Valvular heart disease: a perspective on the asymptomatic patient with severe valvular aortic stenosis†

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Early in 2006, the European Society of Cardiology (ESC) assigned the 2006 Denolin lecturer to provide a broad perspective on the asymptomatic patient with severe calcific valvular aortic stenosis (AS) in the older patient. Subsequently, in late 2006, American College of Cardiology/American Heart Association Guidelines and in 2007 ESC Guidelines have given the Class I recommendation to ‘primary’ aortic valve replacement (AVR) for asymptomatic patients with AS only to those with left ventricular dysfunction at rest and to those who only become symptomatic on exercise testing. Indications for AVR in classes IIa and IIb were provided. However, almost all of the recommendations in classes I and II were based on level of evidence C. ‘Primary’ AVR is that which is recommended for severe AS as opposed to AVR secondary to surgery for other cardiovascular disease.

Keywords
Aortic valve replacement • Sudden death • Left ventricular dysfunction • Exercise • Elderly

Progression in valvular heart disease

Clinical status of patients and application of interventional therapeutic procedures progress in opposite directions (Figure 1). Valve replacement started in 1960 in patients in NYHA Class IV. Later it was extended to patients in Class III and in the 1980’s and 1990’s to those in class II. In 1983, a suggestion was made for aortic valve replacement (AVR) in selected asymptomatic (Class I) patients with severe AS.1 In the early 1990’s, it was still an area of disagreement.2,3

Clinical challenge

Symptomatic patients with severe AS have a high mortality.4,5 In these patients AVR is associated with an improvement in survival, left ventricular ejection fraction (LVEF) and functional class, and regression of LV mass.5–7 In those with LV dysfunction, LVEF is improved or normalized; the improved results can be dramatic in those in clinical heart failure.5 Results of AVR have further improved remarkably, operative mortality and morbidity are low, and long-term durability of some prosthetic heart valves is excellent. Natural progression is to consider primary AVR earlier in the course of the disorder; however, AVR is still associated with complications but asymptomatic patients are also at an increased risk for untoward events. The ‘clinical challenge’ is to determine subgroups of asymptomatic patients with severe AS in whom, primary AVR is better, or likely to be better, than later AVR.

Asymptomatic patient with severe aortic stenosis

When the asymptomatic patient with severe AS is seen by a cardiologist, the clinical issues that need to be considered are (Figure 2):

(i) the incidence of sudden death;
(ii) the early risks faced by the patient and when are they likely to occur;
(iii) prediction of high-risk by the previous clinical course of the patient; and
(iv) the likely clinical course of patients with severe AS during the intermediate and long-term follow-up if initially they do not have AVR.

1DENOLIN LECTURE 2006.

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Sudden death

Prospective studies of small numbers of asymptomatic patients (three and 10) showed a 33% incidence of sudden death. Subsequent prospective studies showed an incidence of 0–4.1% (Table 1). Review of autopsy data of 387 asymptomatic young athletes, who died suddenly, found AS as the only abnormality in 2.6% emphasizing that sudden death occurs in these patients. Amato et al. followed 66 patients with severe AS, no coronary artery disease (CAD) on coronary arteriography, no other co-morbid conditions and who did not have early AVR. Incidence of sudden death was 4.5% at 6 months and 6.2% at 18 months; all four patients who experienced sudden death initially had a positive exercise test and an aortic valve area (AVA) ≤ 0.6 cm².

Precise annual incidence of sudden death determined by actuarial analysis, and all predictors of those at high-risk for sudden death, still needs to be defined.

Early risks

The mean ages of patients ranged from 63 to 71 years (Table 2). In the Amato study, mean age was 49 years and all patients had no CAD; patients in other studies did not have routine coronary arteriography at time of entry into the study. Incidence of LV systolic dysfunction in three studies was 0, 2, and 3% and in other studies is not described. Two studies reported early AVR in 17, 21%; they had more severe AS with smaller AVA’s 0.61 vs. 0.69 and 0.69 vs. 0.9 cm² and were excluded from the follow-up data. In a third study, 72/694 (10%) were excluded because of early AVR and their AVA was 0.69 ± 0.17 cm².

Exercise tests revealed symptoms in 46/125 asymptomatic patients (37%). At 2 years, early risks of AVR and/or death in those with severe AS ranged from 44 to 79% (Table 2). The incidence of ‘cardiac events’ was 28% at 15 ± 7 months. In one study, perioperative mortality was 8.5%; in patients with moderate/severe AS the incidence of AVR and/or death was lower at 26 and 37% and of symptoms at 1 year was 29%.

