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Valvular Heart Disease (J Dal-Bianco, Section Editor)

Contemporary Workup and Management of Asymptomatic Patients with Severe Aortic Stenosis

Jasleen K Tiwana, MD
Catherine M Otto, MD[*]

Address
[*]Division of Cardiology, Department of Medicine, University of Washington School of Medicine, Box 356422, 1959 NE Pacific St, HSB AA522, Seattle, WA, 98195, USA
Email: cmotto@uw.edu

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Abstract

Purpose of review Appropriate management of asymptomatic patients with severe aortic stenosis (AS) is increasingly debated given recent improvements in options for aortic valve replacement (AVR). The goal of this review is to provide an updated approach to evaluation and management of patients with asymptomatic severe AS and to discuss the rationale for early AVR.

Recent findings Registry data, retrospective studies, and one small randomized controlled clinical trial suggest a mortality benefit to AVR before symptom onset, although larger randomized trials are needed given potential biases of observational data. Other promising approaches to risk stratification of asymptomatic adults with severe AS include cardiac biomarkers (such as serum B-type natriuretic peptide levels), left ventricular global longitudinal strain, and myocardial fibrosis detected on cardiac magnetic resonance imaging.

Summary Routine close clinical follow-up, periodic imaging, patient education, and shared decision-making are essential in caring for asymptomatic patients with severe AS but there is not yet enough evidence to support early AVR in most patients. Ongoing clinical trials and evaluation of biomarkers will illuminate whether intervention before symptom onset will improve the length or quality of life in adults with severe AS.

Introduction

Disease overview

The prevalence of calcific aortic stenosis (AS) increases with age, with severe AS affecting up to 3.4% of people 75 years of age or older [1, 2]. Moderate AS is even more common and typically progresses to severe AS within 5 to 10 years. At the time of diagnosis, 30–50% of patients with severe AS are asymptomatic [3, 4]. Morbidity and mortality are closely linked to AS disease severity and the emergence of symptoms in patients who initially are asymptomatic [5]. Generally, the goals of aortic valve replacement (AVR) for severe AS are to prolong life, reduce symptoms, and prevent heart failure long-term. Although AVR is clearly indicated in patients with symptoms from valve obstruction, the balance of risks and benefits is less clear in patients who are asymptomatic. After all, patients without symptoms will not have symptomatic benefit with AVR. The hypothesis that asymptomatic patients with severe AS may benefit from AVR before symptom onset is often referred to as "early AVR."

In addition to procedural morbidity and mortality, a bioprosthetic AVR carries the long-term risk of valve degeneration, often requiring reintervention, especially in adults under 65 years of age. If a mechanical prosthesis is implanted, the risks of bleeding and thrombosis must be considered in addition to the inconvenience and life-style limitations with long-term vitamin-K antagonist anticoagulation. Thus, AVR is recommended primarily for symptomatic patients with severe AS because this population most clearly derives benefit from an intervention that justifies the short and long-term risks [6–8]. AVR for asymptomatic patients with severe AS is not routinely recommended unless the patient has a low left ventricular (LV) ejection fraction, very severe AS, rapid disease progression, symptoms provoked on exercise testing, or is undergoing other cardiac surgery [6, 8] (Table 1). However, some data suggest a possible mortality benefit with early surgery [4, 9–13]. Therefore, determining whether patients and which patients may benefit from earlier intervention is increasingly debated with several randomized trials now underway aimed at addressing these questions.

In this review, we will discuss the definition of "severe" AS, consider the challenges in ensuring patients are truly asymptomatic, and review current guidelines for intervention. We then go on to present the research rationale for early AVR and emerging parameters to identify patients most likely to benefit from early intervention. We also discuss the current clinical management of patients with asymptomatic severe AS, with practical guidance, including a framework for shared decision-making regarding the risks and considerations related to valve intervention. Lastly, we will summarize the ongoing trials testing the hypothesis that early AVR might be beneficial for prolonging life and reducing long-term adverse outcomes.

Defining severe aortic stenosis

Severe AS might best be defined as the degree of valve obstruction that results in symptom onset in each patient. However, there is no single numerical measure of AS severity that reliably predicts symptoms in all patients. In addition, there is evidence of adverse effects of valve obstruction on the left ventricle, even before the onset of symptoms. Our current definition of severe AS is derived from natural history studies showing that the rate of symptom onset corresponds closely with the degree of valve obstruction, with symptom onset occurring within a short time period once aortic velocity reaches 4 m/s or higher [14–18].

