




Treating Moderate Aortic Stenosis: Too Early or Too Late?

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Abstract

Purpose of review It is well established that symptomatic severe aortic stenosis (AS) carries a poor prognosis and requires valvular replacement for definitive treatment. While moderate AS has traditionally been thought of as a benign prelude to the aforementioned, recent data suggests that it is associated with increased morbidity and mortality. This article will consider treatment strategies for moderate AS, including early surgical and transcatheter aortic valve replacement and medical therapy.

Recent findings There are few randomized controlled trials dedicated to medical and surgical therapies for moderate AS. Statins, antihypertensive agents and bisphosphonates have not consistently demonstrated an effect on AS progression, timing of aortic valve replacement, or improvement in patient outcomes. Early surgical intervention for patients with concomitant left ventricular dysfunction has been studied in a retrospective manner and appears promising.

Summary Aside from the routine management of comorbidities (i.e., coronary artery disease, hypertension, hyperlipidemia), no specific treatment is recommended that is exclusively directed towards moderate AS. Clinicians should maintain a high vigilance for AS progression and the development of symptoms. Given the safety and efficacy of transcatheter aortic valve replacement, a randomized controlled trial is underway to evaluate its benefits in patients with moderate AS and left ventricular systolic dysfunction.

Introduction

Over the past half-century, the landscape of aortic stenosis (AS) has changed tremendously. Once dominated by younger patients with rheumatic disease, AS now primarily affects older adults through calcific valvular degeneration [1]. Approximately 4% of patients over the age of 65 have moderate or severe AS, a number that is expected to more than double in both the United States and Europe by the year 2050 [2]. Moreover, as aortic valve (AV) calcification progresses with age, elderly patients (> 75 years old) are at greatest risk.

It is well known that untreated, symptomatic severe AS necessitates valvular intervention given its significant morbidity and poor survival [3, 4]. While surgical aortic valve replacement (SAVR) has been the mainstay of therapy for this patient population for years, transcatheter aortic valve replacement (TAVR) has demonstrated similar or improved outcomes since its initial approval by the Food and Drug Administration in 2011 [5–9]. Indeed, in 2017 over 50,000 TAVR procedures were performed in the United States [10].

The time honored “watchful waiting” strategy for moderate AS (defined as an aortic valve area [AVA] > 1.0 cm² with a mean AV gradient of 20–39 mmHg or a peak velocity of 3.0–3.9 m/s) has recently come under scrutiny. Average rates of progression for moderate AS are a decrease in AVA by 0.1 cm²/year, an increase in mean gradient by 7 mmHg/year, and an increase of peak velocity by 0.3 m/s per year [11]. While these data suggest that careful monitoring with serial echocardiography should be satisfactory to avoid a transition to severe AS, these values vary widely among patients. Moreover, moderate AS itself has been associated with significant mortality, particularly in conjunction with a reduced left ventricular ejection fraction (LVEF) [12••, 13••]. Patients with moderate AS present with a high degree of cardiovascular comorbidities and exhibit reduced survival compared to age- and sex-matched patients without AS [14]. Given the potential clinical ramifications, a paradigm shift towards earlier treatment clearly needs to be investigated. As such, we aim to review the evidence in support of available medical, surgical, and interventional treatments for moderate AS.

Aortic stenosis and ventricular maladaptation

Much like severe AS, alterations in LVEF play an important role in prognostication for patients with moderate AS. Patients are typically grouped into those with preserved left ventricular function (LVEF ≥ 50%) and those with systolic dysfunction (LVEF < 50%).

Patients with moderate AS and left ventricular (LV) systolic dysfunction have worse survival compared to those with preserved LVEF [15]. It has been hypothesized that the failing LV is a “double-loaded ventricle” with significantly higher afterload due to increased arterial stiffness (in an elderly population) and a greater *relative* (and therefore more detrimental) effect of “only” moderate AS [16••]. The clinical implications are significant with one study demonstrating death or heart failure hospitalization in 48% of patients over 4 years [13••]. Moreover, 1-year aortic valve replacement (AVR) rates were higher than those historically reported for patients with asymptomatic severe AS or moderate AS with a preserved LVEF (13% vs. 5–9%, and 4–8%, respectively), suggestive of accelerated rates of clinical deterioration. Importantly, in the setting of a reduced LVEF, low aortic valve gradients and an AVA ≤ 1.0 cm², low-flow low-gradient severe AS must be distinguished from moderate AS due to differences in current guideline recommendations for surgical or transcatheter valve replacement [11, 17]. Interestingly, the presence of a low-normal LVEF (50–60%) has also been demonstrated to predict further LVEF deterioration in patients with moderate AS, even after adjustment for confounders [18].

