WHITE PAPER

Stress Testing in Asymptomatic Aortic Stenosis

ABSTRACT: Aortic stenosis is 1 of the most common heart valve diseases among adults. When symptoms develop, prognosis is poor, and current guidelines recommend prompt aortic valve replacement. Depending of the severity of the aortic stenosis and the presence of concomitant heart disease and medical comorbidities, stress testing represents a reasonable strategy to help better risk stratify asymptomatic patients. The present report provides a comprehensive review of the current available data on stress testing in aortic stenosis and subsequently summarizes its potential for guiding the optimal timing of aortic valve replacement.

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Aortic stenosis (AS) is 1 of the most common heart valve diseases in developed countries, affecting 1 in 20 persons >65 years of age.[1–6] Once symptomatic, the prognosis of AS is extremely poor unless aortic valve replacement (AVR) is performed.[7–19] AVR is therefore recommended by current guidelines for patients with severe AS who are symptomatic (class I indication).[20,21] Many patients who develop symptoms remain undetected in clinical practice because of lack of follow-up or access to care, or because they have subconsciously, often unconsciously, adapted by decreasing their level of activity to avoid symptoms. They may also not recognize what constitutes significant symptoms, often underestimate their severity, and only report symptoms when they become extremely limiting. Dyspnea, 1 of the most prognostically important symptoms in patients with AS, may be particularly difficult to detect as patients may relate their shortness of breath to other medical conditions or poor stamina. Self-reported symptoms may also be difficult to interpret by treating physicians.

In clinical practice, ≈50% of patients with severe AS report no symptoms at initial diagnosis.[22–25] Among these patients, irreversible myocardial damage or sudden cardiac death can occur if symptoms are overlooked and treatment is deferred. Similarly, a considerable proportion (≤30%) of patients identified as having moderate AS have been reported to exhibit an abnormal response to exercise, including test-limiting symptoms.[26] Current guidelines recommend AVR (class 1) for patients with spontaneous symptoms or symptoms occurring during a stress test (Table 1).[20,21] Stress testing with adjunctive imaging may further unmask other unfavorable characteristics that are not apparent at rest; recent data imply that several of these indices might be useful in risk stratification.[27–35] The present report will review the available data on stress testing in AS and summarize its potential role in guiding decision making for the optimal timing of AVR. We surveyed the PubMed database through August 31, 2016, for the search terms listed in Table I in the online-only Data Supplement and manually searched the references of the included articles. Articles pertaining to patients with AS who underwent stress testing were reviewed.

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Table 1. Stress Test-Related Recommendations for the Timing of Valve Replacement, Diagnostic Evaluation, and Follow-Up in Patients With Asymptomatic, Severe Aortic Stenosis

Variable	AHA/ACC[20]	ESC/EACTS[21]
Indications for surgical aortic valve replacement		
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
Increase of mean pressure gradient with exercise by >20 mm Hg and low surgical risk	—	IIb, C
Diagnostic evaluation		
Exercise testing	IIa, B	—
Exercise echocardiography*	—	—
Follow-up		
No recommendations related to stress testing	—	—

ACC indicates American College of Cardiology; AHA, American Heart Association; AVA, aortic valve area; EACTS, European Association for Cardio-Thoracic Surgery; and ESC, European Society of Cardiology.

Low-dose dobutamine stress testing using echocardiographic or invasive hemodynamic measurements is reasonable (class IIa per ACC/AHA guidelines) in symptomatic patients presenting with left ventricular ejection fraction <50% and low-flow, low-gradient findings (AVA <1 cm^2 and mean gradient <40 mm Hg or aortic velocity < 4.0 m/second), and clear evidence of a calcific aortic valve with reduced systolic opening.

DEFINITION AND DIAGNOSTIC EVALUATION

AS severity is defined by the aortic valve area (AVA) and the velocity of blood flow across the valve as assessed by transthoracic echocardiography. In patients with preserved left ventricular systolic function, severe AS is defined as (1) AVA ≤1.0 cm^2 or AVA index ≤0.6 cm^2/m^2, (2) peak aortic jet velocity ≥4.0 m/second, or (3) a mean transvalvular pressure gradient ≥40 mm Hg. Moderate AS is defined as (1) AVA 1.0 to 1.5 cm^2, (2) peak aortic jet velocity 3.0 to 3.9 m/second, or (3) a mean transvalvular pressure gradient 20 to 39 mm Hg. Mild AS is defined as a peak aortic jet velocity 2.0 to 2.9 m/second. Because AS progression can be unpredictable, it is important to follow patients closely and to be vigilant for the onset of symptoms.[20,21,36] Similarly, by acknowledging some of the technical challenges, variability, and discordances in echocardiographic acquisition of currently recommended severity grading criteria, symptoms might develop before classical echocardiographic criteria for severe AS are met.[37–44] Last, some entity presenting with an AVA <1.0 cm^2 but nonsevere gradient (paradoxical low-flow/low-gradient with normal ejection fraction) may also represent a challenging situation and area of discrepancy in AS severity assessment.[45]

STRESS TESTING IN AS

Stress testing can be performed with exercise or by pharmacological means. Exercise testing is considered more physiological and has considerably stronger support in the medical literature; it is therefore considered the optimal method for risk stratifying patients with AS who are able to exercise.[20,21] Exercise testing has been demonstrated to be safe for asymptomatic patients with AS.[46–49] It is important to rule out the following contraindications before performing the test: (1) an established indication for AVR, (2) uncontrolled hypertension, (3) symptomatic or hemodynamically significant arrhythmias, and (4) inability to perform the test such as orthopedic limitations or global disabilities.[50–53] Typically, a symptom-limited exercise protocol with the goal of reaching 80% to 85% of the age-predicted maximum heart rate is recommended. The most commonly used exercise test in North America and the United Kingdom is the treadmill test. This test is typically performed using a modified Bruce protocol in accordance with the American College of Cardiology/American Heart Association guidelines.[20] Available treadmill stress test protocols are included in Table II in the online-only Data Supplement. In most European Union countries other than the United Kingdom, the most common test is the upright bicycle test. When combined with echocardiography, the test is better performed on a dedicated tilted (semisupine) bicycle.

The traditional symptom-oriented exercise test has been studied most extensively. It is also methodologically relatively simple and can be performed by most cardiologists. The newer complimentary techniques, such as stress echocardiography and cardiopulmonary exercise testing, are more technically demanding and not as well supported; however, they have the potential to add detailed information on valve structure and function as well as the impact of AS on cardiac and other organ function. Although this additional information has been shown to be prognostically important, none has acquired an evidence base that would justify a class I indication for surgery.

Definition of an Abnormal Exercise Test

The definitions of what constitutes serious enough symptoms and signs to qualify for an abnormal stress test differ among reported studies. Typical criteria include AS-related symptoms, a drop or an insufficient rise in blood pressure, significant ventricular arrhythmias, or horizontal or down-sloping ST-depressions; however, many experts do not consider isolated abnormalities in

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the ST-segment sufficient for considering the test abnormal. Studies have also been heterogeneous in terms of exercise protocol (Table 2),[28–31,34,35,54–65] study end points (Tables 3 and 4),[29–31,33–35,54–67] and patient selection (ie, AS severity) (Tables 2, 3, and 4). These discrepancies complicate to some extent the interpretation of the available literature.

All 20 publications in Table 3 reported criteria for an abnormal stress test. Exercise-induced symptoms were included in all studies. A fall in systolic blood pressure was also included in all studies. Most studies defined this as a lack of increase or a ≤20 mm Hg increase in systolic blood pressure, but some studies used other definitions. A minority of the studies also stated that the absence of an increase in systolic blood pressure was considered abnormal. Most but not all studies reported that the occurrence of an arrhythmia qualified as an abnormal test; however, the definition of what constituted a significant arrhythmia differed among the studies, and some studies did not provide a definition. Seventeen studies included ischemic ECG changes in the definition of an abnormal stress test. This was typically defined as ≥2 mm ST-depression, but some studies used alternative definitions; however, ST-depression in the context of severe AS and associated left ventricular hypertrophy is, most of the time, nonspecific.

Eighteen of the publications in Table 3 contained information on which symptoms were used to define an abnormal stress test. Angina was reported by all. Dizziness, presyncope, or syncope was also reported by all studies. Dyspnea was reported by most studies, and fatigue was included in a minority of studies. Some studies stated that symptoms had to be limiting or occur at a low workload. Others made no mention of how symptoms such as fatigue and dyspnea were interpreted. Because the focus of most of the manuscripts was on other aspects of AS, only a few sentences were devoted to describing the criteria for an abnormal stress test; therefore, some investigators may have used somewhat different criteria than is implied by their published work. Regardless, it appears that definitions of abnormal stress tests differed across studies, complicating the interpretation of the data.

Acknowledging the inherent difficulty in deciphering between what constitutes AS-related symptoms versus deconditioning, frailty, or other causes of exercise-induced dyspnea at low workloads, a traditional exercise test should be considered abnormal if the patient experiences AS-related symptoms or displays signs of hemodynamic decompensation. The incidence of an abnormal stress test will vary depending of the severity of AS, ranging from 15% to 65% in the reviewed studies (Tables 2 and 3). As many as half of patients with severe asymptomatic AS who undergo exercise testing will have an abnormal stress test (Table 2).

Prognostic Implications of the Exercise Test

An abnormal stress test has been consistently shown to be associated with a considerably increased risk of death or adverse events over follow-up.[29,30,48,55,58] It should be noted that most studies included symptom-driven AVR as an adverse event. Because a positive stress test may lead to referral bias in the form of closer follow-up with a higher likelihood of referring the patient for AVR, the prognostic value of the exercise test in terms of the risk of an adverse event may be overestimated. That being said, a recent meta-analysis reported good sensitivity of a positive exercise test with regard to predicting adverse cardiac events and excellent sensitivity for predicting sudden cardiac death.[48] The specificity of the stress test appears to be lower for older patients (57% for patients ≥70 years versus 79% for patients <70 years), with similar sensitivity.[46] These data clearly demonstrate that many patients with asymptomatic AS are not truly asymptomatic and emphasize the benefit of performing stress testing in these patients who do not report symptoms. It is therefore concerning that relatively few patients with asymptomatic AS undergo routine stress testing.[68]

Because the criteria used to define an abnormal stress test differed between the studies and only a few studies reported outcomes according to which criteria were met, it is not clear which exercise-induced sign or symptom carries the most ominous prognosis. However, some data indicate that the development of symptoms has greater prognostic importance than blood pressure or ST-segment abnormalities.[30,55,57,58,69] It is interesting to note that a recent study showed that poor exercise capacity, defined as percentage of age- and sex-predicted metabolic equivalents achieved, as well as a slow heart rate recovery after exercise, were independently associated with increased mortality among a population of severe AS initially deemed asymptomatic.[27] Pending validation by other studies, these parameters, allowing for a better objective and quantitative stratification of exercise capacity, could be clinically useful. Notwithstanding the differences in definitions of an abnormal test and the uncertainty regarding the relative importance of the different signs and symptoms, the strong association between an abnormal stress test and prognosis makes stress testing an integral part of the risk stratification of patients with AS.[29,30,48,55,58]