In current guidelines, severe AS is defined as a maximum aortic valve velocity (V_{max}) ≥ 4 m/s or mean aortic valve gradient (mean ΔP) ≥ 40 mmHg. Typically, aortic valve area (AVA) is 1.0 cm^2 or less (or aortic valve area indexed to body surface area (AVAi) ≤ 0.6 cm^2/m^2) but may be higher with mixed stenosis and regurgitation or with a high cardiac output. A high aortic velocity (or pressure gradient) alone is adequate for diagnosis of severe AS, regardless of valve area calculations. In addition to high-gradient severe AS, some patients with severe AS have a calcified immobile valve with a small AVA but a lower velocity and gradient due to a low transaortic flow rate. Low-gradient, low-flow severe AS may be associated with a low LV ejection fraction (< 50%) or with a normal ejection fraction but low transaortic stroke volume (< 35 ml/min/m^2) [6, 19].

Identification of symptoms is critical in the evaluation of patients with severe AS. The initial symptoms are reduced exercise tolerance and exertional dyspnea; frank angina, syncope, and heart failure are end-stage

Table 1. Current guidelines and indications for valve replacement

	Definition	Hemodynamics	Testing	Indications for replacement (class of recommendation)	Type of replacement
ACC/AHA 2017 guidelines [6, 7]	Asymptomatic severe AS	Aortic $V_{max} \geq 4$ m/s or mean $\Delta P \geq 40$ mmHg and AVA typically $\leq$ 1.0 cm^2 (or AVAi ≤ 0.6 cm^2/m^2)	• TTE every 6–12 months • Exercise testing to assess physiological changes and symptoms with exercise	• Decreased exercise tolerance or fall in systolic blood pressure with exercise testing (IIa) • LVEF < 50% with low surgical risk (I) • Undergoing other cardiac surgery (I) • $\Delta V_{max} > 0.3$ m/s/year and low surgical risk (IIb)	• Surgical AVR for low to intermediate risk • TAVR not recommended in asymptomatic patients
	Asymptomatic very severe AS	Aortic $V_{max} \geq 5$ m/s or mean $\Delta P \geq 60$ mmHg	• Same as above	• Low surgical risk (IIa)	• Surgical AVR
ESC/EACTS 2017 guidelines [8••]	Asymptomatic severe AS	Aortic $V_{max} \geq 4$ m/s or mean $\Delta P \geq 40$ mmHg	• TTE + exercise testing every 6 months • Consider serial BNP	• LVEF < 50% (I) • Exercise test with symptoms (I) or fall in blood pressure below baseline (IIa) • Undergoing other cardiac surgery (I) • Low surgical risk and 1 risk factor ($\Delta V_{max} >$ 0.3 m/s/year, markedly elevated BNP, PASP > 60 mmHg) (IIa)	• Weigh risks and benefits and if patient eligible for surgery than surgical AVR recommended • TAVR not recommended in asymptomatic patients.
	Asymptomatic very severe AS	Aortic $V_{max} \geq 5.5$ m/s		• Low surgical risk (IIa)	Surgical AVR

ACC American College of Cardiology, *AHA* American Heart Association, *AS* aortic stenosis, *AVR* aortic valve replacement, *AVA* aortic valve area, *AVAi* aortic valve area indexed to body surface area, *BNP* brain natriuretic peptide, *EACTS* European Association for Cardio-Thoracic Surgery, European Society of Cardiology, *LVEF* left ventricular ejection fraction, *PASP* pulmonary artery systolic pressure, *TTE* transthoracic echocardiogram, V_{max} peak velocity, ΔP pressure gradient

symptoms. Even if mild symptoms are present, candidacy for AVR is pursued. However, determining exercise tolerance and the presence of mild symptoms is challenging in many older patients. Patients and providers alike may have difficulty in recognizing the early onset of subtle symptoms, particularly in an elderly population, because of limited mobility and patient adaptation to decreased exercise tolerance [20]. Conversely, there are many alternate causes for reduced exercise capacity or exertional dyspnea in older adults. For patients with unclear exercise tolerance or ambiguous symptoms, exercise tolerance testing allows the assessment of physiological changes and symptoms with exercise. An abnormal exercise test—fall in blood pressure, decreased exercise tolerance, symptoms of severe AS, marked ST-depression, or ventricular arrhythmias—predicts symptom onset and cardiac events at 1 year [21–23]. Therefore, exercise testing is reasonable in selected patients to confirm the absence of symptoms and exclude high-risk features in patients with severe AS who deny overt symptoms [6, 8]. Of course, given the demographics of patients with severe AS, many patients are unable to undergo exercise testing secondary to limited exercise capacity, comorbidities, frailty, or advanced age [24]. In the USA, only about 30–40% of patients with severe asymptomatic AS undergo exercise treadmill testing [11, 25, 26]. Whether this is an appropriate level of exercise testing or whether more exercise testing would improve clinical outcomes has not been studied.

