Aortic Stenosis: an Overview

Clinical Evaluation, Guidelines and Treatment: from Surgery to Current Indications for TAVI
Aortic Stenosis

Aortic stenosis (AS) is a life-threatening valvular heart disease, most commonly occurring in elderly patients due to age-related aortic valve calcification.

More than one in eight people over the age of 75 years have moderate or severe valve disease and the prevalence of AS is 2.8%.¹

AS is a narrowing of the aortic valve that prevents normal opening. As aortic valve calcification worsens, obstruction to blood flow forces the heart to work harder to pump blood across the narrowed valve.²

AS is often asymptomatic when the stenosis is mild to moderate in severity. No effective drug therapy exists, and surgical treatment is limited to patients who have progressed to symptomatic AS.³
Diagnosis of Aortic Stenosis

Timely and accurate diagnosis of AS is essential. After onset of symptoms, average survival in patients with severe AS is 50% at 2 years, and 20% at 5 years. Because asymptomatic patients have a lower risk of mortality and surgical treatment of AS carries its own risks, decisions to operate require careful weighting of both benefits and risks.

**Clinical Evaluation and Auscultation:** typical symptoms of AS (e.g. shortness of breath, chest pain or tightness) alongside the identification of a systolic murmur during auscultation.

**Echocardiography:** the key non-invasive tool for diagnosis and evaluation of severe AS, echocardiography is indicated in any patient with a confirmed heart murmur following auscultation and suspicion of heart valve disease. Doppler echocardiography is preferred when assessing AS severity. Combined evaluation is the best approach for diagnosis of AS and should include an examination of valvular function and anatomy, hemodynamics and indices of left ventricular (LV) anatomy and function.

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Echocardiographic criteria for the definition of severe AS according to the ESC/EACTS guidelines:

- Aortic valve area: <1.0 cm²
- Indexed valve area: <0.6 cm²/m² (body surface area)
- Mean gradient: >40 mmHg
- Maximum jet velocity: >4.0 m/s
- Velocity ratio: <0.25
Additional Examinations: in some patients, the severity of AS may be difficult to quantify, e.g. in patients with a small valve area and low–normal pressure gradient/cardiac output. In such cases, the following tests may be utilized:

- **Electrocardiogram:** monitor for signs of LV hypertrophy.

- **Exercise Testing:** this may help to unmask symptoms in asymptomatic patients with AS, but is contraindicated in symptomatic patients and may be difficult to interpret in those with an abnormal baseline 12-lead ECG.

- **Chest X-Ray:** monitor for signs of LV hypertrophy, post-stenotic dilatation of ascending aorta, or potential signs of pulmonary edema.

- **Multi-slice Computed Tomography:** this is a cornerstone in the per-interventional work-up of patients considered for transcatheter aortic valve implantation (e.g. evaluation of the severity of aortic disease).

- **Invasive Evaluation:** coronary angiography and/or right heart catheterization, the latter is used for a more accurate assessment of hemodynamics when non-invasive tests are inconclusive.

To ensure safety during the test, patients should be monitored for changes in 12-lead ECG, blood pressure, and carefully observed for the appearance of symptoms associated with AS. Stress echocardiography may provide additional prognostic information in selected patients as to changes in hemodynamics and/or global LV function.

Patients with asymptomatic severe AS should be re-evaluated at least every 6 months for changes in echocardiographic parameters or exercise tolerance, and occurrence of symptoms.

**Electrocardiogram of a patient with severe aortic stenosis** (Paper speed 50mm/s; 10mm/mV; Filter 40Hz). Signs of left ventricular hypertrophy (i.e. positive Sokolow-Lyon index) and T-wave depression in the inferolateral leads can be observed in the presence of normal conduction time intervals.

