Controversies in cardiovascular medicine

Risk stratification in asymptomatic severe aortic stenosis: a critical appraisal

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Aortic stenosis is one of the most common forms of acquired valvular heart disease. The development of symptoms, namely syncope, angina, or heart failure, in patients with severe aortic stenosis predicts a high likelihood of mortality. Aortic valve replacement is the current standard of care. In truly asymptomatic patients, the risk of sudden death is perceived to be low; therefore many advocate conservative management of these patients until symptoms develop. Emerging data suggest that certain markers may identify subsets of asymptomatic patients who are at a high risk of cardiac events. This review critically appraises the growing plethora of adverse prognostic markers that have been identified and evaluates how these parameters may influence clinical practice and potentially identify patients in whom early surgical intervention is warranted.

Keywords Aortic valve • Stenosis • Echocardiography

Introduction

Calcific aortic stenosis (AS) is one of the most common forms of valvular heart disease.¹ For >40 years it has been recognized that the presence of syncope, angina, or heart failure in patients with severe AS predicts a grave prognosis.² Aortic valve replacement (AVR) is the only therapy to significantly improve both survival and symptoms.³ The management of the asymptomatic patient is controversial. As the risk of sudden death in asymptomatic patients is relatively low,⁴ many advocate conservative management of these patients as the immediate risk of AVR may be higher. However, patients with asymptomatic severe AS are a heterogeneous group with some being at a much higher risk of sudden death than others. Over the past decades, several investigators have tried to establish which factors may help identify those patients at higher risk of sudden death. The vast majority of studies have used parameters identified by non-invasive imaging modalities. This review considers how these parameters may influence clinical practice and potentially identify patients that warrant early surgical intervention.

Risk of sudden death in asymptomatic patients

Pelikka et al.⁵ identified 622 patients with severe asymptomatic AS (defined as a peak velocity of ≥4 m/s). After a median follow-up of 5 years, 11 (4.1%) out of 270 patients who did not undergo AVR experienced sudden death without preceding symptoms (~1% per year). Other prospective studies reported an overall annual rate of sudden death in patients with asymptomatic severe AS of approximately up to 3% (Table 1).⁵–¹³ There is one study that provides a different insight. In a retrospective analysis of 338 initially asymptomatic AS patients, over a mean of 3.5 years, there were 157 deaths and 99 patients underwent AVR.¹³ Therefore, the overall rate of death was ~13% per year. This is a higher mortality rate than quoted by other studies. However, the retrospective design of this study does not allow us to know how many of the patients developed symptoms prior to death but did not undergo AVR (e.g. due to the risk of surgery, patient choice, etc.) which would confound the study results.
Clinical risk factors

Clinical risk factors are poor predictors of sudden death in patients with severe asymptomatic AS. Several observational cohort studies have failed to consistently identify independent clinical risk factors.\(^7\) Major predictors seem to be echocardiographic, exercise testing, and biochemical markers.

Evaluation of the aortic valve

Valve morphology: calcification

Echocardiography

The degree of aortic valve calcification (AVC) is a strong predictor of cardiac events. Rosenhek et al.\(^7\) followed 106 patients (mean age 57 years) with severe asymptomatic AS for 27 months. Mild calcification was defined as small, isolated spots, while heavily calcified valves were defined as extensive thickening and calcification of all cusps (Figure 1). Four-year event-free survival (death or AVR) was 75 ± 9% in patients with no/minimal calcification compared with 20 ± 5% in patients with moderate or severe valve calcification (Figure 2). From a total of 67 events, only 6 were cardiac deaths and only 1 death occurred without preceding symptoms. Therefore, although patients with moderate/heavy calcification are a high risk group for the development of symptoms and subsequent need for AVR, the risk of sudden death without preceding symptoms is modest. Furthermore, the value of this marker to risk stratify the large population of elderly patients with predominately calcific AS will be limited as the majority of these patients will have at least moderate calcification.