Current indications for AVR in patients with asymptomatic severe aortic stenosis

American and European guidelines for evaluation and management of asymptomatic patients with severe AS are shown in Table 1 [6–8]. Indications for valve replacement include LVEF < 50%, abnormal exercise tolerance test, rapidly progressing valve obstruction ($\Delta V_{max} > 0.3$ m/s/year), or if a patient is already planned to undergo cardiac surgery for another reason. Surgical aortic valve replacement (SAVR) rather than transcatheter aortic valve implantation (TAVI) is recommended in asymptomatic patients requiring intervention. The European guidelines also specify that valve replacement should be considered for patients with a markedly elevated BNP or pulmonary artery systolic pressure > 60 mmHg and low surgical risk. Generally, patients with very severe AS and low surgical risk are recommended to undergo SAVR, rather than TAVI, although the definitions for very severe AS differ slightly between European and American guidelines. In the European guidelines, the definition of very severe AS is an aortic $V_{max} \geq 5.5$ m/s whereas the breakpoint in the American guidelines is an aortic $V_{max} \geq 5$ m/s or mean $\Delta P \geq 60$ mmHg. Both guidelines likely will be updated soon with possible changes in the recommendations for the timing of AVR and the choice between SAVR versus TAVI. Fig. 1

Rationale for early aortic valve replacement

Prevention of left ventricular dysfunction

A key element underlying the rationale for early AVR in asymptomatic patients with severe AS is the concept that removing the high afterload due to valve obstruction might prevent end-organ LV damage and thus reduce long-term symptoms and adverse outcomes from diastolic and systolic heart failure. Advanced cardiac imaging demonstrates that subclinical LV damage occurs early in the disease course of adults with AS [27]. Many of these changes persist or fail to fully resolve after valve replacement [28]. Chronic pressure overload leads to LV myocyte hypertrophy which contributes to reduced coronary flow reserve and chronic ischemia [29]. Apoptosis of ischemic myocytes with subsequent irreversible replacement fibrosis leads to changes in LV myocardial longitudinal function, even when global ejection fraction is maintained. These subclinical LV myocardial changes contribute to diastolic dysfunction, pulmonary hypertension, heart failure, and cardiac death [30]. With early AVR, the hope is to prevent these LV changes and eventual heart failure.

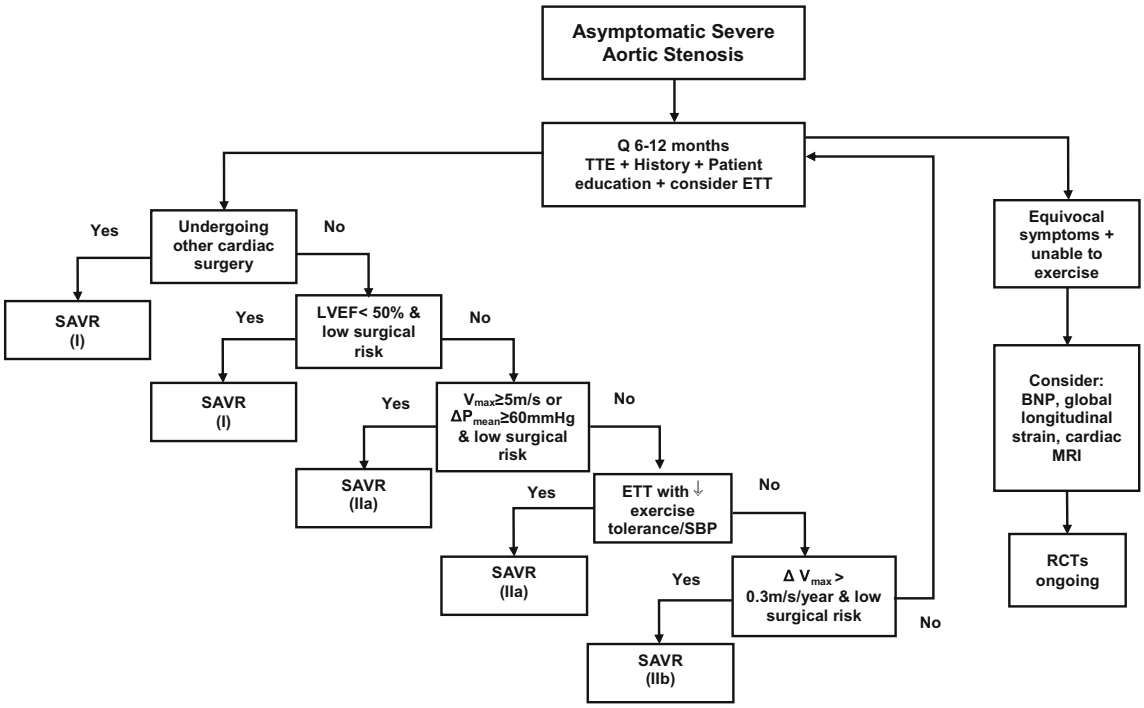

Fig. 1. Approach to evaluation and management of asymptomatic severe aortic stenosis

