Aortic stenosis and aging
SY Soh1, DTL Wong2*

Abstract
Introduction
Aortic stenosis (AS) develops when the effective area of valve opening becomes progressively narrow. In the elderly population, it is most frequently due to calcification. It is a common disease with an estimated prevalence of 2% in those 65 years and above. Without intervention, the prognosis is poor with more than 50% two year mortality once symptoms developed. The new ACC/AHA guidelines classify AS into: patients at risk of aortic stenosis (stage A), with progressive haemodynamic obstruction (stage B), severe asymptomatic (stage C) and severe symptomatic aortic stenosis (stage D). Once symptoms develop, treatment is generally recommended. For patients with estimated low to intermediate operative risk, surgical aortic valve replacement is the current standard treatment. Transcatheter aortic valve intervention (TAVI) has developed as an effective and comparable alternative to surgical aortic valve replacement in patients who have high or prohibitive operative risk. Compared to conservative therapy, it improves symptoms and functional status, and reduces mortality by 20% at one year. However, it has increased vascular complications, stroke and major bleeding. The decision making of who should receive TAVI is a complex one and requires meticulous assessment of operative risks, procedural suitability, comorbidities, life expectancy and frailty. The long term durability and safety is still being evaluated. Conservative management includes a holistic approach in patient and family counselling, symptoms management with medications or valvuloplasty and palliative service involvement. The aim of this review was to discuss aortic stenosis and aging.

Conclusion
Aortic stenosis has a huge disease burden in the elderly population. The development of TAVI offers an effective alternative to patients who have excessive operative risk. Patient selection is the key for a successful TAVI. Such complex decision making should ideally be carried out by a multidisciplinary specialist team. Conservative management remains a suitable option for patients who are too ill and too frail.

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Introduction
Aortic stenosis develops when the effective area of valve opening becomes progressively narrow due to various disease processes. In the elderly population, aortic valve leaflets thickening and calcification of either normal trileaflet valve or congenital bicuspid valve is the most common aetiology1. The pathogenesis of calcific aortic valve disease is characterised by lipoprotein deposition, chronic inflammation and active leaflet calcification2. Not surprisingly, it is associated with increased cardiovascular deaths3.

The prevalence of calcific aortic valve disease increases with age. It was previously estimated that aortic stenosis present in 2% of adults age 65 years and above3,4. More recently, a systematic search inclusive of 7 studies (9723 subjects above age 75 years) in Europe and North America, demonstrated a prevalence of 12.4% of all aortic stenosis and 3.4% of severe aortic stenosis5. The natural history of aortic stenosis is that of a prolonged asymptomatic phase6, but once symptoms developed, the prognosis is extremely ominous with a mortality of 26%, 48% and 57% at one, two and three years respectively7. Even in asymptomatic patients with severe aortic stenosis (defined as an aortic jet velocity ≥4m/sec), event free survival (defined as death or aortic valve replacement for symptoms) was 67% at one year, 56% at two years and 33% at 4 years6. The average rate of increase in the mean systolic pressure gradient is 4 to 7mmHg per year, valve area reduces at 0.1cm² per year and aortic jet velocity increases by 0.3m/sec per year. However, these changes vary widely among individual patients8 and therefore close follow up and tailored assessment to individual patient is required. Here we discuss the association of aortic stenosis with aging.

Assessment
The assessment of patients with aortic stenosis includes history taking focusing on exertional symptoms such as dyspnoea, dizziness, angina or reduced exercise tolerance. The classic symptoms of heart failure, syncope and angina at rest are more reflective of end stage disease. Other comorbid medical conditions and overall functional capacity assessment are crucial too. Chest X ray and electrocardiography findings are generally non-specific and baseline blood work up to assess other major organ functions are part of the assessment. Pulmonary function tests may be required, especially in patients with smoking history, to delineate if symptom is more likely due to pulmonary cause or aortic stenosis. Transthoracic echocardiography is the most readily available modality in assessing the aortic valve (number of leaflets, calcification, valve opening), haemodynamic parameters (jet velocity, systolic pressure gradient, peak velocity and regurgitant fraction), valve morphology, left ventricle size and function and left atrial size and function. Mitrval valve regurgitation, pericardial effusion and paravalvular regurgitation should also be noted.

Competing interests: declared in the article.
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mean pressure gradient across aortic valve, derived valve area, LV wall and function (systolic and diastolic) and pulmonary artery pressure. Dobutamine stress transthoracic echocardiography and invasive cardiac catheterisation may be indicated in patients with severe aortic stenosis with low flow (stroke volume index ≤35ml/m²), low aortic valve gradient (<40mmHg) and low EF (<50%).