The reason why some patients experience ventricular maladaptation in the presence of moderate AS and others do not remains unclear. While prior studies have suggested that women are more likely to respond to the pressure load imposed by valvular stenosis with concentric hypertrophy, clinical predictors of systolic dysfunction have been challenging to identify. Pathology studies have implicated two distinct types of LV fibrosis in response to the increased afterload from valvular stenosis—reactive interstitial fibrosis and replacement fibrosis [19•, 20, 21]. The former, characterized by myofibroblast activity and collagen deposition, occurs in the early stages of AS and has been demonstrated to regress following AVR [22]. Conversely, replacement fibrosis occurs later and is permanent. The extent of both forms of maladaptive left ventricular fibrosis appears to worsen as AS progresses and is emblematic of the detrimental effects of even early stages of AS [23].

Unsurprisingly, greater degrees of replacement fibrosis have been associated with impaired LV recovery after AVR and poorer outcomes [19•]. In a longitudinal observational study of 674 patients with severe AS, the presence of late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (a marker of replacement fibrosis) was associated with higher all-cause mortality (26.4% vs. 12.9%, $p < 0.001$) and cardiovascular mortality (15.0% vs. 4.8%, $p < 0.001$) regardless of surgical or transcatheter intervention [24]. Moreover, greater degrees of LGE correlated with higher rates of all-cause and cardiovascular mortality. In a prospective study of 203 patients (of which 166 had at least mild AS), the extent of myocardial fibrosis was observed to gradually worsen across the progression of AS from mild to moderate to severe [23]. Thus, the obstructive aortic valve lesion may adversely impact left ventricular remodeling, even before symptoms or severe AS develop, thereby providing an important pathologic basis for the need for early intervention. The prospective EVOLVE trial (NCT03094143) will seek to answer this question for patients with asymptomatic severe AS, randomizing 400 patients with midwall LGE to early AVR as compared to medical therapy [25]. If in fact the presence of LGE identifies patients that benefit from early AVR for asymptomatic severe AS, future studies will be needed to investigate whether this strategy should be expanded to moderate AS.

Surgical and transcatheter aortic valve replacement

In light of the aforementioned data regarding the adverse consequences of moderate AS, the question of whether these patients should undergo valve replacement gains relevance (see Fig. 1). While moderate AS imposes a significant hemodynamic load on the left ventricle (with increased wall stress and myocyte fibrosis), this load is manageable for the normal heart. Moreover, for asymptomatic patients with moderate AS and a normal LVEF, the finite durability and life span of bioprosthetic valves in addition to the periprocedural risks of AVR are important considerations. Given our inability to accurately predict the progression of AS, it remains inappropriate and unnecessary to globally recommend surgical intervention for all patients with moderate AS in the absence of some evidence of cardiac or clinical decompensation.

In patients with existing LV dysfunction, however, relief of fixed valvular stenosis may improve left ventricular hemodynamics and limit

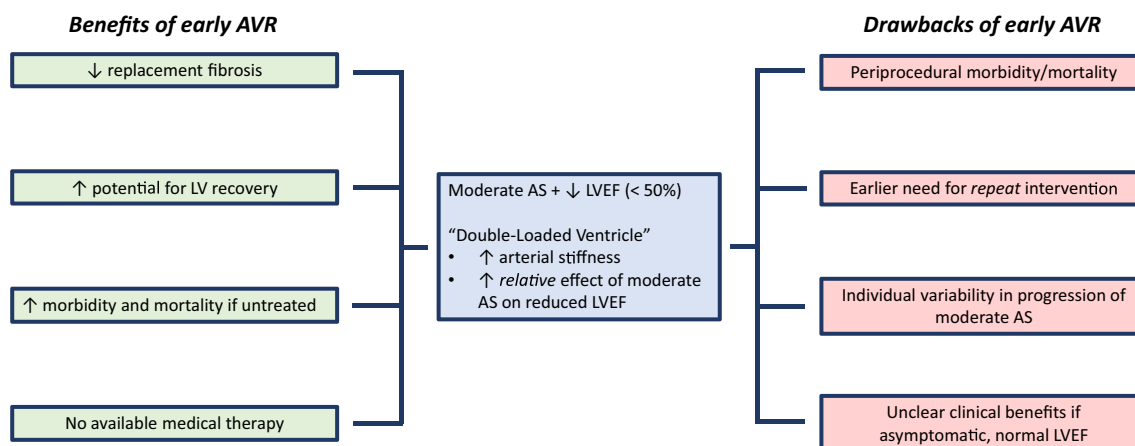


Fig. 1. Flowchart depicting the potential benefits and drawbacks associated with early AVR in patients with moderate AS and reduced LVEF. Abbreviations: AS, aortic stenosis; AVR, aortic valve replacement; LV, left ventricle; LVEF, left ventricular ejection fraction.

