NATURAL HISTORY OFAORTIC STENOSIS

Rheumatic Aortic valve disease

- fusion of the commissures between the leaflets, with a small central orifice.
- The rheumatic process typically involves the mitral valve as well
- most patients with rheumatic AS also have mitral stenosis and/or mitral regurgitation.

Aortic Valve Disease-AS

- Aortic valve sclerosis-valve thickening and calcification without a significant gradient (defined as an aortic jet velocity <2 m/sec).
- Aortic stenosis (AS)- antegrade velocity across an abnormal valve is at least 2 m/sec.
- The stages of AS are defined by symptoms, valve anatomy, valve hemodynamics, and left ventricular function

A

AORTIC VALVE ANATOMY

B

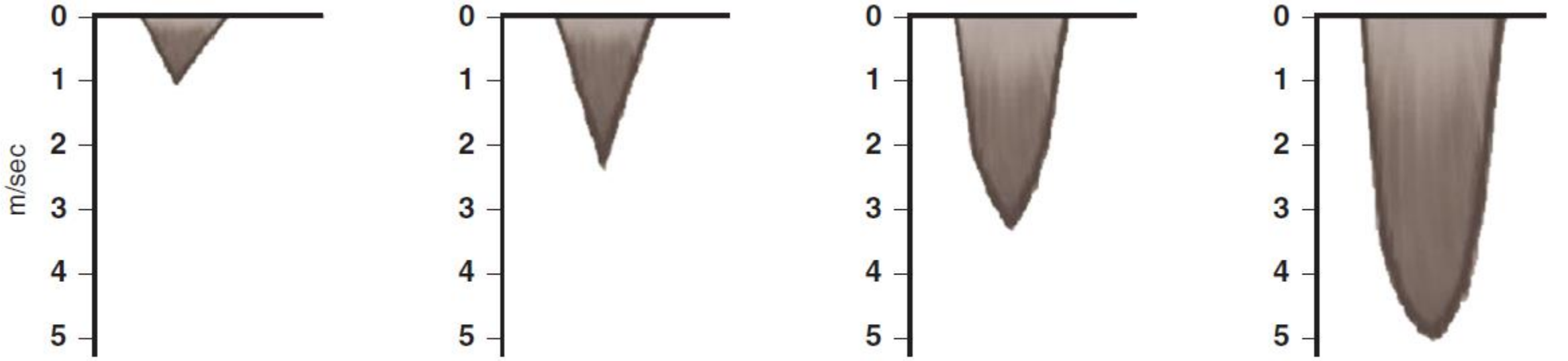
Normal

Aortic sclerosis

Mild to moderate aortic stenosis

Severe aortic stenosis

DOPPLER AORTIC JET VELOCITY



NORMAL

AORTIC SCLEROSIS
<2.5 m/sec

MILD TO MODERATE AORTIC STENOSIS
2.5-4.0 m/sec

SEVERE AORTIC STENOSIS
>4 m/sec

C

STAGE	DEFINITION	VALVE ANATOMY	VALVE HEMODYNAMICS	HEMODYNAMIC CONSEQUENCES	SYMPTOMS
A	**At risk of AS**	Bicuspid aortic valve (or other congenital valve anomaly) Aortic valve sclerosis	Aortic Vmax <2 m/sec	None	None
B	**Progressive AS**	Mild to moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion or Rheumatic valve changes with commissural fusion	***Mild AS:*** Aortic Vmax 2.0-2.9 m/sec or mean ΔP <20 mm Hg ***Moderate AS:*** Aortic Vmax 3.0-3.9 m/sec or mean ΔP 20-39 mm Hg	Early LV diastolic dysfunction may be present Normal LVEF	None
C	**Asymptomatic severe AS**				
C1	Asymptomatic severe AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	***Severe AS:*** Aortic Vmax ≥4 m/sec or mean ΔP ≥40 mm Hg AVA typically is ≤1 cm^2 (or AVAi ≤0.6 cm^2/m^2) Very severe AS is an aortic Vmax ≥5 m/sec, or mean ΔP ≥ 60 mm Hg	LV diastolic dysfunction Mild LV hypertrophy Normal LVEF	None–exercise testing is reasonable to confirm symptom status
C2	Asymptomatic severe AS with LV dysfunction	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	Aortic Vmax ≥4 m/sec or mean ΔP ≥40 mm Hg AVA typically is ≤1 cm^2 (or AVAi ≤0.6 cm^2/m^2)	LVEF <50%	None

