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Moderate aortic stenosis: culprit or bystander?

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ABSTRACT

Non-rheumatic aortic stenosis (AS) is among the most common valvular diseases in the developed world. Current guidelines support aortic valve replacement (AVR) for severe symptomatic AS, which carries high morbidity and mortality when left untreated. In contrast, moderate AS has historically been thought to be a benign diagnosis for which the potential benefits of AVR are outweighed by the procedural risks. However, emerging data demonstrating the substantial mortality risk in untreated moderate AS and substantial improvements in periprocedural and perioperative mortality with AVR have challenged the traditional risk/benefit paradigm. As such, an appraisal of the contemporary data on morbidity and mortality associated with moderate AS and appropriate timing of valvular intervention in AS is warranted. In this review, we discuss the current understanding of moderate AS, including the epidemiology, current surveillance and management guidelines, clinical outcomes, and future studies.

INTRODUCTION

Non-rheumatic aortic stenosis (AS) is among the most common valvular pathologies affecting older adults in developed countries, with rates expected to increase with the ageing of the population.[1] Aortic valve replacement (AVR) is currently advocated for those with severe symptomatic AS based on substantial morbidity and mortality without intervention.[2] By contrast, imaging surveillance is currently recommended for patients with moderate AS.[3]

The decision to recommend non-operative treatment in moderate AS has historically been based on (1) observation of a low overall risk for sudden cardiac death with moderate rather than severe AS and (2) high procedural risk associated with AVR. Advances in surgical and catheter-based approaches to aortic valve intervention have led to improved procedural outcomes, with contemporary procedural mortality for low-risk patients with AS as low as 0.4% after transcatheter aortic valve replacement (TAVR) and 0.9% after surgical aortic valve replacement (SAVR).[4] Furthermore, mounting evidence suggests a worse prognosis associated with moderate AS than previously appreciated.[5–11] These developments bring into question whether the current risk/benefit paradigm has shifted in favour of earlier intervention for AS.

In this review, we summarise the contemporary understanding of moderate AS, including the epidemiology, current surveillance and management guidelines, clinical outcomes, and future areas of investigation.

DEFINITION OF MODERATE AS

The 2020 American College of Cardiology/American Heart Association (ACC/AHA) guidelines divide AS into four stages based on valve anatomy, valve haemodynamics, haemodynamic consequences and symptoms.[12] By comparison, the 2017 European Society of Cardiology and European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines delineate AS severity according to aortic valve area, velocity and gradient.[13] Table 1 further details these comparisons.

Moderate AS is defined as a maximal aortic jet velocity (Vmax) of 3.0–3.9 m/s and/or mean pressure gradient (MPG) of 20–39 mm Hg and/or aortic valve area (AVA) of >1 cm^2. Patients with low forward stroke volume (eg, stroke volume index ≤35 mL/m^2) may have valve haemodynamics in the moderate range despite an AVA <1.0 cm^2. These haemodynamic characteristics are often referred to as 'low-flow, low-gradient' AS and may exist in the setting of both preserved and reduced systolic function.[12 13] In cases of low-flow, low-gradient AS, dobutamine stress echocardiography, CT calcium scoring, and cardiac catheterization can be used to distinguish moderate from severe AS.[12 14–16]

EPIDEMIOLOGY AND PROGRESSION OF MODERATE AS

The prevalence of AS increases with age, with about 12.4% of adults over age 75 with mild, moderate or severe AS.[17] The Tromsø Study prospectively studied 3273 individuals with

