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STATE-OF-THE-ART REVIEW

Natural History, Diagnostic Approaches, and Therapeutic Strategies for Patients With Asymptomatic Severe Aortic Stenosis

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ABSTRACT

Aortic stenosis (AS) is one of the most common valvular diseases encountered in clinical practice. Current guidelines recommend aortic valve replacement (AVR) when the aortic valve is severely stenotic and the patient is symptomatic; however, a substantial proportion of patients with severe AS are asymptomatic at the time of first diagnosis. Although specific morphological valve features, exercise testing, stress imaging, and biomarkers can help to identify patients with asymptomatic severe AS who may benefit from early AVR, the optimal management of these patients remains uncertain and controversial. The current report presents a comprehensive review of the natural history and the diagnostic evaluation of asymptomatic patients with severe AS, and is followed by a meta-analysis from reported studies comparing an early AVR strategy to active surveillance, with an emphasis on the level of evidence substantiating the current guideline recommendations. Finally, perspectives on directions for future investigation are discussed.
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Aortic stenosis (AS) affects ~5% of adults above the age of 65 years (1). It is one of the most common valvular diseases in developed countries, and its prevalence is projected to increase over the next decade with an aging population (2,3). Untreated, symptomatic severe AS is associated with a dismal prognosis (4-6), with as many as half of patients dying within 1 or 2 years (7-9). Aortic valve replacement (AVR), either surgical or via a transcatheter approach, is the only treatment shown to improve survival (10-14). Current guidelines recommend surgical AVR (SAVR) as a Class I indication for appropriate patients with severe symptomatic AS. Transcatheter AVR (TAVR) is recommended with a Class I indication for severe symptomatic AS patients who are not candidates for SAVR and with a Class IIa recommendation as an alternative to SAVR in "high-risk" AS patients (15,16).

As many as 50% of patients with severe AS report no symptoms at the time of diagnosis (17-19). The optimal timing of intervention for these patients is uncertain and controversial (17,19-28). Although current guidelines recommend AVR for selected patients with asymptomatic severe AS (**Table 1**) (15,16),

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ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

3D = 3-dimensional

ΔP = mean pressure difference across the valve

ACC = American College of Cardiology

AHA = American Heart Association

AS = aortic stenosis

AVA = aortic valve area

AVR = aortic valve replacement

BNP = B-type natriuretic peptide

CI = confidence interval

CMR = cardiac magnetic resonance

CT = computed tomography

EACTS = European Association of Cardio-Thoracic Surgery

ESC = European Society of Cardiology

HR = hazard ratio

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

NT-proBNP = N-terminal pro-B-type natriuretic peptide

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

V_{max} = peak velocity of blood flow across the valve

Zva = valvuloarterial impedance

in practice, a "watchful waiting" or active surveillance strategy is adopted for the vast majority of asymptomatic patients, with intervention planned once symptoms emerge or left ventricular (LV) systolic dysfunction develops. This strategy has some practical challenges: 1) interpreting symptoms or the lack thereof is notoriously difficult, particularly in elderly sedentary patients; 2) with AS progression being highly variable and unpredictable, rapid deterioration may occur; 3) a standardized algorithm for active surveillance has not been defined or validated; 4) late symptom reporting may result in irreversible myocardial damage with worsened prognosis, despite AVR; 5) operative risk increases with patient age and LV dysfunction; and 6) the risk of sudden death in patients with severe AS without classic symptoms is ~1% to 1.5% per year. Given the current low periprocedural mortality rates for isolated SAVR and TAVR, earlier intervention has been increasingly advocated (11-14,18,19,25-31); however, the current conservative strategy of watchful waiting in patients with asymptomatic severe AS has never been compared with early AVR in a randomized trial.

The present report will review the natural history of asymptomatic severe AS and subsequently summarize the potential roles of exercise testing, biomarker assessment, and imaging to guide the optimal timing of AVR. A meta-analysis from reported studies comparing an AVR strategy with a watchful waiting approach will also be presented. Finally, perspectives on directions for future investigation are discussed.

NATURAL HISTORY AND DIAGNOSTIC EVALUATION OF PATIENTS WITH ASYMPTOMATIC SEVERE AS

DEFINITION OF SEVERE AS AND CURRENT RECOMMENDATIONS FOR AVR. Current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines describe 4 stages of AS (15). A patient is at risk of AS (stage A) if a bicuspid aortic valve or aortic valve sclerosis is identified. A patient is classified as having progressive AS (stage B) if echocardiographic evidence of mild or moderate AS is present. Stage C and stage D refer to hemodynamically severe AS without symptoms (stage C) and with symptoms (stage D). Hemodynamically severe AS is defined as: 1) peak aortic jet velocity ≥4 m/s or a mean transvalvular pressure gradient ≥40 mm Hg; or 2) aortic valve area (AVA) ≤1.0 cm^2 or ≤0.6 cm^2/m^2.

AVR for symptomatic and hemodynamically severe AS is a Class I recommendation. In the presence of symptomatic low-flow/low-gradient AS (defined as severely calcified and restricted leaflet with AVA ≤1.0 cm^2 and resting peak aortic jet velocity <4 m/s or mean gradient <40 mm Hg), AVR is a Class IIa recommendation, given that dobutamine (in case of left ventricular ejection fraction [LVEF] <50%) demonstrated true severe AS or, in the case of LVEF ≥50%, clinical, anatomic, and hemodynamic features (restricted leaflet motion, severe calcification, indexed valve area ≤0.6 cm^2/m^2, stroke volume index <35 ml/m^2) support severe valve obstruction. Finally, AVR is also a Class IIa recommendation for patients with moderate AS (stage B) with an aortic velocity between 3.0 m/s and 3.9 m/s or mean pressure gradient between 20 mm Hg and 39 mm Hg who are undergoing cardiac surgery for other indications.

Asymptomatic severe AS is divided into 2 subcategories (C1 and C2), distinguished by whether LV systolic function is impaired (i.e., LVEF <50%). Patients with asymptomatic AS and reduced LV systolic function (C2) also have a Class I recommendation for AVR (**Table 1**, **Central Illustration**).

For patients with asymptomatic AS and LVEF >50% (stage C1), AVR should be considered with a Class I recommendation if the patient is scheduled to undergo other cardiac surgery or if clearly valve-related symptoms are unmasked by stress test, and is reasonable with a Class IIa recommendation with evidence of an abnormal exercise stress test or if the AS is hemodynamically very severe (peak aortic jet velocity ≥5 m/s [15] or ≥5.5 m/s [16]) (**Table 1**). For stage C1 patients who do not fulfill those criteria, a strategy of watchful waiting is recommended, with clinical and echocardiographic assessment every 6 to 12 months (**Central Illustration**).

Of note, the level of evidence substantiating each of these recommendations is either B or C, meaning that they are on the basis of small, retrospective, observational studies or expert consensus opinions, with no randomized clinical trial available. The data regarding which stage C1 patients might benefit from early AVR are especially sparse. Most of the studies supporting current guideline recommendations include approximately 100 to 200 patients and originate mainly from single-center experiences (32-35). Also, the following stress test criteria are commonly used to qualify a stage C1 patient for AVR: development of exercise-limiting symptoms at low workload or an abnormal blood pressure response

(i.e., hypotension or <20 mm Hg increase). These findings are derived from studies of approximately 100 patients (34,36-39). These studies show that patients who experience any of the criteria mentioned earlier are more likely over time to develop symptoms, undergo AVR, or die than patients who do not display these criteria; however, the number of deaths in these studies is low, and it is not clear whether these patients would benefit from early AVR (before they progress to stage D). Similarly, although patients with peak aortic velocity ≥5 m/s or ≥5.5 m/s have an increased event rate, the events are usually development of symptoms and not sudden cardiac death while asymptomatic (25,35,40). Whether the low rate of sudden death would be reduced with early AVR is unknown, an important consideration given the morbidity and cost of the procedure in an asymptomatic population.

TABLE 1 Recommendations for the Diagnostic Evaluation, Follow-up, and Timing of Surgical AVR in Patients With Asymptomatic, Severe, High-Flow, High-Gradient AS

	AHA/ACC (15) Class (LOE)	ESC/EACTS (16) Class (LOE)
Indications for surgical aortic valve replacement		
Left ventricular ejection fraction <50%	I (B)	I (C)
Undergoing other cardiac surgery	I (B)	I (C)
Symptoms on exercise test clearly related to aortic stenosis	I (B)	I (C)
Decreased exercise tolerance	IIa (B)	IIa (C)
Exercise fall in blood pressure	IIa (B)	IIa (C)
Very severe (aortic velocity ≥5.0 m/s [AHA/ACC]; >5.5 m/s [ESC/EACTS]) aortic stenosis and low surgical risk	IIa (B)	IIa (C)
Rate of peak transvalvular velocity progression ≥0.3 m/s/year and low surgical risk	IIb (C)	IIa (C)
Repeated markedly elevated natriuretic peptide and low surgical risk	–	IIb (C)
Increase of mean pressure gradient with exercise by >20 mm Hg and low surgical risk	–	IIb (C)
Excessive left ventricular hypertrophy in the absence of hypertension and low surgical risk	–	IIb (C)
Diagnostic evaluation		
Transthoracic echocardiography as the initial diagnostic modality	I (B)	–
Exercise testing	IIa (B)	–
Exercise echocardiography	IIa (B)	–
Follow-up		
Echocardiography every 6-12 months	I (C)	–

ACC = American College of Cardiology; AHA = American Heart Association; AS = aortic stenosis; AVR = aortic valve replacement; EACTS = European Association for Cardio-Thoracic Surgery; ESC = European Society of Cardiology; LOE = Level of Evidence.

NATURAL COURSE OF ASYMPTOMATIC SEVERE AS

Patients with asymptomatic severe AS have a better prognosis than those with symptomatic severe AS (40); however, 5 years after receiving the diagnosis, approximately two-thirds of conservatively managed patients with asymptomatic AS will develop symptoms, and 75% will have either died or undergone AVR (18).