The extremely high incidence of 79% for AVR and/or death at 2 years for 26 patients with severe AS out of a total of 123 patients with AS merits additional assessment. In this study, coronary arteriography was subsequently performed in 42% of 123 patients and 50% of them had associated significant CAD (Table 3). Thus, in this study it is not known if the events were due to AS and/or associated CAD.

Prediction of high-risk

Event rate at 1 year in those with a positive vs. a negative exercise test was 60 and 10%, respectively, and those with AVA of <0.7 vs. ≥ 0.7 cm² was 45 and 22%, respectively. Event rate at 2 years in those with AVA <0.75 vs. ≥ 0.75 cm² was 60 vs. 28%, respectively. In one study, 18/26 (69%) patients with positive exercise test had a cardiac event in 15 ± 7 months.

The event rate at 1 year in patients aged >50 vs. ≤ 50 years was 41 ± 6 and 15 ± 6%, respectively; and in those with moderate/severe valve calcification and no or mild calcification was 40 ± 6 and 8 ± 5%, respectively.

In those with clinical events vs. with no clinical events, the aortic jet velocity was 4.66 ± 0.62 and 4.41 ± 0.38 m/s/year, respectively, \( P = 0.03 \). In those with the progression of aortic jet velocity at a rate of ≥ 0.5 m/s/year, there was a very low predictive sensitivity for cardiac event (Figure 3).

Outcome on intermediate and long-term follow-up

(i) In three studies symptoms developed in 29% in ≤12 months, in 47% (59/128) in 22 ± 18 months, and in 50% in 5.4 ± 4.0 years, respectively.
If patients did not have AVR initially, event rate on intermediate
and long-term follow-up is 1.5–3% per month (Table 4). The
events start occurring very early and the rate is almost linear
up to 7 years. In the largest study, 622 patients who did not have AVR initially were followed for 7–10
years. Symptoms developed in 297 (47.7%); 207/297 (70%)
had AVR in whom the event rate was lower than with no
AVR, 21.7 vs. 77.7%, respectively; 325 (52.3%) remained
asymptomatic, 145/325 (45%) had AVR and 180/325 (55%)
who had no AVR; the mortality after AVR was lower than with
no AVR, 28 vs. 57%, respectively. Events began occurring in
the first few months (Figure 4).

Limitations of above studies
The above studies are important and valuable but have significant
limitations that must be kept in mind when extrapolating their
findings to clinical decision-making in all asymptomatic patients. The limitations are as follows.

(i) Some studies included patients with severe as well as
moderate AS.

(ii) In some studies patients with more severe AS had early
AVR and were excluded from the study, the exclusion
criteria were not predefined. Thus, for the study of natural
history of all asymptomatic patients their data is of concern.

(iii) In only one study, the absence of CAD on angiography was an
entry criteria. In other studies, the status of CAD at baseline
is not known. In the USA, Veterans Administration study
of 643 patients and from Mayo Clinic of 618 patients
undergoing valve replacement the incidence of associated
CAD was 49 and 52%, respectively. A more recent study
from Germany of 282 patients with severe AS the incidence
of associated CAD was 59%. Thus, patients in the cited
studies who were in their 60’s and 70’s it is
likely the incidence of associated CAD was about ≥50%.

**Table 2** Event-rate in asymptomatic patients by severity of aortic stenosis: prospective studies after non-invasive testing

<table>
<thead>
<tr>
<th>First author</th>
<th>References</th>
<th>Patients, n</th>
<th>Age (years) Mean ± SD</th>
<th>Peak velocity (m/s) or AVA (cm²)</th>
<th>At 2 years AVR and/or death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe AS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otto</td>
<td>15</td>
<td>26</td>
<td>63 ± 16</td>
<td>&gt;4.0 m/s</td>
<td>79 ± 18%</td>
</tr>
<tr>
<td>Rosenhek</td>
<td>10</td>
<td>128</td>
<td>71 ± 12</td>
<td>≤0.8 cm²</td>
<td>44 ± 5%</td>
</tr>
<tr>
<td>Amato</td>
<td>14</td>
<td>66</td>
<td>49 ± 15</td>
<td>≤1.0 cm²</td>
<td>62 ± 6%</td>
</tr>
<tr>
<td>Lancellotti</td>
<td>12</td>
<td>69</td>
<td>66 ± 12</td>
<td>≤1.0 cm²</td>
<td>28%</td>
</tr>
<tr>
<td>Moderate/severe AS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pellikka</td>
<td>2</td>
<td>143</td>
<td>70</td>
<td>≥4.0 m/s</td>
<td>26 ± 6%</td>
</tr>
<tr>
<td>Pellikka</td>
<td>11</td>
<td>622</td>
<td>71 ± 11</td>
<td>≥4.0 m/s</td>
<td>37%</td>
</tr>
<tr>
<td>Das</td>
<td>16</td>
<td>125</td>
<td>65</td>
<td>≤1.2 cm²</td>
<td>(29%)</td>
</tr>
</tbody>
</table>