Cardiac computed tomography

An AVC score, assessed by electron beam computed tomography, has been shown to correlate well with both echocardiography derived aortic valve area and peak velocity. Messika-Zeitoun et al.\(^14\) demonstrated, in a study of 100 patients with varying degrees of AS (mean aortic valve area 1.8 cm\(^2\) ± 0.9), that an AVC score ≥ 1100 Agaston Units provided 93% sensitivity and 82% specificity for diagnosis of severe AS (AVA ≤ 1 cm\(^2\)). Over a mean follow-up of 2 years, an AVC score was an independent predictor of event-free survival (death, AVR, or symptoms). More recently, an AVC score of ≥ 1651 using multi-slice computed tomography provided 82% sensitivity for diagnosis of severe AS. However, long-term data specific to patients with asymptomatic severe AS are lacking.\(^15\)

Jet velocity

The effect of various Doppler parameters on survival has been studied. The most validated is maximal jet velocity across the aortic valve. Otto et al.\(^12\) prospectively followed 123 patients with a mean aortic jet velocity at a baseline of 3.6 m/s. The study demonstrated an increasing maximal jet velocity correlated with worsening likelihood of remaining alive without AVR (Figure 3). In those with a peak velocity of > 4 m/s, only 21% were alive without AVR compared with 66% with a velocity of 3–4 m/s. However, the number of events in this study was low. There were only four cardiac deaths, all of which were admitted with symptoms of heart failure prior to death. Secondly, the need for AVR was dictated by individual clinicians rather than by strict criteria.

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Number of patients</th>
<th>Mean follow-up ± SD (months)</th>
<th>Criteria for severe aortic stenosis</th>
<th>Events</th>
<th>Cardiac death</th>
<th>Hospitalization</th>
<th>Aortic valve replacement</th>
<th>Mean aortic valve area (cm(^2))</th>
<th>Mean peak aortic valve velocity (m/s)</th>
<th>Sudden death rate per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenhek et al.(^7)</td>
<td>Prospective</td>
<td>128</td>
<td>22 ± 18</td>
<td>Peak AV Vel ≥ 4 m/s</td>
<td>59</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1.8</td>
<td>3.6</td>
<td>1/1000</td>
</tr>
<tr>
<td>Amato et al.(^11)</td>
<td>Prospective</td>
<td>66</td>
<td>23.6 ± 12.5</td>
<td>AVA ≤ 1 cm(^2)</td>
<td>12</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1.2</td>
<td>3.6</td>
<td>1/1000</td>
</tr>
<tr>
<td>Lancellotti et al.(^9)</td>
<td>Retrospective</td>
<td>69</td>
<td>15 ± 7</td>
<td>Peak AV Vel ≥ 4 m/s</td>
<td>42</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1.2</td>
<td>3.6</td>
<td>1/1000</td>
</tr>
<tr>
<td>Pae et al.(^12)</td>
<td>Prospective</td>
<td>622</td>
<td>48.4 ± 48</td>
<td>AVA ≤ 0.8 cm(^2)</td>
<td>99</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0.8</td>
<td>3.6</td>
<td>1/1000</td>
</tr>
<tr>
<td>Lancellotti et al.(^10)</td>
<td>Prospective</td>
<td>318</td>
<td>42</td>
<td>AVA ≤ 0.6 cm(^2)</td>
<td>57</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0.6</td>
<td>3.6</td>
<td>1/1000</td>
</tr>
<tr>
<td>Cioffi et al.(^6)</td>
<td>Prospective</td>
<td>209</td>
<td>20 ± 13</td>
<td>Peak AV Vel ≥ 4 m/s</td>
<td>72</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1.0</td>
<td>3.6</td>
<td>1/1000</td>
</tr>
<tr>
<td>Roseheik et al.(^8)</td>
<td>Prospective</td>
<td>116</td>
<td>41 ± 63</td>
<td>AVA ≤ 0.6 cm(^2)</td>
<td>90</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0.6</td>
<td>3.6</td>
<td>1/1000</td>
</tr>
</tbody>
</table>

AVA, aortic valve area; AV Vel, aortic valve velocity; N/A, data not available; SD, standard deviation.

Sudden death rate per year calculated by equation: (death without preceding symptoms/number of patients)/mean follow-up (years).