Pharmacological Stress Testing in AS

One in 6 (≈15%) patients with AS is unable to exercise.[54] Inability to exercise is particularly common among the elderly, in whom the prevalence of AS is the highest.[70] Despite the lack of robust data to support its routine use, pharmacological (dobutamine) stress testing with concomitant cardiac imaging may be considered in these patients. Symptom development after dobutamine

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Table 2. Abnormal Stress Test Among Large Observational Series of Aortic Stenosis

Studies	Type of Stress Test	Abnormal Stress Test	Aortic Stenosis Severity		
			Mild	Moderate	Severe
Treadmill stress test					
Otto et al[54]	Treadmill, Bruce	15% (N=104)*		×	×
Amato et al[55]	Treadmill, Ellestad	67% (44/66)			×
Das et al[56]†	Treadmill, modified Bruce	29% (19/65)‡		×	×
Das et al[57]	Treadmill, modified Bruce	37% (46/125)		×	×
Peidro et al[58]	Treadmill, modified Naughton	63% (67/106)		×	×
Lafitte et al[59]	Treadmill, modified Bruce	65% (39/60)			×
Rajani et al[60]	Treadmill, modified Bruce	26% (10/38)		×	×
Stress echocardiogram					
Takeda et al[28]	Dobutamine stress echo	27% (13/49)		×	×
Alborino et al[29]	Dobutamine stress echo	60% (18/30)		×	×
Lancellotti et al[30]	Exercise echocardiography, bicycle	38% (26/69)			×
Maréchaux et al[31]	Exercise echo, bicycle	48% (24/50)			×
Lancellotti et al[32]	Exercise echocardiography, bicycle	47% (60/128)			×
Maréchaux et al[33]	Exercise echocardiography, bicycle	27% (51/186)		×	×
Donal et al[34]	Exercise echocardiography, bicycle	34% (69/205)		×	×
Sonaglioni et al[35]§	Exercise echocardiography, bicycle	36% (32/90)	×	×	
Cardiopulmonary testing					
Olaf et al[61]†	Bicycle, cardiopulmonary testing	23% (9/39)		×	×
Dulgheru et al[62]	Treadmill, modified Bruce, cardiopulmonary testing	N=62		×	×
Levy et al[63]	Bicycle, cardiopulmonary testing	28% (12/43)			×
Dulgheru et al[64]	Treadmill, modified Bruce, cardiopulmonary testing	N=44		×	×
van Le et al[65]§	Bicycle, cardiopulmonary testing	19% (25/130)		×	×

*Two hundred and seventy-four stress tests were performed on 104 subjects; 15% of the stress tests were abnormal.
†Dobutamine stress echocardiography was also performed, but symptoms were not reported.
‡An additional 4 patients had minor symptoms at high workload.
§Symptoms only.

administration has been associated with future spontaneous symptom onset in AS.[28] The most commonly used dobutamine stress protocol consists of continuous infusion of dobutamine, starting at 5 μg/kg/minute, with stepwise increase to 10, 20, 30, and 40 μg/kg/minute in 3-minute increments.[46]

Stress Echocardiography in AS

Stress echocardiographic protocols focus on valve or left ventricle (LV)-related parameters and hemodynamics. Stress echocardiography can be performed during exercise or pharmacological stress. Exercise echocardiography is more demanding and requires more training and experience than pharmacological stress echocardiography; it is also considered more physiological and is therefore preferred in patients with asymptomatic AS, whereas dobutamine stress echocardiography is the test of choice for patients with low-gradient, reduced ejection fraction AS that is deemed severe based on AVA calculation.[71] Echocardiography after exercise can be performed after traditional treadmill or bicycle ergometer exercise, but bicycle exercise is the recommended exercise technique when stress echocardiography is performed. With supine or semisupine bicycle stress echocardiography, imaging and Doppler assessment can be performed continuously throughout the testing period.[34]

Studies that used stress echocardiography to risk stratify patients with AS are summarized in Table 5.[27,28,30–35,56,61,66] In moderate or severe AS, a considerable exercise-induced increase in mean pressure gradient is associated with an increased risk of adverse events (cardiac death or development of symptoms, including symptom-driven AVR), with an increase >18 mm Hg or >20 mm Hg considered pathological.[30,33] Exercise-induced changes

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Table 3. Studies Evaluating Treadmill Exercise Tests in Patients With Aortic Stenosis

Authors	N	Patients	Test Protocol	Criteria for Abnormal Test	Specified Symptoms	% Abnormal Exercise Test	Findings
Otto et al[54]	123	AS with peak velocity >2.5 m/s	Bruce	Symptoms Fall in systolic blood pressure >10 mm Hg ST-depression >5 mm Significant arrhythmias	—	Abnormal stress test: 15% Fall in systolic blood pressure >10 mm Hg: 9% >2 mm ST-depression persisting >5 min into recovery: 2%	Rate of hemodynamic progression and clinical outcome was predicted by peak velocity, rate for change in peak velocity, and functional status
Amato et al[55]	66	Severe AS with AVA ≤1 cm^2	Ellestad protocol Age-related peak heart rate was determined using the formula (210 – Age). Submaximal frequency corresponded to 85% of this value.	Symptoms of AS (precordial chest pain or near syncope) Upsloping ST-segment depression of >3 mm in men. Upsloping ST-segment depression in women was considered negative. Horizontal or downsloping ST-segment depression of >1 mm in men or >2 mm in women Complex ventricular arrhythmia SBP failed to rise by ≥20 mm Hg	Precordial chest pain Presyncope	Abnormal stress test: 44/66 (67%) Limiting symptoms: 20/66 (30%) Dizziness (7/20) Chest pain (12/20) Dizziness and chest pain (1/20) Arrhythmia: 3/66 (5%)	Of the 38 patients who reached 1 of the end points of the study, 35 (92.1%) had a positive stress test and 3 (7.9%) had a negative stress test. After 24 mo, 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. 6% of the patients (4/66) experienced sudden death; all these had a positive exercise test and an AVA ≤0.6 cm^2 Positive exercise test was the strongest predictor of death or developing symptoms at follow-up
Das et al[56]	65	AS with effective orifice area <1.2 cm^2	Bruce protocol modified by 2 warmup stages	Significant limiting symptoms (clear symptoms preventing continuation of exercise at <80% of predicted maximum workload) ST-depression of >5 mm >3 consecutive ventricular premature beats Fall in SBP >20 mm Hg	Dyspnea (limiting) Chest discomfort (limiting) Dizziness (limiting)	Abnormal stress test: 19/65 (29%) 19/65 (29%) limiting symptoms (16 dyspnea or chest pain and 3 dizziness) (11/19 severe AS and 8/19 moderate AS) 18/65 (28%) abnormal SBP	Exertional symptoms are better predicted by compliance than resting effective orifice area, mean pressure drop, or peak transaortic velocity
Das et al[57]	125	Moderate-severe AS with effective orifice area <1.4 cm^2 (42% severe)	Bruce protocol modified by 2 warmup stages	Stopped prematurely because of symptoms ST-segment depression of >5 mm More than 3 consecutive ventricular premature beats SBP fall of >20 mm Hg from baseline	Dyspnea (limiting) Chest discomfort (limiting) Dizziness (limiting)	46/125 (37%) stopped because of limiting symptoms (28 dyspnea, 12 chest discomfort, and 6 dizziness) Other criteria: 29/125 (23%) had an abnormal SBP response (same or drop compared with baseline)	36 (29%) developed spontaneous symptoms within 12 mo. Of these, 26 (72%) had symptoms revealed by exercise testing. Exercise-limiting symptoms were the only independent predictors of outcome at 12 mo, and an abnormal blood pressure response or ST-segment depression did not improve the accuracy of the exercise test

(*Continued*)

Table 3. Continued

Authors	N	Patients	Test Protocol	Criteria for Abnormal Test	Specified Symptoms	% Abnormal Exercise Test	Findings
Das et al[57] (Continued)						33/125 (26%) had ST-segment depression >2 mm	Spontaneous symptoms at 12 mo developed in 5/6 (83%) patients with exertional dizziness, 6/12 (50%) patients with chest tightness, and 15/28 (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 Symptoms during exercise testing were superior to clinical history and echocardiography in predicting the imminent onset of spontaneous symptoms
Peidro et al[58]	106	AS with mean gradient >30 mm Hg	Modified Naughton protocol	Limiting symptoms Dyspnea or maximal exhaustion to functional capacity ≤5 METs in patients <70 y or ≤4 METs in patients >70 y Drop in SBP ≥10 mm Hg Downsloping ST-segment depression >1 mm Frequent coupled ventricular beats or ventricular tachycardia during exercise or recovery	Angina Presyncope Syncope Dyspnea (at lower than expected exertion)	Abnormal stress test 67/102 (66%) Angor or dyspnea: 37.2% ST-segment depression: 42.1% Drop SBP: 26.5% Ventricular arrhythmia: 3.9%	Abnormal stress test: 35/67 (52%) AVR 2/67 (3%) death Normal stress test: 10/35 (29%) AVR 0/35 (0%) death Predictors of cardiovascular death or AVR: Symptoms during exercise test Drop in SBP ST-segment depression
Lafitte et al[59]	60	Severe AS with AVA <1 cm^2	Bruce protocol modified by 2 warmup stages	Limiting symptoms ST-segment depression of >2 mm >3 consecutive ventricular premature beats Fall in SBP of >20 mm Hg	Angina Dyspnea Dizziness	Abnormal stress test: 39/60 (65%) Limiting symptoms: 37% Abnormal blood pressure response: 35% Significant ST-segment depression: 13%	42 (70%) patients underwent AVR Cardiovascular death: 2 (3.3%) patients; heart failure or atrial fibrillation: 5 (8.3%) patients 65% of patients had a positive stress test: 37% had limiting symptoms, 35% had an abnormal blood pressure response, 13% had significant ECG ST-segment depression

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Table 3. Continued

Authors	N	Patients	Test Protocol	Criteria for Abnormal Test	Specified Symptoms	% Abnormal Exercise Test	Findings
Lafitte et al[59] (Continued)							Global longitudinal strain and basal longitudinal strain values of −18 and −13 were associated with a sensitivity of 68% and 75%, and a specificity of 77% and 83%, respectively, in predicting an abnormal exercise response Unoperated patients demonstrated a significant relationship between basal longitudinal strain and cardiac events; no event occurred in patients with basal longitudinal strain >−13%
Rajani et al[60]	38	Moderate-severe AS (effective orifice area <1.5 cm²)	Bruce protocol modified by two warmup stages	Symptoms ST-depression >5 mm >3 consecutive ventricular premature beats A fall in SBP >20 mm Hg from baseline	Angina Dyspnea Dizziness	10/38 (26%) with limiting symptoms during stress test Severe AS: 7/18 (39%) Moderate AS: 3/20 (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 B-type natriuretic peptide level
Dulgheru et al[62]	62	AVA <1.5 cm² and LVEF >50%	Modified Bruce protocol (Multistage symptom-limited treadmill cardiopulmonary imaging)	Symptoms Sustained ventricular arrhythmias Inadequate rise (<20 mm Hg) or drop in SBP ≥2 mm ST-depression	Angina Dizziness	N/A	45% had VO_2 <84% of predicted
Dulgheru et al[64]	44	AVA <1.5 cm² and LVEF >50%	Modified Bruce protocol (Multistage symptom-limited treadmill cardiopulmonary imaging)	Symptoms Sustained ventricular arrhythmias Inadequate rise (<20 mm Hg) or drop in systolic blood pressure ≥2 mm ST-depression	Angina Dizziness	The study included only patients who were asymptomatic on the exercise test	Baseline longitudinal deformation (speckle tracking) was associated with maximum VO_2