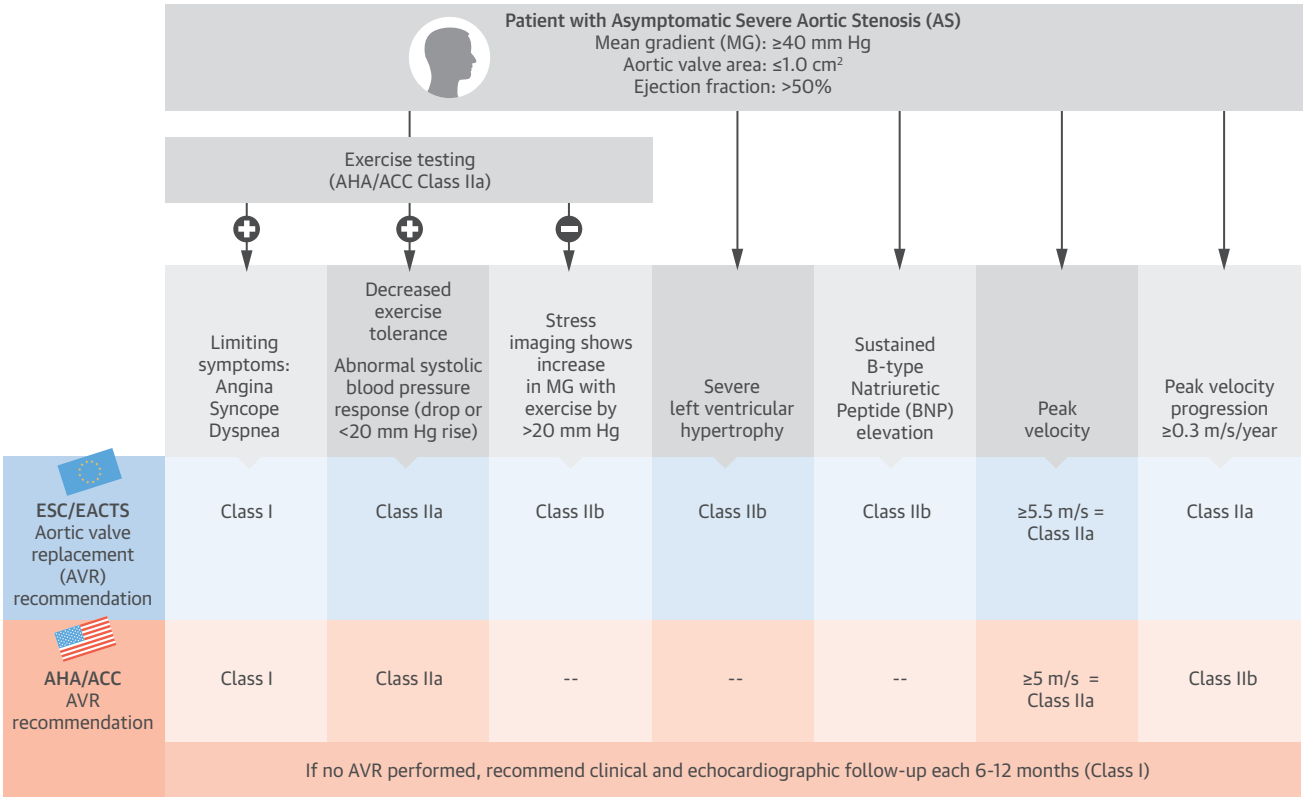
The rate of hemodynamic progression of severe AS is variable and unpredictable. The average annual increase in aortic jet velocity has been estimated to be 0.3 m/s, and the annual decrease in AVA has been estimated at 0.1 cm^2 (32). Several predictors of rapid hemodynamic progression have been reported, including smoking, dyslipidemia, male sex, diabetes mellitus, hypertension, chronic kidney disease, and coronary artery disease (41). To what extent these factors contribute to AS progression is unknown. The aortic valve calcium load is the most powerful predictor of rapid stenosis progression (42).

In patients with asymptomatic severe AS, 1-year and 5-year survival rates have been reported to range from 67% to 97% and 38% to 83%, respectively (19,26,33,40,43). A recent retrospective analysis of 1,517 conservatively treated patients with asymptomatic severe AS by Taniguchi et al. (26), the largest study to date, reported 1-year and 5-year survival rates of 92.8% and 73.6%, respectively. However, many patients who died did so after first developing symptoms and were not referred for AVR. The risk of dying in asymptomatic patients is directly related to the severity of AS and its rate of progression (18,32). Patients with limiting symptoms on exercise testing are significantly more likely to develop spontaneous symptoms or die than those without exercise-limiting symptoms (39,44). Other reported predictors of death or subsequent need for AVR include age, chronic heart failure, chronic renal insufficiency, and inactivity (18,32). Beta-blocker use and higher LVEF have been associated with better prognosis (19). Although statin use in patients with AS has been shown to decrease the rates of ischemic cardiovascular events (mainly the need for coronary artery bypass graft), its role in preventing major clinical valve-related outcomes (such as the need for AVR) has never been demonstrated (45).

DEVELOPMENT OF SYMPTOMS AND THE NEED FOR AVR

The median time to symptom onset, AVR, or death has ranged between 1 and 4 years (Table 2); however, the definitions of what constitutes "symptoms" have differed across studies, and some studies reported only cardiac death and/or hospitalization, rather than death and/or symptom onset. Furthermore, some studies included patients with moderate AS (stage B)

CENTRAL ILLUSTRATION Treatment Algorithm for Asymptomatic Severe Aortic Stenosis: Basis of Current American and European Guidelines



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ACC = American College of Cardiology; AHA = American Heart Association; AS = aortic stenosis; AVA = aortic valve area; ESC = European Society of Cardiology; MG = mean gradient; PV = peak velocity; SBP = systolic blood pressure.

as well as more severe AS. Median time to symptom onset would likely be shorter if these studies had only included patients with severe AS. Recently, from 582 propensity-matched patients with asymptomatic severe AS, Taniguchi et al. (26) reported the emergence of AS-related symptoms in 46.3% of patients undergoing medical observation compared with 3.2% for patients undergoing early AVR ($p < 0.001$) at a median follow-up of 1,361 days. Importantly, up to 19.9% in the observation group compared with 3.8% in the early AVR cohort were hospitalized for heart failure ($p < 0.001$). Also, among the 291 patients treated with the conservative approach, AVR was performed in 118 patients (41%) during follow-up, with a median interval of 780 days from diagnosis.

Hemodynamic severity of AS, the degree of aortic valve calcification, positive stress test results, and LV hypertrophy have been associated with more rapid symptom onset (18,19,32) (**Table 3**). Other factors that influence the development of symptoms include baseline functional status and level of activity, and the presence of comorbidities (33,35,41,46). An important drawback to basing treatment decisions on whether or not a patient reports symptoms relates to the subjective nature of "symptoms." It is difficult to decipher whether patients who do not report symptoms in everyday life and/or report no symptoms on an exercise test are truly asymptomatic. AS typically progresses slowly, and symptoms may be nonspecific. Patients may therefore relate their symptoms to poor overall stamina. They may also relate their symptoms to a concomitant medical condition. Alternatively, they may adjust their activity and/or exercise level to avoid symptoms. Finally, interpreting dyspnea as a definite cardiac symptom is often equally difficult in an aging, deconditioned, and overweight population.

TABLE 2 Observational Studies of Patients With Asymptomatic Severe AS

First Author (Ref. #)	Year	Design	AS Definition	N	Age (Yrs)	Female Patients	Severity	Follow-Up	Clinical Outcomes and Findings
Pellikka et al. (17)	1990	Retrospective, observational, comparative study	Severe AS; Doppler PV ≥4 m/s	143 (23 AVR, 5 valvuloplasty, and 2 surgical decalcification within 3 months following echocardiography vs. 113 no AVR)	72 (mean) 40 to 94	38%	Entire cohort PV: 4.4 m/s 4.0 to 6.4 m/s MG: 51 mm Hg AVR PV: 4.6 m/s MG: 63 mm Hg No AVR PV: 4.3 m/s (significantly <AVR group) MG: 47 mm Hg	AVR 21 months (mean) No AVR 20 months	AVR: 2 of 30 (6.7%) deaths (cardiac). Freedom from cardiac death or re-AVR was 90% at 6 months, 1 yr, and 2 yrs. No AVR: 14 of 113 (12.4%) deaths (6 [5.3%] cardiac). Survival was 96%, 94%, and 90% at 6 months, 1 yr, and 2 yrs, respectively. 37 of 113 (32.7%) developed symptoms. Freedom from symptoms was 94%, 86%, and 62% at 6 months, 1 yr, and 2 yrs, respectively. 20 of 113 (17.7%) had AVR. Freedom from cardiac death or AVR was 95%, 93%, and 74% at 6 months, 1 yr, and 2 yrs, respectively.
Otto et al. (32)*	1997	Prospective, observational, single-arm	Moderate-severe AS; Doppler PV ≥2.5 m/s	123	63 ± 16 22 to 84	30%	AVA: 1.3 ± 0.5 cm^2 PV: 3.6 ± 0.6 m/s MG: 29 ± 11 mm Hg	2.5 ± 1.4 yrs	8 of 123 (6.5%) deaths (4 cardiac) 48 of 123 (39/0%) had AVR. 2-yr freedom from death and AVR: PV >4.0 m/s = 21%. PV 3.0 to 4.0 m/s = 66%; PV <3.0 m/s = 84% Freedom from cardiac death or AVR for symptoms was 93% at 1 yr, 67% at 3 yrs, 34% at 5 yrs.
Rosenhek et al. (43)*	2000	Prospective, observational, single-arm	Severe AS; Doppler PV ≥4 m/s	128 (22 AVR <3 months while asymptomatic; data censored at time of AVR)	60 ± 18	46%	PV: 5.0 ± 0.6 m/s	22 ± 18 months	8 of 128 (6.3%) deaths (6 [4.7%] cardiac) AVR for symptoms: 59 of 128 (46.1%). AVR with no symptoms: 22 of 128 (17.2%). Freedom from death or AVR was 67% at 1 yr, 56% at 2 yrs, 33% at 4 yrs.
Amato et al. (38)	2001	Prospective, observational, single-arm	Severe AS undergoing exercise testing; AVA ≤1 cm^2	66	44.2 ± 13.7	33%	AVA: 0.61 ± 0.17 cm^2	14.77 ± 11.93 months	44 of 66 (66.7%) had a positive stress test. 4 of 66 (6.1%; 1.2%/yr) had sudden death; all 4 had a positive exercise test and an AVA of <0.6 cm^2. 35 of 44 (79.5%) with positive stress test developed symptoms or sudden death. 3 of 22 (13.6%) with negative stress test developed symptoms or sudden death. Patients with positive stress test had a 7.6-fold increased risk of developing symptoms or sudden death at follow-up.

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TABLE 2 Continued

First Author (Ref. #)	Year	Design	AS Definition	N	Age (Yrs)	Female Patients	Severity	Follow-Up	Clinical Outcomes and Findings
Das et al. (39)	2005	Prospective, observational, single-arm	AS with EOA <1.4 cm^2	125	65 (IQR: 56–74)	32%	Mild: 11 patients (8%) Moderate: 62 patients (50%) Severe: 52 patients (42%), defined as EOA ≤ 0.8 cm^2	12 months	46 (37%) patients had stress-test limiting symptoms. 36 (29%) patients developed spontaneous symptoms. Symptom-free survival at 12 months was 49% for patients with limiting symptoms on exercise testing and 89% for those without. By multivariable analysis, limiting symptoms on exercise testing was the strongest independent predictor of symptom onset within 12 months. Patients with a positive stress test had a 7.7-fold increased risk of developing symptoms with 12 months.
Lancellotti et al. (37)	2005	Prospective, observational, single-arm	Severe AS with AVA ≤ 1 cm^2	69 degenerative: 96%; rheumatic: 4%	66 $\pm$ 12	30%	AVA: 0.81 $\pm$ 0.15 cm^2 MG: 40 $\pm$ 12 mm Hg PG: 65 $\pm$ 16 mm Hg	15 $\pm$ 7 months	26 (38%) patients had a positive stress test. 18 (26.1%) patients had cardiac events, including symptoms in 2 (2.9%), HF in 2 (2.9%), AVR in 12 (17.4%), and cardiac death in 2 (2.9%). 14 of 18 (77.8%) patients with abnormal stress test had cardiac events during follow-up. Independent predictors of cardiac events: 1) Increase in MG by $\geq$18 mm Hg during exercise; 2) An abnormal exercise test; 3) AVA <0.75 cm^2.
Pellikka et al. (18)	2005	Retrospective, observational, single-arm	Severe AS with Doppler PV >4 m/s	622	72 $\pm$ 11	38%	AVA: 0.9 $\pm$ 0.2 cm^2 PV: 4.4 $\pm$ 0.4 m/s MG: 45.8 $\pm$ 11.0 mm Hg	5.4 $\pm$ 4.0 yrs	Symptoms developed in 297 (48%) patients; AVR in 352 (52%); death in 265 (43%); cardiac death in 117 (19%). Sudden death without preceding symptoms occurred in 11 (4.1%; ~1%/yr) among 270 unoperated patients. Freedom from cardiac symptoms while unoperated was 82%, 67%, and 33% at 1, 2, and 5 yrs, respectively. Independent predictors of developing symptoms were AVA and LVH. Independent predictors of death were age, chronic renal failure, inactivity, and PV.
Pai et al. (19)	2006	Retrospective, observational, single-arm	Severe AS AVA <0.8 cm^2	338	71 $\pm$ 15	49%	AVA: 0.72 $\pm$ 0.17 cm^2	3.5 yrs	AVR in 99 (29%) patients; death in 157 (46%) patients. Death occurred in 10% AVR vs. 54% no AVR patients. Survival at 1, 2, and 5 yrs in no-AVR patients were 67%, 56%, and 38%, compared with 94%, 93%, and 90%, respectively, in AVR patients ($p < 0.0001$). Adjusted HR for death with AVR was 0.17 (95% CI: 0.10–0.29).