\(^a\)Median and inter-quartile range quoted.
More recently, Rosenhek et al. extended this observation to patients with very severe AS. In a prospective study of 119 patients with a peak aortic valve jet velocity of >5 m/s, it was shown that patients with peak aortic velocities >5.5 m/s had a 1-year event-free survival (death or AVR) of only 44% compared with 76% for those patients with a peak velocity between 5 and 5.5 m/s. Ninety out of the 99 events were due to AVR. Only five events were cardiac deaths in patients without preceding symptoms. Although both studies clearly demonstrate that an increasing jet velocity predicts a high likelihood of the need for AVR, the risk of cardiac death is less well defined.

Both the studies from Otto et al. and Rosenhek et al. have shown the rate of change of jet velocity is an important predictor of events. The rate of change of aortic valve velocity was significantly greater in patients who had cardiac events than in those who did not in both studies. Rosenhek et al. demonstrated that patients with a moderate/heavily calcified valve and an increase in jet velocity of >0.3 m/s/year had a particularly poor prognosis. Seventy-nine per cent of these patients required valve replacement or died within 2 years. The reproducibility of serial measurements of this parameter to detect small changes in velocity has not been validated and may be unreliable. Furthermore, data in the increasingly elderly population are sparse.

The contribution of concomitant coronary artery disease (CAD) as a cause of sudden death in patients with asymptomatic severe AS remains uncertain. The prevalence of CAD varies from 25 to 50% in patients with severe AS. However, neither of these studies identified CAD as an independent risk factor for cardiac events. In both studies, there was a lack of systematic evaluation for the presence of CAD.

**Myocardial response to physiological effects of aortic stenosis**

Over time patients with severe AS develop a pressure overloaded left ventricle (LV) with subsequent LV hypertrophy, sub-endocardial fibrosis, and elevated LV mass. This leads to impaired myocardial relaxation, impaired left ventricular filling, and eventual LV systolic dysfunction. Several studies have used a variety of imaging techniques to identify the significance of these pathological processes.

**Indices of left ventricular myocardial function**

**Left ventricular mass/hypertrophy/geometry**

The prognostic significance of an inappropriately high LV mass (>110% of that expected for body size, gender, and wall stress)
was studied in 209 patients with severe, asymptomatic AS. The presence of an inappropriate LV mass heralded a 4.5 increased risk of mortality independent of other known risk factors. One may argue an early intervention strategy may be beneficial because of the deleterious effect of LV hypertrophy; however, there is no current data to support this strategy.

In a study of 70 patients with AS, LV systolic dysfunction (identified by lower longitudinal deformation) was associated with both increased LV mass and also normal LV mass but with concentric left ventricular remodelling. The prognostic value of LV remodelling in patients with asymptomatic AS remains unknown.

Left ventricular systolic function

Left ventricular ejection fraction

It is now recognized that the LV ejection fraction (LVEF) is an imperfect marker of intrinsic myocardial dysfunction and reduced LVEF bears a poor prognosis. Several investigators have demonstrated that AVR in patients with severe AS and severe impairment of the LVEF is associated with improved functional class and LVEF albeit at a higher surgical risk. However improvement in the LVEF is not universal. Connolly et al. found almost a quarter of patients at the Mayo Clinic undergoing AVR who had severe LV dysfunction did not show improvement in the LVEF postoperatively. Furthermore, Vaquette et al. demonstrated that those patients without improvements in the LVEF have a poorer prognosis. Therefore, AVR prior to the onset of LV dysfunction may be recommended; however, data in patients with purely asymptomatic AS are lacking.

Strain and strain rate

Cramariuc et al. studied 1591 patients with asymptomatic AS. One-third of asymptomatic patients with AS and preserved LVEF demonstrated reduced mid-wall shortening. Speckle tracking to measure the strain and the strain rate is a newer echocardiographic modality which is able to assess longitudinal, circumferential, and radial myocyte function. Ng et al. identified 420 patients with varying degrees of AS (including 112 patients with severe AS) with an LVEF >50%. There was a stepwise impairment in longitudinal, circumferential, and radial strain and strain rate with increasing severity of AS. These indices were significantly more impaired in patients with symptomatic moderate or severe AS compared with patients who were asymptomatic. One of limitations of this technique, which currently limits clinical use, is the high inter- and intra-observer variability of strain measurements. The absolute difference in longitudinal strain and circumferential strain between patients with moderate and severe AS was 2 and 1.8%, respectively. In comparison, the absolute intra-observer variability quoted by this study’s authors was 1.2%. Therefore, the changes in the strain were small in comparison with intra-observer variability.