*aSudden death and symptom.
*bCardiac events as at 15 ± 7 months.
*cCardiac deaths.
*dOnly symptoms at 12 months.
*eAVA available in 47% of patients, and was 0.9 ± 0.2 cm²
fAVA, aortic valve area.

Valvular heart disease

**Table 3** Coronary artery disease in asymptomatic patients with severe aortic stenosis

<table>
<thead>
<tr>
<th>Severe AS (peak aortic velocity &gt;4 m/s)</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>63 ± 16 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVR and/or death at 2 years</td>
<td>79 ± 18%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of patients in study</td>
<td>123</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subsequent coronary arteriography</td>
<td>52/123 (42%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Significant coronary artery disease</td>
<td>26/52 (50%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Left main 7, 3 vessel 5, 2 vessel 4 and 1 vessel 10</td>
<td></td>
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</tbody>
</table>

*aMean ± SEM by actuarial analysis.
Adapted from Otto et al.

**Figure 3** Relationship of rate of aortic jet velocity progression to cardiac events. Adapted from Rosenhek et al.
(iv) Associated LV dysfunction, not described in most studies, will result in a higher event rate.

(v) One study reported 'cardiac death' and not all deaths. This study is from a large excellent referral centre; nevertheless, it is difficult to accurately determine cause of death in patients who are being followed in their own local communities.

(vi) Adverse patient outcomes are reported as ‘Death/AVR’. Rate of onset of symptoms and whether it led to AVR was not always reported.

(vii) Indications for AVR were usually not predefined. Indication for AVR and death after AVR were often not reported.

(viii) Did all patients who became symptomatic have AVR? In one study, all patients who developed symptoms had AVR, but not in at least one study possibly because patients were followed in their own local communities.

(ix) Therapy of associated co-morbid conditions and its success may have influenced patient outcomes but were not described.

(x) Patients considered not at ‘high-risk’ also had an increased event rate (~10–20%) even up to 1 year of follow-up.

(x) Rate of progression by: (a) aortic jet velocity has a low sensitivity for predicting clinical events and did not predict 73% of those who had an event; and by: (b) the severity of calcification which was subjectively estimated from visual assessment of echocardiogram is problematic. It correlates poorly (r = 0.34) with Agatston score on EBCT.

(xii) Other studies defining high-risk subgroups

Ischaemia

In animals with experimental severe AS, O2 supply to the endocardium is limited because myocardial O2 extraction reserve is exhausted. Total myocardial blood flow is increased but is mal-distributed, that to the subendocardium does not increase by the same amount as to the epicardium; as a result, the normal ratio of subendocardial to epicardial myocardial blood flow of 1 is changed to <1.

In patients with severe AS and normal coronary arteries, the same phenomenon occurs (Figure 5). Myocardial blood flow per unit of LV muscle is reduced implying subendocardial blood flow is reduced because when coronary flow is reduced that to the subendocardium is affected first. Moreover, coronary flow reserve is also reduced. These findings are not unique to AS but also occur in conditions with LV hypertrophy, that is increased LV mass with wall thickening.

On the ECG, changes of depolarization and repolarization due to LV hypertrophy are increased QRS voltage and T wave changes. Additional finding of ST depression is evidence of subendocardial ischaemia but is not a sensitive finding. However,
in clinical practice subendocardial ischaemia is difficult to image accurately in the hypertrophied heart.

**Coronary artery disease**

In animals with LV hypertrophy from experimental hypertension, occlusion of the left anterior descending coronary artery results in a four-fold increase of mortality at 48 h when compared with left anterior descending occlusion in the control animals. Coronary artery occlusion in patients with severe AS can be expected to result in a significant increase of mortality and morbidity. Prevalence of associated CAD with severe AS in these age groups is ≥ 50%.