AS indicates aortic stenosis; AVA, aortic valve area; BNP, B-type natriuretic peptide, CP, cardiopulmonary exercise testing performed; E, diastolic mitral inflow velocity; e’, peak diastolic mitral annulus velocity; FEV_1, forced expiratory volume in 1 second; LVEF, left ventricular ejection fraction; MET, metabolic equivalent; N/A, not available; ΔP, pressure gradient; pVO_2, peak oxygen consumption; SBP, systolic blood pressure; SE, stress echocardiography performed; Vco_2, carbon dioxide elimination rate; VE/CO_2, ventilatory equivalent for carbon dioxide; and Vo_2, oxygen uptake rate.

in pressure gradient have incremental value over the traditional exercise test and baseline echocardiographic parameters.[30,33] From a pathophysiological perspective, the increase in pressure gradient during exercise can occur because the AS is severe at baseline, which results in a greater increase in the gradient for a given flow rate during exercise or because the aortic valve is noncompliant and rigid and does not increase its orifice area during stress.[72] Because of the intimate relationship between pressure gradient and flow rate, exercise-induced changes in gradient should be interpreted in the context of changes in stroke volume. If the stroke volume increases markedly during exercise, then the gradient can increase considerably even in the presence of a compliant valve. Assessment of exercise-induced changes in stroke volume has additional value because the change

Table 4. Studies Evaluating Bicycle Ergometer Exercise Tests in Patients With Aortic Stenosis

Authors	N	Patients	Test Protocol	Criteria for Abnormal Test	Specified Symptoms	% Abnormal Exercise Test	Findings
Alborino et al[29]	30	Asymptomatic moderate-to-severe AS (mean gradient ≥30 mm Hg)	Upright maximal bicycling exercise test Baseline ≥25 Watts and then increase by 10–50 Watts every 2 min	Symptoms (angina, syncope) Malign arrhythmias Fall ≥20 mm Hg of SBP at peak intensity Ischemic ST changes Exhausted at low workload (<6 METs in men ≤70 y of age, or <5 METs in men >70 y of age or in women)	Angina Syncope	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 10/18 (56%) had symptoms at 1 y 14/18 (78%) had symptoms at 3 y Patients with normal stress test 0/12 (0%) had symptoms at 1 y 2/12 (17%) had symptoms at 3 y 3-year freedom of cardiac death or AVR was 83% for normal stress test and 33% for abnormal stress test
Lancellotti et al[30]	169	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 Watts; increase by 25 Watts every 2 min	Symptoms >2 mm ST-segment depression Fall or small (20 mm Hg) rise in SBP compared with baseline Significant arrhythmias	Angina Dyspnea Syncope	Abnormal stress test: 26/69 (38%) Angina: 4 (6%) Dyspnea: 2 (3%) >2 mm ST-depression: 13 (19%) Fall or <20 mm Hg rise in SBP: 6 (9%) Nonsustained ventricular tachycardia: 1 (1.5%) 18 (26.1%) patients had cardiac events at 15±7 mo follow-up	Stress test was abnormal in 14/18 (78%) of patients with cardiac events and in 12/51 (24%) in pts with no cardiac events at follow-up (*P*=0.0008). All 6 of the patients who developed hypotension or had an inadequate rise in systolic arterial pressure during exercise experienced a cardiac event at follow-up Independent predictors of cardiac events: Increase in mean gradient by ≥18 mm Hg during exercise An abnormal exercise test AVA <0.75 cm^2
Maréchaux et al[31]	50	Severe AS with AVA ≤1 cm^2	Symptom-limited exercise on a semirecumbent bicycle exercise Initial workload of 25 Watts; increase by 25 Watts every 3 min	Symptoms ≥2 mm ST-segment depression Fall or no increase in SBP at peak exercise Ventricular arrhythmias Abnormal left ventricular response to exercise ΔLVEF from rest to peak exercise <0%	Angina Presyncope Syncope Dyspnea	Abnormal stress test: 24/50 (48%; 20/24 [83%] had AVR) Symptoms: 24/50 (48%) Fall or no increase in SBP at peak exercise: 7/50 (14%)	7/50 (14%) had spontaneous symptoms at median of 11-mo follow-up (2 normal LVEF at exercise and 5 abnormal) Decrease LVEF at exercise was associated with development of cardiovascular death or spontaneous symptoms at follow-up

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Table 4. Continued

Authors	N	Patients	Test Protocol	Criteria for Abnormal Test	Specified Symptoms	% Abnormal Exercise Test	Findings
Maréchaux et al[31] (Continued)						≥2 mm ST-segment depression: 5/50 (10%) Normal stress test: 26/50 (52%) 10/26 (38%) had AVR	3 patients who experienced symptoms during exercise developed functional mitral regurgitation
Maréchaux et al[33]	186	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 semisupine position on a tilting exercise table Initial workload of 20–25 Watts maintained for 3 min; workload increased every 3 min by 20–25 Watts	Symptoms Fall in SBP below baseline Complex ventricular arrhythmia	Dyspnea Angina Dizziness Syncope Fatigue at low workload	Abnormal stress test: 51/186 (27%) Normal stress test: 135/186 (73%)	Normal exercise test subgroup: 67/135 (50%) cardiovascular events (time to occurrence of cardiovascular death or symptom-driven AVR or by LVEF<50%) Predictors of cardiovascular events: Age ≥65 y (HR=1.96) Diabetes mellitus (HR=3.20) LVH (HR=1.96) Resting mean gradient >35 mm Hg (HR=3.60) Exercise-induced increase in mean gradient >20 mm Hg (HR=3.83) The combination of a rest mean gradient >35 mm Hg and an exercise-induced increase in mean gradient >20 mm Hg was associated with markedly increased risk of event (HR=9.6; *P*<0.0001)
Donal et al[34]	205	Moderate and severe with AS ≤1.2 cm^2	Symptom-limited graded bicycle exercise test in a semisupine position on a tilting exercise table	Symptoms ≥2 mm ST-segment depression Rise of SBP <20 mm Hg or a fall in SBP Complex ventricular arrhythmias	Angina Dyspnea at low workload Dizziness Presyncope Syncope	Abnormal stress test: 69/205 (34%)	Independent predictor of abnormal response to exercise: Lower global longitudinal strain at rest Higher increase in mean gradient at exercise

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Table 4. Continued

Authors	N	Patients	Test Protocol	Criteria for Abnormal Test	Specified Symptoms	% Abnormal Exercise Test	Findings
Donal et al[34] (Continued)			Initial workload of 30 Watts. Workload increased by 20 Watts every 2 min, depending on physical training				Smaller exercise-induced changes in global longitudinal strain ROC curve analysis best cutoff: Global longitudinal strain at rest of <15.5% (AUC, 0.58) Global longitudinal strain change by <−1.4% at exercise (AUC, 0.77) Increase in mean gradient ≥14 mm Hg (AUC, 0.72)
Lancellotti et al[66]	191	Severe AS with indexed AVA <0.6 cm^2/m^2	Symptom-limited graded bicycle exercise test in a semisupine position on a tilting exercise table Initial workload of 25 Watts maintained for 2 min. Workload increased by 25 Watts every 2 min	Symptoms ≥2 mm ST-segment depression Rise of SBP <20 mm Hg or a fall in SBP Complex ventricular arrhythmias	Angina Dizziness Presyncope Syncope	45/191 (23.5%) Only patients who were asymptomatic and who had measurable systolic pulmonary artery pressure on exercise were included in subsequent analyses	Ex-PHT (systolic pulmonary arterial pressure >60 mm Hg) was associated with reduced cardiac event-free (cardiovascular death or need for AVR) survival (at 3 y, 22±7% vs. 55±9%; P=0.014) Ex-PHT was identified as an independent predictor of cardiovascular 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%
Olaf et al[61]	39	AVA <1.0 cm^2 or ΔP >35 mm Hg	Symptom-limited semisupine bicycle exercise test with assessment of cardiopulmonary function. Patients were exercised until they developed symptoms or reached a respiratory quotient ≥1.1 Stepwise dobutamine-stress echocardiography to a maximum heart rate of 120/min	Symptoms Inadequate blood pressure response ST depression >2 mm VO_2 peak <80% of predicted	Reference to recommendations by Lung et al[104]: Angina Dyspnea Presyncope Syncope	Abnormal stress test: 11/39 (28.2%) Symptoms: 9/39 ST-depression: 6/39	Cardiopulmonary imaging and dobutamine stress test both associated with exercise intolerance. Note that patients with AS were grouped together with patients with other valvular heart disease when these associations were assessed

(*Continued*)

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Table 4. Continued

Authors	N	Patients	Test Protocol	Criteria for Abnormal Test	Specified Symptoms	% Abnormal Exercise Test	Findings
Capoulade et al[67]	211	Moderate or severe AS (Vmax >2.5 m/s and AVA <1.5 cm^2)	Graded bicycle test Doppler echocardiography	Symptoms ≥2 mm ST-segment depression Rise of SBP <20 mm Hg or a fall in SBP Complex ventricular arrhythmias	Angina Dizziness Pre-syncope Syncope	N/A	Resting as well as peak-exercise BNP levels were associated with increased risk of death or AVR in patients with severe AS (N=157)
Levy et al[63]	43	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 Watts/min or 10 Watts/min) after a 1-minute warmup at 20 Watts	Symptoms Peak SBP at or below the baseline level Complex ventricular arrhythmia	Limiting dyspnea Fatigue at low workload Angina Dizziness Syncope	Abnormal stress test: 12/43 (28%) Limiting dyspnea: 11/43 Angina: 11/43 ST-depression >1 mm: 7/43	Independent predictors of AVR or AS-related symptoms: peak VO_2 ≤14 mL/kg/min, VE/VCO_2 slope >34
Sonaglioni et al[35]	90	Asymptomatic ΔP <40 mm Hg LVEF ≥55% No concomitant moderate or severe mitral valve disease Absence of coronary artery disease and renal failure	Ergometer exercise test with an initial workload of 25 W that was increased every 2 min until age-related maximum heart rate, fatigue, complex ventricular arrhythmias, blood pressure fall ≥20 mm Hg, ST-depression ≥2 mm compared with baseline or symptoms	Symptom Blood pressure falls ≥20 mm Hg ST-depression ≥2 mm compared with baseline or symptoms Complex ventricular arrhythmias	Test stopped if any: Angina Dyspnea Fatigue Dizziness Syncope	32/90 (35.6%) had symptoms on exercise	Three patients died suddenly, 11 underwent AVR, 26 were hospitalized (arrhythmias with hemodynamic instability, N=10; heart failure, N=7; acute coronary syndromes, N=9). Adverse cardiac events (cardiovascular hospitalization, AVR or cardiac death) occurred in 29.4% of patients with mild and 53.5% of patients with moderate AS The change in E/e’ ratio predicted adverse events
van Le et al[65]	131	AVA <1.3 cm^2 Asymptomatic (n=38) or equivocally symptomatic (n=92)	Cardiopulmonary exercise testing on an upright bicycle ergometer The load was calculated for each patient to reach a predicted pVO_2 in 8–10 min	Exercise-induced symptoms Blood pressure increase <20 mm Hg ST-depression >2 mm	Angina Dyspnea Dizziness	25/131 (19.2%) had symptoms. 35/131 (26.9%) had <20 mm Hg blood pressure increase 12/131 (9.2%) had ST-depression >2 mm	26.1% (n=34) had subnormal pVO_2 (<83%). Correlates of reduced pVO_2 were low stroke volume, low peak heart rate, low FEV_1 decreased VE/VCO_2, mean ΔP, AVA index, E/e’, and elevated BNP