Lancellotti et al. examined a cohort of 163 patients with at least moderate to severe, asymptomatic AS (aortic valve area ≤0.6 cm²). They demonstrated that impaired longitudinal myocardial deformation was an independent predictor of survival. Those patients with longitudinal strain >15.9% had significantly better outcome than patients with the strain below 15.9% (4-year survival of 63 vs. 22, P < 0.001).

These studies suggest that impaired myocyte function occurs even in mild or moderate AS and progresses in patients with severe AS in patients with preserved LVEF. It is unclear whether there is a threshold where the degree of impairment of myocyte contractility (defined by longitudinal, circumferential or radial strain) causes symptomatic decompensation or significantly increased risk of sudden death. Further prospective studies are needed to investigate the utility and prognostic value of this technique in patients with severe asymptomatic AS.

Left ventricular diastolic dysfunction

Trans-mitral inflow and tissue Doppler

The use of trans-mitral inflow Doppler to measure parameters of diastolic function (E/A ratio) has not been shown to predict either the onset of symptoms or prognosis. Tissue Doppler is used to assess longitudinal myocyte contractile function. Stewart et al.
examined the value of tissue Doppler parameters on determining symptomatic deterioration in 183 patients with moderate or severe AS (the median aortic valve area in this study was 0.81 cm²) who were initially free of symptoms. Tissue Doppler parameters including peak systolic and diastolic mitral annular velocities were measured. Of the total, 106 patients (58%) developed symptoms during the median 31-month follow-up. No association between diastolic parameters and symptomatic deterioration was found. The most powerful independent predictor of symptom onset remained peak aortic velocity.

**Left atrial volume**
The left atrial size is a parameter associated with the chronic elevation of the left ventricular filling pressure (diastolic dysfunction). Two studies have identified that either the left atrial diameter or the area is an important predictor of mortality. Lancellotti et al. identified indexed left atrial area as being a significant marker of impaired prognosis in asymptomatic patients. A left atrial area of 12.2 cm²/m² or above was found to have the best predictive value for cardiac events. The Mayo Clinic reviewed their cohort of 622 asymptomatic AS patients. They confirmed that the left atrial size (using left atrial diameter as a surrogate for the atrial size) predicts mortality in these patients.23

**Cardiac magnetic resonance imaging**
Severe aortic valve disease is characterized by the accumulation of interstitial myocardial fibrosis. Diffuse interstitial fibrosis is characterized by progressive collagen synthesis by myofibroblasts within the interstitium and is potentially reversible. In the later stages of disease, this process ultimately leads to replacement fibrosis, which is irreversible.24

Several groups have shown a correlation between the degree of myocardial interstitial fibrosis identified on cardiac magnetic resonance (CMR) with that found by histopathological examination in patients with severe AS undergoing AVR. The degree of myocardial fibrosis correlates with worsening functional New York Heart Association Class and impaired longitudinal systolic function.25 Azevedo et al. demonstrated a modest inverse correlation between the degree of myocardial fibrosis and the improvement in left ventricular function seen after AVR. Importantly the degree of myocardial fibrosis was an independent predictor of survival after AVR.

Currently, there are multiple techniques to quantify and measure myocardial fibrosis by CMR. Late gadolinium enhancement sequences demonstrate a multi-focal mid-wall pattern in aortic valve disease. The increase in gadolinium concentration in fibrotic tissue appears as a bright signal intensity and contrasts with normal myocardium. Although the qualitative assessment of fibrosis is feasible, the lack of standardized signal intensity parameters prevents absolute quantitative measurement of myocardial fibrosis. Secondly, the sensitivity for diffuse interstitial fibrosis is limited as differentiation between normal and fibrotic myocardium is problematic when the fibrosis is diffuse. The use of T1 mapping may overcome these problems as this technique enables direct myocardial signal quantification (in milliseconds) on a standardized scale. However, to date there are few data using this method. Currently there are no studies relating quantification of myocardial fibrosis to cardiac risk/sudden death in the asymptomatic patient. Further standardization of methods and research needs to be undertaken before this technique can be used to guide clinical decisions.