**Chest X-ray of a patient with severe aortic stenosis.**
Patient Evaluation

It is critical that patients in need of treatment are promptly identified and referred. Once symptoms appear, untreated patients have a poor prognosis.1,8

Key Considerations During Patient Examination5
- Does the patient have symptoms?
- Are symptoms most likely related to the present degree of AS?
- Is AS severe?
- What is the patient’s wish? Interventional versus surgical aortic valve replacement (sAVR) versus no intervention given the eligibility for the first two options
- What is the patient’s life expectancy and quality of life?
  - Life expectancy should be estimated according to age, gender and comorbidities.

In the absence of serious comorbidities, sAVR is indicated in the majority of symptomatic patients with severe AS, and should be performed promptly due to the risk of sudden death if such patients are left untreated.5,9

Prevalence and Impact of Comorbidities
Comorbidities become more prevalent with increasing age and are common in elderly patients with severe AS. Cardiovascular (CV) diseases, such as hypertension and coronary artery disease, are amongst the most prevalent while hypercholesterolemia, a CV risk factor, is also common in patients with severe symptomatic AS.10

Risk Assessment
Comorbidities place patients with severe symptomatic AS at risk of procedural complications and mortality, and are a key consideration in risk assessment and treatment decisions.5,10
Routine risk assessment should be based on the clinical judgement of the ‘heart team’ with consideration of established scoring systems (logistic EuroSCORE and STS score).5

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Prevalence in patients with severe symptomatic AS</th>
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<tbody>
<tr>
<td>Peripheral artery disease</td>
<td>10–30%</td>
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<tr>
<td>Left ventricular dysfunction</td>
<td></td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>Diabetes</td>
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<td>Cancer</td>
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<td>Previous coronary artery bypass graft</td>
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<tr>
<td>Coronary artery disease</td>
<td>30–50%</td>
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<tr>
<td>Mitral regurgitation</td>
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<tr>
<td>Atrial fibrillation</td>
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<tr>
<td>Cerebrovascular disease</td>
<td></td>
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<tr>
<td>Pulmonary hypertension</td>
<td>50–70%</td>
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<tr>
<td>Chronic kidney disease</td>
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<tr>
<td>Hypercholesterolemia</td>
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<tr>
<td>Hypertension</td>
<td>&gt;70%</td>
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Management of Severe Aortic Stenosis

According to current ESC/EACTS 2012 guidelines, operative and interventional treatment options should be carefully considered in all patients with severe AS.\(^5\)

**ESC/EACTS AS Treatment Guidelines**

Medication may be prescribed to regulate heart rhythm, prevent clotting, and reduce symptoms. Surgical AVR (aortic valve replacement) is recommended for symptomatic patients with severe AS.\(^5\)

Based on the excellent results of the PARTNER Trial,\(^11,12\) transcatheter aortic valve implantation (TAVI) is indicated in patients with severe symptomatic AS not suitable for surgery.\(^5\) Among high-risk patients who are still candidates for surgery, TAVI should be considered as an alternative in individuals for whom the heart team favors TAVI.\(^5\)
**Treatment Options**

**Surgical Aortic Valve Replacement**
Surgical aortic valve replacement has been the established treatment of choice for many years in the treatment of symptomatic patients with severe AS.\(^5,13\)

This non-beating heart procedure is performed via a full sternotomy or via a minimal invasive surgery (MIS) requiring general anesthesia and a heart-lung machine.

**Transcatheter Aortic Valve Implantation**
TAVI has emerged as an option for the treatment of inoperable patients with severe AS following heart team assessment. Clinical characteristics and anatomy considered as contraindications for surgery include porcelain aorta, deleterious effects of chest-wall irradiation, oxygen-dependent respiratory insufficiency and frailty.\(^11\)

This less-invasive, beating heart procedure is commonly performed via transfemoral (TF) access, which requires no general anesthesia and reduces patient time in intensive care.\(^14\) Two other alternatives, the transapical (TA) or transaortic (TAo) approaches, can be used if TF access is not feasible, due to anatomical contraindications.\(^5\)

TAVI is also a therapeutic alternative in high\(^5\) and intermediate-risk patients considered suitable for surgery, but where TAVI is preferred based on individual risk profile assessed by a heart team.\(^5\) The PARTNER Trials, large randomized studies using the Edwards SAPIEN valves, supported this established treatment option in symptomatic patients with severe AS.\(^5\)
The PARTNER Trials – Placement of AoRtic TraNscathetER Valve

The PARTNER Trial

The first PARTNER Trial led to a paradigm shift in clinical investigation of AS patient outcomes.