BNP levels

There are emerging methods and indices which show promise in detecting subclinical LV dysfunction which are not yet routine clinical practice but may be recommended in the future and can be used in individual cases when needed to identify patients that might benefit from early interventions. In patients with AS and a preserved LV ejection fraction, B-type natriuretic peptide (BNP) elevation is associated with heart failure hospitalization, need for AVR, and increased risk of mortality [31–34]. Elevations in BNP greater than or equal to three times the upper limit of normal for age and sex may be most predictive of adverse outcomes [32]. Notably, BNP is influenced by a patient's comorbidities, age, and sex; thus, if measured, clinicians must be reasonably sure that elevations are secondary to valvular disease rather than an alternative etiology. In European guidelines, markedly elevated BNP and low surgical risk for a patient with severe asymptomatic AS is an indication to consider valve replacement. Although it was not included in the 2017 American guidelines, an update is in progress and there remains significant clinical interest in using this biomarker for risk stratifying patients with asymptomatic severe AS.

Global longitudinal strain

Two-dimensional echocardiographic LV strain imaging also has prognostic ability in aortic stenosis. In patients with asymptomatic severe AS and a normal LV ejection fraction, LV global longitudinal strain (GLS) is reduced compared with patients without AS, supporting the concept that myocardial damage occurs before symptom onset [35]. In addition, impaired LV GLS in

asymptomatic patients with severe AS is associated with an increased risk of mortality, suggesting this might be a useful biomarker for identifying which patients might benefit from earlier AVR [36–38]. However, it is challenging to identify a specific absolute strain value reliable enough to be considered a trigger for valve replacement. Additionally, technical differences among vendors in the measurement of GLS, as well as intra- and interobserver variability in recording and measuring the data, further contribute to the lack of reliability in using GLS for decision-making in patients with severe AS. It is hoped that 3D echocardiographic strain imaging might avoid some of the limitations of 2D strain imaging, with preliminary studies suggesting that 3D GLS is a predictor of major adverse events including death, ventricular arrhythmias, and hospital admission in patients with AS [39].

Myocardial fibrosis

LV myocardial fibrosis on cardiac magnetic resonance imaging (CMR) is another promising approach to risk stratification of asymptomatic patients with severe AS. Late gadolinium enhancement (LGE) identifies regions of replacement fibrosis, with a mid-wall LGE pattern identifying myocardial scarring distinct from infarct, and is associated with an increased risk of mortality in patients with AS [40–44]. Mid-wall LGE is present in the ventricle of patients with severe AS, even when ejection fraction is normal, and remains unchanged after AVR suggesting that subclinical myocardial fibrosis is irreversible, at least in the short-term [45]. Unfortunately, despite the association of mid-wall LGE with mortality in patient with AS, it is difficult to define a specific level of LGE that might justify early valve replacement. Variability between studies contributes to this uncertainty with differing approaches to the quantification of the amount of myocardium affected (absolute or relative) as well as some studies simply reporting the presence or absence of LGE. CMR T1 mapping is also abnormal in patients with AS. Interstitial fibrosis, secondary to myofibroblast infiltration and extracellular expansion, accompanies the earlier pathological changes of myocyte hypertrophy and ischemia and can be detected with T1 mapping [45].

Similar to LGE, T1 mapping also predicts mortality after AVR [28]. Interstitial fibrosis, as identified by T1 mapping, appears reversible and thus has the potential to detect reversible subclinical LV dysfunction [46]. In contrast, LGE identifies replacement fibrosis, which remains unchanged even after AVR [28]. Currently, LGE and T1 mapping are not commonly used for clinical decision-making in patients with AS but given their prognostic ability, they remain the focus of ongoing research.

Reduction in mortality

The other major hypothesis underlying clinical trials of valve intervention before symptom onset in adults with severe asymptomatic AS is that early AVR will improve long-term survival. Asymptomatic patients with severe AS generally have a low risk of sudden cardiac death (< 1% per year) [47–52]. In data from one contemporary registry that included 861 asymptomatic patients with severe AS treated conservatively, cardiovascular death–free survival rate was 96% at 2 years, 87% at 4 years, and 71% at 8 years with nearly all patients undergoing AVR during the follow-up period [26]. There were 64 deaths during

medical management, 50% were due to a cardiovascular cause but only 4 were classified as sudden death [26].