**The role of exercise testing**

**Dynamic exercise testing**
Determination of whether a patient has symptoms associated with severe AS is pivotal to management. It has become increasingly recognized that many, particularly elderly, patients may restrict their activities to prevent symptoms or not report symptoms. Amato et al.11 studied a cohort of 66 patients with a mean age of 49.5 years who were reported to have severe, asymptomatic AS. Exercise testing using a treadmill was reported to be positive in this study if the patient developed symptoms, complex ventricular arrhythmias, the blood pressure failed to rise by 20 mmHg, or the development of horizontal or down-sloping ST depression (1 mm or more in men, 2 mm or more in women). Twenty of the 66 patients (30.3%) developed symptoms on exercise testing. The difference in prognosis between those with a positive test and those with a negative is striking. Two-year event-free survival was only 19% in those with a positive test compared with 85% in patients with a negative test (Figure 4). Das et al.28 reported the positive predictive value of symptoms invoked during an exercise test for developing spontaneous symptoms during the next 12 months to be just 57%. However, when only patients <70 years old were included this increased to 79%. Therefore the value of exercise testing in elderly patients may be limited.11,28

**Stress echocardiography**
Lancellotti et al.9 investigated the value of Doppler echocardiography during exercise testing. Sixty-nine patients with severe asymptomatic AS underwent a symptom-limited bicycle exercise stress test. Quantitative Doppler echocardiography was performed at rest and peak exercise. In accordance with the previous study of Amato et al.,11 an abnormal exercise stress test, an aortic valve area < 0.75 cm², and a mean increase of ≥ 18 mmHg were independent predictors of poor prognosis (symptoms, AVR, or death) (Figure 5). The exercise Doppler data had incremental prognostic value over both resting echocardiographic and exercise electrocardiographic parameters. A major limitation of this study was the need for AVR was assessed by individual clinicians and not necessarily the development of symptoms. Secondly, when measuring valve gradients post-exercise, there is considerable beat to beat variation in the Doppler signals recorded. Although the study-based measurements on the average of three cycles, further data on the reproducibility of the measurements for each patient would be desirable.

Further evidence to support this early study is emerging. A recent multi-centre study prospectively assessed the value of exercise stress echocardiography in 186 asymptomatic patients with at least moderate AS.29 Approximately 50% of patients had severe...
**Figure 4** Event-free survival over 5 years in severe aortic stenosis stratified according to positive or negative results of exercise testing. Figure taken from Amato et al.¹¹

**Figure 5** Exercise stress echocardiogram. (A and B) Peak and mean gradient across aortic valve 66 and 36 mmHg, respectively. Aortic valve area 1 cm². Patient exercised for 8 min of the Bruce protocol before complaining of significant dyspnoea. (C and D) Post-exercise Doppler assessment. Peak gradient increased to 82 mmHg and mean gradient to 47 mmHg. The patient was referred for aortic valve replacement on the grounds of developing symptoms during the exercise test. There was an increase in the mean gradient across the aortic valve of 11 mmHg.
AS. A mean increase of the aortic valve gradient $\geq 20$ mmHg after exercise was associated with a 3.8-fold increase in cardiovascular events (death or AVR) independent of other risk factors and whether moderate or severe AS was present. In this study, the AVR was performed only if the patient developed symptoms. Clinicians may be reluctant to perform exercise testing in patients with severe asymptomatic AS due to a perceived risk of sudden death on exertion. However, no adverse events occurred during or immediately after stress testing in any of the studies discussed.9,11,29

**Assessment of myocardial perfusion reserve**

In a prospective study of 46 patients with severe AS,30 myocardial perfusion reserve (MPR) (quantified by CMR) was associated with aerobic capacity. Furthermore, LV remodelling was a more important determinant of MPR than stenosis severity per se. Myocardial contrast echocardiography can also assess MPR.31 Prospective studies are needed to determine whether MPR is useful to risk stratify patients with severe, asymptomatic AS.