AS indicates aortic stenosis; AVA, aortic valve area; BNP, B-type natriuretic peptide; CP, cardiopulmonary exercise testing performed; E, diastolic mitral inflow velocity; e’, peak diastolic mitral annulus velocity; FEV_1, forced expiratory volume in 1 second; LVEF, left ventricular ejection fraction; MET, metabolic equivalent; ΔP, pressure gradient; pVO_2, peak oxygen consumption; SBP, systolic blood pressure; SE, stress echocardiography performed; V_{CO_2}, carbon dioxide elimination rate; VE/CO_2, ventilatory equivalent for carbon dioxide; and V_{O_2}, oxygen uptake rate.

Table 5. Studies Evaluating Stress Echocardiography in Patients With Aortic Stenosis

Authors	Patients	Stress Protocol	% Abnormal Exercise Test	Findings
Takeda et al[28]	AS with peak velocity >2.5 m/s	Dobutamine stress echocardiography Dobutamine was infused from 5 up to a maximum of 40 mg/kg/min in 5-min stages	Significant symptoms: 13/49 (27%) Sustained fall in SBP: 5/49 (10%) Arrhythmia: 1/49 (2%)	23/49 (47%) developed symptoms at follow-up Symptoms during stress test: 10/13 (77%) developed symptoms Normal stress test: 13/36 (36%) developed symptoms Mean time to first symptoms: 8 mo Predictors of development of symptoms: Peak velocity, peak pressure gradient, pressure drop/flow slope 83% AVR or symptoms at 2 yr if peak velocity >4 m/s
Das et al[56]	AS with effective orifice area <1.2 cm^2	Dobutamine stress echocardiography Treadmill exercise test using a Bruce protocol modified by 2 warmup stages Abnormal stress test: Significant limiting symptoms ST-depression of >5 mm >3 consecutive ventricular premature beats Fall in SBP >20 mm Hg	Abnormal stress test: 19/65 (29%) 19/65 (29%) limiting symptoms (11/19 severe AS and 8/19 moderate AS) 18/65 (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) $cm^2/100\ mL.s^{-1}$ than in those without at 0.25 (0.10) $cm^2/100\ mL.s^{-1}$ Peak effective orifice area and the absolute increase in area from rest to peak were also lower in patients with symptoms
Lancellotti et al[30]	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 Watts; increased every 2 min by 25 Watts	Abnormal stress test: 26/69 (38%) Angina 4 (6%); dyspnea in 2 (3%); >2 mm ST-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: 14/26 (54%) with event Normal stress test: 4/43 (9%) with event Independent predictors of cardiac events: Increase in mean gradient by ≥18 mm Hg during exercise An abnormal exercise test AVA <0.75 cm^2
Maréchaux et al[31]	Severe AS with AVA ≤1 cm^2	Symptom-limited exercise on a semirecumbent bicycle exercise Initial workload was 25 W that was increased by 25 W increment every 3 min Abnormal stress test: Angina, shortness of breath, near syncope or syncope ≥2 mm ST-segment depression Fall or no increase in SBP at peak exercise when compared with baseline level Ventricular arrhythmias Abnormal left ventricular response to exercise: ΔLVEF from rest to peak exercise <0%	Abnormal stress test: 24/50 (48%); 20/24 (83%) had AVR Normal Stress test: 26/50 (52%); 10/26 (38%) had AVR 7/50 (14%) had spontaneous symptoms at median of 11 mo follow-up (2 normal LVEF at exercise and 5 abnormal)	Decrease LVEF at exercise was associated with development of cardiovascular death or spontaneous symptoms at follow-up

(*Continued*)

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Table 5. Continued

Authors	Patients	Stress Protocol	% Abnormal Exercise Test	Findings
Lancellotti et al. 2008[32]	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 Watts; increased every 2 min by 25 Watts	Abnormal stress test: 60/128 (47%) Symptoms during stress test: 30/128 (23%)	Independent predictors of abnormal stress test: Higher increase in mean gradient (best cutoff value was ≥17 mm Hg) Decrease or lower increase in LVEF Independent predictors of symptoms during stress test: Higher increase in mean gradient Smaller exercise-induced change in SBP Lower LVEF at peak test: Independent predictors of fall or a <20 mm Hg increase SBP: Presence of MR at rest Decrease or lower increase in LVEF Independent predictors of ≥2 mm ST-segment depression: Smaller AVA at rest Higher increase in mean gradient
Maréchaux et al[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 semisupine position on a tilting exercise table Initial workload of 20–25 Watts maintained for 3 min. Workload increased every 3 min by 20–25 Watts Abnormal stress test: Occurrence of limiting breathlessness, fatigue at low workload, angina, dizziness, syncope. Fall in SBP below baseline Complex ventricular arrhythmia	Abnormal stress test: 51/186 (27%) Normal stress test: 135/186 (73%)	Normal exercise test subgroup: 67/135 (50%) cardiovascular events (time to occurrence of cardiovascular death or symptom-driven AVR or by LVEF <50%) Predictors of cardiovascular events: Age ≥65 y (HR=1.96) Diabetes mellitus (HR=3.20), LVH (HR=1.96) Resting mean gradient >35 mm Hg (HR=3.60) Exercise-induced increase in mean gradient >20 mm Hg (HR=3.83) The combination of a rest mean gradient >35 mm Hg and an exercise-induced increase in mean gradient >20 mm Hg was associated with markedly increased risk of event (HR=9.6; *P*<0.0001)
Donal et al[34]	Moderate and severe with AS ≤1.2 cm^2	Symptom-limited graded bicycle exercise test in a semisupine position on a tilting exercise table Initial workload of 30 Watts. Workload increased by 20 Watts every 2 min depending on physical training Abnormal stress test: Angina, shortness of breath at low workload level (50 Watts), dizziness, syncope, or near-syncope ≥2 mm ST-segment depression Rise of SBP <20 mm Hg or a fall in SBP Complex ventricular arrhythmias	Abnormal stress test: 69/207 (34%)	Independent predictor of abnormal response to exercise: Lower global longitudinal strain at rest Higher increase in mean gradient at exercise Smaller exercise-induced changes in global longitudinal strain ROC curve analysis best cutoff: Global longitudinal strain at rest of <15.5% (AUC, 0.58) Global longitudinal strain change by <−1.4% at exercise (AUC, 0.77) Increase in mean gradient ≥14 mm Hg (AUC, 0.72)

(*Continued*)

Table 5. Continued

Authors	Patients	Stress Protocol	% Abnormal Exercise Test	Findings
Lancellotti et al[66]	Severe AS with indexed AVA <0.6 cm^2/m^2	Symptom-limited graded bicycle exercise test in a semisupine position on a tilting exercise table Initial workload of 25 Watts maintained for 2 min. Workload increased every 2 min by 25 Watts Abnormal stress test: Angina, shortness of breath at low workload level (50 Watts), dizziness, syncope, or near syncope ≥2 mm ST-segment depression Rise of SBP <20 mm Hg or a fall in SBP Complex ventricular arrhythmias	-	Ex-PHT was associated with reduced cardiac event-free (cardiovascular death or need for AVR) survival (at 3 y, 22±7% vs. 55±9%; *P*=0.014) Ex-PHT was identified as an independent predictor of cardiovascular 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%
Olaf et al[61]	AVA <1.0 cm^2 or ΔP >35 mm Hg	Symptom-limited semisupine bicycle exercise test with assessment of cardiopulmonary function. Patients were exercised until they developed symptoms or reached a respiratory quotient ≥1.1 Stepwise dobutamine-stress echocardiography to a maximum heart rate of 120/min	Abnormal stress test: 28.20%	Predictors of exercise tolerance: Cardiopulmonary imaging and dobutamine stress test both associated with exercise intolerance. Note that patients with AS were grouped together with patients with other valvular heart disease when these associations were addressed
Sonaglioni et al[35]	Asymptomatic ΔP <40 mm Hg LVEF ≥55% No concomitant moderate or severe mitral valve disease Absence of coronary artery disease and renal failure	Cardiopulmonary exercise testing on an upright bicycle ergometer The load was calculated for each patient to reach a predicted pVO_2 in 8–10 min	19.2% (n=25) had symptoms, 26.9% (n=35) had <20 mm Hg blood pressure increase, 9.2% (n=12) had ST-depression >2 mm	Correlations between cardiopulmonary and stress echocardiographic indices 26.1% (n=34) had subnormal pVO_2 (<83%). Correlates of reduced pVO_2 were low stroke volume, low peak heart rate, low FEV_1, decreased VE/VCO_2, mean ΔP, AVA index, E/e', and elevated BNP.
Masri et al[27]	Asymptomatic severe AS (indexed AVA <0.6 cm^2/m^2) Excluded if unable to exercise or had more than moderate tricuspid/ mitral stenosis/ regurgitation, LVEF <50% or underwent TAVR	Treadmill echocardiography using Bruce, modified Bruce, Cornell, or Naughton protocol. Peak stress echocardiographic images obtained immediately after exercise Test terminated if symptoms	6% (n=31) had abnormal blood pressure response. 0.6% (n=3) experienced dizziness, 1% (n=8) had significant arrhythmia	50% achieved 100% of age-gender predicted METs Number of ischemic left ventricular territories: 0: 89% (n=473) 1: 9% (n=48) 2: 2% (n=8) 3: 0.8% (n=4) Correlation between % age-sex predicted METs and outcome Patients who achieved <85% of the predicted METs had significantly worse prognosis than patients who achieved ≥85% Other independent correlates of poor prognosis: Other predictors of mortality were: No AVR vs. AVR Slower heart rate recovery after exercise STS score

AS indicates aortic stenosis; AUC, area under the curve; AVA, aortic valve area; AVR, aortic valve replacement; HR, hazard ratio; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; PHT, pulmonary hypertension; pVO2, peak oxygen consumption; SBP, systolic blood pressure; STS, Society of Thoracic Surgeons; and TAVR, transcatheter aortic valve replacement.