**Left ventricular systolic dysfunction**

LV systolic dysfunction, measured as an abnormal LVEF, is associated with a worse outcome. Clinically, the extreme clinical manifestation of LV dysfunction is clinical heart failure. In patients in clinical heart failure, AVR with or without associated coronary artery bypass graft (CABG) surgery, is associated with an improvement in survival, LVEF, and functional class. Outcomes are better if there is no previous myocardial infarction and AVR + CABG is performed early in the course of the disease. Reduced LVEF is a high-risk situation which can be improved/corrected by early AVR.

**Afterload mismatch**

LV afterload is integrated intra-myocardial tension in systole and is determined by LV pressure, volume, and mass. Afterload mismatch is a term coined by Ross Jr from acute animal experiments in which LV volume was kept constant, acutely LV mass is constant and increasing aortic pressure resulted in increased contractility. At a certain stage of increasing aortic pressure, contractility began to decrease, that is, contractile state was mismatched to the afterload. In the clinical situation increasing severity of AS is matched by increasing LV mass and contractility; when these are inadequate (clinical afterload mismatch) LV volume begins to increase and LVEF begins to decrease even though they are still in the normal range. This is the earliest stage of LV dysfunction in severe AS.

**Excessive left ventricular mass**

Some patients develop more LV mass than is needed for the same degree of severe AS. In patients aged ≥ 60 years this occurred in 41% of women compared with 14% of men. LV radius to wall thickness ratio is markedly decreased and LVEF is increased, is ‘supernormal’. Excessive mass is associated with an increased operative mortality and post-operatively LV mass may not regress sufficiently or not at all (Figure 6). At that time the LV has no outflow obstruction but only diastolic dysfunction with severe compliance problems and has haemodynamics similar to hypertrophic cardiomyopathy without outflow obstruction. Greater LV mass than is necessary for severity of AS should be dealt with early. Early, excess LV mass is wall thickness ≥ 12–14 mm in smaller people, e.g. women, and ≥ 14–16 mm in larger people, e.g. men.

**Left ventricular diastolic dysfunction**

LV diastolic dysfunction, if severe and of ‘long’ duration, leads to severe pulmonary hypertension, and eventually to severe tricuspid regurgitation and clinical heart failure. At that late stage, mortality after AVR is very high and without AVR is excessive. LV diastolic dysfunction due to reduced LV compliance is manifested clinically in the early stage by normal LVEF and increased left atrial (mean ≥ 15 mmHg) and pulmonary artery pressures (mean ≥ 20 mmHg; systolic > 30 mmHg). Pulmonary congestion (first stage of pulmonary oedema) is of concern; it begins at a mean left atrial pressure of ~ 18 mmHg, at which time mean and systolic pulmonary artery pressures are about ≥ 24 and
> 35 mmHg, respectively. Interstitial pulmonary oedema (second stage) is of serious concern; it begins at mean left atrial pressure of about >24 mmHg, at which time mean and systolic pulmonary artery pressures are about >30 and >40 mmHg, respectively.

**Older age**

Symptomatic patients aged >60 years are benefited by AVR. Older age is associated with an increased event rate partly because older people have more co-morbid conditions and a shorter life expectancy. Over all, older patients always have a poorer survival than younger patients. There is no perfect way to correct for this, but one method is to compare a patient to an age and gender matched person in the population, that is, obtaining ‘relative survival’. At 10 years, older patients had a better relative survival than younger patients. Their survival was not significantly different from 100% (Figure 7) indicating that in symptomatic patients AVR had eliminated or markedly reduced the mortality due to severe AS. Older patients are at higher risk and have better results with AVR.

**The dilemma**

Clinicians responsible for the care of asymptomatic patients with severe AS face the ‘dilemma of balancing’ the immediate (1–30 days) risks of primary AVR vs. the early (1–12/24 months) risks of no AVR. Additional factors need to be considered: (a) assessing severity of AS; (b) operative mortality; and (c) choice of prosthetic heart valve.

**Assessing severity of aortic stenosis**

One has to be careful about assessing severity of AS only by gradients. Gradient, a per beat function, is determined by stroke volume and systolic ejection time, both are influenced by heart rate, LV preload, afterload, and myocardial contractility, and also by systolic pressure in the ascending aorta. Thus, gradients are subject to considerable change from one time to another. Mean gradient >50 mmHg by cardiac catheterization had a high specificity for severe AS. A suggested grading of severity of AS is shown in Table 5.