(or allow reversal of) myocyte fibrosis, thereby theoretically precluding the worsening (or onset) of LV dysfunction [26]. In heart failure with reduced LVEF, the mainstay of therapy is afterload reduction—alleviation of the fixed afterload imposed by moderate AS may therefore provide therapeutic benefit. Similarly, the morbidity and mortality conferred by progressive AS should be alleviated with valve replacement. Unfortunately, no prospective randomized controlled trials have evaluated the role of AVR (surgical or transcatheter) in patients with moderate AS (with a preserved or reduced LVEF). In a retrospective study of 263 patients ≥ 70 years old with moderate AS who were referred for coronary artery bypass grafting (CABG), performance of a concomitant SAVR compared to CABG alone conferred no additional in-hospital mortality (4.2% vs. 6.0%, $p = 0.8$), change in 5-year survival ($62.3 \pm 5.5\%$ vs. $64.2 \pm 4.3\%$), or freedom from AVR ($98.9 \pm 1.1\%$ vs. $97.8 \pm 1.2\%$, $p = 0.13$) [27]. In a more recent study of 1634 patients with moderate or severe AS and an LVEF $\leq 50\%$, the effect of SAVR with or without CABG was compared to medical therapy [28]. In the subgroup of patients with moderate AS (classified by either mean gradient or AVA), SAVR was associated with a lower mortality over a 5-year follow-up period (hazard ratio [HR] 0.58, 95% confidence interval [CI] 0.39–0.89, $p < 0.001$).

With the advent of TAVR, the morbidity, mortality, and recovery times associated with AVR have markedly improved, making early utilization of AVR a potentially advantageous therapeutic strategy. Given the poor prognostic implications of moderate AS with a reduced LVEF, the prospective TAVR-UNLOAD trial (NCT02661451) is ongoing and seeks to randomize 300 patients (≥ 18 years old) with heart failure (defined as heart failure hospitalizations or an elevated serum BNP/NT-proBNP), moderate AS, and a reduced LVEF (20–50%) to either TAVR plus optimal medical therapy or optimal medical therapy alone [29]. The primary endpoint of the study is a composite outcome of all-cause mortality, disabling stroke, cardiovascular hospitalization (due to heart failure, stroke or symptomatic aortic valve disease), and change in Kansas City

Cardiomyopathy Questionnaire relative to baseline. With TAVR-UNLOAD on the horizon, we will soon learn whether early valve replacement for moderate AS will change the trajectory of heart failure progression.

Medical therapy

Beyond valve replacement, several pharmaceutical agents have been evaluated for their potential role in slowing the progression of moderate AS. It should be noted that the majority of trials included patients with varying degrees of stenosis rather than moderate AS exclusively. Further, while there are numerous retrospective and observational studies, randomized, prospective trials are few and far between (see Table 1).

Diet and lifestyle

AS has been identified as an active process of lipid retention, chronic inflammation, and osteoblast activation within the aortic valve. Similarly, metabolic syndrome is characterized by proinflammatory and prothrombotic abnormalities secondary to insulin resistance, often in the setting of abdominal obesity and increased visceral adiposity. It was hypothesized that both obesity and metabolic syndrome could therefore be linked to worsening progression and mortality in patients with AS. In a retrospective study of 105 patients with at least moderate AS, metabolic syndrome was associated with more rapid progression of valvular stenosis ($-0.14 \pm 0.13 \text{ cm}^2/\text{year}$ vs. $-0.08 \pm 0.08 \text{ cm}^2/\text{year}$, $p = 0.008$) and decreased 3-year event-free survival ($44 \pm 8\%$ vs. $69 \pm 6\%$, $p = 0.002$) [38]. In a substudy of the prospective ASTRONOMER (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin) trial, 243 patients with mild to moderate AS were evaluated for the effects of metabolic syndrome on AS progression [39]. Metabolic syndrome was an independent predictor of AS progression, particularly in patients younger than 57 years old. This effect of metabolic syndrome has been similarly identified in patients with bioprosthetic aortic valves, with increased rates of deterioration [40].

There is debate, however, on the role of obesity as a stand-alone risk factor for the progression of AS. Earlier studies suggested an inverse relationship of body mass index (BMI) and aortic valve calcification (i.e., an “obesity paradox”), whereas others have implied either a neutral or negative effect [41–43]. In a substudy of the randomized controlled SEAS (Simvastatin Ezetimibe in Aortic Stenosis) trial, neither being overweight nor obese was associated with AS progression in patients with asymptomatic mild to moderate AS [44].