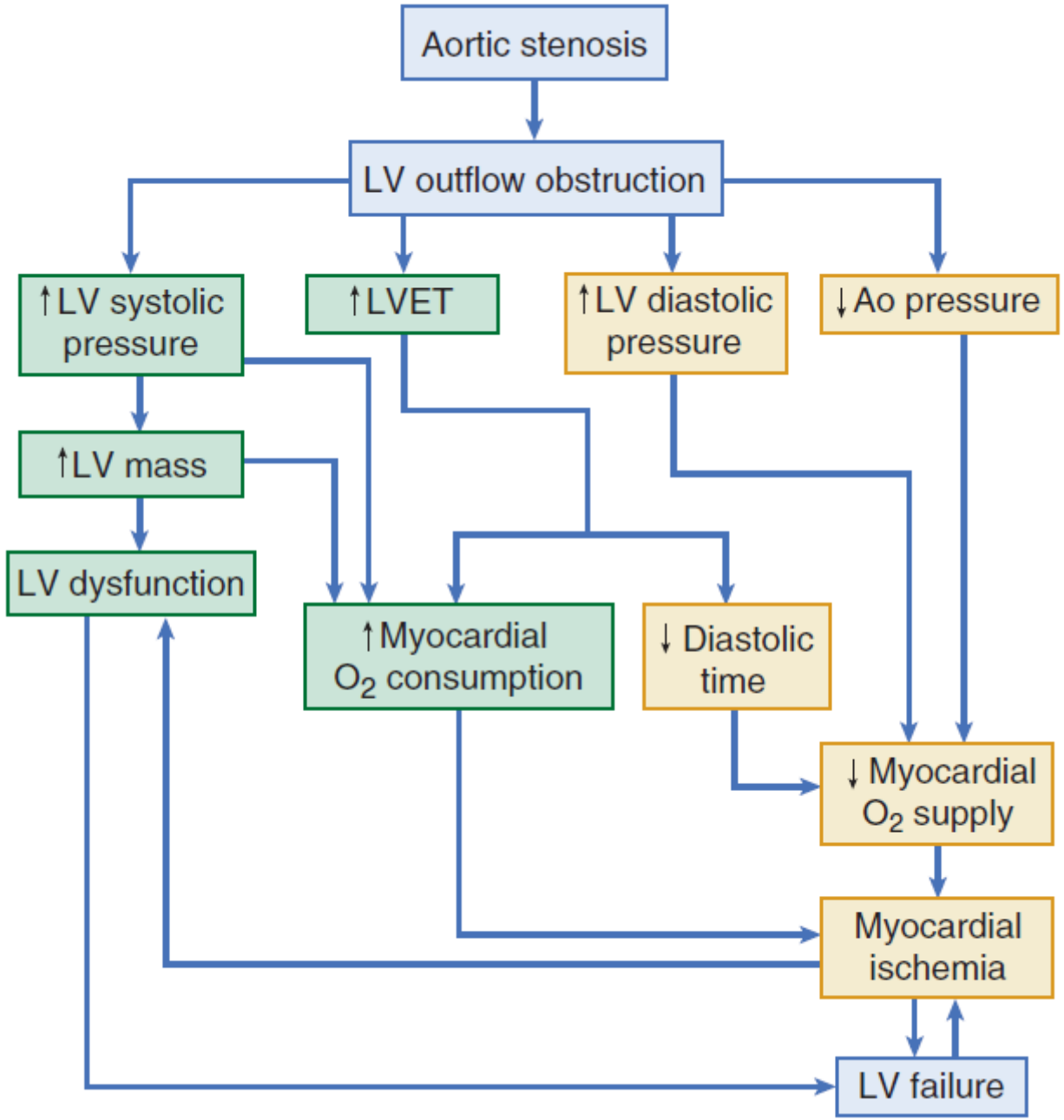
D	**Symptomatic severe AS**				
D1	Symptomatic severe high-gradient AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	***Severe AS:*** Aortic Vmax ≥4 m/sec, or mean ΔP ≥40 mm Hg AVA typically is ≤1 cm^2 (or AVAi ≤0.6 cm^2/m^2), but may be larger with mixed AS/AR	LV diastolic dysfunction LV hypertrophy Pulmonary hypertension may be present	Exertional dyspnea or decreased exercise tolerance Exertional angina Exertional syncope or presyncope
D2	Symptomatic severe low-flow/ low-gradient AS with reduced LVEF	Severe leaflet calcification with severely reduced leaflet motion	AVA ≤1 cm^2 with resting aortic Vmax <4 m/sec, or mean ΔP <40 mm Hg Dobutamine stress echo shows AVA ≤1 cm^2 with Vmax ≥4 m/sec at any flow rate	LV diastolic dysfunction LV hypertrophy LVEF <50%	HF, Angina, Syncope or presyncope
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	Severe leaflet calcification with severely reduced leaflet motion	AVA ≤1 cm^2 with aortic Vmax <4 m/sec, or mean ΔP <40 mm Hg AVAi ≤0.6 cm^2/m^2 Stroke volume index <35 mL/m^2 Measured when the patient is normotensive (systolic BP <140 mm Hg)	Increased LV relative wall thickness Small LV chamber with low-stroke volume. Restrictive diastolic filling LVEF ≥50%	HF, Angina, Syncope or presyncope