**Biochemical risk markers**

**Brain natriuretic peptides**

Gerber et al.32 found median levels of brain natriuretic peptides (BNP) were significantly more elevated in patients with symptomatic severe AS compared with those who were asymptomatic. Furthermore, the levels of these markers increased with worsening symptom status (New York Heart Association Class). Bergler-Klein et al.33 corroborated these findings and also found patients who developed symptoms during the follow-up had higher levels of these biomarkers compared with those who remained asymptomatic. This study identified a significant prognostic value of BNP in patients with severe asymptomatic AS. Patients with BNP $< 130$ pg/mL had a significantly better symptom-free survival compared with those with BNP $> 130$ pg/mL, 66 vs. 34%, respectively. The clinical utility of BNP is yet to be defined. It may be of diagnostic value in patients who predominately have symptoms of dyspnoea, which may be attributable to other co-morbidities such as chronic obstructive lung disease or obesity. An elevated BNP in these cases may help decide whether symptoms are due to AS.

**Effect of valvular and systemic loading factors**

Up to 50% of patients with AS also have concomitant hypertension. The effect of hypertension and the increased afterload it imposes on the LV and subsequent outcomes of AS have been investigated by Hachicha et al.34 They developed the concept of valvulo-arterial impedance. It is calculated by dividing the estimated left ventricular systolic pressure (systolic arterial pressure — mean trans-valvular gradient) by the stroke volume index (SVI). This equation takes into account both the effect of systemic vascular resistance, which is related to blood pressure, and the effect of valvular stenosis.

In a retrospective analysis of 544 patients with moderate or severe AS, the investigators found that, after a median 2.1 years, follow-up survival was significantly reduced in patients with high valvulo-arterial impedance compared with patients with medium or low levels. There was a step-wise increase in risk as valvulo-arterial impedance increased. A value of 4.5 mmHg/mL/m² was associated with a 3.71-fold increased risk of mortality. Lancellotti et al.35 confirmed these finding in a prospective study of 163 patients with moderate to severe asymptomatic AS. A valvulo-arterial impedance $\geq 4.9$ mmHg/mL/m² was associated with the worst prognosis. These studies highlight the importance of blood pressure control in patients with severe AS and its impact on clinical outcomes.

**Integration of risk markers: risk score**

A range of markers have shown prognostic value in severe asymptomatic AS. For the clinician, integrating the data to balance the risk of valve replacement vs. watchful waiting is problematic. Monin et al.35 prospectively followed a cohort of 107 patients with moderate to severe AS (peak velocity $> 3$ m/s). A score based on a combination of major risk factors including jet velocity, BNP, and female sex was developed. The score was [peak velocity (m/s) $\times 2] + \left(\text{natural logarithm of B-type natriuretic peptide} \times 1.5\right) + 1.5$ (if female sex). The results of the score were divided into four quartiles. A progressive, stepwise reduction in event-free survival was demonstrated from the first quartile (20-month survival 80%) to the fourth quartile (20-month survival 7%). The study suggests that the use of the risk score may help identify patients with a higher risk and thereby warrant early surgery. However, one of the major limitations of the data is the inclusion of patients with moderate AS. A large proportion of patients with a good prognosis (i.e. patients in the first quartile with a mean score 12.9) would have moderate AS (peak velocity $< 4$ m/s) rather than severe AS. Therefore, it is difficult to demonstrate the utility of this score to differentiate risk in patients with asymptomatic severe AS.

**Cardiovascular surgery**

Recent data from the Society of Thoracic Surgeons suggest the risk of isolated AVR is between 3 and 4%.36 Furthermore, consideration needs to be given to the longer term risks of valve replacement including infective endocarditis, thromboembolism, anti-coagulation-related bleed, and valve degeneration.37,38 The overall risk of sudden death in asymptomatic patients per year is $\sim 1\%$. One may argue that the risk–benefit ratio favours waiting until symptoms develop. Several recent studies have emerged which challenge this view, suggesting that an early operation in an asymptomatic patient is both safe and improves prognosis.