Despite the aforementioned, there is no available data on the role of diet and/or exercise in prevention or treatment of moderate AS. For competitive athletes with mild to moderate AS, the ACC/AHA recommend continued participation in low and moderate static or dynamic sports *if* exercise testing to at least the level of activity achieved in competition and training demonstrates satisfactory exercise capacity without symptoms, ST segment depression, ventricular arrhythmias, or abnormal blood pressure response (class IIa, level of evidence C) [45]. For non-athletes, however, there are no recommendations with regard to exercise. In terms of diet, we recommend following the

Table 1. Randomized controlled trials of medical therapies evaluated in patients with moderate aortic stenosis

Study	Inclusion criteria	Treatment arms	Duration of follow-up	Hemodynamic outcomes (intervention vs. placebo)	Clinical outcomes (intervention vs. placebo)
SEAS [30]	Asymptomatic, mild to moderate AS (V_{peak} 2.5–4.0 m/s)	Simvastatin 40 mg/day + ezetimibe 10 mg/day ($n = 944$) vs. placebo ($n = 929$)	Median, 52.2 months	Change in V_{peak} (m/s) <ul style="list-style-type: none"> • 0.61 ± 0.59 vs. 0.62 ± 0.61 ($p = 0.83$) Change in mean gradient (mmHg/year) <ul style="list-style-type: none"> • 2.7 ± 0.1 vs. 2.8 ± 0.1 (<i>no statistical analysis</i>) Change in AVA (cm^2/year) <ul style="list-style-type: none"> • -0.03 ± 0.01 (both groups; <i>no statistical analysis</i>) Change in peak gradient (mmHg/year) <ul style="list-style-type: none"> • 6.3 ± 6.9 vs. 6.1 ± 8.2 ($p = 0.83$) Change in mean gradient (mmHg/year) <ul style="list-style-type: none"> • 3.8 ± 4.4 vs. 3.9 ± 4.9 ($p = 0.79$) Change in AVA (cm^2/year) <ul style="list-style-type: none"> • -0.07 ± 0.15 vs. -0.08 ± 0.21 ($p = 0.87$) Change in peak gradient (mmHg/year) <ul style="list-style-type: none"> • 6.48 ± 7.43 vs. 6.56 ± 7.10 ($p = 0.85$) Change in AVA (cm^2/year) <ul style="list-style-type: none"> • -0.079 ± 0.107 vs. -0.083 ± 0.107 ($p = 0.68$) 	Major CV events <ul style="list-style-type: none"> • 38.2% vs. 35.3% ($p = 0.59$) AVR <ul style="list-style-type: none"> • 29.9% vs. 28.3% ($p = 0.97$) All-cause mortality <ul style="list-style-type: none"> • 11.1% vs. 10.8% ($p = 0.80$)
ASTRONOMER [31]	Asymptomatic, mild to moderate AS (V_{peak} 2.5–4.0 m/s)	Rosuvastatin 40 mg/day ($n = 134$) vs. placebo ($n = 135$)	Median, 3.5 years	Change in peak gradient (mmHg/year) <ul style="list-style-type: none"> • 6.3 ± 6.9 vs. 6.1 ± 8.2 ($p = 0.83$) Change in mean gradient (mmHg/year) <ul style="list-style-type: none"> • 3.8 ± 4.4 vs. 3.9 ± 4.9 ($p = 0.79$) Change in AVA (cm^2/year) <ul style="list-style-type: none"> • -0.07 ± 0.15 vs. -0.08 ± 0.21 ($p = 0.87$) Change in peak gradient (mmHg/year) <ul style="list-style-type: none"> • 6.48 ± 7.43 vs. 6.56 ± 7.10 ($p = 0.85$) Change in AVA (cm^2/year) <ul style="list-style-type: none"> • -0.079 ± 0.107 vs. -0.083 ± 0.107 ($p = 0.68$) 	Composite of CV death or AVR <ul style="list-style-type: none"> • 29% vs. 35% ($p = 0.45$)
SALTIRE [32]	Aortic valve calcification on echocardiography + $V_{\text{peak}} \geq 2.5$ m/s	Atorvastatin 80 mg/day ($n = 77$) vs. placebo ($n = 78$)	Median, 25 months	Change in peak gradient (mmHg/year) <ul style="list-style-type: none"> • 6.48 ± 7.43 vs. 6.56 ± 7.10 ($p = 0.85$) Change in AVA (cm^2/year) <ul style="list-style-type: none"> • -0.079 ± 0.107 vs. -0.083 ± 0.107 ($p = 0.68$) 	Composite of CV death, AVR, or hospitalization for severe AS <ul style="list-style-type: none"> • 17% vs. 27% ($p = 0.19$)