PROGRESSION OF AORTIC STENOSIS

- reduction in the aortic valve area and
- increase in transvalvular systolic pressure gradient.
- In normal aortic valves, the effective area of valve opening equals 3-4 cm^2 in adults.

PROGRESSION OF AORTIC STENOSIS

- As aortic leaflet thickening and calcification develop, the antegrade velocity remains normal
- and there is a minimal valve gradient until the orifice area reaches less than half of normal.


Aortic stenosis
LV outflow obstruction
↑LV systolic pressure
↑LVET
↑LV diastolic pressure
↓Ao pressure
↑LV mass
LV dysfunction
↑Myocardial O_2 consumption
↓ Diastolic time
↓ Myocardial O_2 supply
Myocardial ischemia
LV failure

Natural history of AS

- begins with a prolonged asymptomatic period.
- symptoms in patients with AS and normal LVEF rarely occur until the stenosis is severe

➢valve area is <1 cm^2,

➢the jet velocity is over 4 m/sec,and/or

➢mean transvalvular gradient exceeds 40 mmHg

Natural history of AS

- Many patients do not develop symptoms until critical valve obstruction is present,
- while some patients become symptomatic when the stenosis is less severe, particularly if there is coexisting aortic regurgitation.

Natural history of AS

- Most develop symptoms before the onset of LV systolic dysfunction.
- In some reduction in LV systolic function occurs before the onset of symptoms.
- At this point, the left ventricle fails, resulting in reductions in stroke volume and cardiac output,
- and eventually signs and symptoms of heart failure.

Natural history of AS

- Patients with mild disease (ie, aortic jet velocity<3 m/sec) unlikely to develop symptoms due to AS over the ensuing five years.
- Though substantial number severe AS are not symptomatic
- but patients with asymptomatic severe AS have low event-free survival rates
- 56-63 % at 2 years and 25-33 % at 4-5 years

ASYMPTOMATIC PATIENTS

- The severity of outflow tract obstruction gradually increases over 10 to 15 years,
- long latent period during which stenosis severity is only mild to moderate
- clinical outcomes are similar to those for age-matched normal patients

ASYMPTOMATIC PATIENTS

- Of patients with mild valve thickening (e.g., aortic sclerosis)
- 16% will have valve obstruction at 1 year of follow-up,
- only 2.5% will develop severe valve obstruction at an average of 8 years after the diagnosis of aortic sclerosis.
- Disease progression may be related to different factors than initiation of disease

ASYMPTOMATIC PATIENTS

- Once moderate to severe AS is present, prognosis remains excellent so long as the patient remains asymptomatic.
- The progressive nature of the disease, however, warrants close follow-up.
- The strongest predictor of progression to symptoms is the Doppler aortic jet velocity.

