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BCS Editorial

Asymptomatic severe aortic stenosis: what do we know and where we are going?

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Take Home Messages

- 1/3 of patients with severe aortic stenosis are asymptomatic
- Timing of aortic valve replacement is critical to balance irreversible myocardial damage and sudden cardiac death against short and long-term intervention complications
- This review highlights multiple features that should alert the clinician of a patient at high risk of progression or poor long-term prognosis
- Numerous ongoing studies are aimed at making a paradigm shift in the management of this challenging cohort

Introduction

Valvular heart disease (VHD) is increasing in incidence (1) and it is expected that the number of patients affected is due to double by 2046. Aortic stenosis (AS) is the most common valvular lesion requiring intervention (2) in the United Kingdom (UK) and Europe, even in the pre-transcatheter aortic valve replacement (TAVR) era. In the UK from 2018-2019 there were >10,000 TAVR or isolated surgical aortic valve replacements (SAVR), of which TAVR has now surpassed SAVR (3).

AS is often caused by progressive fibro-calcific thickening and remodelling of the aortic valve (AV) leaflets that leads to restriction and obstruction (4). This subsequently induces increased afterload on the left ventricle (LV) and LV hypertrophy. This initially adaptive response eventually decompensates resulting in heart failure and death (**figure 1**).

The prognosis of symptomatic severe AS is dire, with a 1-year mortality of ~50% (5). At present there are no medications that ameliorate the disease progress, therefore timely valve replacement is essential for long term survival.

With regards to the management of asymptomatic AS, there is debate around the timing of AVR. Intervention should ideally take place when the risks of the disease process (irreversible myocardial damage and sudden cardiac death (SCD)) outweigh the periprocedural and long-term complications from intervention. This editorial will discuss the high-risk features of asymptomatic severe AS and future research aimed at optimising outcomes in this group.

About the author

Dr Jonathan Bennett is a Cardiology trainee in South London, and is currently undertaking his PhD at University College London/Bart's Health. He has an interest in valvular heart disease, multi-modality imaging, and preventive cardiology.

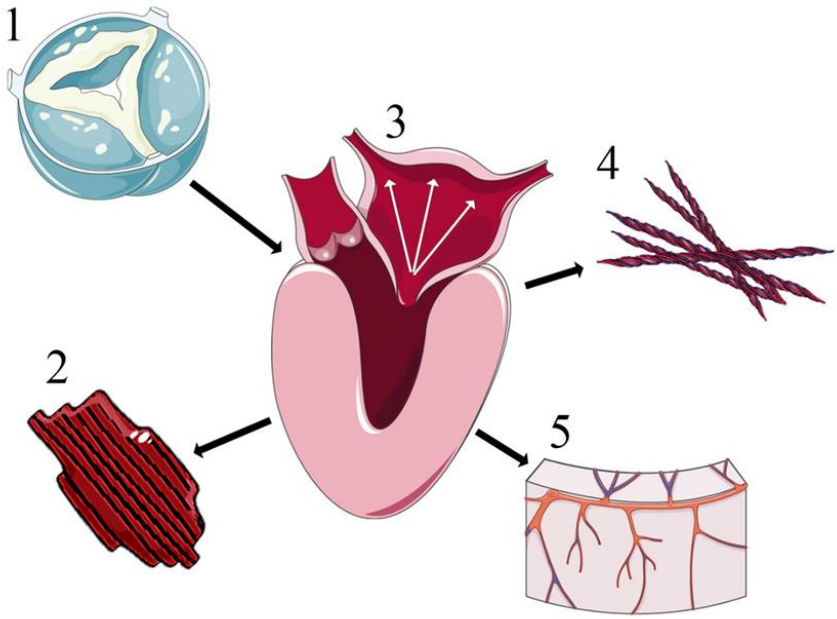

Figure 1. **Myocardial impact of AS.** 1. Fibrocalcific degeneration and progressive obstruction 2. Left ventricular hypertrophy 3. Diastolic dysfunction, raised left atrial pressure, and pulmonary hypertension 4. Focal and diffuse fibrosis 5. Microvascular dysfunction. Royalty free images from smart.servier.com

Current guidelines

The most recent iterations of major society guidelines (9,10) advise intervention in AS for those symptomatic with severe haemodynamic parameters, or left ventricular systolic dysfunction attributed to the valve. A new addition acknowledges that those asymptomatic with very severe AS (Vmax >5m/s, mean gradient >60mmHg), severe valve calcification, Vmax progressing >0.3m/s/year, elevated brain natriuretic peptide (BNP)) can be considered for intervention. This is categorised as class IIa and level B evidence in both European and North American guidelines.

