Aortic Stenosis: an Overview

Clinical Evaluation, Guidelines and Treatment: from Surgery to Current Indications for TAVI
### 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.

**Clinical Evaluation and Auscultation:** Typical symptoms of AS (i.e. signs of heart failure) alongside the use of auscultation and identification of a systolic murmur.

**Echocardiography:** The key diagnostic tool. It confirms the presence of AS, assesses the degree of valve calcification, left ventricular (LV) function and wall thickness, and provides prognostic information. Doppler echocardiography is preferred when assessing AS severity. A stepwise integrated approach is the best approach for diagnosis of AS and should include an examination of valvular function and anatomy, haemodynamics and indices of LV anatomy and function.

### Aortic Stenosis

Aortic stenosis (AS) is potentially 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%.

#### Aortic Stenosis

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.

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.

#### Prevalence of AS by Age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Prevalence of moderate to severe aortic stenosis (%)</th>
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<tbody>
<tr>
<td>&lt;45</td>
<td>1</td>
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<td>45–54</td>
<td>2</td>
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<td>55–64</td>
<td>4</td>
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<tr>
<td>65–74</td>
<td>5</td>
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<td>≥75</td>
<td>6</td>
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#### Echocardiographic criteria for the definition of severe AS according to the ESC/EACTS guidelines

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<tr>
<th>Valve morphology by echocardiography suspicious of AS</th>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>Valve morphology suspicious of AS</td>
<td>AVA ≤1.0 cm²</td>
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<tr>
<th>Assess velocity/gradient</th>
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<tr>
<td>Assess AVA</td>
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<td>AVA ≤1.0 cm²</td>
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**LOW-GRADIENT AS**

- Vmax < 4 m/s, \( \Delta Pm < 40 \text{ mmHg} \)
- Low flow: \( \text{SVi} \leq 35 \text{ mL/m}^2 \)
- Normal flow: \( \text{SVi} > 35 \text{ mL/m}^2 \)

**HIGH-GRADIENT AS**

- Vmax ≥ 4 m/s, \( \Delta Pm ≥ 40 \text{ mmHg} \)
- \( \text{AVA} > 1.0 \text{ cm}² \)

**Management of asymptomatic AS remains controversial, requiring careful weighing of benefits and risks. In the absence of predictors for symptom development, watchful waiting is recommended, as treatment is unlikely to be beneficial.**

#### 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.

#### 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%.

#### Aortic Stenosis

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.
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.

**Key Considerations During Patient Examination**

- 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? Minimally invasive transcatheter valve replacement versus surgical valve replacement versus no intervention.
- What is the patient’s life expectancy and quality of life?
  - Life expectancy should be estimated according to age, gender, comorbidities and country-specific life expectancy.
- What would post-procedural recovery look like for the patient?

Based on the 2017 ESC/EACTS guidelines, patients over 75 years and STS ≥ 4% should be considered for TAVI, while for patients < 4% STS score sAVR is preferred. In light of the latest clinical evidence, SAPIEN 3 TAVI is now approved for all symptomatic patients with severe AS, independent of their STS score. Regardless, AVR should be performed promptly due to the risk of sudden death if such patients are left untreated.

**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 hypercholesterolaemia, a CV risk factor, is also common in patients with severe symptomatic AS.

**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. 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).
Management of Severe Aortic Stenosis

According to current ESC/EACTS 2017 guidelines, operative and interventional treatment options should be carefully considered in all patients with severe AS.\(^5\)

**ESCAPE AS Treatment Guidelines\(^5\)**

<table>
<thead>
<tr>
<th>Management of severe AS</th>
<th>Treatment options</th>
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<td><strong>Symptoms</strong></td>
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<td><strong>SAVR or TAVI</strong></td>
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<td><strong>Contraindications</strong></td>
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Based on the latest clinical evidence, SAPIEN 3 TAVI is now approved for severe aortic stenosis patients, independent of their surgical risk.\(^21\)

In patients at low surgical risk (STS <4%), the 2017 ESC/EACTS guidelines recommend SAVR as the preferred treatment. However, the recent release of the PARTNER 3 trial proves SAPIEN 3 TAVI is superior to surgery for low-risk patients.\(^21\) This may impact future guidelines updates.

The ESC/EACTS treatment guidelines for AS were updated in 2017: following consideration of noteworthy clinical trial data, including those from PARTNER II.\(^13\) The 2017 guidelines recommend that the choice for aortic valve intervention must be based on careful individual evaluation of technical suitability and weighing of the risks and benefits of each treatment modality. Furthermore, the local expertise and outcomes data for the given intervention must be considered when selecting the optimal treatment.