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in stroke volume is a prognostic marker in AS. The absence of an exercise-induced increase in stroke volume or ejection fraction is considered abnormal and associated with reduced cardiac event-free survival (with cardiovascular death and AVR constituting an event).[30,31,33]

Beyond pressure gradient and left ventricular functional parameters, 2 novel exercise echocardiographic indices are emerging. First, development of pulmonary hypertension (systolic pulmonary arterial pressure >60 mm Hg) at peak exercise has been associated with a 2-fold increased adjusted risk of cardiac events (cardiovascular death or need for AVR due to symptoms or LV dysfunction).[66] Whereas pulmonary hypertension at baseline is a strong predictor of worse outcomes even if the patient undergoes AVR, and is often associated with symptoms, pulmonary hypertension that develops only during exercise represents an earlier disease stage. Intervention before chronic pulmonary hypertension develops may improve prognosis. Second, impaired global longitudinal strain (using various cutoffs values as well as a linear metric) has been observed in patients with severe AS and is believed to reflect subendocardial cardiomyocyte dysfunction secondary to concentric remodeling and myocardial fibrosis.[59,69,73–75] Recently, the magnitude of exercise-induced changes in global longitudinal strain, as assessed by tissue Doppler imaging or 2-dimensional speckle-tracking, predicted reduced contractile reserve; however, these studies did not examine the relationship between exercise-induced changes in global longitudinal strain and clinical events.[34,76] Hence, the association between changes in global longitudinal strain during exercise and clinical outcomes needs to be confirmed.

In summary, among asymptomatic AS patients, exercise echocardiography is a diagnostic modality that has the potential for continuous assessment during exercise of key parameters related to valve anatomy and physiology. It appears to offer incremental value over the traditional exercise test and baseline echocardiography, but its value in asymptomatic AS needs to be proven in more robust studies. The European Society of Cardiology/European Association for Cardio-Thoracic Surgery but not the American College of Cardiology/American Heart Association guidelines recommend that for asymptomatic severe AS patients with normal ejection fraction and high gradient, AVR could be considered for patients with >20 mm Hg increase in mean gradient during exercise (class IIb).[21]

Cardiopulmonary Exercise Testing in AS

Cardiopulmonary exercise testing complements the traditional stress test by adding information on respiratory gas exchange, including maximum oxygen uptake (VO_2). This is achieved by measuring airflow rates (transducers) and the partial pressures of O_2 and CO_2 (gas analyzers).[77,78] Maximum VO_2 reflects the body's highest attainable rate of transport and use of oxygen. Thus, in AS the maximum VO_2 reflects the impact of AS on the heart's primary objective, the delivery of oxygen and nutrients to the tissues. A strong association between maximum VO_2 and the risk of adverse clinical outcomes has been demonstrated in other forms of heart failure.[79]

In a study by Dulgheru et al,[62] ≈50% of patients with asymptomatic severe AS had markedly reduced VO_2 (defined as <84% of the age- and sex-predicted peak VO_2). van Le et al[65] performed cardiopulmonary exercise testing in 130 patients with asymptomatic or equivocally asymptomatic moderate or severe AS (AVA <1.3 cm^2). Patients with VO_2 <83% of the predicted value and in whom the reduced VO_2 could only be explained by the AS were referred to an independent heart team for possible AVR. Cardiopulmonary exercise testing was safe, and subsequent adverse event rates were low; however, the study design (patients were referred to AVR based on their maximum VO_2 value) complicates interpretation of the value of the cardiopulmonary exercise test. The relationship between decreased VO_2 and other cardiopulmonary exercise parameters with clinical outcomes needs to be addressed.

Neurohormones During Exercise Testing in AS

Plasma B-type natriuretic peptide concentration at baseline is a complimentary tool to exercise testing for risk stratifying patients with AS.[80–83] A recent study in 211 patients showed that increased peak-exercise plasma B-type natriuretic peptide levels are independently associated with adverse outcomes among asymptomatic patients with AS.[67] Similarly, baseline cardiospecific troponin levels are associated with worse prognosis in AS, and troponin levels after stress correlate with myocardial ischemia in patients with coronary artery disease.[84–86] Additional studies are required to establish whether B-type natriuretic peptide, troponin, or other biomarkers measured at peak exercise have a role in the risk stratification of patients with AS.

Limitations of Exercise Testing in AS

An inherent limitation with the exercise test is that the symptoms and signs that may develop during exercise are not specific for AS, and exercise capacity can be influenced to varying degrees by other cardiac or noncardiac conditions.[87–89] Concomitant coronary artery disease is common among patients with AS and increases with age.[87] Whether symptoms such as chest pain and dyspnea are caused predominantly by the coronary obstruction or the AS is difficult to discern. Similarly, chronic obstructive pulmonary disease may cause these symptoms.[88,89] Exercise echocardiography and cardiopulmonary imaging can provide more disease-specific information that may help to differentiate between AS and non–AS-related symptoms.[30,33,62,77–79] Furthermore, cardiac MRI, computed tomography, and biomarker assessment can provide additional information that can help in assessing the physiological significance of the AS[36,39,80–83,90–97]. However, it is not possible to fully exclude the possibility that concomitant diseases contribute considerably to the symptomatology and results of an exercise test. That being said, it may be reasonable to treat the AS in many situations where concomitant disease contributes to patient symptomatology because effective treatment of significant AS is likely to provide symptom relief in the setting of concomitant disease.[98]

THE ROLE OF STRESS TESTING IN CLINICAL DECISION MAKING

The most important decision a physician faces when caring for a patient with asymptomatic AS is when to recommend AVR.[20,21] Traditional symptom-limited exercise testing is helpful to determine whether patients with severe AS and preserved LV systolic function who do not report symptoms are truly asymptomatic. Asymptomatic patients with severe AS and reduced or subnormal LV systolic function should be referred for surgery (class I). If the patient with preserved LV function develops spontaneous valve-related symptoms during follow-up or exercise stress testing, then both European Society of Cardiology/European Association for Cardio-Thoracic Surgery and American College of Cardiology/American Heart Association guidelines recommend referral for AVR (class I). If an abnormal physiological response such as a lack of blood pressure increase or ventricular arrhythmia occurred during exercise stress testing, then AVR is recommended (class IIa).[20,21] Exercise testing should be considered in any asymptomatic patient with severe AS and preserved LV systolic function, especially if there is a concern regarding the accuracy of the history or a need to establish the safety of daily physical activities or occupational work. If the patient is unable to perform an exercise test, then other stratification methods, such as baseline and follow-up biomarkers (eg, B-type natriuretic peptide), could be useful.

If the exercise test is normal (the patient does not report symptoms or fulfills the other criteria for an abnormal test), then a short-term prognosis is reasonable, and clinical/echocardiographic follow-up can continue per current guidelines. Recognition and reporting of symptoms between visits is essential to reduce not only the risk of sudden cardiac death (which is low among this population), but also disease progression, irreversible myocardial damage, and the development of other major complications, including atrial fibrillation and heart failure hospitalization. Current guidelines recommend repeat echocardiography every 6 to 12 months for severe AS and every 12 to 24 months for moderate AS but are silent as to whether an exercise test should be repeated at each follow-up.[20,21] Given the variability in symptom reporting and the assiduousness of clinical follow-up, repeat stress testing could be seen as reasonable. Exercise echocardiography and cardiopulmonary exercise testing may add incremental prognostic information, and high-risk features such as an exercise-induced increase in mean pressure gradient ≥20 mm Hg may motivate closer follow-up.[33,99] In fact, given the currently low procedural mortality and morbidity rates for isolated surgical AVR and transcatheter AVR, earlier intervention may be favorable for at least a subset of these patients.[15,16,100–102] As discussed earlier, the European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines acknowledge that AVR can be considered for patients in whom the mean gradient increases by ≥20 mm Hg during exercise (class IIb).[21] Further studies are needed to confirm these asso-

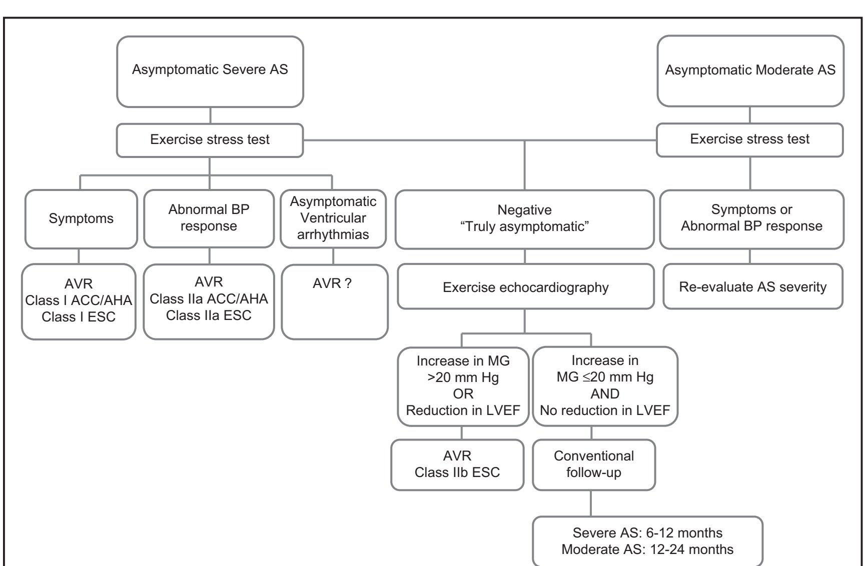

Figure. Proposed algorithm for follow-up of patients with aortic stenosis.
ACC/AHA indicates American College of Cardiology/American Heart Association; AS, aortic stenosis; AVR, aortic valve replacement; BP, blood pressure; ESC, European Society of Cardiology; LVEF, left ventricular ejection fraction; and MG, mean gradient.

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ciations and develop criteria or risk scores for predicting prognosis in asymptomatic patients who perform well on exercise testing. Ideally, future large-scale randomized controlled trials comparing AVR to a conservative approach may help identify asymptomatic patients for whom intervention can be justified.

Last, given the inherent limitations and challenges of the current anatomic and valve-centric grading system (mild, moderate, severe) and the poor prognosis associated with a positive stress test among patients with moderate or severe AS,[103] a multimodal stratification scheme incorporating both anatomic (echocardiogram) grading criteria and physiological (stress test) assessment of AS might represent a more appropriate investigational strategy when facing patients with severe or even moderate asymptomatic AS. Advantages of such a novel and more aggressive strategy in which early screening of potential AVR candidate is performed using a multimodal approach includes the balancing of intrinsic limitations associated with each modality and the identification of early AS-related repercussions not captured by more conventional anatomic criteria. Further prospective studies are needed to validate such approach (Figure; AVATAR, NCT02436655; EARLY TAVR).