Table 1 Comparison of ACC/AHA and ESC/EACTS classification of AS severity

	2020 ACC/AHA	2017 ESC/EACTS
Characteristics determining AS severity	**Valve anatomy, valve haemodynamics, haemodynamic consequences and symptoms**	**Aortic valve area, velocity and gradient**
Classification of AS	Stage A (at risk): ► Aortic valve Vmax <2 m/s. ► Bicuspid aortic valve or aortic sclerosis. Stage B (progressive): ► Mild AS: Vmax 2.0–2.9 m/s or MPG <20 mm Hg. ► Moderate AS: Vmax 3.0–3.9 m/s or MPG 20–39 mm Hg. ► Mild to moderate calcification or rheumatic valve changes with commissural fusion. ► Early LV diastolic dysfunction with LVEF ≥50%. Stage C (asymptomatic severe), C1 and C2 subgroups: ► Vmax ≥4 m/s or MPG ≥40 mm Hg. ► AVA ≤1.0 cm^2 or AVAi ≤0.6 cm^2/m^2. ► Severe calcification or congenital stenosis with severely reduced leaflet opening. ► C1: LVEF ≥50%; C2: LVEF <50%. Stage D (symptomatic severe), D1, D2, D3 subgroups: ► D1: Vmax ≥4 m/s or MPG ≥40 mm Hg. ► D2 (classic low-flow/low-gradient AS): AVA <1 cm^2, Vmax <4 m/s or MPG <40 mm Hg and LVEF <50%. ► D3 (paradoxical low-flow/low-gradient AS): AVA <1 cm^2, Vmax <4 m/s or MPG <40 mm Hg, SVI <35 mL/m^2 and AVAi <0.6 cm^2/m^2 measured when normotensive (systolic blood pressure <140), and LVEF ≥50%. ► Symptoms for all subgroups: HF, angina, presyncope or syncope.	Low-gradient AS with normal flow (moderate AS): ► Vmax <4 m/s. ► MPG <40 mm Hg. ► SVI >35 mL/m^2. ► AVA >1.0 cm^2. Low-flow, low-gradient AS with reduced flow: ► Vmax <4 m/s. ► MPG <40 mm Hg. ► SVI ≤35 mL/m^2. ► AVA ≤1.0 cm^2. ► LVEF <50%. ► Pseudo-severe AS: AV >1.0 cm^2 with dobutamine. ► True severe AS: mean gradient ≥40 mm Hg with dobutamine. Severe high gradient AS: ► Vmax ≥4 m/s. ► MPG ≥40 mm Hg. ► AVA ≤1.0 cm^2.
Indications for AS intervention	Class I indications: ► Severe AS (stage D1) with symptoms of HF, syncope, exertional dyspnea, angina or presyncope. ► Asymptomatic severe AS (stage C1) with LVEF <50%. ► Asymptomatic severe AS (stage C1) undergoing cardiac surgery. ► Symptomatic low-flow, low-gradient severe AS (stage D2). ► Symptomatic paradoxical low-flow, low-gradient severe AS if AS most likely the cause of symptoms (severe D3). Class II indications: ► Asymptomatic severe AS (stage C1) and decreased exercise tolerance or fall in SBP (≥10 mm Hg) on exercise test who are at low surgical risk. ► Asymptomatic very severe AS (Vmax ≥5 m/s) and low surgical risk. ► Asymptomatic severe AS (stage C1) and low surgical risk with BNP >3 times the normal. ► Asymptomatic severe AS (stage C1) and low surgical risk with an increase in Vmax ≥0.3 m/s per year. ► Asymptomatic severe AS (stage C1) with progressive decline in LVEF <60% on three serial imaging studies. ► Moderate AS (stage B) who are undergoing cardiac surgery.	Class I indications: ► Severe AS with symptoms. ► Symptomatic patients with low-flow, low-gradient AS with reduced LVEF and evidence of flow reserve. ► Asymptomatic severe AS with low LVEF. ► Asymptomatic severe AS and symptoms with exercise test. ► Severe AS in patients undergoing cardiac surgery. Class II indications: ► Symptomatic low-flow, low-gradient AS with normal LVEF. ► Symptomatic low-flow, low-gradient AS with low LVEF without flow reserve. ► Asymptomatic severe AS and low blood pressure with exercise test. ► Very severe AS, Vmax >5.5 m/s. ► Severe AS with severe valve calcification, with rate of progression of Vmax ≥0.4 m/s per year, or BNP >3× normal, or PASP >60 mm Hg at rest. ► Moderate AS in patients undergoing cardiac surgery.

