instead of LVOT in the present study because the former has been shown to be similar in size but less eccentric.[23] Finally, an increase in systemic blood pressure may decrease transvalvular pressure gradient.[24] As a result, more patients will be diagnosed with low-gradient "severe" aortic stenosis, which, in turn, may explain the increased number of patients with elevated blood pressure in the low-gradient "severe" aortic stenosis group in the present analysis. However, the effects of blood pressure on the echocardiographic assessment of mean pressure gradient and aortic valve area remain controversial.[25]

Clinical Implications

The echocardiographic constellation of low-gradient "severe" aortic valve stenosis in patients with normal ejection fraction is a clinically challenging finding observed in ≈30% of consecutive, unselected patients evaluated for aortic stenosis,[1,3,4] The present study and a previous study[26] demonstrate that it is also present in 29% of asymptomatic patients, of whom many remain event free over a considerable period of time independently of calculated stroke volume index. Therefore, management of asymptomatic patients similar to those with moderate stenosis is reasonable, including clinical and echocardiographic follow-up every 6 months, as in the SEAS trial, or yearly, as recommended by current guidelines. Functional capacity of the asymptomatic patient may be assessed by exercise testing.[27,28]

In patients with low-gradient severe stenosis presenting with dyspnea suffering from comorbidities such as chronic obstructive pulmonary disease, hypertension, or obesity, the relation between aortic stenosis and symptoms needs clarification and further evaluation, particularly when surgery is considered, because a higher perioperative risk may have to be anticipated, and aortic stenosis may not be the reason for their symptoms. An accurate estimation of the severity of aortic stenosis, assessment of comorbidities, particularly the presence of coronary artery disease, and the risk carried by the individual patient is warranted. Hence, if "the numbers don't add up,"[29,30] all echocardiographic measurements should be rechecked carefully. This is especially true for the

measurement of the LVOT diameter, representing the Achilles' heel of the calculation of aortic valve area by the continuity equation. Other diagnostic tools should be considered to assess morphology and hemodynamics of the stenotic valve. This may include transesophageal echocardiography,[31] magnetic resonance imaging,[32] and, rarely, cardiac catheterization,[33] as outlined in the American Heart Association/American College of Cardiology and European Society of Cardiology guidelines.[10–12] Several additional echocardiographic parameters have been proposed for a better definition of the severity of aortic stenosis and imminent risk (energy loss index,[34,35] stroke work loss,[36,37] resistance,[38] and valvuloarterial impedance[39,40]), but their utility and prognostic impact still must be proven in larger-scale, prospective studies. Indication for valve replacement in patients with low-gradient "severe" aortic stenosis may currently be restricted to those in whom symptoms can clearly be attributed to aortic valve disease. The remainder requires close clinical monitoring for development of symptoms and disease progression.

Limitations

Although the data were collected prospectively, the current analysis was performed retrospectively with all its inherent limitations. In the present study, only patients with an ejection fraction ≥55% were included, which in the presence of left ventricular hypertrophy may not be entirely normal. Therefore, some patients may have had undetected left ventricular compromise. Patients in the SEAS trial were scheduled for surgical valve replacement according to current guidelines. However, echocardiographic calculation of mean pressure gradient and aortic valve area may have influenced the decision. Yet, patients with low-gradient "severe" aortic stenosis had an outcome comparable to that of patients with moderate stenosis in both surgically and conservatively managed patients. The comparison to patients with severe aortic stenosis is limited because the SEAS study was designed to include patients with mild to moderate aortic stenosis. The 35 patients identified as having severe aortic stenosis after review of the echocardiographic data at the core laboratory therefore represent a subgroup of patients at the lower end of the spectrum of severe aortic stenosis. Although these patients already have markedly higher event rates than patients with moderate and low-gradient "severe" aortic stenosis, patients with "very severe"[9] aortic stenosis can be expected to have an even worse outcome.