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TABLE 2 Continued

First Author (Ref. #)	Year	Design	AS Definition	N	Age (Yrs)	Female Patients	Severity	Follow-Up	Clinical Outcomes and Findings
Brown et al. (31)	2008	Prospective, observational, single-arm study	Severe AS with PV >4 m/s	622 total; subanalysis on 263 patients undergoing AVR driven by symptoms vs. no symptoms	72 ± 11	34%	AVR with symptoms AVA: 0.90 ± 0.3 cm^2 PV: 4.30 ± 0.4 m/s AVR with no symptoms AVA: 0.87 ± 0.2 cm^2 PV: 4.37 ± 0.4 m/s	7.8 ± 5.3 yrs	Subanalysis of Pellikka et al. 2005 (18) At 3 yrs, 52% of asymptomatic patients with severe AS had symptoms develop, had AVR, or died. Operative mortality was 2% for symptomatic patients and 1% for asymptomatic patients ($p = 0.43$). 10-yr survival was 64% for symptomatic patients and 64% for asymptomatic patients ($p = 0.92$) undergoing AVR. Among patients with asymptomatic severe AS, the omission of AVR was the most important risk factor for late mortality (HR: 3.53; $p < 0.001$).
Avakian et al. (124)	2008	Prospective, observational, single-arm	Severe AS with peak gradient ≥60 mm Hg	133	66.2 ± 13.6	48%	No event at follow-up AVA: 0.70 ± 0.16 cm^2 PV: 4.35 ± 0.41 m/s Event at follow-up AVA: 0.66 ± 0.18 cm^2 PV: 4.46 ± 0.49 m/s	3.30 ± 1.87 yrs	Symptoms: 64 (48%) patients; sudden death: 7 (5%; ~1%/yr) patients; AVR 5 (4%) patients. Event-free survival was 90.2% at 1 yr, 73.4% at 2 yrs, 70.7% at 3 yrs, 57.8% at 4 yrs, 40.3% at 5 yrs, and 33.3% at 6 yrs. Mean follow-up period until the development of sudden death was 1.3 ± 1.1 yrs. 3 deaths occurred in patients with preceding symptoms; 4 deaths occurred in patients without preceding symptoms.
Hachicha et al. (58)	2009	Retrospective, observational, single-arm	Moderate-severe AS; PV ≥2.5 m/s	544	70 ± 14	23%	Varying across Zva severity subgroups	2.5 ± 1.8 yrs	Increased mortality and cardiac events with Zva >3.5, and especially when >4.5.
Monin et al. (48)	2009	Prospective, observational single-arm	Moderate-severe AS; PV ≥3.0 m/s and/or AVA ≤1.5 cm^2	107	Median: 72 (IQR: 63-77)	33%	AVA: 0.9 cm^2 (0.8-1.1 cm^2) PV: 4.1 m/s (3.5-4.4 m/s); MG: 40 mm Hg (31-50 mm Hg)	24 months in 97% of patients	Events in 61 (57%) patients; 3 (2.8%) deaths, 58 (54%) AVRs; 1 patient refused AVR despite symptoms. 56 of 61 (90%) events occurred within 20 months.

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TABLE 2 Continued

First Author (Ref. #)	Year	Design	AS Definition	N	Age (Yrs)	Female Patients	Severity	Follow-Up	Clinical Outcomes and Findings
Lafitte et al. (68)	2009	Prospective, observational study with a normal control group	Severe AS with AVA <1 cm^2	60 AS 60 control	AS: 70 ± 12 control: 66 ± 15	18%	AS group AVA: 0.7 ± 0.2 cm^2 PV: 4.4 ± 0.6 m/s MG: 54 ± 15 mm Hg	12 months	42 (70%) patients underwent AVR; 18 (30%) did not undergo non-AVR. CV death: 2 (3.3%) patients; HF or AFib: 5 (8.3%) patients. 65% of patients had a positive stress test: 37% had limiting symptoms; 35% had an abnormal BP response; 13% had significant ECG ST-segment depression. GLS and BLS values of −18 and −13 were associated with a sensitivity and specificity of 68% and 75%, and 77% and 83%, respectively, in predicting an abnormal exercise response. Unoperated patients demonstrated a significant relationship between BLS and cardiac events; no event occurred in patients with BLS ≥13%.
Kang et al. (25)	2010	Prospective, observational, comparative study	Very severe AS with AVA ≤0.75 cm^2 AND PV ≥4.5 m/s or an MG ≥50 mm Hg	197 102 early AVR; 95 medical	63 ± 12	50%	Early AVR AVA: 0.61 ± 0.10 cm^2 PV: 5.1 ± 0.5 m/s MG: 65 ± 13 mm Hg Medical AVA 0.62 ± 0.09 cm^2 PV: 4.9 ± 0.4 m/s MG: 59 ± 12 mm Hg	Early AVR Median: 1,265 days (IQR: 2,325–947 days) Medical 1,769 days (IQR: 2,423–1,020 days)	Early AVR 0 operative mortality; 0 cardiac death; 3 (2.9%) noncardiac death. Initial medical therapy (conservative) 18 (18.9%) cardiac death; 10 (10.5%) noncardiac death; 46 (70.8%) AVR; 59 (62.1%) developed symptoms. 7 (7%) patients with sudden cardiac death were asymptomatic at the last examination performed within 1 yr before death, and the estimated actuarial 6-yr rate of sudden death not preceded by symptoms was 10%. Propensity score matched paired comparison (n = 57 pairs): all-cause mortality was significantly lower in the early AVR group than in the medical treatment group (HR: 0.14; 95% CI: 0.03-0.60; p = 0.008). 6-yr survival and cardiac mortality-free survival rates were 98% and 100% in the early surgery group and 68% and 76% in the medical treatment group respectively, both p < 0.001. The survival rates free of cardiac mortality in the conventional treatment group were 91% at 2 yrs, 83% at 4 yrs, and 76% at 6 yrs.
*Lancellotti et al. (34)	2010	Prospective, observational, single-arm	Moderate-to-severe AS with Indexed AVA ≤0.6 cm^2/m^2	163	70 ± 10	60%	Indexed AVA: 0.45 ± 0.09 cm^2/m^2 PV: 4.2 ± 0.6 m/s MG: 46 ± 14 mm Hg	20 ± 19 months	6 (3.7%) deaths and 57 (35%) AVR. 11 (6.8%) of patients who refused AVR had symptoms.
Le Tourneau et al. (46)	2010	Retrospective, observational, single-arm	Severe AS with PV ≥4 m/s	694 160 AVR <1 yr; 514 medical therapy; 20 valvuloplasty <1 yr (excluded)	71 ± 11	40%	AVA: 0.86 ± 0.23 cm^2 PV: 4.4 ± 0.5 m/s MG: 46 ± 11 mm Hg	Mean >5 yrs	1-yr death: 35 (5%); >1-yr death: 289 (41.6%) 248/514 (48.2%) had AVR among medical group. Operative mortality: early AVR: 1.9% vs. late AVR 2.8%

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TABLE 2 Continued

First Author (Ref. #)	Year	Design	AS Definition	N	Age (Yrs)	Female Patients	Severity	Follow-Up	Clinical Outcomes and Findings
Maréchaux et al. (33)*	2010	Prospective, observational, single-arm	Moderate and severe AS, with AVA <1.5 cm^2 and indexed AVA <0.9 cm^2/m^2	135 with moderate-to-severe AS (53% severe)	64 ± 15	36%	AVA: 0.97 ± 0.22 cm^2 PV 3.8 ± 0.8 m/s MG: 36 ± 15 mm Hg	20 ± 14 months	58 (43.0%) AVR; 4 (3.0%) symptoms but no AVR because multiple comorbidities; 3 (2.2%) CV deaths; 3 (2.2%) non-CV deaths. Median time between events (CV death or need for AVR motivated by symptoms or LVEF<50%) and occurrence of endpoint was 13 months (range: 0.6–50 months).
Rosenhek et al. (35)*	2010	Prospective, observational, single-arm	Very severe AS with PV >5 m/s	116	67 ± 15	49%	AVR within 3 months AVA: 0.61±0.13 cm^2 PV: 5.0 ± 0.7 m/s No AVR AVA: 0.69 ± 0.10 cm^2 PV: 4.5 ± 0.5 m/s	Median: 41 months (IQR: 26–63 months)	79 (68.1%) AVR; 9 (7.8%) deaths; 6 (5.2%) cardiac deaths; 73 (62.9%) developed symptoms (all asymptomatic and not meeting guideline criteria for AVR before death).
Stewart et al. (49)	2010	Prospective, observational, single-arm	Moderate-to-severe AS with PV >3 m/s	183	70 (IQR: 61–76)	35%	AVA: 0.81 cm^2 (0.64–1.01 cm^2) PV: 3.77 m/s (3.27–4.35 m/s)	Median: 31 months (IQR: 14–40 months)	106 (58%) had symptoms, 95 (51.9%) AVR; 3 sudden deaths. PV was the only significant predictor of symptomatic deterioration. The average rate of increase in peak aortic velocity was greater for patients who became symptomatic compared with those who remained asymptomatic (31 ± 55 cm/s/yr vs. 13 ± 32 cm/s/yr).
Cioffi et al. (53)	2011	Retrospective, observational, single-arm	Severe AS with AVA <1 cm^2 and MG >40 mm Hg	218 (209 with available follow-up)	75 ± 11	42%	–	22 ± 13 months	Death: 20 (9.6%) patients; AVR: 72 (34.5%) patients; hospitalization: 15 (7.2%) patients. Event-free survival was 77% at 1 yr, 54% at 2 yrs, 37% at 3 yrs, 30% at 4 yrs, and 28% at 5 yrs.
Kitai et al. (40)	2011	Retrospective, observational, single-arm	Severe and very severe AS with PV ≥4 m/s or MG ≥40 mm Hg, or AVA <1 cm^2 (54% were symptomatic)	166 108 severe; 58 very severe	70 ± 11	58%	Severe AVA: 0.89 ± 0.13 cm^2 PV: 3.8 ± 0.5 m/s MG: 37 ± 9 mm Hg Very severe AVA: 63 ± 20 cm^2 PV: 5.0 ± 0.8 m/s MG: 62 ± 18 mm Hg	5.5 ± 3.0 yrs	Among 166 patients, 76 (46%) were asymptomatic. 39 (23.5%) deaths, 22 (13.3%) cardiac deaths, 64 (38.6%) AVR, 22 (13.3%) hospitalizations for H. Overall survival at 3 and 5 yrs was 77% and 69% in very severe AS, and 88% and 83% in severe AS, respectively. Patients with symptomatic very severe AS had the worst overall survival and valve-related event-free survival. Both overall survival and valve-related event-free survival of asymptomatic very severe AS were comparable with those of symptomatic severe AS, but they were significantly worse than asymptomatic severe AS.
Lancellotti et al. (81)	2012	Prospective, observational, single-arm	Severe AS with indexed AVA <0.6 cm^2/m^2	105	71 ± 9	41%	AVA: 0.89 ± 0.10 cm^2 MG: 45 ± 15 mm Hg	19 ± 11 months	7 (6.7%) CV death; 49 (46.7%) AVR. Event-free survival of 72%, 50%, and 34% at 1-yr, 2-yr, and 3-yr follow-up, respectively. The rate of cardiac events was significantly higher in patients with exercise PHT (67% vs. 36%; p = 0.002). Patients with exercise PHT had lower cardiac event-free survival (1 yr: 65% vs. 81%; 2 yrs: 43% vs. 59%; 3 yrs, 22% vs. 55%; p = 0.01).