CONCLUSIONS

Approximately half of patients diagnosed with severe AS do not report symptoms. Exercise testing is helpful to identify whether patients are truly asymptomatic. Traditional treadmill exercise testing or bicycle ergometer are safe, and it is well established that patients with AS and an abnormal exercise test have a worse prognosis unless AVR is performed. Exercise echocardiography and cardiopulmonary exercise testing can complement the traditional symptom-based exercise test with detailed information on valve structure and function and capacity for adequate oxygen delivery, but more experience with these techniques is necessary.

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Dr Pibarot has received research grants (echo core laboratory analyses) from Edwards Lifesciences. Dr Gillam has received Core Laboratory contracts with Edwards Lifesciences and Medtronic and served as consultant for Edwards Lifesciences. Dr Burkhoff is a consultant to HeartWare division of Medtronic, BackBeat Medical, Cardiac Implants, Corvia Medical, and Sensible Medical; has received unrestricted educational grant support from Abiomed; is on the Heart Failure Advisory Board of LivaNova; and is the founder of PVLoops LLC. Dr Bax has received research grants from Medtronic, Biotronik, Edwards Lifesciences, and Boston Scientific. Dr Lindman is on the scientific advisory board for Roche Diagnostics and has received research grants from Edwards Lifesciences and Roche Diagnostics. Dr Leon has worked on the Executive Committee—PARTNER Trial (Edwards Lifescience [nonpaid]). Dr Généreux has received speaker's fee from Edwards Lifescience. The other authors report no conflicts of interest.

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FOOTNOTES

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REFERENCES

1. Otto CM, Prendergast B. Aortic-valve stenosis–from patients at risk to severe valve obstruction. *N Engl J Med*. 2014;371:744–756. doi: 10.1056/NEJMra1313875.
2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368:1005–1011. doi: 10.1016/S0140-6736(06)69208-8.
3. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, Borger MA, Carrel TP, De Bonis M, Evangelista A, Falk V, Iung B, Lancellotti P, Pierard L, Price S, Schafers HJ, Schuler G, Stepinska J, Swedberg K, Takkenberg J, Von Oppell UO, Windecker S, Zamorano JL, Zembala M. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012;33:2451–2496.
4. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Judd SE, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Mackey RH, Magid DJ, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Mussolino ME, Neumar RW, Nichol G, Pandey DK, Paynter NP, Reeves MJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Wong ND, Woo D, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2014 update: a report from the American Heart Association. *Circulation*. 2014;129:e28–e292. doi: 10.1161/01.cir.0000441139.02102.80.
5. Bonow RO, Greenland P. Population-wide trends in aortic stenosis incidence and outcomes. *Circulation*. 2015;131:969–971. doi: 10.1161/CIRCULATIONAHA.115.014846.
6. Martinsson A, Li X, Andersson C, Nilsson J, Smith JG, Sundquist K. Temporal trends in the incidence and prognosis of aortic stenosis: a nationwide study of the Swedish population. *Circu-*

lation. 2015;131:988–994. doi: 10.1161/CIRCULATIONAHA.114.012906.
7. Ross Jr R, Braunwald E. Aortic stenosis. *Circulation*. 1968;37:61–67.
8. Turina J, Hess O, Sepulcri F, Krayenbuehl HP. Spontaneous course of aortic valve disease. *Eur Heart J*. 1987;8:471–483.
9. Kelly TA, Rothbart RM, Cooper CM, Kaiser DL, Smucker ML, Gibson RS. Comparison of outcome of asymptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. *Am J Cardiol*. 1988;61:123–130.
10. Bach DS, Siao D, Girard SE, Duvernoy C, McCallister BD Jr, Gualano SK. Evaluation of patients with severe symptomatic aortic stenosis who do not undergo aortic valve replacement: the potential role of subjectively overestimated operative risk. *Circ Cardiovasc Qual Outcomes*. 2009;2:533–539. doi: 10.1161/CIRCOUTCOMES.109.848259.
11. Varadarajan P, Kapoor N, Bansal RC, Pai RG. Clinical profile and natural history of 453 nonsurgically managed patients with severe aortic stenosis. *Ann Thorac Surg*. 2006;82:2111–2115. doi: 10.1016/j.athoracsur.2006.07.048.
12. Dichtl W, Alber HF, Feuchtner GM, Hintringer F, Reinthaler M, Bartel T, Süssenbacher A, Grander W, Ulmer H, Pachinger O, Müller S. Prognosis and risk factors in patients with asymptomatic aortic stenosis and their modulation by atorvastatin (20 mg). *Am J Cardiol*. 2008;102:743–748. doi: 10.1016/j.amjcard.2008.04.060.
13. Busseuil D, Shi Y, Mecteau M, Brand G, Kernaleguen AE, Thorin E, Latour JG, Rhéaume E, Tardif JC. Regression of aortic valve stenosis by ApoA-I mimetic peptide infusions in rabbits. *Br J Pharmacol*. 2008;154:765–773. doi: 10.1038/bjp.2008.122.
14. Rajamannan NM, Subramaniam M, Springett M, Sebo TC, Niekrasz M, McConnell JP, Singh RJ, Stone NJ, Bonow RO, Spelsberg TC. Atorvastatin inhibits hypercholesterolemia-induced cellular proliferation and bone matrix production in the rabbit aortic valve. *Circulation*. 2002;105:2660–2665.
15. Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG, Cigarroa JE, Disesa VJ, Hiratzka LF, Hutter AM Jr, Jessen ME, Keeley EC, Lahey SJ, Lange RA, London MJ, Mack MJ, Patel MR, Puskas JD, Sabik JF, Selnes O, Shahian DM, Trost JC, Winniford MD. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124:e652–e735. doi: 10.1161/CIR.0b013e31823c074e.
16. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB; PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. *N Engl J Med*. 2012;366:1686–1695. doi: 10.1056/NEJMoa1200384.
17. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597–1607. doi: 10.1056/NEJMoa1008232.
18. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, Gleason TG, Buchbinder M, Hermiller J Jr, Kleiman NS, Chetcuti S, Heiser J, Merhi W, Zorn G, Tadros P, Robinson N, Petrossian G, Hughes GC, Harrison JK, Conte J, Maini B, Mumtaz M, Chenoweth S, Oh JK; U.S. CoreValve Clinical Investigators. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370:1790–1798. doi: 10.1056/NEJMoa1400590.
19. Lund O. The effect of aortic valve replacement on survival. *Circulation*. 1990;82:124–139.
20. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:e521–e643. doi: 10.1161/CIR.0000000000000031.
21. The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*. 2012;33:2451–2496.
22. Pellikka PA, Nishimura RA, Bailey KR, Tajik AJ. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. *J Am Coll Cardiol*. 1990;15:1012–1017.
23. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, Barnes ME, Tajik AJ. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation*. 2005;111:3290–3295. doi: 10.1161/CIRCULATIONAHA.104.495903.
24. Pai RG, Kapoor N, Bansal RC, Varadarajan P. Malignant natural history of asymptomatic severe aortic stenosis: benefit of aortic valve replacement. *Ann Thorac Surg*. 2006;82:2116–2122. doi: 10.1016/j.athoracsur.2006.07.043.
25. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, Kitai T, Kawase Y, Izumi C, Miyake M, Mitsuoka H, Kato M, Hirano Y, Matsuda S, Nagao K, Inada T, Murakami T, Takeuchi Y, Yamane K, Toyofuku M, Ishii M, Minamino-Muta E, Kato T, Inoko M, Ikeda T, Komasa A, Ishii K, Hotta K, Higashitani N, Kato Y, Inuzuka Y, Maeda C, Jinnai T, Morikami Y, Sakata R, Kimura T; CURRENT AS Registry Investigators. Initial surgical versus conservative strategies in patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol*. 2015;66:2827–2838. doi: 10.1016/j.jacc.2015.10.001.
26. Généreux P, Stone GW, O'Gara PT, Marquis-Gravel G, Redfors B, Giustino G, Pibarot P, Bax JJ, Bonow RO, Leon MB. Natural history, diagnostic approaches, and therapeutic strategies for patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol*. 2016;67:2263–2288. doi: 10.1016/j.jacc.2016.02.057.
27. Masri A, Goodman AL, Barr T, Grimm RA, Sabik JF, Gillinov AM, Rodriguez LL, Svensson LG, Griffin BP, Desai MY. Predictors of long-term outcomes in asymptomatic patients with severe aortic stenosis and preserved left ventricular systolic function undergoing exercise echocardiography. *Circ Cardiovasc Imaging*. 2016;9:e004689.
28. Takeda S, Rimington H, Chambers J. Prediction of symptom-onset in aortic stenosis: a comparison of pressure drop/flow slope and haemodynamic measures at rest. *Int J Cardiol*. 2001;81:131–137.
29. Alborino D, Hoffmann JL, Fournet PC, Bloch A. Value of exercise testing to evaluate the indication for surgery in asymptomatic patients with valvular aortic stenosis. *J Heart Valve Dis*. 2002;11:204–209.
30. Lancellotti P, Lebois F, Simon M, Tombeux C, Chauvel C, Pierard LA. Prognostic importance of quantitative exercise Doppler echocardiography in asymptomatic valvular aortic stenosis. *Circulation*. 2005;112(9 Suppl):I377–I382. doi: 10.1161/CIRCULATIONAHA.104.523274.
31. Maréchaux S, Ennezat PV, LeJemtel TH, Polge AS, de Groote P, Asseman P, Nevière R, Le Tourneau T, Deklunder G. Left ventricular response to exercise in aortic stenosis: an exercise echocardiographic study. *Echocardiography*. 2007;24:955–959. doi: 10.1111/j.1540-8175.2007.00501.x.
32. Lancellotti P, Karsera D, Tumminello G, Lebois F, Piérard LA. Determinants of an abnormal response to exercise in patients with asymptomatic valvular aortic stenosis. *Eur J Echocardiogr*. 2008;9:338–343. doi: 10.1016/j.euje.2007.04.005.