Conclusion

Outcome and progression rate in patients with low-gradient "severe" aortic valve stenosis are similar to those in patients with moderate stenosis. The echocardiographic finding of an aortic valve area <1.0 cm^2 and a mean pressure gradient ≤ 40 mm Hg is frequent in asymptomatic patients with preserved ejection fraction and in general does not indicate advanced aortic valve disease. Indication for valve replacement may safely be restricted to those in whom symptoms can clearly be attributed to aortic stenosis.

Sources of Funding

Drs Gerdts, Boman, Brudi, Chambers, Rossebø, and Kesäniemi received research support from Merck/Schering-Plough Pharmaceuticals, Inc, North Wales, PA.

Disclosures

Drs Jander, Holme, Boman, Chambers, Kesäniemi, Nienaber, Rossebø, Pedersen, Willenheimer, Skjærpe, Wachtell, and Gohlke-Bärwolf have received honoraria from Merck/Schering-Plough Pharmaceuticals, Inc, North Wales, PA, the funding sponsor of the SEAS study. Drs Pedersen and Willenheimer received honoraria from AstraZeneca Inc, Wilmington, DEL, and Pfizer Inc, New York, NY. Dr Kesäniemi received honoraria from Sanofi-Aventis, Paris, France, and AstraZeneca Inc, Wilmington, DEL. Drs Brudi and Malbecq are employees of Merck/Schering-Plough Pharmaceuticals, Inc, and own stock and/or stock options in the company.

References

1. Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N. Inconsistencies of echocardiographic criteria for the grading of aortic valve stenosis. *Eur Heart J*. 2008;29:1043–1048.
2. Christensen KL, Ivarsen HR, Thuesen L, Kristensen BO, Egeblad H. Aortic valve stenosis: fatal natural history despite normal left ventricular function and low invasive peak-to-peak pressure gradients. *Cardiology*. 2004;102:147–151.
3. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. *Circulation*. 2007;115:2856–2864.
4. Barasch E, Fan D, Chukwu EO, Han J, Passick M, Petillo F, Norales A, Reichek N. Severe isolated aortic stenosis with normal left ventricular systolic function and low transvalvular gradients: pathophysiologic and prognostic insights. *J Heart Valve Dis*. 2008;17:81–88.
5. Dumesnil JG, Pibarot P, Carabello B. Paradoxical low flow and/or low gradient severe aortic stenosis despite preserved left ventricular ejection fraction: implications for diagnosis and treatment. *Eur Heart J*. 2010;31:281–289.
6. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, Kraft CD, Miyake-Hull CY, Schwaegler RG. Prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic, and exercise predictors of outcome. *Circulation*. 1997;95:2262–2270.
7. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, Maurer G, Baumgartner H. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med*. 2000;343:611–617.
8. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, Barnes ME, Tajik AJ. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation*. 2005;111:3290–3295.
9. Rosenhek R, Zilberszac R, Schemper M, Czerny M, Mundigler G, Graf S, Bergler-Klein J, Grimm M, Gabriel H, Maurer G. Natural history of very severe aortic stenosis. *Circulation*. 2010;121:151–156.
10. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, Flachskampf F, Hall R, Iung B, Kasprzak J, Nataf P, Tornos P, Torracca L, Wenink A. Guidelines on the management of valvular heart disease: the Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J*. 2007;28:230–268.
11. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B, Otto CM, Pellikka PA, Quinones M. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *Eur J Echocardiogr*. 2009;10:1–25.
12. Bonow RO, Carabello BA, Kanu C, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Nishimura R, Page RL, Riegel B. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation*. 2006;114:e84–e231.