Classification
The 2014 AHA/ACC Valvular Heart Disease guideline classifies the stages of aortic stenosis into: patients at risk of aortic stenosis (stage A), with progressive haemodynamic obstruction (stage B), severe asymptomatic (stage C) and severe symptomatic aortic stenosis (stage D)

In true stenosis, a dobutamine stress echocardiography with or without invasive haemodynamic measurements will demonstrate an increased flow and mean pressure gradient with similar valve area. On the other hand, a pseudo-stenosis will show increased flow and valve area but modest increased in mean gradient. This group of patients is less likely to benefit from valve replacement. Nevertheless, it has been demonstrated that patients who have increased stroke volume and transaortic flow with dobutamine infusion (preserved LV contractile reserve) have lower operative mortality and better long term survival than those who do not.

Low flow, low gradient severe AS can also be seen in patients with preserved LVEF. The report from Hachicha showed that up to 35% of patients with severe aortic stenosis by valve area criteria had paradoxical low flow output (defined as stroke volume index ≤35ml/m²) despite preserved LV ejection fraction (62%). This group of patients were older, had higher proportion of female, larger LV mass and relative wall thickness, smaller stroke volume, and lower overall three year survival as compared to those with normal flow output.

Treatment
Management of those at risk of (stage A) and progressive (stage B, mild-moderate) aortic stenosis includes regular follow up and interval transthoracic echocardiography. Hypertension should be treated accordingly. Statin therapy is not indicated for prevention of progressive disease. Patients with asymptomatic severe AS (stage C1) requires closer follow up, meticulous assessment of TTE and sometimes exercise stress testing. Patients with symptomatic severe AS (stage D), with LV dysfunction (C2), moderate AS with other cardiac surgery indicated, should be referred for consideration of surgical aortic valve replacement if operative risk is low to intermediate. For patients in whom TAVI or high-risk surgical AVR is being considered, a Heart Valve Team consisting of professionals with expertise in valvular heart disease, cardiac imaging, interventional cardiology, cardiac surgery, cardiac anaesthesia and intensive care should collaborate to provide optimal care (Figure 1).

Surgical aortic valve replacement (SAVR)
SAVR is an established definitive treatment of severe aortic stenosis. According to the published data from Society of Thoracic Surgeons National Cardiac Surgery Database in USA, the operative mortality of isolated aortic valve replacement was 3.2% (in-hospital regardless of timing and 30-day regardless of location) and 5.6% with coronary artery bypass grafts. Although age together with LV function, NYHA functional class, low gradient disease and the volume of procedures performed at the hospital affect survival after surgery, the overall relative survival remains high, with one and five year survival estimated around 89% and 69% respectively for patients aged 80 years and above in one study. In another study, patients of the oldest age group showed decreased observed survival but excellent relative survival (adjusted to age and gender matched expected survival of the similar population), suggesting old age was not a risk factor for excess mortality post SAVR. Therefore, surgical aortic valve replacement is still considered a gold standard treatment for patients with low to intermediate operative risks.

Transcatheter aortic valve implantation (TAVI)
TAVI has now been shown to be a viable alternative for patients with high or prohibitive risk of having SAVR. In brief, it is a procedure in which a bioprosthetic valve is percutaneously through a catheter and implanted within the diseased native aortic valve. In recent years, in a highly selected group of patients who were not suitable for surgical intervention, the PARTNER B trial demonstrated reduced all-cause mortality at 1 year to 30.7% in patients treated with TAVI as compared to 50.7% in patients managed with standard therapy (medical ± valvuloplasty). Among survivors at 1 year, there was less NYHA class III or IV symptoms reported in the TAVI group (25%) compared to standard therapy (58%). However, there was higher incidence of major strokes (5% vs 1.1%, p=0.06), major vascular complications (16.2% vs 1.1%, P<0001) and major bleeding (16.8% vs 3.9% p<0.001) at 30 days. Patients in this trial has an average STS PROM
score of 11.6% or a low STS score with coexisting conditions that would be associated with a predicted risk of death by 30 days after surgery of 15% or higher\textsuperscript{18}. The exclusion criteria of this trial included bicuspid or non-calcified aortic valve, acute myocardial infarction, substantial coronary artery disease requiring revascularisation, left ventricular ejection fraction of less than 20%, aortic annulus diameter of less than 18mm or more than 25mm, severe (3+) mitral or aortic regurgitation, transient ischaemic attack or stroke within 6 months, and severe renal insufficiency\textsuperscript{18}.