Table 1. (Continued)

Study	Inclusion criteria	Treatment arms	Duration of follow-up	Hemodynamic outcomes (intervention vs. placebo)	Clinical outcomes (intervention vs. placebo)
PROCAS [33]	Congenital AS with $V_{\text{peak}} \geq 2.5$ m/s	Rosuvastatin 10 mg/day ($n = 30$) vs. placebo ($n = 33$)	Median, 2.4 years	Change in peak gradient (mmHg/year) <ul style="list-style-type: none"> • 2.5 ± 5.7 vs. 3.5 ± 9.2 ($p = 0.64$) Change in mean gradient (mmHg/year) <ul style="list-style-type: none"> • 1.2 ± 3.3 vs. 1.9 ± 4.8 ($p = 0.52$) Change in AVA (cm^2/year) <ul style="list-style-type: none"> • -0.03 ± 0.11 vs. -0.03 ± 0.18 ($p = 0.99$) Peak gradient at 2 years follow-up (mmHg) <ul style="list-style-type: none"> • 50.7 ± 19.0 vs. 47.0 ± 21.2 ($p = \text{NS}$) Mean gradient at 2 years follow-up (mmHg) <ul style="list-style-type: none"> • 31.3 ± 12.3 vs. 29.9 ± 14.8 ($p = \text{NS}$) Change in peak gradient (mmHg) <ul style="list-style-type: none"> • -3 ± 8 vs. 4 ± 11 ($p = 0.05$) Change in mean gradient (mmHg) <ul style="list-style-type: none"> • -2 ± 4 vs. 2 ± 6 ($p = 0.03$) Change in AVA (cm^2) <ul style="list-style-type: none"> • 0.0 ± 0.1 (both groups, $p = 0.44$) 	AVR <ul style="list-style-type: none"> • 30% vs. 27% ($p = 0.32$) No deaths or AVR-related complications
TASS [34]	Asymptomatic AS with aortic valve calcification on echocardiography, $V_{\text{peak}} \geq 2.0$ m/s and mean systolic gradient ≥ 15 mmHg	Atorvastatin 20 mg/day ($n = 23$) vs. placebo ($n = 24$)	Mean, 2.3 years		No comparisons of clinical outcomes
Hansson et al. [35]	Asymptomatic, moderate to severe AS ($\text{AVA} \leq 1.2$ cm^2) OR $V_{\text{peak}} \geq 3.0$ m/s) + sinus rhythm with HR ≥ 60 bpm	Metoprolol 50–200 mg/day ($n = 19$) vs. placebo ($n = 19$)	22 weeks		Adverse cardiovascular events <ul style="list-style-type: none"> • 2 vs. 0 patients

Table 1. (Continued)

Study	Inclusion criteria	Treatment arms	Duration of follow-up	Hemodynamic outcomes (intervention vs. placebo)	Clinical outcomes (intervention vs. placebo)
RIAS [36]	Asymptomatic moderate to severe AS (AVA < 1.5 cm ² or $v_{\text{peak}} \geq 3.0$ m/s)	Ramipril 10 mg/day ($n = 50$) vs. placebo ($n = 50$)	1 year	Change in v_{peak} (m/s) • 0.0 ± 0.1 vs. 0.1 ± 0.1 ($p = 0.28$) Change in AVA (cm ²) • 0.0 ± 0.1 vs. -0.2 ± 0.05 ($p = 0.067$) Change in v_{peak} (m/s per year) • 0.24 ± 0.37 vs. 0.30 ± 0.41 ($p = 0.9$) Change in AVA (cm ² /year) • -0.11 ± 0.22 vs. -0.18 ± 0.24 ($p = 0.2$)	Change in LV mass (g) • -23.9 vs. 4.5 ($p = 0.006$) Composite of major adverse cardiovascular events and AVR • 18% vs. 14% ($p = 0.52$)
ZEST [37]	Asymptomatic moderate to severe AS ($v_{\text{peak}} \geq 3.0$ m/s) and a normal LVEF (> 50%)	Eplerenone 100 mg/day ($n = 33$) vs. placebo ($n = 32$)	Median, 19 months		Change in LV mass index (g/m ² per year) • -0.3 ± 14.6 vs. 5.1 ± 15.0 ($p = 0.3$)