Continued on the next page

TABLE 2 Continued

First Author (Ref. #)	Year	Design	AS Definition	N	Age (Yrs)	Female Patients	Severity	Follow-Up	Clinical Outcomes and Findings
Saito et al. (50)	2012	Retrospective, observational, single-arm	Severe AS with AVA <1 cm^2	103	72 ± 11	55%	AVA: 0.82 ± 0.15 cm^2 PV: 4.1 ± 0.9 m/s MG: 41 ± 18 mm Hg	36 ± 27 months	31 (30.1%) AVR; 20 (19.4%) cardiac death (16 had no symptoms before cardiac death). Event-free survival rates for all patients was 81%, 74%, 58%, and 48% at 1, 2, 3, and 5 yrs, respectively. Event-free survival rates for patients with an AVAI of ≥0.6 cm^2/m^2 were 100% at 1 yr, 97% at 2 yrs, 86% at 3 yrs, and 71% at 5 yrs. Event-free survival rates for patients with an AVAI <0.6 cm^2/m^2 were 71% at 1 yr, 60% at 2 yrs, 41% at 3 yrs, and 35% at 5 yrs. The differences between these 2 groups were significant $p < 0.01$.
Yingchoncharoen et al. (51)	2012	Prospective, observational, single-arm	Severe AS with AVA <1 cm^2 or PV >4 m/s	79	77 ± 12	51%	AVA: 0.75 ± 0.12 cm^2 PV: 4.4 ± 0.3 m/s MG: 36.8 ± 12.6 mm Hg	23 ± 20 months	7 (8.9%) deaths, 5 (6.3%) cardiac deaths, 49 (62.0%) AVR. Event-free survival was 72 ± 5% at 1 yr, 50 ± 5% at 2 yrs, and 24 ± 5% at 4 yrs. By multivariable analysis, GLS, STS, AV calcification score, AVA, and Zva were associated with events. Absolute GLS >15% had the best performance in predicting events.
Lancellotti et al. (55)	2012	Prospective, observational, single-arm	Severe AS with AVA <1 cm^2 and normal exercise stress test	150	69.7 ± 8	36%	Indexed AVA: 0.5 ± 0.11 cm^2/m^2 4 groups on the basis of indexed LV stroke volume and MG: Normal flow (≥35 ml/m^2) or low flow (<35 ml/m^2) High gradient (≥40 mm Hg) or low gradient (<40 mm Hg)	27 ± 12 months	CV death or need for AVR was motivated by the development of symptoms or LVEF<50%. 76 of 150 (51%) met the pre-defined endpoint: 9 (6%) deaths; 8 (5.3%) cardiac deaths; 3 (2%) sudden deaths without symptoms preceding death. 70 (47%) had indication for AVR: Spontaneous symptoms: 58 (39%); progressive AS: 2 (1.3%); positive stress test during follow-up: 8 (5.3%); LVEF <50%: 2 (1.3%). Event-free survival of CV events was 71%, 51%, and 40% at 1-yr, 2-yr, and 3-yr follow-up, respectively. According to the AS grading classification, 2-yr cardiac event-free survival was 83%, 44%, 30%, and 27% in NF/LG, NF/HG, LF/HG, and LF/LG groups, respectively ($p < 0.0001$). Independent predictors of events: PV, LVEDV, indexed LA area, low flow, low gradient.
Levy et al. (52)	2014	Prospective, observational, single-arm	Severe AS with AVA <1 cm^2 or indexed AVA ≤0.6 cm^2/m^2	43	69 ± 13	28%	AVA: 0.86 ± 0.20 cm^2 PV: 4.3 ± 0.6 m/s MG: 46 ± 15 mm Hg	28 ± 31 months	12 (28%) patients had a positive stress test with an indication for AVR. 0 death; 15 (34.8%) AVR; 4 (9.3%) developed symptoms.

Continued on the next page

TABLE 2 Continued

First Author (Ref. #)	Year	Design	AS Definition	N	Age (Yrs)	Female Patients	Severity	Follow-Up	Clinical Outcomes and Findings
Taniguchi et al. (26) (total cohort)	2015	Retrospective, observational, comparative study	Severe AS with AVA: <1 cm^2; MG: >40 mm Hg; PV: >4 m/s	1,808 (291 AVR; 1,517 conservative treatment)	Early AVR 71.6 ± 8.7 Conservative 77.8 ± 9.4	60%	Early AVR AVA: 0.67 ± 0.16 cm^2 PV: 4.8 ± 0.8 m/s MG: 54 ± 20 mm Hg Conservative AVA: 0.79 ± 0.16 cm^2 PV: 3.8 ± 0.7 m/s MG: 33 ± 14 mm Hg	1.361 days (IQR: 1,055-1,697)	Among 1,517 patients in the conservative group, AVR was performed in 392 (26%) patients with median interval of 788 days. The cumulative 5-yr incidence of sudden death was 7.6% (1.5%/yr) in the conservative group compared with 3.6% (0.7%/yr) in the initial AVR group. Among the 82 sudden deaths, 57 patients (70%) died suddenly without preceding symptoms. Among 679 patients who underwent AVR in the present study, AVR after symptom development during follow-up (n = 247) was associated with higher 30-day operative mortality than AVR while asymptomatic (n = 432) (3.7% vs. 1.2%; p = 0.03).
Taniguchi et al. (26) (propensity-matched cohort)	2015	Retrospective, observational, comparative study	Severe AS with AVA: >1 cm^2; MG: >40 mm Hg; PV: >4 m/s	582 (291 AVR, 291 conservative treatment)	Early AVR 71.6 ± 8.7 Conservative 73.1 ± 9.3	57%	Early AVR AVA: 0.67 ± 0.16 cm^2 PV: 4.8 ± 0.8 m/s MG: 54 ± 20 mm Hg Conservative AVA: 0.75 ± 0.18 cm^2 PV: 4.4 ± 0.9 m/s MG: 45 ± 20 mm Hg	–	Among 291 patients in the conservative group, AVR was performed in 118 patients (41%) during follow-up at a median time of 780 days. The cumulative 5-yr incidence of all-cause death was significantly lower in the initial AVR group than in the conservative group (15.4% vs. 26.4%; p = 0.009). The cumulative 5-yr incidence of sudden death tended to be lower in the initial AVR group than in the conservative group (3.6% vs. 5.8%; p = 0.06). The initial AVR strategy was also associated with markedly lower cumulative 5-yr incidences of emerging symptoms related to AS and HF hospitalization (3.2% vs. 46.3%; p < 0.001, and 3.8% vs. 19.9%; p < 0.001, respectively).

*Referenced in the ACC/AHA 2014 Valvular Heart Diseases guidelines.

AFib = atrial fibrillation; AVA = aortic valve area; AVAI = aortic valve area index; BLS = basal longitudinal strain; BNP = B-type natriuretic peptide; CI = confidence interval; CV = cardiovascular; EOA = effective orifice area; GLS = global longitudinal strain; HF = heart failure; HG = high gradient; HR = hazard ratio; IQR = interquartile range; LA = left atrial; LF = low flow; LG = low gradient; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; MG = mean gradient; MR = mitral regurgitation; NF = normal flow; PHT = pulmonary hypertension; PV = peak velocity; RR = relative risk; STS = Society of Thoracic Surgeons; Zva = valvuloarterial impedance; other abbreviations as in Table 1.

TABLE 3 Predictors of Adverse Events at Follow-up in Patients with Asymptomatic Severe AS

Echocardiographic (Ref. #)	Stress Test (Ref. #)	Stress Imaging (Ref. #)
Peak velocity (18,32,34,48,49,51,53,55,56)	Abnormal stress test (34,36-38) or limiting symptoms during stress test (39)	Increase in mean gradient during exercise by ≥18 mm Hg (37) or >20 mm Hg (33)
Peak velocity >4.0 m/s (50)		Decrease in LVEF at peak exercise (126) Exercise-induced pulmonary hypertension (best cutoff sPAP >60 mm Hg) (81)
Peak velocity >4.5 m/s (17)		Peak Vo_2 ≤14 ml/kg/min, VE/Vco_2 slope >34 (52)
Peak velocity >5 m/s (25,40)		
Peak velocity >5.5 m/s (35)		
Rates of progression of PV (25,32,43,125)		
AVA (18,32,40,51); AVA <0.75 cm^2 (37,50); indexed AVA <0.6 cm^2/m^2 (50)		
Mean gradient (33,40); mean gradient >35 mm Hg (33)		
Calcification severity (43,51,53)		
LVH (18,33,53,58)		
LVEF <50% (17); LVEF (19,31,124)		
Left ventricular mass index (33,58)		
LVEDV (55)		
Mitral regurgitation 3 or 4 (19)		
Left atrial area (34,55)		
LV strain (34,51,60,67,68)		
Valvuloarterial impedance (Zva) (especially >4.5) (34,51,58)		
Low stroke volume (<35 cc/m^2) (55)		
Pressure drop/flow slope (56)		

BP = blood pressure; sPAP = systolic pulmonary artery pressure; VE/Vco_2 = ventilatory equivalent for carbon dioxide; Vo_2 = oxygen uptake rate; other abbreviations as in Tables 1 and 2.

SUDDEN DEATH IN ASYMPTOMATIC SEVERE AS

The risk of sudden death has been reported to be approximately 1% per year in clinically asymptomatic patients with severe AS (17,25,32-34,38,39,43,47-53), with Taniguchi et al. (26) reporting the highest annual sudden death rates (1.5%). However, once symptoms occur, as many as 3% of patients may die suddenly within 3 to 6 months, and as many as 6.5% of symptomatic patients may die while awaiting AVR (29). Importantly, ~70% of sudden deaths in patients with asymptomatic severe AS are not preceded by any of the classical AS symptoms, thus representing the first clinical manifestation of AS (17,25,26,32-34,38,39,43,47-53). The hemodynamic severity of AS has been associated with an increased risk of sudden death in asymptomatic patients (25).