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33. Maréchaux S, Hachicha Z, Bellouin A, Dumesnil JG, Meimoun P, Pasquet A, Bergeron S, Arsenault M, Le Tourneau T, Ennezat PV, Pibarot P. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. *Eur Heart J*. 2010;31:1390–1397. doi: 10.1093/eurheartj/ehq076.
34. Donal E, Thebault C, O'Connor K, Veillard D, Rosca M, Pierard L, Lancellotti P. Impact of aortic stenosis on longitudinal myocardial deformation during exercise. *Eur J Echocardiogr*. 2011;12:235–241. doi: 10.1093/ejechocard/jeq187.
35. Sonaglioni A, Lombardo M, Baravelli M, Trotta G, Sommese C, Anzà C. Exercise stress echocardiography with tissue Doppler imaging in risk stratification of mild to moderate aortic stenosis. *Int J Cardiovasc Imaging*. 2015;31:1519–1527. doi: 10.1007/s10554-015-0724-9.
36. Clavel MA, Pibarot P, Messika-Zeitoun D, Capoulade R, Malouf J, Aggarval S, Araoz PA, Michelena HI, Cueff C, Larose E, Miller JD, Vahanian A, Enriquez-Sarano M. Impact of aortic valve calcification, as measured by MDCT, on survival in patients with aortic stenosis: results of an international registry study. *J Am Coll Cardiol*. 2014;64:1202–1213. doi: 10.1016/j.jacc.2014.05.066.
37. Berthelot-Richer M, Pibarot P, Capoulade R, Dumesnil JG, Dahou A, Thebault C, Le Ven F, Clavel MA. Discordant grading of aortic stenosis severity: echocardiographic predictors of survival benefit associated with aortic valve replacement. *J Am Coll Cardiol Cardiovasc Imaging*. 2016;9:797–805. doi: 10.1016/j.jcmg.2015.09.026.
38. Clavel MA, Malouf J, Messika-Zeitoun D, Araoz PA, Michelena HI, Enriquez-Sarano M. Aortic valve area calculation in aortic stenosis by CT and Doppler echocardiography. *J Am Coll Cardiol Cardiovasc Imaging*. 2015;8:248–257. doi: 10.1016/j.jcmg.2015.01.009.
39. Clavel MA, Messika-Zeitoun D, Pibarot P, Aggarwal SR, Malouf J, Araoz PA, Michelena HI, Cueff C, Larose E, Capoulade R, Vahanian A, Enriquez-Sarano M. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study. *J Am Coll Cardiol*. 2013;62:2329–2338. doi: 10.1016/j.jacc.2013.08.1621.
40. Kamperidis V, van Rosendael PJ, Katsanos S, van der Kley F, Regeer M, Al Amri I, Sianos G, Marsan NA, Delgado V, Bax JJ. Low gradient severe aortic stenosis with preserved ejection fraction: reclassification of severity by fusion of Doppler and computed tomographic data. *Eur Heart J*. 2015;36:2087–2096. doi: 10.1093/eurheartj/ehv188.
41. Mehrotra P, Flynn AW, Jansen K, Tan TC, Mak G, Julien HM, Zeng X, Picard MH, Passeri JJ, Hung J. Differential left ventricular outflow tract remodeling and dynamics in aortic stenosis. *J Am Soc Echocardiogr*. 2015;28:1259–1266. doi: 10.1016/j.echo.2015.07.018.
42. Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N. Inconsistent grading of aortic valve stenosis by current guidelines: haemodynamic studies in patients with apparently normal left ventricular function. *Heart*. 2010;96:1463–1468. doi: 10.1136/hrt.2009.181982.
43. Ng AC, Yiu KH, Ewe SH, van der Kley F, Bertini M, de Weger A, de Roos A, Leung DY, Schuijf JD, Schalij MJ, Bax JJ, Delgado V. Influence of left ventricular geometry and function on aortic annular dimensions as assessed with multi-detector row computed tomography: implications for transcatheter aortic valve implantation. *Eur Heart J*. 2011;32:2806–2813. doi: 10.1093/eurheartj/ehr237.
44. Simard L, Côté N, Dagenais F, Mathieu P, Couture C, Trahan S, Bossé Y, Mohammadi S, Pagé S, Joubert P, Clavel MA. Sex-related discordance between aortic valve calcification and hemodynamic severity of aortic stenosis: is valvular fibrosis the explanation? *Circ Res*. 2017;120:681–691. doi: 10.1161/CIRCRESAHA.116.309306.
45. Clavel MA, Magne J, Pibarot P. Low-gradient aortic stenosis. *Eur Heart J*. 2016;37:2645–2657. doi: 10.1093/eurheartj/ehw096.
46. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, Voigt JU, Zamorano JL; European Association of Echocardiography. Stress echocardiography expert consensus statement: executive summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur Heart J*. 2009;30:278–289. doi: 10.1093/eurheartj/ehn492.
47. Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG; American Society of Echocardiography. American Society of Echocardiography recommendations for performance, interpretation, and application of stress echocardiography. *J Am Soc Echocardiogr*. 2007;20:1021–1041. doi: 10.1016/j.echo.2007.07.003.
48. Rafique AM, Biner S, Ray I, Forrester JS, Tolstrup K, Siegel RJ. Meta-analysis of prognostic value of stress testing in patients with asymptomatic severe aortic stenosis. *Am J Cardiol*. 2009;104:972–977. doi: 10.1016/j.amjcard.2009.05.044.
49. Dhoble A, Sarano ME, Kopecky SL, Thomas RJ, Hayes CL, Allison TG. Safety of symptom-limited cardiopulmonary exercise testing in patients with aortic stenosis. *Am J Med*. 2012;125:704–708. doi: 10.1016/j.amjmed.2012.01.012.
50. Lancellotti P, Magne J, Piérard LA. The role of stress testing in evaluation of asymptomatic patients with aortic stenosis. *Curr Opin Cardiol*. 2013;28:531–539. doi: 10.1097/HCO.0b013e3283632b41.
51. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL Jr. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the ACC/AHA Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation*. 2002;106:1883–1892. doi: 10.1161/01.CIR.0000034670.06526.15.
52. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, Mark DB, Marwick TH, McCallister BD, Thompson PD, Winters WL Jr, Yanowitz FG, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A Jr, Lewis RP, O'Rourke RA, Ryan TJ. ACC/AHA guidelines for exercise testing: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *Circulation*. 1997;96:345–354.
53. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, Mark DB, Marwick TH, McCallister BD, Thompson PD, Winters WL Jr, Yanowitz FG, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A Jr, Lewis RP, O'Rourke RA, Ryan TJ. ACC/AHA guidelines for exercise testing: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *Circulation*. 1997;96:345–354.
54. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, Kraft CD, Miyake-Hull CY, Schwaegler RG. Prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic, and exercise predictors of outcome. *Circulation*. 1997;95:2262–2270.
55. Amato MC, Moffa PJ, Werner KE, Ramires JA. Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. *Heart*. 2001;86:381–386.
56. Das P, Rimington H, Smeeton N, Chambers J. Determinants of symptoms and exercise capacity in aortic stenosis: a comparison of resting haemodynamics and valve compliance during dobutamine stress. *Eur Heart J*. 2003;24:1254–1263.
57. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. *Eur Heart J*. 2005;26:1309–1313. doi: 10.1093/eurheartj/ehi250.
58. Peidro R, Brión G, Angelino A. Exercise testing in asymptomatic aortic stenosis. *Cardiology*. 2007;108:258–264. doi: 10.1159/000096953.

59. Lafitte S, Perlant M, Reant P, Serri K, Douard H, DeMaria A, Roudaut R. Impact of impaired myocardial deformations on exercise tolerance and prognosis in patients with asymptomatic aortic stenosis. *Eur J Echocardiogr*. 2009;10:414–419. doi: 10.1093/ejechocard/jen299.
60. Rajani R, Rimington H, Chambers JB. Treadmill exercise in apparently asymptomatic patients with moderate or severe aortic stenosis: relationship between cardiac index and revealed symptoms. *Heart*. 2010;96:689–695. doi: 10.1136/hrt.2009.181644.
61. Olaf S, Debora B, Ricarda B, Gunnar B, Jochen K, Schimke I, Halle M, Jaffe A. Exercise tolerance in asymptomatic patients with moderate-severe valvular heart disease and preserved ejection fraction. *Arch Med Sci*. 2012;8:1018–1026. doi: 10.5114/aoms.2012.32409.
62. Dulgheru R, Magne J, Capoulade R, Davin L, Vinereanu D, Pierard LA, Pibarot P, Lancellotti P. Impact of global hemodynamic load on exercise capacity in aortic stenosis. *Int J Cardiol*. 2013;168:2272–2277. doi: 10.1016/j.ijcard.2013.01.205.
63. Levy F, Fayad N, Jeu A, Choquet D, Szymanski C, Malaquin D, Peltier M, Tribouilloy C. The value of cardiopulmonary exercise testing in individuals with apparently asymptomatic severe aortic stenosis: a pilot study. *Arch Cardiovasc Dis*. 2014;107:519–528. doi: 10.1016/j.acvd.2014.06.003.
64. Dulgheru R, Magne J, Davin L, Nchimi A, Oury C, Pierard LA, Lancellotti P. Left ventricular regional function and maximal exercise capacity in aortic stenosis. *Eur Heart J Cardiovasc Imaging*. 2016;17:217–224. doi: 10.1093/ehjci/jev147.
65. van Le D, Jensen GV, Carstensen S, Kjøller-Hansen L. Cardiopulmonary exercise testing in patients with asymptomatic or equivocal symptomatic aortic stenosis: feasibility, reproducibility, safety and information obtained on exercise physiology. *Cardiology*. 2016;133:147–156. doi: 10.1159/000441292.
66. Lancellotti P, Magne J, Donal E, O'Connor K, Dulgheru R, Rosca M, Pierard LA. Determinants and prognostic significance of exercise pulmonary hypertension in asymptomatic severe aortic stenosis. *Circulation*. 2012;126:851–859. doi: 10.1161/CIRCULATIONAHA.111.088427.
67. Capoulade R, Magne J, Dulgheru R, Hachicha Z, Dumesnil JG, O'Connor K, Arsenault M, Bergeron S, Pierard LA, Lancellotti P, Pibarot P. Prognostic value of plasma B-type natriuretic peptide levels after exercise in patients with severe asymptomatic aortic stenosis. *Heart*. 2014;100:1606–1612. doi: 10.1136/heartjnl-2014-305729.
68. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. *Eur Heart J*. 2003;24:1231–1243.
69. Lancellotti P, Donal E, Magne J, Moonen M, O'Connor K, Daubert JC, Pierard LA. Risk stratification in asymptomatic moderate to severe aortic stenosis: the importance of the valvular, arterial and ventricular interplay. *Heart*. 2010;96:1364–1371. doi: 10.1136/hrt.2009.190942.
70. Green P, Cohen DJ, Généreux P, McAndrew T, Arnold SV, Alu M, Beohar N, Rihal CS, Mack MJ, Kapadia S, Dvir D, Maurer MS, Williams MR, Kodali S, Leon MB, Kirtane AJ. Relation between six-minute walk test performance and outcomes after transcatheter aortic valve implantation (from the PARTNER trial). *Am J Cardiol*. 2013;112:700–706. doi: 10.1016/j.amjcard.2013.04.046.
71. Picano E, Pibarot P, Lancellotti P, Monin JL, Bonow RO. The emerging role of exercise testing and stress echocardiography in valvular heart disease. *J Am Coll Cardiol*. 2009;54:2251–2260. doi: 10.1016/j.jacc.2009.07.046.
72. Leurent G, Donal E, de Place C, Chabanne C, Gervais R, Fougerou C, le Helloco A, Daubert JC, Mabo P, Laurent M. Argument for a Doppler echocardiography during exercise in assessing asymptomatic patients with severe aortic stenosis. *Eur J Echocardiogr*. 2009;10:69–73. doi: 10.1093/ejechocard/jen163.
73. Zito C, Salvia J, Cusmà-Piccione M, Antonini-Canterin F, Lentini S, Oreto G, Di Bella G, Montericcio V, Carerj S. Prognostic significance of valvuloarterial impedance and left ventricular longitudinal function in asymptomatic severe aortic stenosis involving three-cuspid valves. *Am J Cardiol*. 2011;108:1463–1469. doi: 10.1016/j.amjcard.2011.06.070.
74. Yingchoncharoen T, Gibby C, Rodriguez LL, Grimm RA, Marwick TH. Association of myocardial deformation with outcome in asymptomatic aortic stenosis with normal ejection fraction. *Circ Cardiovasc Imaging*. 2012;5:719–725. doi: 10.1161/CIRCIMAGING.112.977348.
75. Tongue AG, Dumesnil JG, Laforest I, Theriault C, Durand LG, Pibarot P. Left ventricular longitudinal shortening in patients with aortic stenosis: relationship with symptomatic status. *J Heart Valve Dis*. 2003;12:142–149.
76. Van Pelt NC, Stewart RA, Legget ME, Whalley GA, Wong SP, Zeng I, Oldfield M, Kerr AJ. Longitudinal left ventricular contractile dysfunction after exercise in aortic stenosis. *Heart*. 2007;93:732–738. doi: 10.1136/hrt.2006.100164.
77. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2003;167:211–277.
78. Myers J, Arena R, Franklin B, Pina I, Kraus WE, McInnis K, Balady GJ; American Heart Association Committee on Exercise, Cardiac Rehabilitation, and Prevention of the Council on Clinical Cardiology, the Council on Nutrition, Physical Activity, and Metabolism, and the Council on Cardiovascular Nursing. Recommendations for clinical exercise laboratories: a scientific statement from the American Heart Association. *Circulation*. 2009;119:3144–3161. doi: 10.1161/CIRCULATIONAHA.109.192520.
79. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:1810–1852. doi: 10.1161/CIR.0b013e31829e8807.
80. Gerber IL, Stewart RA, Legget ME, West TM, French RL, Sutton TM, Yandle TG, French JK, Richards AM, White HD. Increased plasma natriuretic peptide levels reflect symptom onset in aortic stenosis. *Circulation*. 2003;107:1884–1890. doi: 10.1161/01.CIR.0000060533.79248.0C.
81. Lim P, Monin JL, Monchi M, Garot J, Pasquet A, Hittinger L, Vanoverschelde JL, Carayon A, Gueret P. Predictors of outcome in patients with severe aortic stenosis and normal left ventricular function: role of B-type natriuretic peptide. *Eur Heart J*. 2004;25:2048–2053. doi: 10.1016/j.ehj.2004.09.033.
82. Weber M, Arnold R, Rau M, Brandt R, Berkovitsch A, Mitrovic V, Hamm C. Relation of N-terminal pro-B-type natriuretic peptide to severity of valvular aortic stenosis. *Am J Cardiol*. 2004;94:740–745. doi: 10.1016/j.amjcard.2004.05.055.
83. Bergler-Klein J, Klaar U, Heger M, Rosenhek R, Mundigler G, Gabriel H, Binder T, Pacher R, Maurer G, Baumgartner H. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. *Circulation*. 2004;109:2302–2308. doi: 10.1161/01.CIR.0000126825.50903.18.
84. Lee G, Twerenbold R, Tanglay Y, Reichlin T, Honegger U, Wagener M, Jaeger C, Rubini Gimenez M, Hochgruber T, Puelacher C, Radosavac M, Kreutzinger P, Stallone F, Hillinger P, Krivoshei L, Herrmann T, Mayr R, Freese M, Wild D, Rentsch KM, Todd J, Osswald S, Zellweger MJ, Mueller C. Clinical benefit of high-sensitivity cardiac troponin I in the detection of exercise-induced myocardial ischemia. *Am Heart J*. 2016;173:8–17. doi: 10.1016/j.ahj.2015.11.010.