The ESC/EACTS treatment guidelines make the following recommendations when selecting the treatment option for patients with symptomatic aortic stenosis:\(^6\)

- Surgical AVR (SAVR) is recommended in patients at low surgical risk (STS or EuroSCORE II <4% or logistic EuroSCORE I <10%) and no other risk factors not included in these scores, such as frailty, porcelain aorta, sequelae of chest radiation)

- TAVI is recommended in patients who are not suitable for SAVR as assessed by the Heart Team

- In patients who are at increased surgical risk (STS or EuroSCORE II ≥4% or logistic EuroSCORE I ≥10%) and other risk factors not included in these scores such as frailty, porcelain aorta, sequelae of chest radiation), the decision between SAVR and TAVI should be made by the Heart Team according to the individual patient characteristics, with TAVI favoured in elderly patients (≥75 years) suitable for transfemoral (TF) access.

### 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.\(^21\)

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

**Transcatheter Aortic Valve Implantation**

This less-invasive, beating heart procedure is commonly performed via TF access, which requires no general anaesthesia and reduces patient time in intensive care.\(^21\) Two other alternatives, the transapical (TA) or transaortic (TAo) approaches, can be used if TF access is not feasible, due to anatomical contraindications.\(^21\)

TAVI is recommended in patients with heart disease due to aortic stenosis who are not suitable for SAVR as assessed by the heart team.\(^5\)

Both SAVR and TAVI are recommended (class I indication) for the treatment of patients at increased surgical risk (STS>4%). The decision for either treatment should be made based upon a thorough assessment that includes different clinical characteristics as well as anatomical and technical aspects. Criteria favouring TAVI include among others previous cardiac surgery, restricted mobility, porcelain aorta, sequelae of chest radiation, oxygen-dependent respiratory insufficiency, frailty.\(^21\)

The PARTNER Trials, large randomised studies using the Edwards SAPIEN valves, evaluated TAVI as a treatment option in all symptomatic patients with severe AS across all risk categories.\(^10,11,14-17,21\)
The PARTNER Trials – Placement of AoRtic TraNscatheterER 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, randomised and controlled Trials for TAVI, studying outcomes in two different cohorts:

- **Cohort A**: sAVR versus TAVI in high-risk patients\(^{15,16}\)
- **Cohort B**: standard therapy versus TAVI in inoperable patients\(^{14,17}\)

### Cohort A – High-risk\(^{15,16}\)

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

**Primary endpoint**: all-cause mortality at 1 year, up to 3 years follow-up (non-inferiority).

**Results at 1 year**: all-cause mortality 67.8% (TAVI) vs. 62.4% (sAVR) \((p = 0.076)\).

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

### Cohort B – Inoperable\(^{14,17}\)

**Methods**: 358 inoperable patients were randomised 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% (sAVR) \((p < 0.001)\).

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

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

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 and 8) or by the Heart Team. The PARTNER II Trial consisted of two cohorts of patients randomised 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.\(^{12,13,16}\) A registry with the new generation valve, SAPIEN 3, was also initiated, using the same in- and exclusion criteria as the randomised study with 1,077 intermediate-risk patients.\(^{11}\) 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.\(^{20,21}\)

### TAVI versus sAVR in Patients at Intermediate-risk (PII A)\(^{10}\)

**Methods**: 2,032 intermediate-risk patients with severe AS were randomised to TAVI \((n = 1,077)\) or sAVR \((n = 955)\).

**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: 21.1% (TAVI) vs. 21.9% (sAVR) – non-inferiority of TAVI as compared to sAVR \((p = 0.901)\).

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

### SAPIEN 3 Valve in Patients at Intermediate-risk (PII S3i)\(^{11,19}\)

**Methods**: 1,077 intermediate-risk patients with severe AS were treated with TAVI via TF \((n = 1,077)\) or sAVR \((n = 955)\).

**Primary endpoint**: composite of all-cause mortality or stroke at 30 days and at 2 years.

**Results at 30 days**: all-cause mortality 1.1% and all strokes 2.7% (disabling stroke 1.0%).

Low rate of paravalvular regurgitation (combined inoperable, high and intermediate risk cohorts): severe 0.0%, moderate 3.4%.

**Propensity score analysis at 1 year**: non-inferiority for the primary endpoint \((p = 0.0001)\).

**Conclusion**: TAVI might be the preferred treatment alternative in intermediate-risk patients with symptomatic severe aortic stenosis.

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The PARTNER 3 Trial

(SAPIEN 3 TAVI in low risk patients)

Previous TAVI RCTs showed that, in patients who were at intermediate or high risk for death with surgery, TAVI was either superior or non-inferior to standard therapies, including sAVR. There was insufficient evidence regarding the comparison of the two procedures in patients who are at low risk.

The study was designed to investigate the safety and effectiveness of the Edwards SAPIEN 3 Transcatheter Heart Valve in patients with severe, calcific aortic stenosis who are at low operative risk (STS<4%).