Several recent retrospective studies have shown a lower all-cause mortality with a strategy of early AVR in adults with severe asymptomatic AS compared with patients who did not undergo AVR [4, 9–13] (Table 2). Additionally, early AVR was associated with fewer heart failure hospitalizations in these studies. However, these observational data are limited by potential differences between those who did or did not undergo AVR and uncertainty about whether AVR was performed promptly once symptoms supervened. Additionally, observational studies can only show an association, not a cause-effect relationship.

The Randomized Comparison of Early Surgery versus Conventional Treatment in Very Severe Aortic Stenosis (RECOVERY) trial is the first randomized trial data for early treatment of asymptomatic patients with very severe AS, defined in this study as an aortic valve area 0.75 cm^2 or less with either an aortic velocity of 4.5 m/s or greater or a mean gradient of 50 mmHg or greater [53•]. The primary endpoint of operative mortality or death from cardiovascular causes was 1% at both 4 and 8 years in the early-surgery group, compared with 6% at 4 years and 26% at 8 years in the conservative-care group ($P = 0.003$). The cumulative incidence of sudden death in the conservative care group was higher than expected—4% at 4 years and 14% at 8 years—with no sudden deaths in the surgical group. These data are very encouraging but may not be directly applicable to most patients with AS seen in our practices. The subjects in this randomized trial, were young (mean age 63.4 years), had a high prevalence of bicuspid aortic valves (54%), had very severe AS (mean V_{max} 5.04 ± 0.44 m/s and mean AVA 0.64 ± 0.09 cm^2), low surgical risk scores (EuroSCORE II 0.9%), and 50% received a mechanical AVR. On the other hand, the reduction in the risk of sudden death in this study should give us pause and certainly supports the current recommendations for AVR in asymptomatic adults with very severe AS.

Treatment

Approach to management of asymptomatic patients with severe AS

When evaluating a patient with asymptomatic severe AS, careful imaging and clinical evaluation are of utmost importance (Table 1). Transthoracic echocardiography at time of diagnosis and routinely thereafter is necessary to determine accurate valve hemodynamics and LV function. Clinical history to determine the presence of even the mildest symptoms is also equally important as symptom onset triggers referral for AVR. These symptoms may present as a slight decrease in exercise tolerance as opposed to the more dramatic symptoms of syncope. Generally, patients are seen every 6 months to 1 year to evaluate echocardiographic data, clinical history, and physical examination. Patient education centered around "red flag" symptom awareness, such as angina, exertional syncope, and dyspnea or simply a gradual reduction in exercise tolerance, takes place at each clinic visit. If the history is ambiguous, an exercise tolerance test may be considered to confirm the absence of symptoms. Additionally, evaluating novel markers such as BNP or GLS may be helpful to determine the presence of subclinical LV dysfunction. Clinicians also need to be alert to the indications for AVR in asymptomatic patients with severe AS to ensure optimal timing of intervention [6, 7]. Even though routine AVR is not

Table 2. Studies of early aortic valve replacement for asymptomatic severe aortic stenosis