The PARTNER Trials were the world’s first prospective, randomized and controlled Trials for TAVI, studying outcomes in two different cohorts:

- Cohort A: sAVR versus TAVI in high-risk patients
- Cohort B: standard therapy versus TAVI in inoperable patients

Cohort A – High-risk

Methods: 699 high-risk patients were randomized to TF/TA TAVI or sAVR.

Primary endpoint: all-cause mortality at 1 year, up to 5 years follow-up (non-inferiority).

Results at 1 year: all-cause mortality 24.2% (TAVI) vs. 26.8% (sAVR) \( (p=0.44) \).

Results at 5 years: all-cause mortality 67.8% (TAVI) vs. 62.4% (sAVR) \( (p=0.76) \).

Clinical implication: comparable clinical outcomes of survival and hemodynamic performances at 1 year and 5 years in high-risk patients with AS treated with TAVI or sAVR.

Conclusion: TAVI is a proven alternative to surgery for treatment of AS in patients with high surgical risk.

Cohort B – Inoperable

Methods: 358 inoperable patients were randomized 1:1 for TF TAVI or standard therapy (medical management with or without balloon aortic valvuloplasty at the discretion of the treating physician).

Primary endpoint: all-cause mortality at 1 year, over length of trial up to 5 years (superiority).

Results at 1 year: all-cause mortality 30.7% (TAVI) vs. 50.7% (standard therapy) \( (p<0.001) \).

Results at 5 years: all-cause mortality 71.8% (TAVI) vs. 93.6% (standard therapy) \( (p<0.0001) \).

Clinical implication: TAVI should be strongly considered in inoperable patients as being more beneficial in terms of improvement of survival and functional status than standard treatment.

Conclusion: TAVI has demonstrated superiority compared with standard medical therapy.
The PARTNER II Trial

The PARTNER II Trial was designed to evaluate, in a larger cohort, TAVI versus surgery in patients with symptomatic severe AS at intermediate-risk – as defined by STS score (between 4 to 8) or by the heart team. The PARTNER II Trial consisted of two cohorts of patients randomized in a 1:1 ratio to either TAVI or sAVR. The primary endpoint was a non-hierarchical composite of death from any cause or disabling stroke at 2 years. A registry with the new generation valve, SAPIEN 3, was also initiated, using the same in- and exclusion criteria as the randomized study with 1,077 intermediate-risk patients. This registry was used to compare the outcomes of patients treated with TAVI (from PARTNER II S3i) and sAVR (from PARTNER IIA), from two arms of the PARTNER II Trial using a propensity score analysis.

TAVI versus sAVR in Patients at Intermediate-risk (PII A)14

Methods: 2,032 intermediate-risk patients with severe AS were randomised to TAVI (n=1,011, 76.3% TF) or sAVR (n=1,021).

Primary endpoint: non-hierarchical composite of all-cause mortality or disabling stroke at 2 years.

Results at 2 years: composite of all-cause mortality or disabling stroke: 19.3% (TAVI) vs. 21.1% (sAVR) – non-inferiority of TAVI as compared to sAVR (p=0.001)

Clinical implication: similar outcomes of death or disabling stroke at 2 years in intermediate-risk patients with AS.

(SAPIEN XT valve has no CE Mark approval in EU for intermediate-risk indication)

SAPIEN 3 Valve in Patients at Intermediate-risk (PII S3i)18,19

Methods: 1,077 intermediate-risk patients with severe AS were treated with TAVI via TF (88%) access.

Primary endpoint: composite of all-cause mortality, all strokes and moderate or severe aortic valve regurgitation at 1 year (non-inferiority propensity score analysis).