In the PARTNER A trial, patients with high operative risks (mean STS scores of 11.8%) but still suitable for SAVR were randomly assigned to receive TAVI or SAVR. The all-cause mortality rate was 3.4% in the TAVI group and 6.5% in the SAVR group at 30 days (P=0.07) and 24.2% and 26.8% respectively at 1 year (P=0.44) in the intention to treat analysis. It was concluded that TAVI was a non-inferior alternative to SAVR in patients with high risks of operative complications and death. At 30 days, TAVI was associated with increased major vascular complications, while SAVR had increased major bleeding, and new onset atrial fibrillation. More patients had improved symptoms in the TAVI group at 30 days, but by one year, the difference was not significant\textsuperscript{19}.

A meta-analysis which included 17 studies comparing TAVI (n=2,267) and SAVR (n=2,392) showed no significant difference in all-cause mortality at 30 days and at 85 weeks (average follow up). There was also no difference in cardiovascular mortality, myocardial infarction, stroke and transient ischaemic attack at averages of 86, 72, 66 and 89 weeks. It concluded similarly that TAVI is a safe alternative to SAVR in selected high-risk elderly patients with severe aortic stenosis\textsuperscript{20}. However, the long term durability of transcatheter bioprosthetic valves is not yet known and long term follow up results of TAVI patients are required.

**Medical therapy and percutaneous balloon valvuloplasty**

Once SAVR or TAVI are considered too high risk, technically unsuitable or futile, a holistic treatment approach including patient and family counselling, medical

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**Figure 1:** Timing of Intervention.
therapy with or without valvuloplasty and palliative service involvement should be initiated. Most medications have the potential of destabilising patients with symptomatic aortic stenosis. Management needs to be targeted on patients symptoms and loading conditions. For example, patients presented with dyspnoea and heart failure, administration of diuretics and ACEI may be appropriate. Otherwise, maintaining normal volume status (preload) and normal blood pressure (afterload) is the key. Occasionally, percutaneous aortic balloon valvuloplasty to temporarily relieve the aortic stenosis can be used as a palliative intervention to relieve symptoms.

From a registry data of 674 patients who had balloon valvuloplasty, 3% died during the procedure, 8% by discharge, and a total of 14% by 30 days. However, of the 86% survivors, symptoms and functional status improvement was generally reported.

**Discussion**

The development of TAVI with compatible survival and complications to SAVR has revolutionised the management of severe aortic stenosis, especially in those who were previously deemed “in-operable” due to high operative risks.

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**Table 1: Stages of AS (Nishimura et al. 2014 ACC/AHA guidelines)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics</th>
<th>Hemodynamic Consequences</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At risk of AS</td>
<td>Bicuspid aortic valve (or other congenital valve anomaly) Aortic valve sclerosis</td>
<td>Aortic $V_{max} &lt; 2 , m/s$</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Progressive AS</td>
<td>Mild-to-moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion or Rheumatic valve changes with commissural fusion</td>
<td>Mild AS: Aortic $V_{max} 2.0–2.9 , m/s$ or mean $\Delta P &lt; 20 , mm , Hg$ Moderate AS: Aortic $V_{max} 3.0–3.9 , m/s$ or mean $\Delta P 20–39 , mm , Hg$</td>
<td>Early LV diastolic dysfunction may be present</td>
<td>Normal LV EF</td>
</tr>
<tr>
<td>C</td>
<td>Asymptomatic severe AS</td>
<td>Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening</td>
<td>Aortic $V_{max} \geq 4 , m/s$ or mean $\Delta P \geq 40 , mm , Hg$ AVA typically is $\leq 1.0 , cm^2$ (or AVAi $\leq 0.6 , cm^2/m^2$) Very severe AS is an aortic $V_{max} \geq 5 , m/s$ or mean $\Delta P \geq 60 , mm , Hg$</td>
<td>LV diastolic dysfunction</td>
<td>Normal LV EF</td>
</tr>
<tr>
<td>D</td>
<td>Symptomatic severe AS</td>
<td>Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening</td>
<td>Aortic $V_{max} \geq 4 , m/s$ or mean $\Delta P \geq 40 , mm , Hg$ AVA typically $\leq 1.0 , cm^2$ (or AVAi $\leq 0.6 , cm^2/m^2$) but may be larger with mixed AS/AR</td>
<td>LV diastolic dysfunction Mild LV hypertrophy Pulmonary hypertension may be present</td>
<td>Exertional dyspnea or decreased exercise tolerance Exertional angina Exertional syncope or presyncope</td>
</tr>
</tbody>
</table>