Study, year	Aim	Study type/size (*n*)	Inclusion	Exclusion	Intervention	Primary endpoints	Results
Taniguchi et al. (2015) [9]	Compare long-term outcomes of initial AVR vs. conservative management for asymptomatic severe aortic stenosis	Retrospective, multicenter/1808	Asymptomatic AVA ≤ 1 cm^2, mean $\Delta P \geq$ 40 mmHg, and/or $V_{max} \geq$ 4 m/s	Hx aortic valve intervention	291 initial AVR, 1517 conservative	All-cause mortality and HF hospitalization	• In propensity matched cohort, all-cause death was lower in the initial AVR group (15.4% vs. 26.4% p0.009) • In propensity matched cohort, HF hospitalizations were lower in the initial AVR group (3.8% vs. 19.9% $p < 0.001$)
Miyake et al. (2018) [10]	Evaluate post-operative mortality after AVR comparing initial AVR vs. eventual AVR after conservative management for asymptomatic severe AS	Retrospective, multicenter/1808	Asymptomatic AVA ≤ 1 cm^2, mean $\Delta P \geq$ 40 mmHg, and/or $V_{max} \geq$ 4 m/s	Hx aortic valve intervention	286 initial AVR, 377 AVR after watchful waiting	All-cause death, cardiovascular death, HF hospitalization	• Patients with $V_{max} \geq 4.5$ m/s in watchful waiting group had higher cumulative incidence of HF hospitalization at 5 years (56.1% vs. 18.8%, $p = 0.005$) • Overall survival and CV death-free survival was similar at 5 years between initial AVR and watchful waiting group (86% vs. 84.1%, $P = 0.34$ and 91.3% vs. 91.1, $p = 0.61$) • In subgroup $V_{max} \geq 4.5$ m/s, initial AVR group had better 5 year overall and cardiovascular death-free survival (88.4% vs. 70.6%, $p = 0.003$ and 91.9% vs. 81.7%, $p = 0.023$)
Campo et al. (2019) [11]	Determine outcomes for patients with severe AS, stratified by treatment recommendations	Retrospective/265	Asymptomatic AVA ≤ 1 cm^2, mean $\Delta P \geq$ 40 mmHg, and/or $V_{max} \geq$ 4 m/s	Inoperable, no known clinical recommendation	104 AVR, 161 watchful waiting	All-cause mortality	• At 2 and 3 years, all-cause mortality was higher in watchful waiting group (respectively 16.1% vs. 7.5% $p = 0.04$; 21.1% vs. 9% $p = 0.01$). • For both groups, undergoing AVR was associated with higher survival (AVR: HR 0.17 95% CI 0.03–0.91; $p = 0.08$; watchful waiting HR 0.39 95% CI 0.16–0.97; $p = 0.044$)
Kim et al. (2019) [12]	Evaluate impact of AVR on long-term survival in patients with asymptomatic severe AS taking into account surgical timing using time-dependent Cox analyses.	Retrospective/468	Asymptomatic AVA ≤ 1 cm^2, mean $\Delta P \geq$ 40 mmHg, and/or $V_{max} \geq$ 4 m/s	Prior aortic valve intervention, infectious etiology of aortic disease, concomitant mitral valve or tricuspid valve disease requiring surgery, genetic aortopathy, LVEF < 50%	221 AVR, 247 medical management	All-cause death, cardiac death	• AVR independently associated with decreased all-cause mortality (HR 0.62 95% CI 0.4–0.97, $p = 0.036$) • AVR independently associated with decreased incidence of cardiac death (HR 0.59, 95% CI 0.35–0.995, $p = 0.048$)
Kang et al., RECOVERY trial, (2020) [53•]	Evaluate outcomes of early SAVR in patients with asymptomatic very severe AS compared with conservative care	Multicenter, randomized, parallel-group, open label trial/145	Asymptomatic AVA ≤ 0.75 cm^2, mean $\Delta P \geq$ 50 mmHg, and/or $V_{max} \geq$ 4.5 m/s	Symptomatic aortic stenosis, LVEF < 50%, significant AR or MR, history of cardiac surgery, positive exercise test, non-surgical candidates	73 early surgery, 72 conservative management	Composite of operative mortality or death from cardiovascular causes.	• Operative mortality or death from cardiovascular cause favored early surgery (1% vs. 15%, HR 0.09, 95% CI 0.01–0.67, $P = 0.003$) • Secondary endpoint of death from any cause was also lower in early surgery group (7% vs. 21% HR 0.33, 95% CI 0.12–0.9) • Conservative care group had cumulative incidence of sudden death at 4% at 4 years and 14% at 8 years

Table 2. (Continued)

Study, year	Aim	Study type/size (*n*)	Inclusion	Exclusion	Intervention	Primary endpoints	Results
Kushiyama et al. (2020) [4]	Evaluate effect of AVR vs. conservative management on long-term outcomes stratified by age among patients with asymptomatic severe AS.	Retrospective, multicenter/1808	Asymptomatic AVA ≤ 1 cm^2, mean $\Delta P \geq$ 40 mmHg, and/or $V_{max} \geq$ 4 m/s	Symptomatic patients	1166 ≥ 75 years old, 642 < 75 years old	All-cause death and HF hospitalization	• All-cause death is lower in the AVR group at 5 years for patients ≥75 years (HR 0.35, 95% CI 0.2–0.61, $P = 0.0003$) but not for patients < 75 years (HR 0.69, 95% CI 0 .41–1.16, $P = 0.16$) with significant interaction ($p = 0.016$) • HF hospitalizations were lower in patients undergoing AVR regardless of age stratification: for patients ≥ 75 years (HR 0.13, 95% CI 0.05–0.34, $P < 0.0001$) for < 75 years (HR 0.37, 95% CI 0.14–0.99, $P = 0.047$)
Lee et al. (2020) [13]	Evaluate survival with early AVR vs. conventional treatment among patients with asymptomatic very severe AS over 20 year follow-up	Multicenter, prospective, propensity analysis/256	Asymptomatic AVA ≤ 0.75 cm^2, mean $\Delta P \geq$ 50 mmHg, and/or $V_{max} \geq$ 4.5 m/s	Symptomatic patients, LVEF < 50%	119 early surgery, 137 conventional treatment; 93 propensity score-matched pairs	Cardiac mortality	• 7 cardiac deaths in early surgery cohort vs. 41 in conventional treatment group • In propensity score-matched cohort, estimated actuarial cardiac mortality rates were 2.7 ± 1.9% vs. 31.2 ± 5.5% at 12 years, $p < 0.001$, favoring early surgery