13. Rossebo AB, Pedersen TR, Allen C, Boman K, Chambers J, Egstrup K, Gerdts E, Gohlke-Barwolf C, Holme I, Kesaniemi VA, Malbecq W, Nienaber C, Ray S, Skjaerpe T, Wachtell K, Willenheimer R. Design and baseline characteristics of the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. *Am J Cardiol*. 2007;99:970–973.
14. Rossebo AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, Gerdts E, Gohlke-Barwolf C, Holme I, Kesaniemi YA, Malbecq W, Nienaber CA, Ray S, Skjaerpe T, Wachtell K, Willenheimer R. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359:1343–1356.
15. Zoghbi WA, Farmer KL, Soto JG, Nelson JG, Quinones MA. Accurate noninvasive quantification of stenotic aortic valve area by Doppler echocardiography. *Circulation*. 1986;73:452–459.
16. Cramariuc D, Rieck AE, Staal EM, Wachtell K, Eriksen E, Rossebo AB, Gerdts E. Factors influencing left ventricular structure and stress-corrected systolic function in men and women with asymptomatic aortic valve stenosis (a SEAS Substudy). *Am J Cardiol*. 2008;101:510–515.
17. Carabello BA. Clinical practice: aortic stenosis. *N Engl J Med*. 2002;346:677–682.
18. Jander N. Low-gradient 'severe' aortic stenosis with preserved ejection fraction: new entity, or discrepant definitions? *Eur Heart J Suppl*. 2008;10:E11–E15.
19. Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N. Inconsistent grading of aortic valve stenosis by current guidelines: haemodynamic studies in patients with apparently normal left ventricular function. *Heart*. 2010;96:1463–1468.
20. Baumgartner H, Kratzer H, Helmreich G, Kuehn P. Determination of aortic valve area by Doppler echocardiography using the continuity equation: a critical evaluation. *Cardiology*. 1990;77:101–111.
21. Doddamani S, Bello R, Friedman MA, Banerjee A, Bowers JH Jr, Kim B, Vennalaganti PR, Ostfeld RJ, Gordon GM, Malhotra D, Spevack DM. Demonstration of left ventricular outflow tract eccentricity by real time 3D echocardiography: implications for the determination of aortic valve area. *Echocardiography*. 2007;24:860–866.
22. Burgstahler C, Kunze M, Loffler C, Gawaz MP, Hombach V, Merkle N. Assessment of left ventricular outflow tract geometry in non-stenotic and stenotic aortic valves by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2006;8:825–829.
23. Ng AC, Delgado V, van der Kley F, Shanks M, van de Veire NR, Bertini M, Nucifora G, van Bommel RJ, Tops LF, de Weger A, Tavilla G, de Roos A, Kroft LJ, Leung DY, Schuijf J, Schalij MJ, Bax JJ. Comparison of aortic root dimensions and geometries before and after transcatheter aortic valve implantation by 2- and 3-dimensional transesophageal echocardiography and multislice computed tomography. *Circ Cardiovasc Imaging*. 2010;3:94–102.
24. Kadem L, Dumesnil JG, Rieu R, Durand LG, Garcia D, Pibarot P. Impact of systemic hypertension on the assessment of aortic stenosis. *Heart*. 2005;91:354–361.
25. Little SH, Chan KL, Burwash IG. Impact of blood pressure on the Doppler echocardiographic assessment of severity of aortic stenosis. *Heart*. 2007;93:848–855.
26. Cramariuc D, Cioffi G, Rieck AE, Devereux RB, Staal EM, Ray S, Wachtell K, Gerdts E. Low-flow aortic stenosis in asymptomatic patients: valvular-arterial impedance and systolic function from the SEAS substudy. *J Am Coll Cardiol Imaging*. 2009;2:390–399.
27. Amato MC, Moffa PJ, Werner KE, Ramires JA. Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. *Heart*. 2001;86:381–386.
28. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. *Eur Heart J*. 2005;26:1309–1313.
29. Flachskampf FA. Severe aortic stenosis with low gradient and apparently preserved left ventricular systolic function: under-recognized or overdiagnosed? *Eur Heart J*. 2008;29:966–968.
30. Weyman AE, Scherrer-Crosbie M. Aortic stenosis: physics and physiology: what do the numbers really mean? *Rev Cardiovasc Med*. 2005;6:23–32.
31. Hoffmann R, Flachskampf FA, Hanrath P. Planimetry of orifice area in aortic stenosis using multiplane transesophageal echocardiography. *J Am Coll Cardiol*. 1993;22:529–534.
32. Kupari M, Hekali P, Keto P, Poutanen VP, Porkka L, Turto H, Nieminen MS, Toivonen L, Ikonen T, Ventila M. Assessment of aortic valve area in aortic stenosis by magnetic resonance imaging. *Am J Cardiol*. 1992;70:952–955.
33. Gorlin R, Gorlin SG. Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. *Am Heart J*. 1951;41:1–29.
34. Garcia D, Pibarot P, Dumesnil JG, Sakr F, Durand LG. Assessment of aortic valve stenosis severity: a new index based on the energy loss concept. *Circulation*. 2000;101:765–771.
35. Bahlmann E, Cramariuc D, Gerdts E, Gohlke-Baerwolf C, Nienaber CA, Eriksen E, Wachtell K, Chambers J, Kuck KH, Ray S. Impact of pressure recovery on echocardiographic assessment of asymptomatic aortic stenosis: a SEAS substudy. *J Am Coll Cardiol Cardiovasc Imaging*. 2010;3:555–562.
36. Bermejo J, Odreman R, Feijoo J, Moreno MM, Gomez-Moreno P, Garcia-Fernandez MA. Clinical efficacy of Doppler-echocardiographic indices of aortic valve stenosis: a comparative test-based analysis of outcome. *J Am Coll Cardiol*. 2003;41:142–151.
37. Tobin JR Jr, Rahimtoola SH, Blundell PE, Swan HJ. Percentage of left ventricular stroke work loss: a simple hemodynamic concept for estimation of severity in valvular aortic stenosis. *Circulation*. 1967;35:868–879.
38. Ho PP, Pauls GL, Lamberton DF, Portnoff JS, Pai RG, Shah PM. Doppler derived aortic valve resistance in aortic stenosis: its hemodynamic validation. *J Heart Valve Dis*. 1994;3:283–287.
39. Briand M, Dumesnil JG, Kadem L, Tongue AG, Rieu R, Garcia D, Pibarot P. Reduced systemic arterial compliance impacts significantly on left ventricular afterload and function in aortic stenosis: implications for diagnosis and treatment. *J Am Coll Cardiol*. 2005;46:291–829.
40. Hachicha Z, Dumesnil JG, Pibarot P. Usefulness of the valvuloarterial impedance to predict adverse outcome in asymptomatic aortic stenosis. *J Am Coll Cardiol*. 2009;54:1003–1011.