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**Valve Anatomy**

- **Bicuspid aortic valve (or other congenital valve anomaly)**
- **Aortic valve sclerosis**
- **Mild-to-moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion**
- **Rheumatic valve changes with commissural fusion**

**Valve Hemodynamics**

- **Aortic $V_{max}$**
- **Mean $\Delta P$**

**Hemodynamic Consequences**

- **LV diastolic dysfunction**
- **Mild LV hypertrophy**
- **Pulmonary hypertension**

**Symptoms**

- **Normal LV EF**
- **LV EF $< 50$**
- **Exertional dyspnea**
- **Exertional angina**
- **Exertional syncope or presyncope**

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**Competing interests:** declared in the article.

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**FOR CITATION PURPOSES:** Soh SY, Wong DTL. Aortic stenosis and aging. OA Elderly Medicine 2014 Jan 18;2(1):1.
mortality and morbidity. However, the majority of these patients who may benefit from TAVI also have multiple co-morbidities, advanced age, and are commonly frail with limited function. In face of an aging population across most developed world, the disease burden will increase and resource allocation needs to be considered. How do we select those who would benefit most from the intervention and prevent those who would not from receiving an expensive futile treatment?

The key lies in stringent patient selection. Frailty, defined as a state of functional decline with increased vulnerability to stressors and decreased physiologic reserve, is independently predictive of disability, hospitalisation and mortality. It has been associated with increased post-operative complications in a general surgical population and more recently associated with increased 1 year mortality (hazard ratio 3.5) post TAVI.(26) The 2014 AHA/ACC Valvular Heart Disease Guideline incorporates the Society of Thoracic Surgeon (STS) risk estimate, frailty, major organ dysfunction, and procedure specific impediments into the surgical and interventional risk assessment.

The functional status assessment includes independence or dependence of seven indices such as the Katz Activities of Daily Living index (feeding, bathing, dressing, transferring, toileting, urinary continence) and mobility (no walking aid, assist required, or 5 meter walk in <6s). Patients are classified as moderate-severely frail if they are dependent on ≥2 of the indices and would be considered as high risk, if valvular intervention is required. As a comparison, patients with two major organ dysfunctions (including severe LV/RV dysfunction, pulmonary hypertension, CKD stage III or above, pulmonary dysfunction with FEV1 <50% or DLCO <50% of predicted, dementia, Parkinson’s disease or CVA with persistent physical limitation, GI – ulcerative colitis, nutritional impairment, active malignancy and chronic liver disease) who needs valve surgery would also be considered as high risk. This demonstrates the emphasis placed on frailty and functional capacity assessment of patients before cardiac surgery. Of interest, 5-Meter-Walk-Test has gained popularity in assessing frailty after Afilalo and colleagues showed that patients who took longer than 6 seconds to walk 5 meters at a self-selected gait speed were at an increased risk of major morbidity and mortality from cardiac surgery and it was found to be a good predictor of dependent functional status in a group of patients with severe aortic stenosis. TAVI is currently recommended for patients who are functionally limited due to severe AS and a life expectancy of >1 year and in whom surgery is considered high risk or contraindicated. How can we truly separate patients who are dying from severe AS and those dying from other co-morbid disease? Clearly, with an overall survival of 70%-80% at two year in the earlier trials and majority of late death due to co-morbid diseases, this remains one important area of research. The decision of which patients should receive TAVI in a heterogenous population of elderly is a complex one. There are currently no validated tools that combined surgical risks predictions (for example Euroscore and STS-PROM score in cardiac surgery), life expectancy, functionality and co-morbid assessment to predict risks and long term outcomes in this unique TAVI population.

Conclusion

Aortic stenosis has a huge disease burden in the elderly population and carries grave prognosis if left untreated. SAVR remains the treatment of choice for those who have low to intermediate operative risks. The development of TAVI offers an effective alternative to patients who have excessive operative risks. Patient selection is the key for a successful TAVI. Such complex decision making should ideally be carried out by a multidisciplinary specialist team. Conservative management remains a suitable option for patients who are too ill and too frail.

Funding

DW is supported by NHF (Australia) Post-Doctoral fellowships and Robertson Family Research Cardiologist Fund.

Competing interests

DW is supported by NHF (Australia) Post-Doctoral fellowships and Robertson Family Research Cardiologist Fund

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Critical review