AR aortic regurgitation, *AS* aortic stenosis, *AVA* aortic valve area, *AVR* aortic valve replacement, *CI* confidence interval, *CV* cardiovascular, *HF* heart failure, *HR* hazard ratio, *LVEF* left ventricular ejection fraction, *MR* mitral regurgitation, *SAVR* surgical aortic valve replacement, V_{max} peak velocity, ΔP pressure gradient

recommended for most asymptomatic patients with severe AS, clinical decision-making in an individual patient also includes other clinical and nonclinical factors. For example, patients who need treatment for other conditions, such as cancer, may benefit from AVR to improve hemodynamics during chemotherapy. Similarly, AVR might be considered before symptom onset in a young woman considering pregnancy. Another example is the patient who lives in a remote location with likely long delays in access to clinical care when symptoms occur and thus may benefit from consideration of earlier AVR. AS is a progressive disease; once severe AS is present, hemodynamic progression and symptom onset are inevitable. Many factors enter the decision to consider AVR earlier in the disease course than recommended in guidelines. We recommend both active patient involvement in decision-making and referral to a Comprehensive Valve Center when this option is being considered [54].

Risks and considerations of valve replacement

When considering valve replacement, the risk of intervention must be balanced against the benefit. SAVR and TAVI both carry periprocedural risk. In a population with low surgical risk, SAVR has low periprocedural mortality risk (~ 1%), ~ 1–3% stroke risk, and 21–40% risk of atrial fibrillation [53, 55, 56]. Life-threatening or disabling bleeding risk is as high as 12% [56]. Conversely, TAVI has a periprocedural mortality ~ 0.4–0.8%, 0.6–3% stroke risk, ~ 2% risk of life-threatening or disabling bleed, and carries a risk for permanent pacemaker placement (6–17% depending on the type of valve deployed) [55, 56]. These data are predominantly from studies on symptomatic patients and thus may not reflect the risks for an asymptomatic patient population. With higher risk patients, the risks of intervention increase with both SAVR and TAVI. In asymptomatic populations, since the patient is not pursuing intervention for symptomatic relief, the onus of determining true benefit from early intervention falls heavily on the clinician.

Choice of valve type and valve durability is also important to evaluate when considering AVR. The main risks to balance include the risk of anticoagulation versus risk of valve degeneration when considering mechanical or bioprosthetic valve replacement. For patients under 60 years of age, mechanical aortic valve replacement is generally recommended over bioprosthetic valves [6–8]. Mechanical prostheses have lower rates of valve degeneration, lower rates of reoperation, and better rates of survival in patients < 60 years [57–64]. The risk of bioprosthetic valve degeneration is higher in patients who are implanted at a younger age [65]. However, mechanical prostheses carry the lifelong risk of anticoagulation and thus bleeding risk and contraindications to anticoagulation should be evaluated. In elderly patients, bioprosthetic SAVR or TAVI may be considered since valve degeneration requiring reintervention may not occur in the patient's lifetime. Overall, national trends show an increase in bioprosthetic valve use, even in younger populations [66, 67]. Therefore, a careful discussion including risks, benefits, and patient preference is required.

Aortic valve replacement timing: ongoing trials

There are currently at least six trials underway to determine the benefit of early valve replacement for patients with asymptomatic severe AS [68–73] (Table 3). The EARLY TAVR trial will compare TAVR versus clinical

Table 3. Ongoing trials with early aortic valve replacement for asymptomatic severe aortic stenosis