CLINICAL PERSPECTIVE

This is the first prospective study to determine the outcome of patients with low-gradient "severe" aortic valve stenosis, defined as a severe stenosis based on aortic valve area (<1.0 cm^2) and a nonsevere stenosis based on mean pressure gradient (≤ 40 mm Hg). In an analysis of 1525 patients with preserved ejection fraction from the Ezitimibe/Simvastatin in Aortic Stenosis (SEAS) trial, we confirm that this clinically challenging finding is also present in 29% of asymptomatic patients, similar to the percentage observed in unselected patients evaluated for aortic stenosis. The associated echocardiographic characteristics (eg, left ventricular mass) denote no more than moderate aortic valve disease. Comparison to patients with moderate stenosis (aortic valve area 1.0–1.5 cm^2/mean pressure gradient 25–40 mm Hg) shows a similar progression rate to truly severe stenosis (aortic valve area <1.0 cm^2/mean pressure gradient >40 mm Hg) and overall outcome during 46 months of follow-up (aortic valve events 48.5% vs 44.6%; $P=0.37$). These results indicate a markedly better prognosis in patients with low-gradient "severe" aortic stenosis than suggested in recent retrospective studies. According to our results, patients with low-gradient "severe" aortic stenosis can be managed with serial clinical and echocardiographic evaluations. Surgery is recommended only when symptoms can clearly be attributed to aortic stenosis or other indications according to prevailing guidelines.