AS aortic stenosis, *ASTRONOMER* Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin, AVA aortic valve area, AVR aortic valve replacement, CV cardiovascular, HR heart rate, LV left ventricular, LVEF left ventricular ejection fraction, *PROCAS* Progression of Stenosis in Adult Patients with Congenital Aortic Stenosis, *RIAS* Ramipril in Aortic Stenosis, *SALTIRE* Study Investigating the Effect of Drugs Used to Treat Osteoporosis on the Progression of Calcific Aortic Stenosis, *SEAS* Simvastatin and Ezetimibe in Aortic Stenosis, *TASS* Ticlopidine Aspirin Stroke study, v_{peak} peak aortic valve velocity, *ZEST* Zostavax Efficacy and Safety Trial

2019 ACC/AHA guidelines on the primary prevention of cardiovascular disease given the frequency with which cardiovascular comorbidities occur in conjunction with moderate AS [46].

Statin therapy

The pathogenesis of valvular calcification in AS is similar to that of atherosclerosis; with damage to the valvular endothelium, there is lipid deposition (e.g., lipoprotein(a) [Lp(a)] and low-density lipoprotein [LDL]) resulting in inflammation, macrophage infiltration, and ultimately calcification [47]. Indeed, AS and atherosclerosis share many of the same risk factors for progression, including long-term elevations in cholesterol levels [43, 48]. As such, it is reasonable to postulate that statins may have a beneficial effect in the treatment of AS.

The SEAS trial was the largest trial to evaluate this question. 1873 patients with asymptomatic mild to moderate AS and no other indication for lipid-lowering therapy were randomized to simvastatin plus ezetimibe versus placebo [30]. After a median of 52 months, there was no difference in major adverse cardiac events, rates of AVR, or AS progression. Similarly, the ASTRONOMER trial was a randomized, double-blind, placebo-controlled trial examining 269 patients with mild to moderate AS and no indication for lipid-lowering therapy [31]. After a median follow-up of 3.5 years, no change in rates of AS progression were noted. These findings have been replicated in other smaller randomized controlled trials using different statin agents [32–34]. A meta-analysis of 4 major prospective randomized controlled trials showed no differences in mean or peak aortic valve gradients, AVA, freedom from AVR, or death from cardiovascular causes if a statin was used compared to placebo [49].

As such, current US and European guidelines do not recommend statin therapy to slow progression or treat moderate AS [11, 17].

Alternative lipid-lowering therapies

Like LDL, high levels of Lp(a) have been associated with aortic valve calcification [48, 50, 51]. In one prospective study of 145 patients with AS (peak velocity > 2.0 m/s), patients in the top Lp(a) tertile had increased progression of valvular calcium score, faster hemodynamic progression on echocardiography, and higher risk of death and AVR compared to those in the lower tertile [52]. While a central role of Lp(a) in the pathogenesis of AS could explain the lack of benefit seen with statins, we await the results of ongoing randomized controlled trials evaluating therapies that target Lp(a), including PCSK9 inhibitors, niacin, and antisense oligonucleotides against apo(a) mRNA [50, 53, 54].

Antihypertensive agents

Hypertension is a major risk factor for the development and progression of AS and has been estimated to account for up to one quarter of incident cases [55–57]. Pathologically, hypertension results in concentric left ventricular remodeling and diastolic dysfunction. In patients with mild to moderate AS, the presence of a higher left ventricular mass index has been shown to increase rates of cardiovascular morbidity and mortality [58, 59]. Moreover, the synergistic load imposed on the left ventricle by reduced arterial compliance and an increased transvalvular gradient, quantified by the valvuloarterial impedance index (Z_{va}), have also been shown to correlate with an increased risk of left ventricular dysfunction and increased

mortality in patients with at least moderate AS [60, 61].

In this section, we will briefly review the available evidence in support of different classes of antihypertensive therapies for patients with moderate AS.

β-Blockers

While there is an abundance of data in support of β-blockers for use in coronary artery disease, arrhythmia, and heart failure with a reduced ejection fraction (HFrEF), there are a dearth of studies evaluating their efficacy and safety in patients with AS. Mechanistically, β-blockers decrease afterload, heart rate and myocardial oxygen demand. As one retrospective study has demonstrated higher resting heart rates in patients with mild valvular stenosis, β-blockers can theoretically hit multiple targets associated with the development and progression of AS [62].