Displayed are the ACC/AHA and ESC/EACTS guidelines for classification of AS severity.[12 13]
ACC, American College of Cardiology; AHA, American Heart Association; AS, aortic stenosis; AV, aortic valve; AVA, aortic valve area; AVAi, index AVA; BNP, b-type natriuretic peptide; EACTS, European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; MPG, mean pressure gradient; PASP, pulmonary artery systolic pressure; SBP, systolic blood pressure ; SVI, stroke volume index; Vmax, maximal aortic jet velocity.

serial echocardiography over 14 years and found that the estimated point prevalence of AS steadily rose with age: 0.2%, 1.3%, 3.9% and 9.8% for those aged 50–59, 60–69, 70–79, and 80–89 years.[18] A more recent study of all patients who underwent echocardiogram at a single medical centre found that 2.4% of adults had moderate AS (mean age 78).[19]

The rate of progression of AS varies between individuals. In a 1997 prospective study by Otto *et al*,[20] 123 patients with asymptomatic mild to moderate AS followed for 2–3 years had an annual increase in Vmax of 0.32±0.34 m/s, increase in MPG of 7±7 mm Hg and decrease in AVA of 0.12±0.19 cm^2/year. More recent studies suggest a slower annual progression of AS with Vmax increase of 0.24±0.3 m/s, increase in MPG of 3.2–6.4 mm Hg and decrease in AVA of 0.068±0.004 cm^2/year.[5 20–23]

Severity of AS at presentation is an important predictor of progression rate. Kearney *et al*[22] found that MPG and AVA progression were strongly dependent on initial AS severity on enrolment. A 2013 prospective study of 147 Veterans Affairs patients with AS similarly found that independent predictors of rapid haemodynamic progression (defined as MPG >5.1 mm Hg/year) included worse baseline AS severity (>mild vs mild AS, OR 2.63, 95% CI

1.52 to 4.53, p=0.001) and aortic valve calcification (OR 2.07, 95% CI 1.33 to 3.22, p=0.01).

Certain demographic features also associate with the rapidity of AS progression. Recent data suggest that progression may be faster in men than in women (decrease in AVA cm^2/year 0.078±0.004 in men vs 0.065±0.004 in women, p=0.02).[1 23] Disease progression was also found to occur more rapidly in Caucasians than African Americans (decrease in AVA cm^2/year 0.075±0.005 in Caucasians vs 0.062±0.004 in African Americans, p=0.03). This finding may be attributable to the higher prevalence of bicuspid aortic valve in Caucasians than in the general population.[23]

Current guidelines account for the crescendo progression pattern of AS by recommending more frequent surveillance echocardiograms when the disease progresses from mild to moderate (from every 3–5 years to every 1–2 years). There are no specific recommendations to shorten surveillance intervals based on patient demographics. More investigation is needed to determine whether individuals with moderate AS who are expected to be fast progressors require more frequent echocardiograms.

CONTEMPORARY MANAGEMENT

The 2020 ACC/AHA guidelines for the management of patients with valvular heart disease and the 2017 ESC/EACTS guidelines for the management of valvular heart disease both recommend consideration for valvular replacement for moderate AS in patients who are already undergoing open heart surgery (class IIa, level of evidence C for both guidelines).[12 13] The major rationale for this recommendation is the elevated perioperative risk and potential for damage to bypass grafts (if present) during repeat sternotomy should the moderate AS progress and require operative intervention in the future. The ACC/AHA guidelines recommend screening patients with moderate AS with echocardiography every 1–2 years to assess for progression versus the ESC/EACTS guidelines which recommend yearly screening. Currently, guidelines do not recommend stratification of individuals at risk of rapid progression.