Outcome of Patients With Low-Gradient "Severe" Aortic Stenosis and Preserved Ejection Fraction

Nikolaus Jander, Jan Minners, Ingar Holme, Eva Gerdts, Kurt Boman, Philippe Brudi, John B. Chambers, Kenneth Egstrup, Y. Antero Kesäniemi, William Malbecq, Christoph A. Nienaber, Simon Ray, Anne Rossebø, Terje R. Pedersen, Terje Skjærpe, Ronnie Willenheimer, Kristian Wachtell, Franz-Josef Neumann and Christa Gohlke-Bärwolf

Circulation. 2011;123:887-895; originally published online February 14, 2011;
doi: 10.1161/CIRCULATIONAHA.110.983510
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

압력차가 낮은 '중증' 대동맥판협착증과 중등도 대동맥판협착증의 임상 경과는 같다

강 덕 현 교수 서울아산병원 심장내과

Summary

배경

대동맥 판막면적이 1.0cm^2 미만인 중증 대동맥판협착증에서 좌심실 수축기능 저하로 심박출량이 감소하면서 평균 압력차(pressure gradient)가 기준치보다 낮을 수 있다. 그러나 좌심실 수축기능이 정상인 환자에서도 심초음파 검사의 대동맥 판막면적 기준으로는 중증에 해당되지만, 평균 압력차 기준으로는 중증에 도달하지 못하는 경우가 30%에 이르는데, 후향적 관찰연구들에서는 이러한 low-gradient 환자들이 중증 대동맥판협착증 중에서도 대동맥판막질환이 보다 진행된 경우로 일회박출량이 저하되고, 예후가 불량하며 수술적 치료가 필요한 특성이 있음을 제시하였다. 무증상의 대동맥판협착증 환자들을 전향적으로 포함한 Simvastatin and Ezetimibe in Aortic Stenosis(SEAS) 연구 자료를 이용하여 대동맥 판막면적이 1.0cm^2 미만이고 평균 압력차가 40mmHg 이하인 low-gradient '중증' 대동맥판협착증 환자들의 임상 경과를 평가하였다.

방법 및 결과

대동맥 판막면적이 1.0-1.5cm^2이고 평균 압력차는 25-40mmHg인 중등도 대동맥판협착증과 low-gradient 중증 대동맥판협착증 환자들의 임상 경과를 비교하였다. 연구의 일차 종료점은 심혈관 원인으로 인한 사망, 대동맥판 치환술 시행과 대동맥판협착증에 의한 심부전 등의 대동맥판과 연관된 사건이었고, 이차 종료점들은 주요 심혈관 사건들 및 심혈관 사망이었다. 좌심실 박출률이 55% 이상인 1,523명의 무증상 대동맥판협착증 환자(평균 연령 67±10세) 중 심초음파검사 결과에 근거하여 435명(29%)의 low-gradient 중증 대동맥판협착증 환자들과 184명(12%)의 중등도 대동맥판협착증 환자들을 포함하였다. Low-gradient 중증 대동맥판협착증 환자들의 좌심실 심근량은 중등도 대동맥판협착증 환자들보다 유의하게 적었다(182±64g vs. 212±68g; P<0.01). 46개월간의 추적관찰 기간 동안 대동맥판 사건은 low-gradient 중증 대동맥판협착증 환자들의 48.5% 및 중등도 대동맥판협착증 환자들의 44.6%에서 일어났다(P=0.37; 주요 심혈관 사건, 50.9% vs. 48.5%, P=0.58; 심혈관 사망, 7.8% vs. 4.9%, P=0.19). Low-gradient 중증 대동맥판협착증 환자들 중에서 일회박출량이 35mL/m^2 이하로 저하된 223명 환자들의 대동맥판 사건 빈도는 정상 일회박출량을 가진 환자(n=212)들에서의 사건 빈도와 비슷하였다(46.2% vs. 50.9%; P=0.53).