This approach likely remains suboptimal as there remains significant mortality (22% at 3.5 years (11)) after intervention, the mechanisms of which are under investigation (12). Intervention may occur after irreversible cardiac damage has occurred in asymptomatic severe cases. Symptom assessment can be challenging in this population group due to the high burden of co-morbidities that confound the symptoms of AS, and physical inactivity can limit the reproduction of symptoms in activities of daily living. Here I discuss several features based on imaging, exercise testing and blood biomarkers which have been shown to indicate a high-risk subgroup of asymptomatic AS patients who may benefit from earlier intervention.

High risk features in asymptomatic severe AS

Echocardiographic haemodynamic features

Echocardiography is the cornerstone of diagnosis, surveillance, and can distinguish higher risk individuals without the requirement for additional tests. Those with very severe haemodynamic features on echocardiography in meta-analyses (6,12,13) consistently report better outcomes with early intervention vs a “watchful waiting” strategy though there is a lack of randomised data and these meta-analyses rely heavily upon observational data of wide heterogeneity.

The RECOVERY trial (16) randomised those with very severe AS based on echocardiographic parameters to either early surgery (predominantly SAVR) or watchful waiting. The early surgery group had no operative mortality and 1 cardiovascular death (median follow up >6 years). In comparison, 52 patients (74%) within the conservative group required intervention, of which 17% were urgent operations from unplanned admissions and cardiovascular mortality was significantly higher (n=11, 15%; $p<0.01$) at follow up.

The authors however noted that 1 in 4 of the conservative group did not require surgery during prolonged follow up, highlighting the heterogeneity of this group of patients.

Echocardiographic myocardial features

Myocardial deterioration in response to AS is readily detectable on echocardiography (**figure 2**) and needs attention when decision making in asymptomatic patients.

AVR improves left ventricular ejection fraction (LVEF) by >10% in the majority (65-83%) even when pre-operative LVEF is <40% (20). However subtle deterioration of systolic function is a marker of poor prognosis (21,22) and those with asymptomatic decline to LVEF <55% can be considered for AVR (9). Registry data (18) comparing LVEF at presentation with conservatively managed severe AS shows significant differences in outcomes (all-cause and cardiovascular mortality, heart failure admission, SCD) comparing LVEF 50-59% against >70% (p <0.001). This effect was not seen when comparing LVEF 60-69% against >70%. In those that underwent AVR, the impact of LVEF at presentation between groups became insignificant.

Global longitudinal strain (GLS) is more sensitive at detecting myocardial dysfunction before the overt onset of impaired LVEF(23). Impaired GLS is present in those with asymptomatic severe AS (24) when compared to age- and sex- matched controls and deteriorates significantly (p <0.001) by -1.7% per year with no detectable reduction in LVEF. GLS >-18.2% was significantly associated with development of symptoms and requirement for AVR (23).

Beyond left ventricular structure and function the myocardial impact of AS can be seen with alterations in diastology, atrial abnormalities, atrial fibrillation, pulmonary pressures, and right ventricular dysfunction (25,26). Extra-valvular and cardiac damage has been classified into defined stages by Genereux et al., which correlate with a stepwise progression in mortality and hospitalisation 1 year post AVR. Those within stage 4 have a 5.5 times all-cause mortality compared to stage 0, and at the time of intervention the majority of patients with severe AS (84%) had developed at least stage 2 damage.