PROGNOSIS AND OUTCOMES OF PATIENTS WITH MODERATE AS

Emerging data have revealed that the prognosis of individuals with moderate AS is unfavourable, in some cases approaching that of severe AS, with unchanged event-free survival over the last few decades.[10 24] While cardiovascular outcomes in moderate AS are not as well studied as severe AS, existing data indicate the prognosis is not benign. Table 2 summarises the event-free survival in studies enrolling individuals with moderate AS. Events in the studies are defined as either mortality, or event-free survival from either AVR, heart failure (HF) hospitalization, death or a combination of the aforementioned.

Large observational studies have demonstrated a high overall mortality associated with moderate AS. Strange *et al*[10] identified 3315 patients with moderate AS across 12 sites in Australia and found that despite adjustment for left ventricular (LV) dysfunction, patients with moderate AS had a 5-year mortality of 56%, which was similar to the 67% mortality of patients with severe AS. The study found that Vmax >3.0 m/s and MPG >20 mm Hg were a threshold for increased risk of long-term all-cause and cardiovascular mortality. Delesalle *et al*[6] and Lancellotti *et al*[7] found a mortality for moderate AS of 53% at 6 years and 78% at 8 years, respectively. Factors associated with higher rates of all-cause mortality included age, dyslipidemia, chronic obstructive pulmonary disease, higher systolic blood pressure, peak aortic jet velocity, and left ventricular ejection fraction (LVEF).[7]

Patients with both moderate AS and reduced LVEF have high rates of cardiovascular morbidity and mortality. van Gils *et al*[8] studied 305 patients with moderate AS and LVEF <50% from 2010 to 2015 and found that, over a 4-year follow-up period, 24% of patients underwent AVR, 27% of patients were hospitalised for HF and 36% of patients died from any cause. Factors that were associated with worse prognosis included male sex, New York Heart Association (NYHA) class III–IV HF and higher transaortic velocities.[8]

Retrospective data have suggested patients with moderate AS and reduced ejection fraction could benefit from aortic valve intervention. In a retrospective study of 1090 patients with moderate AS and LVEF <50% in the Duke Echocardiographic Laboratory Database, 26% of patients ultimately underwent AVR, about half of whom also underwent concomitant coronary artery bypass graft over the 5-year study period.[25] There was a 59% reduction in all-cause mortality in those who underwent SAVR compared with those who did not undergo SAVR. A sensitivity analysis excluding patients with known coronary artery disease found that patients with moderate AS who underwent SAVR had a 41% reduction in all-cause mortality compared with patients who did not undergo SAVR. Another study of 262 patients with moderate AS and LVEF <50%, of which 44 patients underwent AVR, found that AVR was associated with improved survival at a median follow-up of 11 months (HR 0.59, 95% CI 0.35 to 0.98, p=0.04). In this study the survival benefit was largely driven by TAVR (HR 0.43, 95% CI 0.18 to 1.00, p=0.05) rather than SAVR (p=0.92).[11]

RATIONALE FOR THE UNFAVOURABLE PROGNOSIS IN PATIENTS WITH MODERATE AS

Several factors can influence the unfavourable prognosis of moderate AS demonstrated in recent studies, including the misclassification of severe AS as moderate AS, the associated LV hypertrophy, the existence of cardiovascular risk factors which colocalize with moderate AS, and the presence of rapid AS progressors.