결론

박출률이 정상인 low-gradient '중증' 대동맥판협착증 환자들은 중등도 협착증과 유사한 임상 경과를 가진다.

Commentary

박출률이 정상인 low-gradient '중증' 대동맥판협착증으로 진단되는 혈역학적 상황으로는 첫째, 좌심실 크기가 정상이고, 좌심실 박출률이 50% 정도로 일회박출량이 약간 감소하는 경우; 둘째, 신체가 작고 좌심실도 작아서 일회박출량이 감소하는 경우; 셋째, 심초음파 검사에서 좌심실 유출로 직경을 과소 측정하면서 대동맥판 면적을 작게 계산하는 오류가 발생하는 경우; 넷째, 동반된 고혈압이 압력차에 영향을 주는 경우; 다섯째, 현재 지침에서 정의하는 중증 대동맥판협착증의 기준치가 되는 대동맥판면적 1.0cm^2가 압력차 및 혈류 최대속도의 기준치와 일치하지 않는 점 등을 들 수 있다. 혈류 최대속도 >4m/s 또는 평균 압력차 >40mmHg에 일치하는 대동맥판 면적은 대략 0.8cm^2이므로 현재 치료지침에서 정한 대동맥판면적 1.0cm^2는 중증 대동맥판협착증을 진단하는데 매우 예민하지만 특이도는 떨어지는 진단 기준이다. 비특이적 증상을 호소하는 환자들이 심초음파 검사상 평균 압력차는 40mmHg 미만이지만 대동맥판면적이 1.0cm^2 미만이어서 '중증' 대동맥판협착증으로 과잉 진단된다면 이러한 환자들이 불필요한 조기 수술을 받는 위험에 노출될 수 있다. SEAS 연구는 경증 및 중등도 대동맥판협착증 환자 1,873명을 포함하여 평균 4.3년의 기간 동안 대동맥판협착증의 진행 및 주요 심혈관 사건의 발생에 대한 Vytorin의 효과를 평가하였는데, statin의 효과에 대해서는 negative result를 보였지만 대동맥판협착증의 진행 및 임상 경과를 평가할 수 있는 가장 큰 규모의 전향적 registry 자료를 제공할 것으로 기대하였다. 박출률이 정상인 low-gradient '중증' 대동맥판협착증의 적절한 치료 방침에 대해 많은 논란이 있었는데, Jander 등이 Circulation에 발표한 본 논문은 SEAS 자료를 활용한 매우 중요한 연구 결과로서 대부분의 low-gradient '중증' 대동맥판협착증 환자들은 중등도 협착증과 유사한 임상경과를 보이므로 수술적 치료가 필요하지 않음을 결정적으로 제시하였다. 본 연구 결과를 임상에 적용할 때 유의할 사항으로는 좌심실 박출률이 50% 정도로 저하되면서 일회박출량이 약간 감소하거나 신체가 작고 좌심실도 작아서 일회박출량이 감소하는 경우에는 대동맥판협착증의 중증도에 비해 압력차가 낮게 나올 수 있으므로, 상대적으로 드물지만 이러한 low-gradient 중증 대동맥판협착증 환자들에서는 특징적인 증상이 동반된다면 수술적 치료가 필요하다는 것이다. 결론적으로 환자의 치료 방침을 결정하는 데 있어서, 현재 대동맥판협착증의 치료 지침에서 정의한 중증 대동맥판협착증의 대동맥판 면적 기준을 기계적으로 적용하기보다는 최대 대동맥 혈류속도, 압력차, 좌심실 비대 및 크기 등을 함께 고려하고, 환자의 증상에 대해서도 대동맥판협착증과 연관된 증상인지를 상세히 조사하여 증상의 동반 여부를 평가해야 할 것이다.