ASYMPTOMATIC PATIENTS

- Survival free of symptoms is 84% at 2 years when jet velocity < 3 m/sec,
- only 21% when jet velocity is > 4 m/sec.
- In adults with severe AS (Doppler velocity >4 m/sec), outcome can be further predicted by:

➢magnitude of the Doppler velocity

➢severity of aortic valve calcification

AYMPTOMATIC TO SYMPTOMATIC AS

- The likelihood of symptom onset increases as AS severity increases
- symptom onset occurs within 3 years in

➢approximately 50% of patients with an aortic velocity between 4 and 5 m/sec,

➢67% of patients with an aortic velocity between 5.0 and 5.5 m/sec, and

➢89% of patients with an aortic velocity>5.5 m/sec

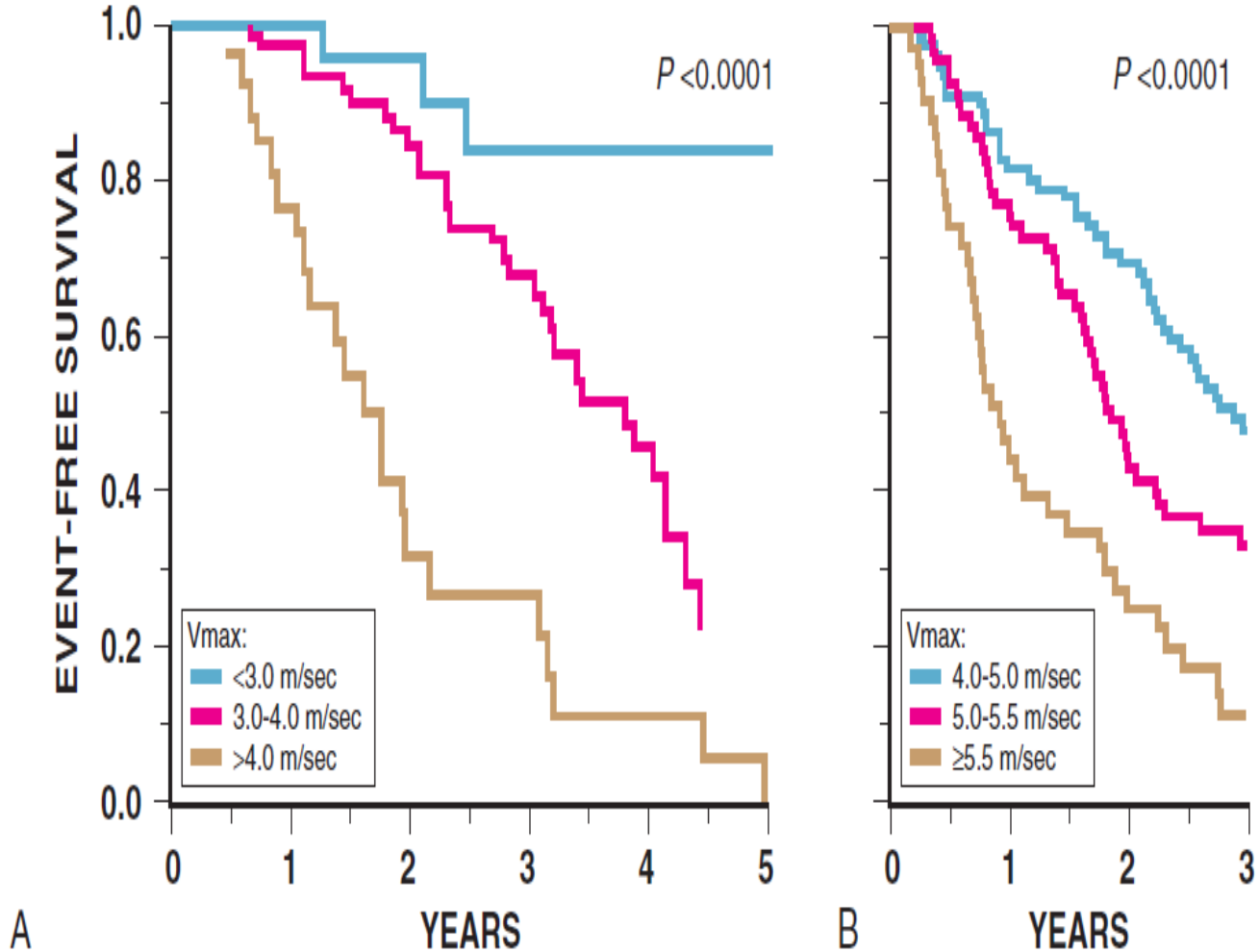


FIGURE 63-6 **A,** Natural history as reflected by event-free survival in asymptomatic patients with AS. Initial aortic jet velocity (Vmax) stratifies patients according to the likelihood that symptoms requiring valve replacement will develop over time. **B**, Outcomes with very severe AS. Kaplan-Meier event-free survival rate for patients with a peak aortic jet velocity of 4.0 m/sec or greater. In both **A** and **B,** most "events" consisted of the onset of symptoms warranting aortic valve replacement. (***A,*** *From Otto CM, Burwarsh IG, Legget ME, et al: A prospective study of asymptomatic valvular aortic stenosis: Clinical, echocardiographic, and exercise predictors of outcome. Circulation 95:2262, 1997.* ***B,*** *From Rosenhek R, Zilberszac R, Schemper M, et al: Natural history of very severe aortic stenosis. Circulation 121:151, 2010.)*

STUDY	NO. OF PATIENTS	SEVERITY OF AORTIC STENOSIS	AGE (YEARS)	MEAN FOLLOW-UP	EVENT-FREE SURVIVAL WITHOUT SYMPTOMS