In a post hoc analysis of the SEAS trial, the use of β-blockers demonstrated lower all-cause mortality (HR 0.5, 95% CI 0.3–0.7, $p < 0.001$), sudden cardiac death (HR 0.2, 95% CI 0.1–0.6, $p = 0.004$), and cardiovascular death (HR 0.4, 95% CI 0.2–0.7, $p < 0.001$) in patients with mild to moderate AS compared to placebo [63]. In another study, 40 patients with asymptomatic moderate to severe AS were randomized to metoprolol or placebo for 22 weeks [35]. Patients who took metoprolol were noted to have lower peak and mean aortic valve gradients, lower myocardial consumption, and lower valvuloarterial impedance with no change in stroke volume. While these data are promising (both in terms of efficacy and safety), the confounding beneficial effects of β-blockade on other common comorbidities (including atherosclerosis, hypertension and arrhythmias) necessitate further dedicated studies for patients with moderate AS.

RAAS inhibitors

The renin-angiotensin-aldosterone system (RAAS) plays an important role in ventricular adaptation in the setting of AS. While myocytes initially hypertrophy to counteract the effects of prolonged increases in afterload and left ventricular wall stress, eventually the left ventricle will decompensate. Angiotensin II and aldosterone signaling have both been implicated in maladaptive ventricular behavior by driving myocyte apoptosis, activating cardiac myofibroblasts and promoting myocardial fibrosis [37, 64, 65]. Indeed, inhibition of these pathways by angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) has well-known benefits on ventricular remodeling and clinical outcomes in patients with HFrEF. The aortic valve also expresses prorenin, renin, ACE, and angiotensin II receptors and they are thereby integrally linked to the RAAS system [53].

Given the connection of the RAAS system to the aortic valve and adverse ventricular remodeling, it is reasonable to suspect that RAAS antagonism could improve clinical outcomes or slow progression of AS. While several randomized controlled trials have investigated patients with *severe* AS, fewer have included the cohort of patients with moderate or less disease. The RIAS (Ramipril In Aortic Stenosis) trial was a randomized controlled trial of ramipril versus placebo in 100 patients with moderate to severe asymptomatic AS. Compared to placebo, ramipril resulted in statistically significant reductions in left ventricular mass and a trend towards a slower rate of AS progression after 1 year of follow-up (0.0cm^2 vs. -0.2cm^2 , $p = 0.067$) [36]. Like the RIAS trial, a substudy of the randomized

controlled SEAS trial also demonstrated reductions in left ventricular mass in patients using ACE inhibitor or ARB therapy [66]. However, after a median follow-up of 4.3 years, there were no differences in AS progression or cardiovascular outcomes, including cardiovascular death and all-cause mortality.

The only randomized controlled trial to date to investigate MRA therapy in AS has been the ZEST trial [37]. Sixty-five patients with asymptomatic moderate to severe AS were randomized to placebo versus eplerenone. After a median follow-up of 19 months, there were no statistically significant differences in the onset of left ventricular dysfunction (systolic or diastolic), left ventricular mass, or progression of AS.

Calcium channel blockers

Like β -blockers, calcium channel blockers (CCBs) have multiple beneficial cardiovascular effects, including a decrease in afterload and myocardial oxygen demand. Neither dihydropyridine (DHP) nor non-DHP CCBs have been studied in a randomized controlled trial for patients with any degree of AS. A retrospective analysis of 314 patients examined the effects of CCBs (DHP and non-DHP) on patients with asymptomatic moderate or severe AS [67]. In this cohort, all-cause mortality was greater in the group of patients taking CCBs, independent of age, hypertension, diabetes, LVEF, and baseline AVA (HR 7.09, 95% CI 2.15–23.38, $p = 0.001$). Importantly, however, the type of CCB was not delineated and the prevalence of coronary artery disease was significantly higher in the group taking CCBs. It is therefore unclear whether CCB therapy poses safety concerns to patients with moderate AS without further randomized control trials.

Antihypertensive agents—a summary

Given the aforementioned, current ACC/AHA guidelines recommend the initiation of antihypertensive therapy in all patients with asymptomatic AS, started at a low dose and gradually uptitrated with frequent clinical monitoring (class I, level of evidence B) [11]. Given a lack of evidence in support of any one class of medication, recommendations suggest initiation of therapies “according to standard guideline directed medical therapy.”

Calcium and phosphorus metabolism

After the initial phases of inflammation and lipid deposition in aortic valve tissue, valvular calcification is dominated by the activation of osteoblast-like cells that develop an osteogenic phenotype [47]. There is upregulation and deposition of extracellular matrix proteins and dysregulation of RANKL/OPG signaling (receptor activator of nuclear factor- κ B ligand and osteoprotegerin, respectively), which normally governs bone demineralization [47]. Similarly, there have been numerous associations established between patients with low bone density and aortic valve calcification [68, 69]. It has therefore been hypothesized that medications designed to prevent and treat osteoporosis may have a role in the management of AS.