ECHOCARDIOGRAPHY IN ASYMPTOMATIC SEVERE AS

Echocardiography has a central role in the risk stratification of patients with AS. The peak velocity of blood flow across the valve (V_{max}) as assessed by Doppler techniques and the AVA largely define the stage of AS. Several specific echocardiographic predictors of adverse events have been reported (**Table 3**). V_{max} is one of the strongest independent echocardiographic predictors of adverse cardiovascular events in patients with AS (17,18,25,32,34,35,40,48-56). Although severe AS is defined as V_{max} ≥4 m/s, patients with a V_{max} ≥5.0 or ≥5.5 cm/s (i.e., very severe AS) have a higher risk of adverse events (25,35). The mean pressure difference across the valve (ΔP), which is also derived from the Doppler blood flow velocities, and the AVA also have strong prognostic relevance (18,32,33,37,40,50,51).

Lancellotti et al. (55) demonstrated that a low flow state, defined as an indexed stroke volume <35 ml/m^2, was associated with worse prognosis among patients with asymptomatic severe AS (defined as AVA <1 cm^2) and a normal exercise test. A dilated left atrium, reflecting chronically elevated LV diastolic pressure, has also been associated with worse prognosis (34). Other echocardiographic indexes linked to a higher risk of adverse events in patients with AS include reduced LVEF, LV hypertrophy, and pulmonary hypertension (33,43,53). Echocardiography can also provide semiquantitative

assessment of the degree of valve calcification and can identify anatomic valve abnormalities, including bicuspid morphology (Table 3).

Valvuloarterial impedance (Zva) and longitudinal strain are emerging as alternative markers for assessing the repercussions of AS on LV function (57,58). Zva, first described in 2005 by Briand et al. (57), is defined as the ratio of the LV systolic pressure to the stroke volume index. The LV systolic pressure is estimated by adding the mean ΔP to the systolic blood pressure (measured by sphygmomanometry) at the time of echocardiography. Zva takes into account both the valvular load, which is determined by AS severity, and the arterial load, which is determined by reduced arterial compliance, and increased systemic valvular resistance. This parameter thus provides an estimate of the global hemodynamic load that is imposed on the LV. Higher Zva has been associated with major cardiovascular events and mortality in populations with asymptomatic AS ranging from mild to severe (57,58). In a series of 544 patients with asymptomatic AS (39% severe: AVA <1.0 cm^2). Hachicha et al. (58) found that Zva was independently associated with mortality. Lancellotti et al. (34) prospectively followed 163 patients with asymptomatic AS and an indexed AVA ≤0.6 cm^2/m^2, and corroborated these findings by showing that Zva was independently associated with adverse cardiac events. Zva cutoff values ranging from 4.5 to 5.0 mm Hg/ml/m^2 identify severely elevated global hemodynamic load and have been shown to predict subsequent death, AVR, and development of symptoms (34,51,59,60).

Assessment of global longitudinal strain is another method to assess the impact of severe AS on the LV and is believed to reflect subendocardial cardiomyocyte dysfunction secondary to concentric remodeling, subendocardial ischemia, and myocardial fibrosis. Up to 50% of patients with asymptomatic severe AS and preserved LVEF have some degree of subclinical myocardial dysfunction, as documented by reduced longitudinal strain (61-63). Myocardial strain is generally measured by 2-dimensional (2D) speckle tracking echocardiography, which measures the deformation of myocardial tissue in 3 directions (longitudinal, circumferential, and radial), by analyzing the naturally occurring speckle pattern in the myocardium (64-66). Low longitudinal strain is an independent predictor of symptom development (67). In patients with asymptomatic severe AS and preserved LVEF, decreased longitudinal strain is associated with an abnormal response to exercise (68,69) and higher rates of cardiac events at follow-up (34,51,60,68). Assessment of global longitudinal strain has been reported to add incremental value to a score consisting of peak pressure gradient, Zva, and aortic calcification for the prediction of adverse events (51).

Three-dimensional (3D) echocardiography, computed tomography (CT), and cardiac magnetic resonance (CMR) imaging are emerging imaging modalities that may improve the accuracy of left ventricular outflow tract (LVOT) and AVA measurements; however, the severity parameters and criteria for these modalities need to be validated with outcome data before they can be used to complement or replace the traditional echocardiographic parameters and criteria of AS severity (70-75).

EXERCISE TESTING IN ASYMPTOMATIC SEVERE AS

The incidence of an abnormal stress test varies, depending of the severity of AS; for patients with asymptomatic severe AS undergoing stress testing, the incidence of abnormal stress test has ranged between 28% and 67%, with a pooled average of 49% (Table 4). An abnormal response to exercise is thought to reflect poor contractile reserve and an increased transvalvular gradient and Zva during effort (76,77). Exercise-induced symptoms or an abnormal blood pressure response are also predictive of worse outcome (Table 5) (44,78,79). Therefore, AVR is recommended (Class I if clear valve-related symptoms occurred during stress test) and may be reasonable (Class IIa for abnormal blood pressure response or poor exercise tolerance) for asymptomatic patients with severe AS by current AHA/ACC

TABLE 4 Abnormal Stress Test Among Large Observational Series of Asymptomatic AS

	Moderate-Severe AS			Severe AS Only		
First Author (Ref. #)	% Abnormal Stress Test	n	N	% Abnormal Stress Test	n	N
Takeda et al. 2001 (56)	27%	13	49	–	–	–
Amato et al. 2001 (38)	–	–	–	67%	44	66
Alborino et al. 2002 (79)	60%	18	30	–	–	–
Das et al. 2003 (78)	29%	19	65	–	–	–
Das et al. 2005 (39)	37%	46	125	–	–	–
Lancellotti et al. 2005 (37)	–	–	–	38%	26	69
Peidro et al. 2007 (36)	66%	67	102	–	–	–
Maréchaux et al. 2007 (126)	–	–	–	48%	24	50
Lancellotti et al. 2008 (76)	–	–	–	47%	60	128
Lafitte et al. 2009 (68)	–	–	–	65%	39	60
Maréchaux et al. 2010 (33)	27%	51	186	–	–	–
Rajani et al. 2010 (127)	15%	3	20	39%	7	18
Donal et al. 2011 (69)	33%	69	207	–	–	–
Levy et al. 2014 (52)	–	–	–	28%	12	43
Total	36.5%	286	784	48.8%	212	434

AS = aortic stenosis.

TABLE 5 Studies Evaluating Exercise Stress Tests in Patients With Asymptomatic Severe AS

First Author (Ref. #)	Patients	Exercise Protocol	Criteria for Abnormal Test	% Abnormal Exercise Test	Findings
Amato et al. 2001 (38)	Severe AS AVA ≤1 cm^2	Treadmill Ellestad protocol Age-related peak heart rate was determined using the formula (210 − age). Submaximal frequency corresponded to 85% of this value.	1) Symptoms of AS: precordial chest pain or near syncope; 2) Up-sloping ST-segment depression >3 mm in men. Up-sloping ST-segment depression in women was considered negative; 3) Horizontal or down-sloping ST-segment depression >1 mm in men or >2 mm in women; 4) Complex ventricular arrhythmia; 5) SBP failed to rise by >20 mm Hg.	Abnormal stress test: 44 of 66 (67%) 20 of 66 (30%) limiting symptoms 3 of 66 (5%) arrhythmia	After 24 months, the probability of a patient with a positive test to have an event (death or symptoms) is 81%, compared with 15% in those with a negative test. Positive exercise test was the strongest predictors of death or developing symptoms at follow-up.
Alborino et al. 2002 (79)	Asymptomatic moderate-to-severe AS (mean gradient ≥30 mm Hg)	Upright maximal bicycling exercise test Baseline ≥25 W, and then increment each 2 min by 10–50 W	1) Symptoms: angina or syncope; 2) Ischemic ST-segment changes; 3) Fall ≥20 mm Hg in SBP at peak intensity; 4) Malign arrhythmias 5) Exhausted at low work load.	Abnormal stress test: 18/30 (60%) Angina: 3% ECG signs of ischemia: 17% Fall in SBP: 10% Dyspnea at low workload: 37% Significant arrhythmia or syncope: 0%	Patients with abnormal stress test 10 of 18 (56%) had symptoms at 1 yr. 14 of 18 (78%) had symptoms at 3 yrs. Patients with normal stress test 0 of 12 (0%) had symptoms at 1 yr. 2 of 12 (17%) had symptoms at 3 yrs. 3-yr freedom of cardiac death or AVR at 3 yrs was 83% for normal stress test and 33% for abnormal stress test.
Das et al. 2005 (39)	Moderate-Severe AS with EOA <1.4 cm^2 (42% severe)	Treadmill Bruce protocol modified by 2 warm-up stages	1) Stopped prematurely because of limiting breathlessness/chest discomfort or dizziness; 2) ST-segment depression >5 mm; 3) More than 3 consecutive ventricular premature beats; 4) SBP fall >20 mm Hg from baseline.	Limiting symptoms: 37% Other criteria: Abnormal SBP (same or drop compared to baseline): 23% ST-segment depression >2 mm: 26%	Limiting symptoms during stress-test was an independent predictor of spontaneous symptoms. Spontaneous symptoms at 12 months developed in 5 of 6 (83%) patients with exertional dizziness, 6 of 12 (50%) patients with chest tightness, and 15 of 28 (54%) with breathlessness. The sensitivity of exercise-limiting symptoms was 72% and the specificity was 78%. Overall, the absence of limiting symptoms had a negative predictive accuracy of 87% among all patients.
Lancellotti et al. 2005 (37)	Severe AS with AVA ≤1 cm^2	Symptom-limited graded bicycle exercise test in a semisupine position on a tilting exercise table. Initial workload of 25 W; increased every 2 minutes by 25 W.	1) Angina or dyspnea; 2) >2-mm ST-segment depression; 3) Fall or small (20 mm Hg) rise in SBP, as compared with baseline; 4) Significant arrhythmias.	Abnormal stress test: 26 of 69 (38%). Angina: 4 (6%); dyspnea: 2 (3%); >2-mm ST-segment depression: 13 (19%); fall or <20 mm Hg rise in SBP: 6 (9%); nonsustained ventricular tachycardia: 1 (1.5%).	Independent predictors of cardiac events: 1) Increase in MG by ≥18 mm Hg during exercise; 2) An abnormal exercise test; 3) AVA <0.75 cm^2.

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and European Society of Cardiology (ESC)/European Association of Cardio-Thoracic Surgery (EACTS) guidelines (**Table 1**) (15,16).