Kelly et al, 1988	51	Vmax >3.6 m/sec	63 ± 8	5-25 months	Overall: 59% at 15 months
Pellikka et al, 1990	113	Vmax ≥4.0 m/sec	40-94	20 months	Overall: 86% at 1 year, 62% at 2 years
Kennedy et al, 1991	66	AVA = 0.7-1.2 cm^2	67 ± 10	35 months	Overall: 59% at 4 years
Otto et al, 1997	123	Vmax >2.6 m/sec	63 ± 16	2.5 ± 1.4 years	Overall: 93% ± 5% at 1 year, 62% ± 8% at 3 years; 26% ± 10% at 5 years *Subgroups:* Vmax <3 m/sec: 84% ± 16% at 2 years Vmax 3-4 m/sec: 66% ± 13% at 2 years Vmax >4 m/sec: 21% ± 18% at 2 years
Rosenhek et al, 2000	128	Vmax >4.0 m/sec	60 ± 18	22 ± 18 months	Overall: 67% ± 5% at 1 year, 56% ± 55% at 2 years, 33% ± 5% at 4 years *Subgroups:* No or mild Ca^{2+}: 75% ± 9% at 4 years Moderate-severe Ca^{2+}: 20% ± 5% at 4 years
Rosenhek et al, 2004	176	Vmax 2.5-3.9 m/sec LVEF >50%	58 ± 19	48 ± 19 months	95% at 1 year 75% at 2 years 60% at 5 years

Pellikka et al, 2005	622	Vmax ≥4.0 m/sec	72 ± 11	5.4 ± 4.0 years	Overall: 82% at 1 year, 67% at 2 years, 33% at 5 years
Rossebo et al, 2008	1873	Vmax 2.5-4.0 m/sec	68 ± 9	52 months (median)	Event-free survival 65% at 5 years No effect of statin therapy on major CV events
Lancellotti et al, 2010	163	AVAi ≤0.6 cm^2/m^2 No AS symptoms LVEF ≥55%	70 ± 10	20 ± 19 months	Event-free survival 50% at 2 years, 44% at 4 years Multivariate predictors of clinical outcome were Vmax ≥4.4 m/sec, LV longitudinal deformation ≤15.9%, valvuloarterial impedance ≥4.9 mm Hg/m^2, LA area ≥12.2 cm^2/m^2
Kang et al, 2010	95	AVA 0.75 cm^2 PLUS Vmax ≥4.5 m/sec or ΔP_{mean} ≥50 mm Hg	63 ± 12	50 months	71% ± 5% at 2 years 47% ± 5% at 4 years 28% ± 6% at 6 years Multivariate predictors of survival were Vmax ≥5 m/sec age, male sex, EuroScore, degree of valve calcification