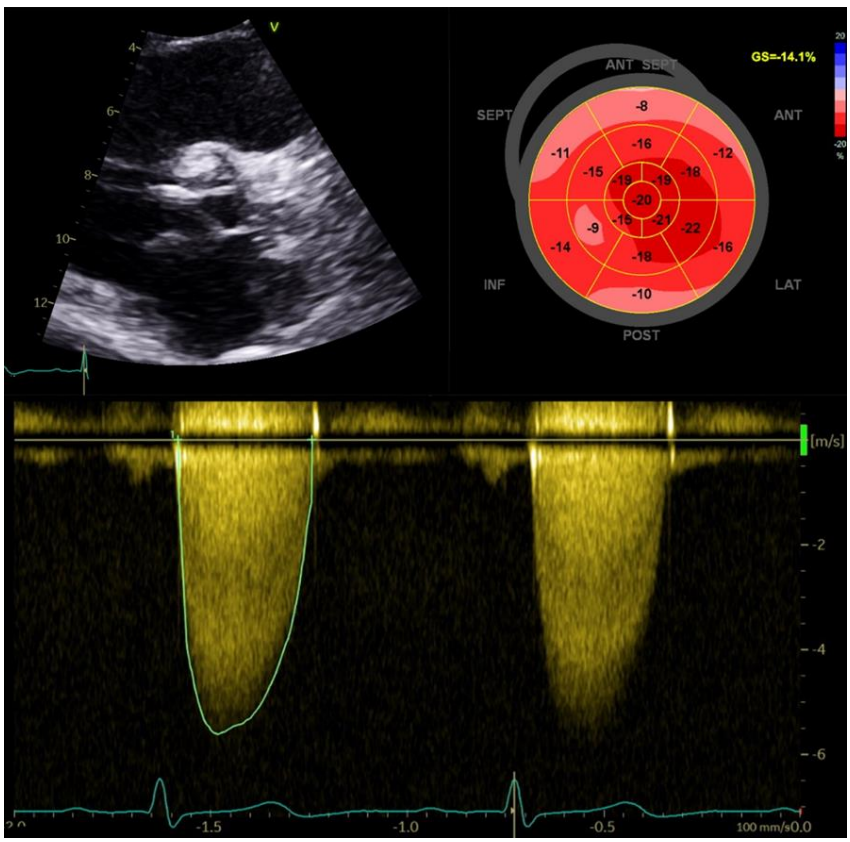

Figure 2. **High risk echocardiographic features of severe AS.** Top left: Severely calcified aortic valve Top right: Impaired global longitudinal strain at -14.1% Bottom: Aortic valve Vmax >5.5 m/s

Machine learning using echocardiography

Machine learning using echocardiography alone can identify high- and low-risk phenotypes that may benefit from earlier valve intervention (29). A machine learning algorithm trained on an echo cohort (n=1052) correctly identified 99% of those with classical concordant severe AS as high-risk, and 64% of inconclusive patients with discordant findings into the high-risk group. When combined with cardiac magnetic resonance imaging (CMR) (n=160) high-risk phenotypes were twice as likely to have replacement fibrosis ($p<0.01$), high LV mass, and diffuse myocardial fibrosis. These high risk patients also had significantly more ($p<0.01$) aortic valve calcification (AVC) on cardiac computed tomography, were more likely to undergo AVR, and had higher mortality risk compared to the low-severity phenotype. Compared to the current standard of care, use of the algorithm resulted in improved prognostication in patients with severe AS.

Exercise testing

Exercise testing has long been used to unmask symptoms; inducible symptoms or a sustained drop of >20mmHg is considered an indication for intervention. However, the discriminatory ability of exercise testing is not particularly impressive; 21% severe AS patients with normal tests suffer adverse cardiac events, and 66% with abnormal tests go on to develop adverse events. In addition to this, 15% of patients cannot undertake exercise testing(32), nor are the potential symptoms it induces specific to AS, especially with concurrent coronary disease. Considering its limited discrimination, the results of exercise testing should be interpreted alongside results from other investigations in order to appropriately identify high-risk AS patients.

Cardiac MRI (CMR)

CMR is not included in either major society guideline, but is increasingly recognised as the modality of choice for evaluation of the myocardial impact of AS (34). CMR yields accurate and reproducible structural, functional, haemodynamic assessment of AS with invaluable addition of tissue characterisation.

CMR planimetry of the aortic valve (**figure 3**) corroborates (within 0.01cm2) with transoesophageal echocardiography, but tends to overestimate (by 0.17cm2) compared to TTE. Peak aortic velocity, via phase contrast imaging, correlates well with TTE (35,36) but with a tendency to under-estimate. Newer 4D-flow measurement sequences can detect higher peak and mean gradients, but long acquisition time and requiring additional software limits routine use.

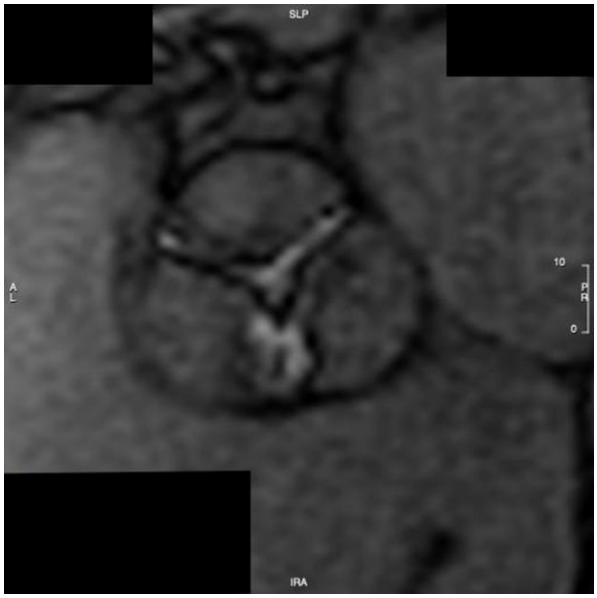

Figure 3. **CMR planimetry of aortic valve.** Cardiac MRI planimetry of a severely stenotic aortic valve. Multiple slices are taken through the valve to determine the minimal orifice area.

CMR can uniquely identify and quantify myocardial fibrosis, a prime driver of myocardial decompensation in AS (37). There are two types of fibrosis observed in AS which can be visualised and quantified on CMR. Diffuse fibrosis, which represents cellular hypertrophy and extracellular matrix expansion (33), can regress post AVR.