In a cohort of 622 patients with symptomatic AS, 10-year survival for asymptomatic patients who did not undergo AVR was 33% compared with 70% for patients who were asymptomatic but underwent AVR.37 Furthermore, the absence of AVR was an independent predictor of late survival. This was a retrospective, non-randomized study. Given the last contact prior to death was
mean gradient. Guidelines define severe AS by an aortic valve area classification criteria of severe AS. Insights from proposed new classification criteria of severe AS

Guidelines define severe AS by an aortic valve area < 1 cm² with a mean gradient > 40 mmHg. More recently it has become recognized that a proportion of patients with severe AS do not fit into these criteria.

Kang et al. 40 interrogated a prospective registry of 197 patients with very severe asymptomatic AS (aortic valve area ≤ 0.75 cm and peak aortic velocity 4.5 m/s, or mean gradient > 50 mmHg). Patients who underwent early surgery had a significant survival benefit (6-year survival free of cardiac death was 100% in the early surgery compared with 76% in the conventional arm. However, the decision of whether to undergo AVR was left to the discretion of treating physicians and not randomized. Secondly, exercise testing was not utilized to assess if patients were truly asymptomatic. Thirdly, the operative mortality in this study was 0% and the mean age of patients just 63 years old; therefore, it is difficult to apply these data to the older patient with higher operative risk more frequently encountered in routine clinical practice.

Insights from proposed new classification criteria of severe AS

Table 2  Risk factors in patients with asymptomatic severe aortic stenosis and corresponding threshold values which put patients at a high risk

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>High-risk values</th>
<th>Guideline recommendation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Valve assessment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak jet velocity</td>
<td>&gt; 5 m/s</td>
<td>AHA (IIb)</td>
<td>Bonow et al. 44, Rosenhek et al. 8</td>
</tr>
<tr>
<td>Aortic valve area</td>
<td>&lt; 0.6 cm²</td>
<td>AHA (IIb)</td>
<td>Bonow et al. 46, Rosenhek et al. 7</td>
</tr>
<tr>
<td>Rate of progression of jet velocity</td>
<td>≥ 0.3 m/s/year</td>
<td>ESC (IIa) if valve calcification moderate to severe</td>
<td></td>
</tr>
<tr>
<td>Degree of valve calcification</td>
<td>Heavily calcified (extensive calcification of all cusps)</td>
<td>Rosenhek et al. 7</td>
<td></td>
</tr>
<tr>
<td>Valvulo-arterial impedance</td>
<td>&gt; 4.5–4.9 mmHg/mm/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LV assessment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular systolic dysfunction</td>
<td>Ejection fraction &lt; 50%</td>
<td>ESC (I) and AHA (I)</td>
<td>Bonow et al. 45, Vahanian et al. 16</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>≥ 15 mm unless this is due to hypertension</td>
<td>ESC (IIb)</td>
<td>Vahanian et al. 16</td>
</tr>
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<td>Left ventricular mass</td>
<td>&gt; 110% of that expected for body size, gender and wall stress</td>
<td>Cioffi et al. 6</td>
<td></td>
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<tr>
<td>Strain imaging</td>
<td>Global Longitudinal strain &lt; 15.9%</td>
<td></td>
<td></td>
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<tr>
<td>Indexed left atrial area</td>
<td>&gt; 12.2 cm²/m²</td>
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<td><strong>Stress testing</strong></td>
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<tr>
<td>Treadmill exercise stress test</td>
<td>Symptoms on exercise. Fall in blood pressure. Complex ventricular arrhythmias on exercise</td>
<td>ESC (I) and AHA (IIb); ESC (IIa) and AHA (IIb); ESC (IIb)</td>
<td>Amato et al. 51, Das et al. 28</td>
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<tr>
<td>Exercise echocardiography</td>
<td>Mean pressure increase of ≥ 18–20 mmHg</td>
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<td>Lancelotti et al. 9, Maréchaux et al. 29</td>
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<td>Biomarkers</td>
<td>BNP &gt; 130 pg/mL</td>
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<td>Bergler-Klein et al. 33</td>
</tr>
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</table>

LV, left ventricle; BNP, B-type natriuretic peptide.