Results at 30 days: all-cause mortality 1.1% and all strokes 2.7% (disabling stroke 1.0%). Low rate of paravalvular regurgitation: severe 0.0%, moderate 3.4%

Propensity score analysis at 1 year: non-inferiority for the primary endpoint (p<0.0001) and superiority of TAVI compared to the surgical cohort with regards to the combined endpoint (p<0.0001).

Clinical implication: In patients with severe aortic stenosis and intermediate surgical risk, TAVI with the SAPIEN 3 valve is associated with low mortality and strokes as well as low rates of moderate or severe paravalvular regurgitation at 30 days and at 1 year.

“TAVI might be the preferred treatment alternative in intermediate-risk patients with symptomatic severe aortic stenosis”19

Vinod H. Thourani, Emory University School of Medicine, Atlanta, USA
Proven Benefits of TAVI

In addition to the excellent results of the PARTNER Trials, further studies have shown that TAVI has both short- and long-term benefits for patient symptoms, recovery and quality of life.

**Benefits of the Procedure**

- **Shorter Procedure Times versus sAVR**
  Mean procedure time of 92–100 minutes for TAVI vs. 183 minutes with sAVR.\(^1\)

- **Shorter Length of Hospital Stays versus sAVR**
  Mean hospital stay of 9.76 vs. 12.01 days with sAVR \((p<0.001)\).\(^2\)
  Time in intensive care 2 vs. 4 days with sAVR \((p<0.001)\).\(^3\)

- **Faster Recovery versus sAVR**
  TAVI is a less invasive treatment and shortens the recovery time compared to sAVR.\(^4\)

- **Better Quality of Life (QoL)**
  Significantly more rapid improvements in measures of QoL vs. sAVR.\(^5\)

- **Low Complication Rate**
  Low risk of major adverse cerebrovascular and cardiac events (MACCE) and life threatening bleeding with TAVI.
  - Considering bias and the higher mortality risk of patients selected for TAVI, risk of MACCEs was not higher with TAVI vs. sAVR.\(^6\)

- **Proven Durability**
  No valve deterioration over 5 years.\(^7\)

**Long-term Benefits to Patients**

- **Preservation or Improvement in LV function**
  Better ejection fraction (50.2%) vs. sAVR (40.9%) \((p=0.003)\) in those with normal baseline ejection fraction (>50%).\(^8\)
  In those with a low baseline ejection fraction (~34%) TAVI patients had better recovery to normal ejection fraction at the 1-year follow-up (58%) vs. sAVR (20%).\(^9\)

- **Alleviation of Symptoms**
  Patients previously symptomatic at rest and unable to exercise (92% in NYHA classes III and IV) became asymptomatic and more mobile (>75% in NYHA classes I and II) in the 2–5 years following TAVI.\(^10\)

- **Extended Life Expectancy**
  Higher rates of survival in inoperable patients with TAVI versus standard treatment at 5 years (28.2% vs. 6.4%, \(p<0.0001\)).\(^11\)
  Increased median survival from 1 year without treatment to 2.5 years following TAVI.\(^12\)
Call for Cooperation: Timely Referral to a Heart Team is Key to Patient Outcomes

General cardiologists play a key role in the diagnosis of symptomatic severe AS and are the link between the patient, the general practitioner and the heart team. Early diagnosis of severe AS and timely referral to a heart team is essential to direct each patient toward their best treatment option.

Patient Journey with Severe AS
Patients may face a long journey from the development, diagnosis and eventual treatment of severe AS. If you have a patient with symptomatic severe AS, refer them for sAVR or TAVI to your local heart team without delay.

Your local heart center can be found here: www.findatavicenter.com/eu
References


17. Thourani VH on behalf of the PARTNER Trial investigators; Three years outcomes after Transcatheter or Surgical AVR in HR patients with aAS; ACC 2013.


20. Thourani VH on behalf of the PARTNER Trial investigators; SAPIEN 3 Transcatheter Aortic Valve Replacement compared with Surgery in Intermediate-Risk Patients: A propensity score analysis; ACC 2016.


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