85. Chin CW, Shah AS, McAllister DA, Joanna Cowell S, Alam S, Langrish JP, Strachan FE, Hunter AL, Maria Choy A, Lang CC, Walker S, Boon NA, Newby DE, Mills NL, Dweck MR. High-sensitivity troponin I concentrations are a marker of an advanced hypertrophic response and adverse outcomes in patients with aortic stenosis. *Eur Heart J*. 2014;35:2312–2321. doi: 10.1093/eurheartj/ehu189.
86. Lindman BR, Breyley JG, Schilling JD, Vatterott AM, Zajarias A, Maniar HS, Damiano RJ Jr, Moon MR, Lawton JS, Gage BF, Sintek MA, Aquino A, Holley CL, Patel NM, Lawler C, Lasala JM, Novak E. Prognostic utility of novel biomarkers of cardiovascular stress in patients with aortic stenosis undergoing valve replacement. *Heart*. 2015;101:1382–1388. doi: 10.1136/heartjnl-2015-307742.
87. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, Kitzman DW, Otto CM. Clinical factors associated with calcific aortic valve disease: Cardiovascular Health Study. *J Am Coll Cardiol*. 1997;29:630–634.
88. Holmes DR Jr, Brennan JM, Rumsfeld JS, Dai D, O'Brien SM, Vemulapalli S, Edwards FH, Carroll J, Shahian D, Grover F, Tuzcu EM, Peterson ED, Brindis RG, Mack MJ, Registry SAT. Clinical outcomes at 1 year following transcatheter aortic valve replacement. *JAMA*. 2015;313:1019–1028.
89. Ludman PF, Moat N, de Belder MA, Blackman DJ, Duncan A, Banya W, MacCarthy PA, Cunningham D, Wendler O, Marlee D, Hildick-Smith D, Young CP, Kovac J, Uren NG, Spyt T, Trivedi U, Howell J, Gray H; UK TAVI Steering Committee and the National Institute for Cardiovascular Outcomes Research. Transcatheter aortic valve implantation in the United Kingdom: temporal trends, predictors of outcome, and 6-year follow-up: a report from the UK Transcatheter Aortic Valve Implantation (TAVI) Registry, 2007 to 2012. *Circulation*. 2015;131:1181–1190. doi: 10.1161/CIRCULATIONAHA.114.013947.
90. Feuchtner GM, Müller S, Grander W, Alber HF, Bartel T, Friedrich GJ, Reinthaler M, Pachinger O, zur Nedden D, Dichtl W. Aortic valve calcification as quantified with multislice computed tomography predicts short-term clinical outcome in patients with asymptomatic aortic stenosis. *J Heart Valve Dis*. 2006;15:494–498.
91. Cueff C, Serfaty JM, Cimadevilla C, Laissy JP, Himbert D, Tubach F, Duval X, Iung B, Enriquez-Sarano M, Vahanian A, Messika-Zeitoun D. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. *Heart*. 2011;97:721–726. doi: 10.1136/hrt.2010.198853.
92. Aggarwal SR, Clavel MA, Messika-Zeitoun D, Cueff C, Malouf J, Araoz PA, Mankad R, Michelena H, Vahanian A, Enriquez-Sarano M. Sex differences in aortic valve calcification measured by multidetector computed tomography in aortic stenosis. *Circ Cardiovasc Imaging*. 2013;6:40–47. doi: 10.1161/CIRCIMAGING.112.980052.
93. Clavel MA, Dumesnil JG, Pibarot P. Discordant grading of aortic stenosis using echocardiography and what it means: new insights from magnetic resonance imaging. *Can J Cardiol*. 2014;30:959–961. doi: 10.1016/j.cjca.2014.06.007.
94. Barone-Rochette G, Piérard S, De Meester de Ravenstein C, Seldrum S, Melchior J, Maes F, Pouleur AC, Vancraeynest D, Pasquet A, Vanoverschelde JL, Gerber BL. Prognostic significance of LGE by CMR in aortic stenosis patients undergoing valve replacement. *J Am Coll Cardiol*. 2014;64:144–154. doi: 10.1016/j.jacc.2014.02.612.
95. Dweck MR, Joshi S, Murigu T, Alpendurada F, Jabbour A, Melina G, Banya W, Gulati A, Roussin I, Raza S, Prasad NA, Wage R, Quarto C, Angeloni E, Refice S, Sheppard M, Cook SA, Kilner PJ, Pennell DJ, Newby DE, Mohiaddin RH, Pepper J, Prasad SK. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. *J Am Coll Cardiol*. 2011;58:1271–1279. doi: 10.1016/j.jacc.2011.03.064.
96. Weidemann F, Herrmann S, Störk S, Niemann M, Frantz S, Lange V, Beer M, Gattenlöhner S, Voelker W, Ertl G, Strotmann JM. Impact of myocardial fibrosis in patients with symptomatic severe aortic stenosis. *Circulation*. 2009;120:577–584. doi: 10.1161/CIRCULATIONAHA.108.847772.
97. Azevedo CF, Nigri M, Higuchi ML, Pomerantzeff PM, Spina GS, Sampaio RO, Tarasoutchi F, Grinberg M, Rochitte CE. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. *J Am Coll Cardiol*. 2010;56:278–287. doi: 10.1016/j.jacc.2009.12.074.
98. Rajappan K, Rimoldi OE, Dutka DP, Ariff B, Pennell DJ, Sheridan DJ, Camici PG. Mechanisms of coronary microcirculatory dysfunction in patients with aortic stenosis and angiographically normal coronary arteries. *Circulation*. 2002;105:470–476.
99. Zamorano JL, Goncalves A. Exercise echocardiography in aortic stenosis: one more piece in the puzzle. *Eur Heart J*. 2010;31:1295–1297. doi: 10.1093/eurheartj/ehq078.
100. Pellikka PA. Observation for mildly symptomatic normal-flow, low-gradient severe aortic stenosis: caution advised. *Heart*. 2015;101:1349–1350. doi: 10.1136/heartjnl-2015-307842.
101. Lund O, Nielsen TT, Emmertsen K, Flø C, Rasmussen B, Jensen FT, Pilegaard HK, Kristensen LH, Hansen OK. Mortality and worsening of prognostic profile during waiting time for valve replacement in aortic stenosis. *Thorac Cardiovasc Surg*. 1996;44:289–295. doi: 10.1055/s-2007-1012039.
102. Society of Thoracic Surgeons. STS Adult Cardiac Surgery Database—Period Ending 3/31/2015 Executive Summary Contents. http://www.sts.org/sites/default/files/documents/2015Harvest2_ExecutiveSummary.pdf. Accessed September 10, 2015.
103. Lancellotti P, Magne J, Donal E, Davin L, O'Connor K, Rosca M, Szymanski C, Cosyns B, Piérard LA. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification. *J Am Coll Cardiol*. 2012;59:235–243. doi: 10.1016/j.jacc.2011.08.072.
104. Iung B, Gohlke-Bärwolf C, Tornos P, Tribouilloy C, Hall R, Butchart E, Vahanian A; Working Group on Valvular Heart Disease. Recommendations on the management of the asymptomatic patient with valvular heart disease. *Eur Heart J*. 2002;23:1253–1266.