Shaded areas show markers already incorporated in guidelines: European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines with class of recommendation.
Sixty-seven per cent of patients with severe AS (defined by an aortic valve area < 1 cm²) had a mean gradient of <40 mmHg. Only an aortic valve area <1 cm² was an independent predictor of survival. These studies highlight the fact that valve gradients are flow-dependent and may not necessarily reflect severity of stenosis.

The recognition of different flow rates and gradients within patients with severe AS has led to a proposal for subdivision of severe AS into categories depending on gradient and flow. Lancellotti et al.,44 performed a prospective, observational study of 150 patients with asymptomatic severe AS for a mean of 27 months. Patients were classified into four groups: NFHG, NFLG, LFLG, and LFHG. The end-point was need for AVR or death. Two-year event-free survival was 83, 44, 30, and 27% in the NF/LG, NF/HG, LF/HG, and LF/LG groups, respectively. The findings of this study are difficult to translate into a clinical decision making process as the patient’s actual risk of cardiac death in each group is difficult to establish as the end-point was a composite of death and AVR. Secondly, the decision to perform AVR was based on individual clinician decisions. Further studies whose primary end-point is mortality and the decision for AVR based on predefined objective criteria are needed.

Figure 6 Algorithm for risk stratification in asymptomatic severe aortic stenosis. Levels of evidence are given in parentheses. European Society of Cardiology (ESC); American Heart Association (AHA); AS, aortic stenosis; AVA, aortic valve area; BP, blood pressure; CAD, coronary artery disease; LV, left ventricle.
International guidelines and current recommendations

International guidelines are based mainly on expert consensus opinion rather than randomized trials (level of evidence C). Both sets of current guidelines recommend (Class I indication) AVR in patients with asymptomatic severe AS where the patient is due to undergo other heart surgery, i.e. coronary artery by-pass grafting or has an LVEF < 50%. European Society of Cardiology (ESC) guidelines also include symptoms on exercise testing as Class I while the American Heart Association (AHA) guidelines classify this as a Class IIb indication.

The guidelines diverge when evaluating the evidence for other parameters (Table 2). The guidelines suggest that it is reasonable to perform AVR for Class Ila indications and it is reasonable to consider AVR for Class IIb indications. A high likelihood of rapid progression of AS and a drop in blood pressure on exercise testing are classified Class Ila and IIb indications by the ESC and AHA guidelines, respectively. The AHA guidelines identify very severe AS (high peak aortic valve jet velocity > 5 m/s, aortic valve area < 0.6 cm²) as a IIb indication while they are not mentioned in the ESC guidelines. The presence of left ventricular hypertrophy > 15 mm and the development of complex ventricular arrhythmia during exercise testing are classified by the ESC guidelines as Class IIb while they are not mentioned in the AHA guidelines.

Both sets of guidelines recommend risk stratification and careful risk benefit analysis with an individualized approach to treatment. Figure 6 illustrates a practical approach synthesizing the guidelines recommendations.

Discussion

In summary, the overall risk of sudden death in patients with asymptomatic, severe AS is relatively low. On this basis, and the fact that valve surgery comes with risks of its own, it has previously been suggested that valve surgery should be delayed until symptoms develop. However, certain factors identify patients who, despite remaining asymptomatic, have a poorer prognosis. Risk stratification of the asymptomatic patient with severe AS has evolved from a simple assessment of clinical history into an assessment of multiple variables which interact to determine the risk profile of a patient.

The plethora of data on poor prognostic markers is increasing. However, many of the studies quote a combined event rate including the need for AVR and death. Therefore, it is difficult to identify which markers predict a high risk of sudden death rather than markers which predict a high likelihood of the development of symptoms and subsequent AVR. Future studies need to provide clearer quantification, identifying an individual’s risk of sudden death. Such information would allow the identification of patients who are likely to have an adverse clinical outcome and would benefit from early valve replacement. Future research should investigate the utility and prognostic value of newer imaging modalities and emerging prognostic markers. Randomized trials testing the benefit of different selection strategies in asymptomatic patients would ultimately be the only way to provide reliable information.

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References