Trial title	Locations	Start/expected completion	Highlighted inclusion criteria	Comparator interventions	Primary outcomes
The Early Valve Replacement in Severe Asymptomatic Aortic Stenosis Study (EASY-AS) [68]	United Kingdom	March 4, 2020/ October 1, 2029	• Asymptomatic AVA ≤ 1 cm^2, mean $\Delta P \geq$ 40 mmHg, and/or $V_{max} \geq 4$ m/s or AVAi ≤ 0.6 cm^2/m^2 • Acceptable intervention risk. • Suitable for AVR or ongoing surveillance	Early intervention (TAVR or SAVR) vs. expectant management	Combined CV death and HF hospitalization
Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis (AVATAR) [69]	Belgium, Croatia, Czechia, France, Ireland, Italy, Lithuania, Poland, Serbia	June 2015/September 2021	• Asymptomatic AVA ≤ 1 cm^2, mean $\Delta P \geq$ 40 mmHg, and/or $V_{max} \geq 4$ m/s or AVAi ≤0.6 cm^2/m^2 • STS <8%	Early intervention with SAVR vs. watchful waiting	• All-cause death • MACE (Acute MI, stroke, unplanned HF hospitalization needing IV treatment)
Evaluation of Transcatheter Aortic Valve Replacement Compared with Surveillance for Patients with Asymptomatic Severe Aortic Stenosis (EARLY TAVR) [70]	USA, Canada	July 12, 2017/December 2021	Asymptomatic severe AS	Early intervention with TAVR (Edwards SAPIEN 3/SAPIEN 3 Ultra THV) vs. clinical surveillance	Freedom from non-hierarchical composite endpoint of all-cause death, all stroke, unplanned CV hospitalization
Danish National Randomized Study on Early Aortic Valve Replacement in Patients with Asymptomatic Severe Aortic Stenosis (DANAVR) [72]	Denmark	September 1, 2019/September 1, 2029	• Asymptomatic severe AS (AVA ≤ 1 cm^2 and $V_{max} \geq 3.5$ m/s) • Candidate for TAVR or SAVR • Signs of increased LV filling pressures or LV dysfunction: • LA volume index > 34 ml/m^2 OR • E/e' avg. > 13 OR	Early intervention (TAVR or SAVR) vs. watchful waiting	All-cause mortality

Table 3. (Continued)

Trial title	Locations	Start/expected completion	Highlighted inclusion criteria	Comparator interventions	Primary outcomes
			• NT-proBNP > 3X upper limit OR • GLS > – 15.5%		
Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients with Severe AS (EVoLVeD) [71]	United Kingdom	July 21, 2017/October 1, 2024	• Severe asymptomatic AS (V_{max} ≥ 4 m/s or AVAi <0.6cm^2/m^2 with V_{max} ≥ 3.5 m/s) • Cardiac MRI evaluating mid-wall fibrosis prior to randomization	Early interventions (TAVR or SAVR) vs. routine care	Composite all-cause mortality or un-planned AS-related hospitalization
Early Surgery for Patients with Asymptomatic Aortic Stenosis (ESTIMATE) [73]	France	January 2016/November 2019	• Asymptomatic mean ΔP ≥ 40 mmHg, and/or V_{max} ≥ 4 m/s • Negative ETT • Low operative risk (EuroSCORE II ≤ 5%) • No class I indications for surgery • Age between 18 and 80 years	Early SAVR vs. delayed SAVR according to guidelines	• Combination of overall mortality and cardiac mortality • Any adverse cardiac event requiring hospitalization

AS aortic stenosis, *AVA* aortic valve area, *AVAi* aortic valve area indexed to body surface area, *AVR* aortic valve replacement, *CV* cardiovascular, *ETT* exercise tolerance test, *GLS* global longitudinal strain, *LA* left atrium, *MACE* major adverse cardiac event, *SAVR* surgical aortic valve replacement, *STS* society of thoracic surgery risk score, *TAVR* transcatheter aortic valve replacement, V_{max} peak velocity, ΔP pressure gradient

surveillance, whereas AVATAR and ESTIMATE will evaluate SAVR compared with watchful waiting [69, 70, 73]. The remaining three trials (DANAVR, EVoLVeD, and EASY-AS) will compare both SAVR and TAVR versus watchful waiting [68, 71, 72]. Notably, the DANAVR trial will aim to recruit patients that have signs of elevated filling pressure or subclinical LV dysfunction including impaired GLS. This may shed light on whether GLS is an appropriate biomarker to use when considering early intervention. Similarly, the EVoLVeD trial will randomize patients after an initial CMR to assess the presence of mid wall fibrosis, and thus will clarify the prognostic value of CMR when determining appropriate timing of AVR.

Conclusions

Asymptomatic patients with severe AS require routine close follow-up to determine onset of signs or symptoms requiring valve replacement. If AVR is required, shared decision-making is critical for determining the choice of valve and implantation approach. There remains ongoing debate of whether early AVR in asymptomatic severe AS is appropriate, with ongoing trials dedicated to this question.

Compliance with Ethical Standards

Conflict of Interest
Jasleen K Tiwana and Catherine M Otto declare that they have no conflict of interest.

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.

Ethical Approval
All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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