It should be noted that the studies reporting a worse prognosis in patients with an abnormal exercise test have been heterogeneous in terms of exercise protocol (e.g., treadmill vs. bicycle, Naughton vs. Bruce, or other), the definition of what constitutes an abnormal exercise test, study endpoints, and AS severity (**Table 5**). Indeed, the criteria for an abnormal stress test have varied across studies, including limiting symptoms, abnormal blood pressure response (lack of an increase or a drop in blood pressure), ventricular arrhythmias, and ST-segment depression. Some studies have indicated that symptom development during exercise is of greater importance than an

TABLE 5 Continued

First Author (Ref. #)	Patients	Exercise Protocol	Criteria for Abnormal Test	% Abnormal Exercise Test	Findings
Peidro et al. 2007 (36)	AS with MG >30 mm Hg	Treadmill modified Naughton protocol.	1) Angor, syncope, or pre-syncope; 2) Dyspnea or maximal exhaustion to functional capacity ≤5 METs in patients <70 yrs of age or ≤4 METs in patients >70 yrs of age; 3) Drop in SBP ≥10 mm Hg; 4) Down-sloping ST-segment depression >1 mm 5) Frequent coupled ventricular beats or ventricular tachycardia during exercise or recovery.	Abnormal stress test 67 of 102 (66%) Angor or dyspnea: 37.2% Down-sloping ST-segment depression: 42.1% Drop in SBP: 26.5% Ventricular arrhythmia: 3.9%	Abnormal stress test 35 of 67 (52%) AVR 2 of 67 (3%) death Normal stress test 10 of 35 (29%) AVR 0 of 35 (0%) death Predictors of CV death or AVR Drop in SBP, down-sloping ST-segment depression, angor or dyspnea on exercise test
Lafitte et al. 2009 (68)	Severe AS with AVA <1 cm^2	Bruce protocol modified by 2 warm-up stages.	1) Limiting breathlessness/chest discomfort or dizziness; 2) ST-segment depression >2 mm; 3) >3 consecutive ventricular premature beats; 4) Fall in SBP >20 mm Hg.	Abnormal stress test: 39/60 (65%) Limiting symptoms: 37% Abnormal BP response: 35% Significant ST-segment depression: 13%	See Table 2
Rajani et al. 2010 (127)	Moderate-Severe AS (EOA <1.5 cm^2)	Treadmill Bruce protocol modified by 2 warm-up stages.	1) Limiting breathlessness, chest discomfort or dizziness; 2) ST-segment depression >5 mm; 3) >3 consecutive ventricular premature beats; 4) A fall in SBP >20 mm Hg from baseline.	10 of 38 (26%) with limiting symptoms during stress test Severe AS: 7 of 18 (39%) Moderate AS: 3 of 20 (15%)	Patients with induced symptoms had lower peak cardiac index, stroke index, and Vo_2 max. The only independent predictor of peak cardiac index was the log BNP level.
Levy et al. 2014 (52)	Severe AS with AVA <1 cm^2 or indexed AVA ≤0.6 cm^2/m^2	Cardiopulmonary exercise testing on an upright cycle ergometer with a ramp protocol. Exercise workload was increased by a ramp protocol (20 W/min or 10 W/min) after a 1-min warm-up at 20 W.	1) Limiting breathlessness or fatigue at low workload, angina, dizziness, or syncope; 2) Peak SBP at or below the baseline level; 3) Complex ventricular arrhythmia.	Limiting dyspnea or angina: 28% Syncope or fall in SBP: 0%	Independent predictors of AVR or AS-related symptoms: Peak Vo_2 ≤14 ml/kg/min, VE/VCO_2 slope >34.

ECG = electrocardiogram; LV = left ventricular; MET = metabolic equivalent; SBP = systolic blood pressure; other abbreviations as in Tables 2 and 3.

abnormal blood pressure response or ST-segment changes; however, these studies were small and heterogeneous, and the optimal criteria for a positive test remain unknown (34,36-39). It is also possible that in these retrospective studies, patients with abnormal stress test results were followed more carefully, with lower thresholds for AVR referral than those with greater exercise capacity or more normal blood pressure responses. Nonetheless these studies have consistently shown that prognosis is considerably worse for patients with an abnormal exercise test. A recent meta-analysis by Rafique et al. (44) reported a 6-fold increased risk of cardiac death for patients with an abnormal stress test, with sensitivity, specificity, and positive and negative predictive values of 75%, 71%, 66%, and 79% for adverse cardiac events and 100%, 51%, 5%, and 100% for sudden cardiac death, respectively (44).

Approximately 15% of patients with asymptomatic AS will not be able to perform an exercise test (32), a proportion that increases with age (80). Pharmacological stress testing (e.g., with dobutamine) may alternatively be used, and can elicit symptoms that have been associated with a worse prognosis (56). Echocardiography can be performed simultaneously and adds prognostic value.

STRESS ECHOCARDIOGRAPHY IN ASYMPTOMATIC SEVERE AS

ESC/EACTS guidelines (but not ACC/AHA guidelines) include stress imaging to inform management of normal-flow/high-gradient, asymptomatic severe AS, with a Class IIb indication that AVR may be considered in such patients with an increase in ΔP >20 mm Hg during exercise (16). This is on the basis

TABLE 6 Studies Evaluating Stress Echocardiography in Patients With Asymptomatic Severe AS

First Author (Ref. #)	Patients	Stress Protocol	% Abnormal Exercise Test	Findings
Takeda et al. 2001 (56)	AS with PV >2.5 m/s	Dobutamine stress echocardiography Dobutamine was infused from 5 mg/kg/min up to a maximum of 40 mg/kg/min in 5-min stages	Significant symptoms: 13 of 49 (27%) Sustained fall in SBP: 5 of 49 (10%) Arrhythmia: 1 of 49 (2%)	23 of 49 (47%) developed symptoms at follow-up. Symptoms during stress test 10 of 13 (77%) developed symptoms Normal stress test 13 of 36 (36%) developed symptoms Mean time to first symptoms: 8 months Predictors of development of symptoms PV, peak pressure gradient, pressure drop/flow slope 83% AVR, or symptoms at 2 yrs if PV >4 m/s
Das et al. 2003 (78)	AS with EOA <1.2 cm^2	Dobutamine stress echocardiography Treadmill exercise test using a Bruce protocol modified by 2 warm-up stages Abnormal stress test: 1) Significant limiting symptoms; 2) ST-segment depression >5 mm; 3) >3 consecutive ventricular premature beats; 4) Fall in SBP >20 mm Hg.	Abnormal stress test: 19/65 (29%) 19 of 65 (29%) limiting symptoms (11 of 19 severe AS and 8 of 19 moderate AS) 18 of 65 (28%) abnormal SBP	No significant differences in resting measures of AS between patients with limiting symptoms and those without. Valve compliance was significantly lower in patients with limiting symptoms, at 0.19 (0.09) $cm^2/100\ ml \cdot s^{-1}$ than in those without, at 0.25 (0.10) $cm^2/100\ ml \cdot s^{-1}$. Peak EOA and the absolute increase in area from rest to peak were also lower in patients with symptoms.
Lancellotti et al. 2005 (37)	Severe AS with AVA ≤1 cm^2	Symptom-limited graded bicycle exercise test in a semi-supine position on a tilting exercise table Initial workload of 25 W; increased every 2 min by 25 W See Table 5 for positivity criteria	Abnormal stress test 26 of 69 (38%) Angina 4 (6%); dyspnea in 2 (3%); >2 mm ST-segment depression in 13 (19%); fall or <20 mm Hg rise in SBP in 6 (9%); nonsustained ventricular tachycardia in 1 (1.5%)	Abnormal stress test; 14 of 26 (54%) with event Normal stress test 4 of 43 (9%) with event Independent predictors of cardiac events 1) Increase in MG ≥18 mm Hg during exercise; 2) An abnormal exercise test; 3) AVA <0.75 cm^2.
Maréchaux et al. 2007 (126)	Severe AS with AVA ≤1 cm^2	Symptom-limited exercise on a semirecumbent bicycle Initial workload was 25 W that was increased by 25 W increment every 3 min Abnormal stress test: 1) Angina, shortness of breath, near syncope or syncope; 2) ≥2-mm ST-segment depression; 3) Fall or no increase in SBP at peak exercise when compared with baseline level; 4) Ventricular arrhythmias Abnormal LV response to exercise ΔLVEF from rest to peak exercise <0%.	Abnormal stress test 24 of 50 (48%) 20 of 24 (83%) had AVR Normal stress test 26 of 50 (52%) 10 of 26 (38%) had AVR 7 of 50 (14%) had spontaneous symptoms at median of 11 months follow-up (2 normal LVEF at exercise and 5 abnormal).	Decreased LVEF at exercise was associated with development of CV death or spontaneous symptoms at follow-up.

Continued on the next page

of 2 relatively small studies. Maréchaux et al. (33) performed echocardiography at rest and during exercise in 72 patients with asymptomatic severe AS. At a median follow-up time of 20 months, an increase in ΔP >20 mm Hg was the only exercise echocardiographic parameter independently associated with clinical events (hazard ratio [HR]: 1.49; 95% confidence interval [CI]: 1.12 to 2.00). Lancellotti et al. (37) reported a similar threshold (>18 mm Hg increase in ΔP at exercise) as an independent predictor of long-term adverse events. Lancellotti et al. (81) subsequently showed that development of pulmonary hypertension (systolic pulmonary arterial pressure >60 mm Hg) at peak exercise also has incremental prognostic value. Other studies that evaluated stress echocardiography in patients with asymptomatic severe AS are summarized in Table 6.

CT AND CMR IMAGING IN ASYMPTOMATIC AS

CT and CMR imaging are increasingly used in patients with AS. Both techniques provide detailed information of valve, aortic root, and aortic morphology and are useful for pre-procedural assessment before SAVR or TAVR.

Multislice CT has the capability of quantifying the degree and severity of aortic valve calcification. The calcium score correlates strongly with actual aortic valve calcium weight as measured post-mortem, with the echocardiographic hemodynamic severity of AS

TABLE 6 Continued

First Author (Ref. #)	Patients	Stress Protocol	% Abnormal Exercise Test	Findings
Lancellotti et al. 2008 (76)	Severe AS with AVA ≤1 cm^2	Symptom-limited graded bicycle exercise test in a semi-supine position on a tilting exercise table Initial workload of 25 W; increased every 2 min by 25 W See Table 5 for abnormal stress test criteria	Abnormal stress test 60 of 128 (47%) Symptoms during stress test: 30 of 128 (23%)	Independent predictors of abnormal stress test: 1) Larger increase in MG (best cutoff value was ≥17 mm Hg); 2) Decrease or smaller increase in LVEF. Independent predictors of symptoms during stress test: 1) Larger increase in MG; 2) Smaller exercise-induced change in SBP; 3) Lower LVEF at peak test. Independent predictors of fall or a <20 mm Hg increase SBP: 1) Presence of MR at rest; 2) Decrease or smaller increase in LVEF. Independent predictors of ≥2 mm ST-segment depression: 1) Smaller AVA at rest; 2) Larger increase in MG.
Maréchaux et al. 2010 (33)	Moderate and severe AS, with AVA <1.5 cm^2 and indexed AVA <0.9 cm^2/m^2	Symptom-limited graded bicycle exercise test in a semi-supine position on a tilting exercise table Initial workload of 20–25 W maintained for 3 min. Workload increased every 3 min by 20–25 W Abnormal stress test: 1) Occurrence of limiting breathlessness, fatigue at low workload, angina, dizziness, syncope; 2) Fall in SBP below baseline; 3) Complex ventricular arrhythmia.	Abnormal stress test: 51 of 186 (27%) Normal stress test 135 of 186 (73%)	Normal exercise test subgroup: 67 of 135 (50%) CV events (time to occurrence of CV death or symptom-driven AVR or by LVEF<50%) Predictors of CV events: 1) Age ≥65 yrs (HR: 1.96); 2) diabetes (HR: 3.20); 3) LVH (HR: 1.96); 4) resting MG >35 mm Hg (HR: 3.60); 5) exercise-induced increase in MG >20 mm Hg (HR: 3.83). The combination of a rest MG >35 mm Hg and an exercise-induced increase in MG >20 mm Hg was associated with a markedly increased risk of event (HR: 9.6; $p < 0.0001$).
Donal et al. 2011 (69)	Moderate and Severe with AS ≤1.2 cm^2	Symptom-limited graded bicycle exercise test in a semi-supine position on a tilting exercise table Initial workload of 30 W. Workload increased by 20 W every 2 min, depending on physical training Abnormal stress test: 1) Angina, shortness of breath at low workload level (50 W), dizziness, syncope, or near-syncope; 2) ≥2-mm ST-segment depression; 3) Rise of SBP <20 mm Hg or a fall in SBP; 4) Complex ventricular arrhythmias.	Abnormal stress test 69 of 207 (34%)	Independent predictor of abnormal response to exercise: 1) Lower GLS at rest; 2) Greater increase in MG at exercise; 3) Smaller exercise-induced changes in GLS. ROC curve analysis best cutoff: 1) GLS at rest of <15.5% (AUC: 0.58); 2) GLS change by ≤1.4% at exercise (AUC: 0.77); 3) Increase in MG ≥14 mm Hg (AUC: 0.72).
Lancellotti et al. 2012 (81)	Severe AS with indexed AVA <0.6 cm^2/m^2	Symptom-limited graded bicycle exercise test in a semi-supine position on a tilting exercise table Initial workload of 25 W maintained for 2 min workload increased every 2 minutes by 25 W Abnormal stress test: 1) Angina, shortness of breath at low workload level (50 W), dizziness, syncope, or near syncope; 2) ≥2-mm ST-segment depression; 3) Rise of SBP <20 mm Hg or a fall in SBP; 4) Complex ventricular arrhythmias.	-	Ex-PHT was associated with reduced cardiac event-free (CV death or need for AVR). survival (at 3 yrs, 22 ± 7% vs. 55 ± 9%; $p = 0.014$) Ex-PHT was identified as an independent predictor of CV events (HR: 2.0; 95% CI: 1.1–3.6; $p = 0.025$). The best cutoff value to predict cardiac events was exercise sPAP >60 mm Hg: sensitivity, 70%; specificity, 62%; positive predictive value, 67%; and negative predictive value, 64%.