The PARTNER 3 study consisted of two patient cohorts, randomised 1:1 to either TAVI or sAVR.

The primary endpoint is a composite of all-cause mortality, all stroke, and re-hospitalization (valve-related or procedure related and including heart failure) at 1-year post procedure.

TAVI versus sAVR in Patients at Low-risk (PIII)

Methods: 1,000 low-risk patients with severe AS were randomised 1:1 to TAVI (n=496) or sAVR (n=454).

Primary endpoint: composite of all-cause mortality, all stroke, and re-hospitalization at 1 year.

Results at 1 year: composite of all-cause mortality, all stroke, and re-hospitalization superior in TAVI (8.5%) vs. sAVR (15.1%) (p=0.001).

Superior to surgery for the outcomes that matter most

PARTNER 3 trial clinical events at 30 days and 1 year

<table>
<thead>
<tr>
<th></th>
<th>30 Days</th>
<th>1 Year</th>
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<tbody>
<tr>
<td>SAPIEN 3 TAVI (n=496)</td>
<td></td>
<td></td>
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<tr>
<td>Surgery (n=454)</td>
<td></td>
<td></td>
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<tr>
<td>All-cause Death</td>
<td>0.4%</td>
<td>1.0%</td>
</tr>
<tr>
<td>All Stroke</td>
<td>0.6%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Re-hospitalization</td>
<td>3.4%</td>
<td>7.3%</td>
</tr>
<tr>
<td>P-value</td>
<td>0.09</td>
<td>0.04</td>
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Quality of Life improvements

With the SAPIEN 3 valve, low-risk patients can expect to resume their everyday lives rapidly post procedure.40,31

Among patients with severe aortic stenosis who were at low surgical risk, the rate of the composite of death, stroke, or re-hospitalization at 1 year was 46% lower with TAVI than with surgery.30,31

TAVI is superior to surgery in patients with severe aortic stenosis at low-risk for surgery.11
Clinical Evaluation, Guidelines and Treatment: from Surgery to Current Indications for TAVI

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.\(^2,1\)

- **Shorter Length of Hospital Stays versus sAVR**
  Median hospital stay of 4 vs. 9 days with sAVR.\(^1,3\)

- **Faster Recovery versus sAVR**
  TAVI is a less invasive treatment and shortens the recovery time compared to sAVR.\(^2,1\)

- **Better Quality of Life (QoL)**
  Significantly more rapid improvements in measures of QoL vs. sAVR.\(^3\)

- **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 up to 1 year.\(^4\)

Durability of TAVI

The PARTNER trial 5-year outcomes data demonstrate valve durability and excellent haemodynamic outcomes. The results showed equivalent preservation of valve haemodynamics, including mean aortic valve areas and mean valve gradients, in TAVI and sAVR groups.\(^5,9\) Registry data investigating outcomes in patients who had undergone successful TAVI reinforced these findings and demonstrated sustained efficacy and excellent haemodynamics at 5 years.\(^6\)

Long-term Benefits to Patients

- **Preservation or Improvement in LV function**
  Higher ejection fraction (50.2% vs. sAVR 40.9% \(^p=0.003\)) in those with normal baseline ejection fraction (>50%).\(^7\)

  In those with a low baseline ejection fraction (<30%) TAVI patients had better recovery to normal ejection fraction at the 1-year follow-up (58%) vs. sAVR (20%).\(^8\)

- **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.\(^9\)

- **Extended Life Expectancy**
  Higher rates of survival in inoperable patients with TAVI versus standard treatment at 5 years (28.2% vs. 6.4% \(^p<0.0001\)).\(^10\)

  Increased median survival from 1 year without treatment to 2.5 years following TAVI.\(^11\)

- **Sustained improvement to health status**
  TAVI is associated with significantly improved disease-specific health status, represented by a change of approximately 19 points in mean KCQ20 score, not only at 1 month but also at 6 and 12 months.\(^12\)

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 centre can be found here: www.findatavicenter.com/eu

Want to know more?

For information about aortic stenosis visit www.TAVI.today

Further material on aortic stenosis can be ordered free of charge via this website.
Indications for TAVI: from Surgery to Current Clinical Evaluation,
Guidelines and Treatment: from Surgery to Current Indications for TAVI

References
18. Theeuwen VH on behalf of the PARTNER Trial investigators. Three years outcomes after transcatheter or surgical aortic valve replacement in high-risk patients with AS. ACC 2013.
32. Baron, S. Effect of SAPIEN 3 Transcatheter Valve Implantation on Health Status in Patients With Severe Aortic Stenosis at Intermediate Surgical Risk. JACC 2018.
34. Data on file at Edwards.