**Operative mortality**

1997 database of the Society of Thoracic Surgeons (STS) showed in 880 Class I (asymptomatic) patients operative mortality was 1.25%. This includes data from almost 500 hospitals. It is likely the operative mortality in Class I patients ranged from close to zero to perhaps 5% or more. Thus, it seems reasonable ‘primary’ AVR may be recommended if the operative mortality at that hospital/surgeon for AVR is <1–2% and for AVR+CABG surgery is <2–4%. Presence of associated co-morbid conditions, both cardiac and non-cardiac, will increase the mortality associated with primary AVR and also that of non-operated AS.

**Choice of prosthetic heart valve**

Use of a mechanical valve is associated with problems of anticoagulant therapy and increased risk of bleeding which is higher in those >60 years and very high in those >75 years of age. Thus, a biological valve is preferred in these patients. Recent data from the STS database of 409 904 valve procedures showed performing aortic root reconstruction for AVR in patients who do not have aortic root pathology doubles the operative mortality. Prostheses that require additional aortic root reconstruction (stentless valves, homografts, and autografts) should be avoided. The choice is a stented bioprosthesis; pericardial valve has

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Table 5: A suggested grading of the severity of aortic stenosis

<table>
<thead>
<tr>
<th>Grading</th>
<th>AVA (cm²)</th>
<th>AVA index (cm²/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&gt;1.5</td>
<td>&gt;0.9</td>
</tr>
<tr>
<td>Moderate</td>
<td>&gt;1.0–1.5</td>
<td>0.6–0.9</td>
</tr>
<tr>
<td>Severe</td>
<td>≤1.0</td>
<td>≤0.6</td>
</tr>
<tr>
<td>Very severe</td>
<td>≤0.7</td>
<td>≤0.4</td>
</tr>
</tbody>
</table>

Patients with borderline values of AVA’s between moderate and severe (0.9–1.1 cm²; 0.35–0.65 cm²/m²) should be individually considered.

AVA, aortic valve area.

Adapted from Rahimtoola.

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**Figure 7** Ten year relative survival after aortic valve replacement in two age groups. Adapted from Lindblom et al.

**Figure 8** Operative mortality for aortic valve replacement in octogenarians was very low in patients with left ventricular ejection fraction >0.50 and in whom aortic valve replacement was not an emergency and/or redo procedure. From Langanay et al.

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Adapted from Rahimtoola.
lower rate of structural valve deterioration than the porcine valve out to 10–20 years.38

Octogenarians
People are living longer and more octogenarians present with severe AS. AVR in symptomatic octogenarians can be performed with very low operative mortality in those with normal LVEF if the AVR is not an emergent and/or re-do procedure41 (Figure 8). They also have an improved survival and functional class.42

Octogenarians face more difficult issues. They have a shorter life expectancy and have a higher incidence of co-morbid conditions, both cardiac and non-cardiac. In the Helsinki Aging Study43 echocardiographic-Doppler studies were performed in 476 randomly selected people aged 75–86 years, 59% of whom were aged ≥80 years (figure 9). At 4 years, the mortality of those with ‘moderate’ AS plus severe AS was 59% and that of those who had no AS was 29%; thus, primary AVR by itself can be expected to reduce ~52% of all deaths. Randomized trials to prove this benefit may need comparatively small number of patients.

Recommendations for aortic valve replacement
It is reasonable to recommend ‘primary’ AVR for asymptomatic patients with severe valvular AS if they are in a higher risk group (Table 6) provided the operative mortality is expected to be low and the correct prosthetic heart valve is chosen. The patient’s informed acceptance of the procedure, after the risks of early AVR vs. no early AVR are carefully explained, is essential.

Conflict of interest: Dr Rahimtoola has received Honoraria for educational lectures from American College of Cardiology Foundation; American College of Physicians; University of California Los Angeles; University of California Irvine; Cornell University; Creighton University; Thomas Jefferson University; Cedars-Sinai Medical Center; Harvard Medical School; University of Wisconsin; University of Hawaii; Cardiologists Association of Hong Kong, China; ATS; St. Jude Medical; Carbomedics; Merck; Pfizer; Edwards Life Sciences.

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