One hypothesis to explain the unfavourable prognosis seen in patients with moderate AS is the misclassification of severe AS as moderate AS. Prior to the routine use of

Table 2 Studies evaluating the natural history of moderate aortic stenosis

	Studies of outcomes in patients with moderate aortic stenosis							
Author	**Years**	**N**	**Echo/cath**	**AV parameter**	**LVEF, % (mean)**	**Symptoms during follow-up**	**Follow-up time**	**Outcomes (mortality or event-free survival)**
Chizner[26]	1966–1971	10	Cath	AVA: 0.71–1.09 cm^2 and MPG: <70 mm Hg	NR	Heart failure, angina, syncope	64 months	57% at 3 years (mortality)
Turina[27]	1963–1983	30	Cath	AVA: 0.95–1.4 cm^2	NR	Dyspnea	10 years	35% at 10 years (event-free survival from AVR and death)
Kennedy[28]	1980–1985	66	Cath	AVA: 0.7–1.2 cm^2	55	Dyspnea	4 years	59% at 4 years (event-free survival from AVR and death)
Horstkotte and Loogen[29]	1978–1988	236	Cath	AVA: 0.8–1.5 cm^2	NR	Heart failure	16 years	65% at 8 years (event-free survival from AVR)
Livanaienen	1990–1991	26	Echo	AVA: 0.9–1.2 cm^2	NR	Angina, syncope dyspnea	4 years	50% at 4 years (mortality)
Kearney[22]	1988–1994	55	Echo	AVA: 1.0–1.5 cm^2 or MPG: 25–40 mm Hg	NR	NR	6.5 years	23% at 5 years (event-free survival from AVR and death)
Roshenhek	1994	176	Echo	Vmax: 2.5–3.9 m/s	>50	Dyspnea	5 years	42% at 5 years (event-free survival from AVR and death)
Otto[20]	1989–1995	68	Echo	Vmax: 3.0–4.0 m/s	>65	Angina, heart failure, syncope	2.5 years	66% at 2 years (event-free survival from AVR)
Minners	2001–2002	948	Echo	Vmax: 3.0–4.0 m/s	66	NR	5 years	49% at 5 years (event-free survival from AVR and death)
Yechoor	2006	104	Echo	AVA: 1.0–1.5 cm^2	49	NR	5 years	15% at 5 years (event-free survival from AVR and death)
Samad[25]	1995–2014	1090	Echo	MPG: 25–40 mm Hg	<50	Heart failure	5 years	74% at 5 years (event-free survival from AVR)
Delesalle[6]	2000–2014	508	Echo	AVA: 1.0–1.5 cm^2	64	Dyspnea, angina, syncope	6 years	53% at 6 years (mortality)
Lancellotti[7]	2001–2014	514	Echo	AVA: 1.0–1.5 cm^2	66	NR	8 years	78% at 8 years (mortality)
van Gils[8]	2010–2015	305	Echo	AVA: 1.0–1.5 cm^2	<50	NYHA class III/IV symptoms	4 years	39% at 4 years (event-free survival from AVR, death, HF hospitalization)
Mann[19]	2011–2016	952	Echo	AVA: 1.0–1.5 cm^2	55	NR	5 years	66% at 5 years (mortality)
Tastet	1998–2017	285	Echo	AVA: >1.0 cm^2	>50	Remained asymptomatic	8 years	32% at 6 years (mortality)
Murphy[9]	2014–2017	151	Echo	Vmax: 3.0–4.0 m/s, MPG: 20–30 mm Hg and AVA: 1.0–1.5 cm^2	>50	NR	50 months	34% at 1 year (event-free survival from AVR, death, HF hospitalization)
Strange[10]	2000–2017	3315	Echo	MPG: 20.0–29.9 mm Hg or Vmax: 3.0–3.9 m/s	63	NR	5 years	56% at 5 years (mortality)

Displayed is a compiled list of studies evaluating the outcomes of moderate AS. Listed are the authors, enrolment dates, number of included individuals (N), modality for defining AS severity (echocardiography versus catheterisation), AV parameter used to define AS severity, mean LVEF of included patients, symptoms developed during follow up, follow-up time and outcomes (reported as either mortality or event-free survival from AVR, death, HF hospitalization or a combination).
AV, aortic valve; AVA, aortic valve area; AVR, aortic valve replacement; HF, heart failure; LVEF, left ventricular ejection fraction; MPG, mean pressure gradient; NR, not recorded; NYHA, New York Heart Association; Vmax, maximal aortic jet velocity.