Stewart et al, 2010	183	Vmax >3 m/sec LVEF >50%	70	31 months (median)	Probability of symptom-free survival at 3 years (95% CI) Vmax <3.5 m/sec: 0.72 (0.61-0.84) Vmax 3.5-4.0 m/sec: 0.46 (0.30-0.62) Vmax >4.0 m/sec: 0.32 (0.20-0.44)
Rosenhek et al, 2010	116	Vmax ≥5.0 m/sec	67 ± 15	41 (median)	Vmax 5.0-5.5 m/sec: 43% at 2 years Vmax ≥5.5 m/sec: 25% at 2 years Vmax but not AVA predicted outcome
Jander et al, 2011	435	*Low-gradient "severe" AS:* AVA <1 cm^2 with ΔP_{mean} ≤40 mm Hg	70 ± 9	46 ± 14 months	No difference in event rates between groups Low-gradient "severe" AS, defined as an AVA <1 cm^2 with ΔP_{mean} ≤40 mm Hg, was NOT a predictor of clinical outcome
	184	*Moderate AS:* AVA 1-1.5 cm^2, ΔP_{mean} 25-40 mm Hg	67 ± 9	46 ± 14 months	
Saito et al, 2012	103	AVA <1.0 cm^2	72 ± 11	36 ± 27	AVA index <0.6 cm^2/m^2: 41% at 3 years AVA index ≥0.6 cm^2/m^2: 86% at 3 years *Multivariate analysis:* AVAi <0.6 cm^2/m^2 (HR 2.6; 95% CI 11.1-6.3) Vmax >4.0 m/sec (HR 2.6; 95% CI 1.2-5.8) AVA <0.75 cm^2 did NOT predict outcome (mean BSA 1.50 ± 0.15 m^2)

“Symptomatic AS”

- most common symptoms are decreased exercise tolerance, or dyspnea on exertion

- End-stage symptoms include

➢heart failure,

➢anginal chest discomfort, and

➢syncope.

SYMPTOMATIC PATIENTS

- Once even mild symptoms are present, survival is poor unless outflow obstruction is relieved.
- interval from the onset of symptoms to the time of death is approximately
- 2 years in patients with heart failure,
- 3 years in those with syncope, and
- 5 years in those with angina.

Symptomatic severe AS

- outlook is poorest when the left ventricle has failed and cardiac output and transvalvular gradient both are low.
- risk of sudden death is high
- promptly referred for surgical intervention.
- In patients who do not undergo surgical intervention,
- recurrent hospitalizations for angina and decompensated heart failure are common

PARTNER (Placement of Transcatheter Aortic Valves) study

- 179 patients with AS with heart failure symptoms were assigned to the standard therapy arm
- outcomes were very poor for patients with severe symptomatic AS deemed unsuitable candidates for surgery randomly assigned to medical therapy with a
- 1-year mortality of 50.9% and a
- 2-year mortality of 68%

Leon MB et al N Engl J Med 2010; 363:1597

Ben-Dor I et al; Circulation 2010; 122:S37

- observational study of symptomatic AS patients
- not eligible for a transcatheter aortic valve implantation trial,
- 274 patients received medical treatment
- Mortality was 32% during median follow-up of one year.

Rate of hemodynamic progression

- annual decrease in aortic valve area of 0.12 cm2/year,
- an increase in aortic jet velocity of 0.32 m/sec/year, and
- an increase in mean gradient of 7 mm Hg/ year.
- The rate of progression is highly variable, however, and difficult to predict in individual patients.

Factors associated with more rapid hemodynamic progression

- older age,
- more severe leaflet calcification,
- renal insufficiency,
- hypertension,
- smoking, and
- hyperlipidemia.
- The role of genetic factors remains unclear.

Exercise testing and serum BNP levels

- Exercise testing monitored by a physician is safe in adults with severe AS when symptom status is unclear, and
- patients who develop symptoms or exhibit a decrease in blood pressure with exertion should be considered to have symptomatic disease.
- An elevated BNP level may be helpful when symptoms are equivocal or when stenosis severity is only moderate