AUC = area under the curve; ROC = receiver-operating characteristic; other abbreviations as in Tables 2, 3, and 5.

(peak velocity and AVA), and with clinical outcomes (42,82–86). Recent studies suggest that lower cut-point values of aortic valve calcium score should be used in women (>1,200 AU [arbitrary units]) versus men (>2,000 AU) to identify severe AS and predict outcomes (42,85). CT measurement of the LVOT may bring incremental value to 2D echocardiography and improve AS severity assessment (72); however, given

that CT measures a larger LVOT cross-sectional area compared with 2D echocardiography, larger cutpoint values of AVA (<1.2 cm^2 vs. 1.0 cm^2) should be used to identify severe AS and predict adverse events if a "hybrid CT-echocardiography method" is used to estimate AVA (72). That being said, given the elliptical geometry of the LVOT, to compare LVOT measurements derived from 3D CT or CMR with 2D echocardiography remains challenging because they may reflect measurement of different anatomic entities (87–92). Integrating dimension measurement derived by CT, CMR, or 3D echocardiography and flow parameters (i.e., velocity time integral) derived by 2D echocardiography may offer some advantages over standard techniques; however, this approach needs further prospective validation and, most importantly, correlation with outcomes, including mortality (72,86,93).

CMR, in addition to assessing cardiac anatomy and function, can quantify the degree of interstitial fibrosis, as detected with late gadolinium enhancement. Interstitial fibrosis is an important feature of the pathological hypertrophic remodeling that the LV undergoes in response to the elevated afterload in severe AS (94,95). A considerable proportion of patients with severe AS have myocardial fibrosis documented by CMR, the presence of which has been associated with a worse prognosis after AVR (96,97). These findings raise the question of whether long-term outcomes would be improved if valve replacement were to be performed before adverse LV remodeling has occurred.

CT and CMR imaging may thus complement echocardiography in the diagnostic evaluation and monitoring of patients with asymptomatic severe AS, and may affect treatment decisions. Nonetheless, the lack of thorough clinical validation of these modalities, paired with economic considerations, has slowed their widespread use in the detection and risk stratification of AS (98).

BIOMARKERS IN ASYMPTOMATIC SEVERE AS

The ESC/EACTS guidelines note that AVR may be considered in patients with asymptomatic severe AS and markedly elevated levels of natriuretic peptides in the absence of an alternative explanation (Class IIb) (16). N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the active hormone B-type natriuretic peptide (BNP) are released in response to ventricular and/or atrial cardiomyocyte stretch (99). These biomarkers have prognostic utility in patients with heart failure (99,100). NT-proBNP levels correlate with AS severity, AVA, V_{max}, and peak gradient (99,101). In asymptomatic severe AS, baseline BNP levels are predictive of an abnormal blood pressure response to exercise, earlier symptom onset, and mortality (54,102–105). One recent study demonstrated that the level of BNP compared to normal reference values (rather than to the absolute value) in patients with moderate-severe AS, both symptomatic and asymptomatic, was associated with excess long-term mortality and that BNP levels added incremental prognostic value to all baseline characteristics (106). Another interesting study demonstrated the usefulness of measuring BNP during exercise stress test (107). A higher peak-exercise BNP level was independently associated with a higher occurrence of adverse events (death or AVR) at a mean follow-up of 1.5 years, suggesting an incremental role beyond its resting value. Reports of NT-proBNP or BNP in severe AS are summarized in **Table 7**. Of note, most of these studies excluded patients with depressed LV function and/or concomitant valve disease that might otherwise cause elevated natriuretic peptide levels (108). Hence, the results and conclusions of these studies apply to AS patients with otherwise normal cardiac structure and function. Importantly, the role and incremental value of novel biomarkers are currently under investigation and could bring meaningful information to better risk stratify asymptomatic patients (109,110).

THERAPEUTIC STRATEGY

MEDICAL THERAPY. Despite the long clinical silent phase of AS, there is currently no treatment to prevent the progression of this disease and delay the need for AVR. Many attempts to demonstrate the benefit of different medical therapies failed to demonstrate clinical value. Indeed, statin therapy, despite histological and genomic evidence of the association of lipoproteins variant with aortic valve calcification (111,112), has repetitively failed to show any clinical benefits to halt AS progression (8,45,113–115), and current ACC/AHA guidelines do not recommend (Class III) statin therapy if AS is the only indication (15). Whether other novel strategies targeting osteogenic and inflammatory pathways will result in meaningful clinical applications in the treatment of early stages of AS remains to be seen in larger prospective and randomized trials (116–120). That being said, on the basis of studies showing the benefit of optimal blood pressure control, especially when using drugs blocking the renin-angiotensin pathway (121–123), current guidelines do recommend the appropriate and optimal treatment of hypertension in patients with asymptomatic or symptomatic AS (15).

TABLE 7 Studies Evaluating BNP in AS

First Author (Ref. #)	Year	N	Restricted to Severe AS	Population	Findings
Gerber et al. (104)	2003	74	No	V_{max} >2.5 m/s No segmental wall motion abnormality	NT-proBNP and BNP both associated with symptoms (AUC: 0.84 and 0.83, respectively)
Bergler-Klein et al. (103)	2004	130	Yes	V_{max} >4 m/s and/or AVA <1.0 cm^2	NT-proBNP and BNP both predicted the presence of symptoms as well as the risk of symptom onset or death 12-month event rate was 31% (NT-proBNP <80 pmol/l) vs. 92% (NT-pro-BNP ≥80 pmol/l)
Lim et al. (105)	2004	70	Yes	AVA <1.0 cm^2 Normal LV function	BNP predicted presence of symptoms (AUC: 0.86) and independently predicted CV death
Weber et al. (101)	2004	146	No	Degenerative AS (any severity)	NT-proBNP predicted severity of AS and predicted occurrence of AVR (AUC: 0.73)
Gerber et al. (128)	2005	29	No	Asymptomatic V_{max} ≥2.5 m/s No segmental wall motion abnormality or concomitant valve disease	NT-proBNP predicted symptoms (cutoff 50 pmol/l)
Nessmith et al. (102)	2005	124	No	AVA <1.2 cm^2	BNP predicted presence of symptoms (AUC: 0.87) Optimal cutoff was 190 pg/ml
Feuchtner et al. (82)	2006	34	No	Asymptomatic AS	BNP predicted poor outcomes
Antonini-Canterin et al. (129)	2008	64	No	Isolated aortic stenosis	BNP predicted NYHA class III-IV status (AUC: 0.78) and event-free survival (cardiac death, AVR, hospitalization for CHF)
Bergler-Klein et al. (108)	2007	69	No	Low-flow low-gradient (indexed EOA < 0.6 cm^2/m^2, MG ≤40 mm Hg, LVEF ≤ 40%	BNP is higher in true AS than pseudosevere AS; BNP ≥550 pg/ml associated with 1-yr mortality (overall and after AVR)
Dichtl et al. (8)	2008	50	No	Asymptomatic ΔP ≥15 mm Hg, V_{max} ≥2 m/s and aortic valve calcification	NT-proBNP predicted MACE (cardiac death, symptom onset, acute coronary syndrome or endocarditis)
Van Pelt et al. (130)	2008	34	No	Asymptomatic Moderate or severe AS (V_{max} >3 m/s)	BNP predicted abnormal BP response on exercise
Poh et al. (131)	2008	53	No	Variable degrees of AS Sinus rhythm and LVEF >50%	NT-proBNP predicted outcomes (cardiac death or symptom-driven AVR)
Monin et al. (48)	2009	107	No	Asymptomatic Moderate-to-severe AS (V_{max} ≥3.0 m/s or AVA ≤1.5 cm^2)	BNP independently predicted outcomes (cardiac death, hospitalization for CHF, or AVR)
Lancellotti et al. (54)	2010	126	No	Asymptomatic Moderate to severe AS (AVA ≤1.2 cm^2) LVEF ≥55%, sinus rhythm	BNP predicted outcomes (cardiac death, symptoms, or AVR) AUC 0.89; best cutoff was 61 pg/ml
Capoulade et al. (107)	2014	211	No	Asymptomatic Moderate-to-severe AS (V_{max}>2.5 m/s AND AVA<1.5 cm^2) Preserved LVEF 157 patients had severe AS	Both baseline BNP and peak BNP during exercise were associated with worst outcomes (death, symptom/LVEF-driven AVR)
Farre et al. (132)	2014	237	No	Asymptomatic Moderate or severe degenerative AS (V_{max}>3.5 m/s and/or AVA <1.25 cm^2)	NT-proBNP predicted outcomes (hospitalization for angina, syncope, or CHF; AVR; or death)
Henri et al. (133)	2016	69	No	Asymptomatic Moderate or severe AS (AVA <1.5 cm^2) LVEF >50%	Annual change in BNP levels predicted outcomes (symptoms, AVR, or death)

ΔP = pressure difference across the aortic valve; AUC = area under the curve; BNP = B-type natriuretic peptide; CHF = congestive heart failure; MACE = major adverse cardiac event; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association functional; V_{max} = maximum Doppler velocity signal across the aortic valve; other abbreviations as in Tables 2, 3, and 5.

AORTIC VALVE REPLACEMENT VERSUS A CONSERVATIVE APPROACH IN ASYMPTOMATIC SEVERE AS: STUDY-LEVEL META-ANALYSIS

METHODS. A systematic review of all prospective and retrospective studies of patients with asymptomatic severe AS was performed from MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and EBM Reviews—Database of Abstracts of Reviews of Effects using the search terms "asymptomatic aortic stenosis" and "asymptomatic severe aortic stenosis." Studies were included that reported all-cause mortality in adult patients (≥18 years of age) with asymptomatic severe AS. The primary search was complemented by a review of references from

identified manuscripts. Case reports, case series, and non-English reports were excluded. Three authors (P.G., G.M.G., and B.R.) abstracted the reported clinical event rates. Because most of the studies described the longitudinal follow-up of a single-arm cohort without a comparator group, quality assessment of studies using a validated assessment scale could not be performed. If 2 or more studies included patients from the same cohort, only the study with the longest follow-up or the largest number of patients was retained.