echocardiography to adjudicate AS severity, moderate AS was defined via parameters ascertained by cardiac catheterisation.[26–29] Notably in the early catheterisation studies moderate AS included patients with AVA <1.0 cm^2, which would now be characterised as severe AS. In clinical practice, misclassification of severe AS as moderate AS can occur due to incorrect measurements of left ventricular outflow tract (LVOT) and time-velocity integrals at the LVOT and aortic valve, geometric variability of the aortic valve and LVOT, and discordant gradients in low-flow states, as previously discussed.[30]

Moderate AS is associated with adverse LV remodelling, which likely contributes to the poor prognosis in patients with AS. Abnormalities in LV structure and function seen in patients with AS include fibrosis, hypertrophy, diastolic dysfunction, left atrial dilation and pulmonary hypertension, all of which are independently associated with significant morbidity and mortality.[31 32] The degree of LV remodelling in moderate AS approaches that of severe AS. In fact, a study by Dweck *et al* [33] using cardiac MRI showed no difference in the degree of LV hypertrophy between individuals with moderate and severe AS (mean

difference in mass 3.9 g/m^2, 95% CI 7.6 to 15.5 g/m^2, p=0.50). Unfortunately, valvular intervention does not necessarily reduce LV hypertrophy, and several studies have shown that LV hypertrophy can persist after AVR and is associated with a worse prognosis.[34–36]

Moderate AS is associated with a number of conditions which can independently result in worse cardiovascular morbidity and mortality, including hypertension, hyperlipidemia, diabetes, and coronary artery disease.[6] Severe renal impairment, hyperlipidaemia, and anaemia have all been associated with faster AS progression.[22 37] Despite the association between hyperlipidemia and AS progression, several large-scale randomized trials have failed to show a reduction in hemodynamic progression, aortic valve calcification, or improved clinical outcomes with lipid-lowering therapy.[38–41] It is possible that these rapid progressors with moderate AS in observational studies may have progressed to severe AS. Indeed, in the Rosenhek *et al* and Lancellotti *et al* [5 7] studies, those who ultimately underwent AVR and had reassessment of AS severity preoperatively had severe AS.

FUTURE DIRECTIONS

Randomised control trials are ongoing to determine whether patients with moderate AS benefit from earlier valvular intervention than the current guideline-recommended approach. The TAVR UNLOAD (Transcatheter Aortic Valve Replacement to UNload the Left Ventricle in Patients with ADvanced Heart Failure; National Clinical Trial [NCT]: 02661451) trial will randomize 300 patients with moderate AS and LVEF <50% to TAVR versus optimal HF therapy to determine whether patients who undergo TAVR have lower rates of all-cause death and HF hospitalizations. The PROGRESS (Prospective, Randomized, Controlled Trial to Assess the Management of Moderate Aortic Stenosis by Clinical Surveillance or Transcatheter Aortic Valve Replacement; NCT: 04889872) trial will randomize 750 adults aged 65 and older with moderate AS to TAVR or clinical surveillance and will study whether a composite outcome of death, stroke or unplanned cardiovascular hospitalization is different between the two groups. The results of these upcoming trials will help inform whether AVR could have a role in select patients with moderate AS.

CONCLUSION

Since 1968, when Ross and Braunwald published their landmark study showing a steep decline in survival in patients with severe AS at the onset of symptoms, management strategies have centred around this pivotal time point.[42] Fifty years later, procedural and surgical interventions for severe AS have improved, while the treatment and prognosis of moderate AS have remained unchanged. Although traditionally thought of as benign, moderate AS has been associated with significant cardiovascular morbidity and mortality in large observational studies. Retrospective studies have suggested improved outcomes for patients with moderate AS with valve replacement, and randomized control trials are ongoing to determine whether select patients with moderate AS could benefit from earlier valve intervention.

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