Focal fibrosis or scar is not reversible and is associated with 3x higher all-cause and cardiovascular mortality in patients with severe AS (38,39). It has been demonstrated in 36% of asymptomatic moderate-severe AS patients (40) at baseline, and 57% at 1-year follow up, despite patients remaining asymptomatic. This shows that irreversible myocardial damage, which impacts on patient prognosis, frequently occurs before the onset of symptoms.

Cardiac CT

Whereas CMR is the gold-standard to assess the myocardial response to AS; CCT can be utilised for AVC, valve and aortic morphology, valve area, and intervention planning. AVC has long been a qualitative measure of AS severity (45) and can be measured via CCT using the Agaston method (46). AVC reliably correlates with disease severity as measured by echocardiography, and can reliably identify severe AS using sex-specific cut-offs with a C-statistic of 0.89 (46). When utilised in asymptomatic AS cohorts (47,48) raised AVC is an independent predictor of adverse outcome. AVC has already been integrated into the ESC guidelines where there is discordance between flow reserve and left ventricular systolic function, but perhaps can be justifiably used in asymptomatic severe AS patients to provide additional risk stratification.

Natriuretic peptides

Widespread and easily available, natriuretic peptide levels (BNP) can help identify high-risk asymptomatic AS patients. Elevated (age and sex adjusted) BNP in asymptomatic patients have a shorter symptom free survival during follow up (50). Elevated BNP has been associated with a statistically significant increase in midterm (6 month to 4 year) mortality (HR1.88, 95% CI, 1.54-2.28; p <0.01) in AS patients before TAVI (51). Periprocedural mortality however is unaffected.

Future directions

There is significant evidence that the current guideline management of asymptomatic severe AS may be suboptimal for optimising long-term outcomes. There is a paucity of randomised trial data to base current guidelines in this challenging group. At present there are numerous large-scale trials designed for this population which are outlined in **Table 1**.

Summary

Patients presenting with asymptomatic severe AS are common, challenging, and heterogenous. The current approach of watchful waiting is supported by recent major society guidelines and there is a lack of rigorous prospective trial data in this group to warrant deviation.

There are however multiple high-risk features that the treating clinician should be wary of that can signal a patient at increased risk of symptom development or persistent long-term risk despite intervention. This includes features readily available on routine echocardiography but also additional imaging modalities and biomarkers. Numerous randomised trials ongoing, aimed at shining light on this complex issue, may cause a paradigm shift in how this patient population is managed.

Table 1: Ongoing trials in asymptomatic severe AS

Trial:	**Design:**	**Target recruitment:**	**Inclusion:**	**Definition asymptomatic:**	**Primary end-point:**	**Expected finish:**
EARLY TAVR(52)	Prospective, randomised control trial, multicentre:	900	Aged >65 AVA <1cm^2 or AVAi <0.6cm^2/m^2 and AV-Vmax >4m/s or MG >40mmhg LVEF >50% STS <10	Negative treadmill test or clinical history if unable to undertake treadmill	All-cause mortality and unplanned cardiovascular hospitalisation	2032
EVOLVED (37)	Prospective, randomised control trial, multicentre	1000	AV-Vmax >4m/s or AVAi <0.6cm^2/m^2 and AV-Vmax >3.5m/s Midwall fibrosis on CMR LVEF >50% on CMR	May include exercise testing depending on attending physicians' usual practice	Composite all-cause mortality or unplanned aortic stenosis related hospitalisation	2024
AVATAR (53)	Prospective, randomised control trial. multicentre	157	AV-Vmax >4m/s or MG >40mmhg and AVA <1cm^2 or AVAi <0.6cm^2/m^2 STS <8% LVEF >50%	Negative exercise test with at least 80% maximal heart rate achieved	All-cause mortality, major adverse cardiac event	2021
DANAVR (54)	Prospective, randomised control trial. multicentre	1700	AVA <1cm^2 and AV-Vmax >3.5m/s and LAVi >34ml/m^2 or E/e' avg >13 or 3x NT-proBNP (age and sex adjusted) or GLS >-15.5	Considered to be asymptomatic by a consultant in cardiology	All-cause mortality	2029
EASY-AS (55)	Prospective, randomised control trial. multicentre	2844	AV-Vmax >4m/s or MG >40mmHg and AVA <1cm^2 or AVAi <0.6cm^2/m^2 LVEF >50%	Recruiting clinician discretion	Cardiovascular death and hospitalisation for heart failure	2029

AVA, aortic valve area. AVAi, indexed aortic valve area. AV-Vmax, aortic valve maximal velocity. MG, mean gradient. LVEF, left ventricular ejection fraction. STS, society of thoracic score. LAVi, left atrial volume index. NT-proBNP, brain naturetic peptide. GLS, global longitudinal strain.

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