META-ANALYSIS. A study-level meta-analysis of studies comparing an AVR strategy to a conservative approach to examine the relative risk of all-cause mortality was performed. We present pooled baseline characteristics. For continuous variables, we present the pooled weighted mean and the composite standard deviation. In regard to the outcome of interest, we performed 2 analyses according to the available data: 1) by pooling the number of events and estimating a pooled unadjusted risk ratio and 95% CI; and 2) by pooling the adjusted treatment effect estimates (when available) and estimating a pooled HR and 95% CI. Both fixed effect (inverse variance weighted) and random effects models (DerSimonian and Laird) were used to assess treatment effect consistency. We assessed heterogeneity across studies with the I^2 statistic: <25% represented mild heterogeneity; 25% to 50% represented moderate heterogeneity; and >50% represented substantial heterogeneity. Due to the presence of substantial heterogeneity in both analyses, only results from random effects models are reported. We deemed p values <0.05 as significant (all p values were 2-sided). Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) was used for statistical analyses.

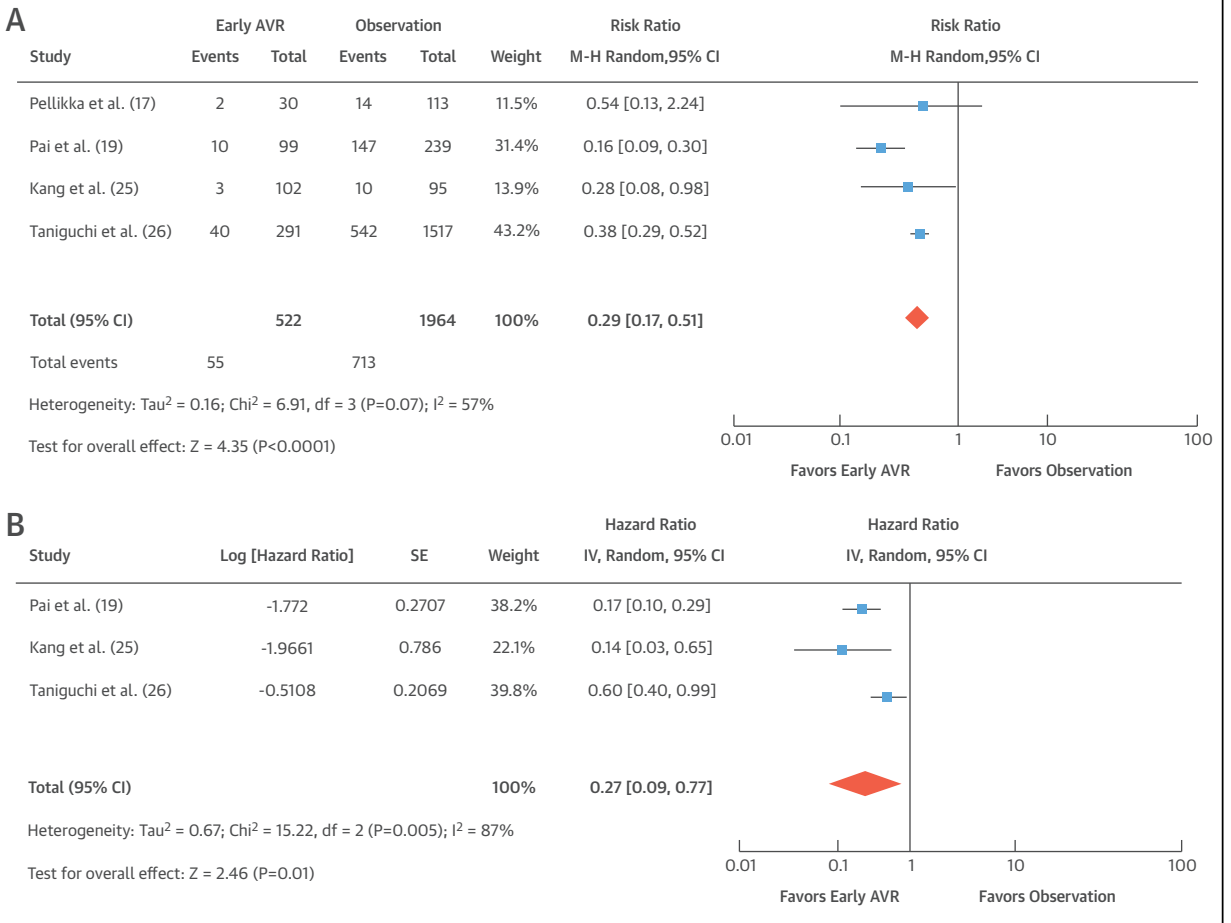
RESULTS. Of 503 potentially relevant studies, 27 observational studies were identified and considered (**Table 2**). No randomized trials were found. Of these 27 observational studies, 4 observational studies including 2,486 patients reported and compared outcomes of patients with asymptomatic severe AS undergoing early AVR to those treated with medical therapy only (17,19,25,26). Five hundred twenty-two (21%) patients underwent early AVR, and 1,964 (79%) patients underwent a conservative approach. The exact timing of early AVR was retrospectively reported in 2 studies (17,25); early AVR was, by definition, performed within 3 months of diagnosis of severe AS. There were similar proportions of women among patients who had early AVR and among patients who were treated medically (54% vs. 57%, $p = 0.28$). Patients who had early AVR were younger (69 ± 11 years vs. 77 ± 10 years; $p < 0.001$), had more severe AS with smaller AVA (0.67 ± 0.15 cm^2 vs. 0.77 ± 0.16 cm^2; $p < 0.001$) and higher mean gradient (54.5 ± 18.0 m/s vs. 35.5 ± 14.0 m/s; $p < 0.001$), but similar ejection fraction (66 ± 10% vs. 65 ± 12%, $p = 0.13$).

Mean or median follow-up time was reported by all 4 studies. Pellikka et al. (17) followed their patients for a mean of 21 months (ranging between 6 and 48 months). Two patients (6.7%) in the AVR group and 14 patients (12.4%) in the medical therapy group died (17). Pai et al. (19) reported a mean follow-up of 42 months. Cumulative mortality rates were 54% in the non-AVR group and 10% in the early AVR group. They reported a total of 17 deaths in the AVR group (17%), but do not report the number of deaths in the medical arm (19). Kang et al. (25) reported a median follow-up of 42.2 months (interquartile range: 31.6 to 77.5 months) and 31 deaths (3 in the AVR group [2.9%] and 28 in the medical therapy group [29.5%]). In the study by Taniguchi et al. (26), median follow up was 45.4 months (interquartile range 35.2 to 56.6 months). Death occurred in 40 patients who had AVR (15.4%) and 542 patients who had medical therapy (41.7%). The pooled unadjusted risk ratio of all-cause mortality for early AVR compared to observation was 0.29 (0.17 to 0.51; $p < 0.001$) (**Figure 1A**). Three studies performed adjusted analysis, with pooled adjusted HR of all-cause mortality of 0.27 (95% CI: 0.09 to 0.77; $p = 0.01$) (**Figure 1B**) (19,25,26).

DISCUSSION. On the basis of 4 retrospective studies, our polled analysis indicated that patients with severe asymptomatic AS have ~3.5-fold higher rate of all-cause death with a watchful-waiting strategy compared with AVR. These findings suggest that early AVR might improve outcomes in patients with asymptomatic severe AS. That being said, these findings have to be considered as hypothesis-generating for several reasons:

1. Patients who underwent medical observation were, in general, older and sicker; it is possible that these patients were not offered AVR in the first place because of their increased operative risk. Indeed, among the population of medically observed patients from the report of Taniguchi et al. (26), >40% at a mean follow-up of 2 years had a Class I indication for AVR, but did not undergo AVR (26,27); more importantly, ~50% of the patients who developed symptoms did not undergo AVR, suggesting that they were not suitable for either SAVR or TAVR at that point in time. This finding illustrates how difficult it could be during follow-up to precisely identify the point at which

FIGURE 1 Study-Level Meta-Analysis



All-cause mortality with surgical aortic valve replacement versus conservative medical therapy for patients with asymptomatic severe aortic stenosis. **(A)** Unadjusted; **(B)** adjusted. AVR = aortic valve replacement; CI = confidence interval; IV = inverse variance; M-H = Mantel-Haenszel test (fixed effects).

patients reach symptomatic status and/or other clear Class 1 indications (e.g., LVEF <50%), and that operative risk may increase substantially over time.

2. Surgical ineligibility (due to frailty, for example) is one of the strongest correlates of mortality, a risk factor that is typically not captured in administrative databases and the pooled studies.
3. Patients included in our pooled analysis were deemed asymptomatic on the basis of patient reporting. No stress tests were performed to identify patients who could have been extremely limited or present high-risk features on a treadmill, despite claiming being asymptomatic. It would have been expected that ~50% of these patients would have been considered for AVR if such stratification had been performed (Table 4).

TABLE 8 Theoretical Pros and Cons of Early AVR in Patients With Asymptomatic Severe AS

Favors Early AVR	Against Early AVR
• Asymptomatic patients have lower operative risk than symptomatic patients. • Potentially reduces the risk of sudden death without preceding symptoms. • May prevent irreversible myocardial damage secondary to excessive afterload. • Eliminates the risk of irreversible complications which can occur if new onset symptoms are reported too late during conservative care.	• The risk of death with conservative treatment may be low in truly asymptomatic patients with normal stress test and stress imaging. • Close follow-up can identify patients who develop indications for AVR before irreversible complications. • Avoids or delays the risks of perioperative morbidity and mortality. • Avoids or delays the long-term complications of AVR; anticoagulation, endocarditis, need for reoperation, thrombosis, and so forth.

Abbreviations as in Table 1.

4. No systematic follow-up was reported, and a more rigorous follow-up, with echocardiogram and, potentially, a stress test, would have led to better outcomes for patients initially observed.
5. Finally, substantial heterogeneity was present across the pooled studies (I^2 >50%) (17,19,25,26). This may not be surprising, as these studies varied in regard to inclusion criteria and even the definition of severe AS. Outcomes beyond mortality were variably reported and not adjudicated.

Given these issues, a large-scale, prospective, randomized clinical trial to evaluate whether routine SAVR or TAVR improves prognosis in patients with asymptomatic severe AS merits strong consideration before adoption of such a strategy can be recommended (27,28). **Table 8** presents the theoretical pros and cons of both approaches.

CONCLUSIONS

Approximately one-half of patients diagnosed with severe AS do not report symptoms. Treatment recommendations for these patients are presently on the basis of data from retrospective analyses, small prospective cohort studies, and expert opinion. On the basis of the current evidence, most asymptomatic patients with severe AS should be managed conservatively, with close monitoring to detect new onset of symptoms, increasing AS severity, deterioration in LV function, or other risk factors that might prompt consideration of early AVR. Exercise testing may be of particular use to identify whether patients are truly asymptomatic. The optimal approach to the individual patient with asymptomatic severe AS is best made by an expert heart team consisting of cardiologists, interventional cardiologists, cardiac surgeons, imaging specialists, and nurses. Given the uncertainty regarding the value of AVR in asymptomatic severe AS and the large number of affected patients, a randomized clinical trial comparing AVR (either surgical and/or transcatheter) to conservative treatment is warranted.

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