Calcium and vitamin D supplementation have not been studied prospectively to determine their effects on progression or outcomes for patients with moderate AS. In a community-based observational study examining 144 women over a 4-year period, calcium supplementation resulted in no differences in aortic valve calcification [70]. However, a recent retrospective study of 2660 patients with mild to moderate AS found that calcium and/or vitamin D

supplementation was associated with faster rates of progression of AS and the need for AVR (44.5% vs. 20.9%, $p < 0.001$) but no differences in overall mortality in a 6-year follow-up period [71].

Bisphosphonates represent one of the mainstays in therapy for osteoporosis. However, they have also been noted to have beneficial effects on vascular and aortic valve calcification through decreased bone resorption (and therefore, decreased release of calcium and phosphate), in addition to pleiotropic effects on inflammation and the reduction of inflammatory cytokines [47]. While no prospective trials have been performed to date, other studies have had mixed results. In an analysis of 3710 women enrolled in the MESA (Multi-Ethnic Study of Atherosclerosis) trial, the use of bisphosphonates was associated with lower degrees of aortic valve calcification in patients ≥ 65 years old [72]. In a retrospective study of 801 female patients with mild to moderate AS, the use of bisphosphonates resulted in no differences in AVA, peak and mean aortic valve gradients, survival, or freedom from AVR over an average 5.1 year follow-up [73]. Conversely, some smaller echocardiographic studies across a range of stenosis severity (i.e., mild to severe) have shown slower rates of progression of valve calcification for patients on bisphosphonates [74–76]. The beneficial effects of bisphosphonates should be interpreted with caution, as the aforementioned trials evaluated patients who were *already* taking these medications for osteoporosis and therefore have dysregulated calcium and phosphate metabolism.

Denosumab, a monoclonal antibody to RANKL and alternative therapy for osteoporosis, has also been proposed as a treatment for AS. While in vitro studies have demonstrated reductions in calcification by valvular interstitial cells, no studies have evaluated this therapy in patients with AS [77].

Clearly, prospective randomized controlled trials are needed to evaluate the efficacy of bisphosphonates and denosumab in patients with AS (and *without* osteoporosis). The SALTIRE II trial (NCT02132026) will hopefully shed some light on this question, comparing the use of alendronic acid, denosumab, and placebo to determine changes in aortic valve calcium score in patients with at least mild AS. At present, however, there are no guideline recommendations for the use of these therapies in patients with moderate AS [11, 17].

Warfarin

While there is an increasing shift towards the use of direct oral anticoagulants (DOAC) for cardiovascular diseases that require anticoagulation, warfarin is still a cornerstone therapy given its widespread availability, affordability, and familiarity. Recently, a retrospective analysis of 303 patients with at least mild AS and a preserved LVEF compared rates of AS progression between patients on warfarin, DOAC, or no anticoagulant therapy [78]. Annualized increases in aortic valve calcium scores and peak aortic valve gradients were higher in the warfarin group compared to the DOAC and no therapy groups. While prospective studies should be performed to confirm the aforementioned, for patients with moderate AS who have the option of either a DOAC or warfarin, we favor the use of the former (if feasible).

Future directions/emerging therapies

Recently, targets of phosphodiesterase type 5 (PDE5) have garnered interest as a therapy for AS. Murine and human hearts have shown increased expression of

myocardial PDE5 in response to transverse aortic constriction and severe valvular AS, respectively [79]. Given the known benefits of PDE5 inhibitors and soluble guanylate cyclase (sGC) inhibitors in patients with pulmonary hypertension, it has been proposed that these therapies may offer benefit in patients with AS [80–84]. While multiple randomized controlled trials were initially underway that included patients with moderate AS, difficulty in enrollment has limited their progress.

A variety of other therapies have been proposed to slow the progression of AS due to their effects on cellular mechanisms and inflammation. These include endocannabinoids, ectonucleotidase inhibitors, disease modifying antirheumatic drugs (DMARDs), and dipeptidyl peptidase-4 (DPP-4) inhibitors [50, 53].

Conclusion

Moderate AS represents more than just a “latent period” before the development of severe AS. Rather, it is an active disease state characterized by inflammation and LV fibrosis and is associated with increased rates of morbidity and mortality when left ventricular function is decreased. While no medical therapies have emerged to slow its progression, there is a signal that early intervention may preclude or reverse maladaptive ventricular remodeling. Randomized controlled trials are underway to evaluate the benefits of early transcatheter valve replacement considering their efficacy and safety profile.

Compliance with Ethical Standards

Conflict of Interest

Dr. Elmariah receives research grants from American Heart Association (19TPA34910170), National Institutes of Health (R01 HL151838), Edwards Lifesciences, Svelte Medical, and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this article to disclose.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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