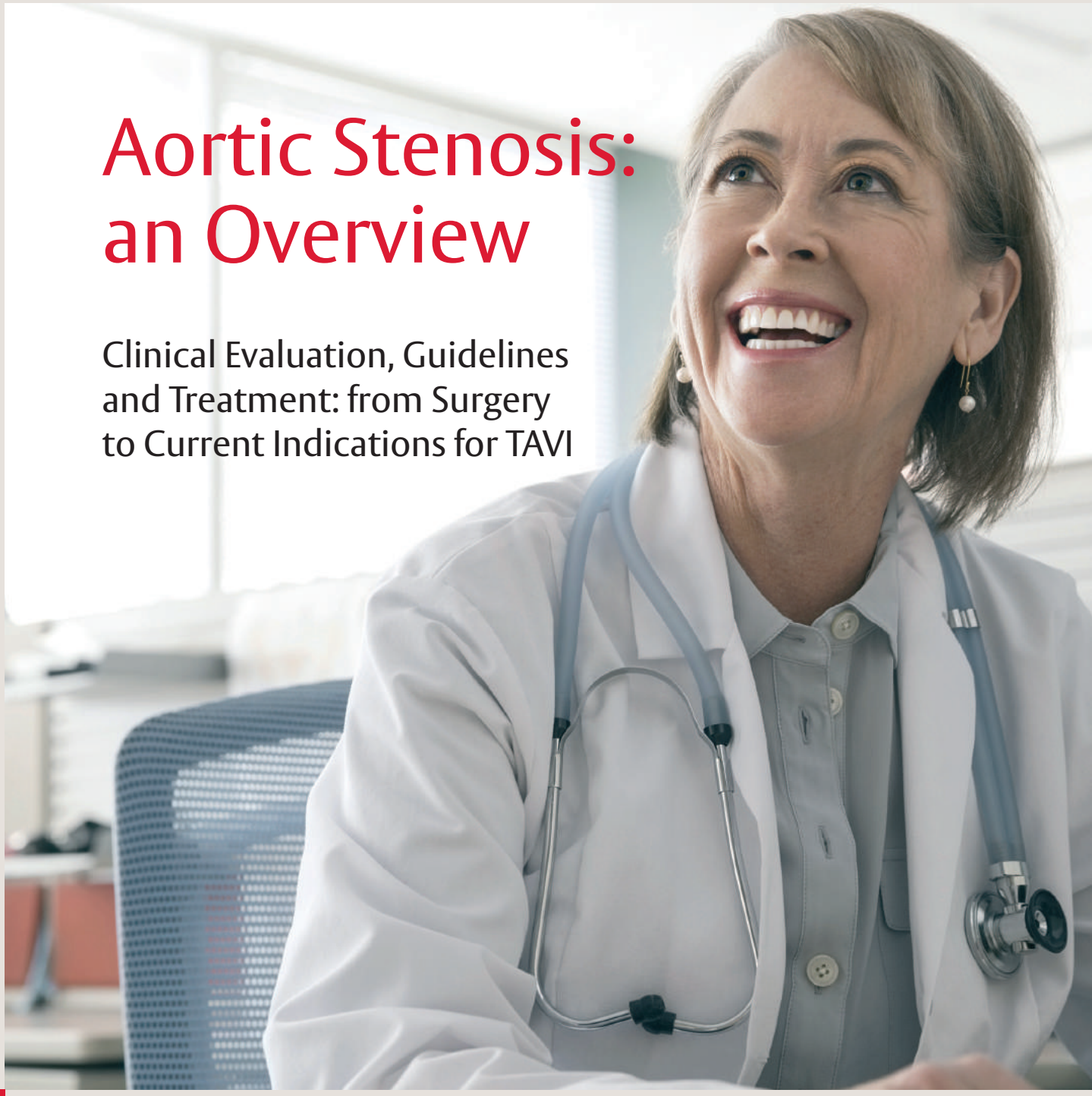
Aortic Stenosis: an Overview

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



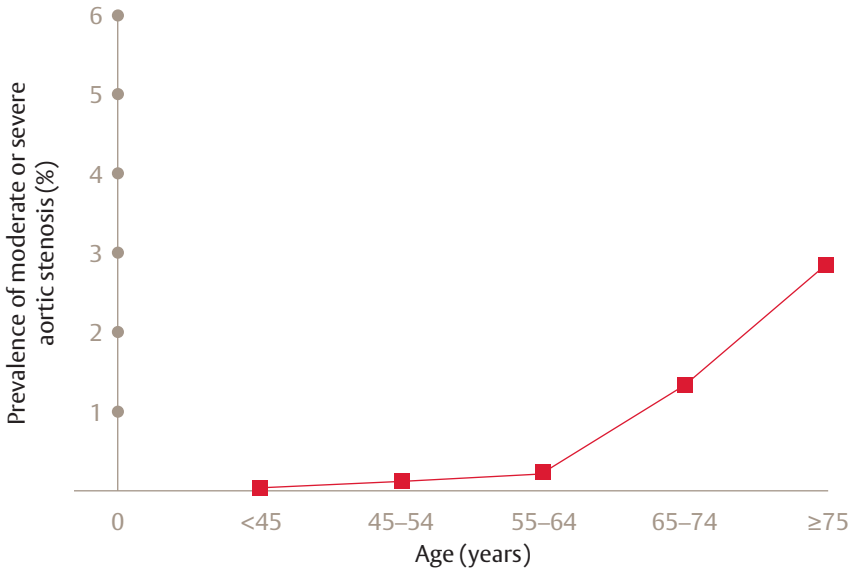
Edwards

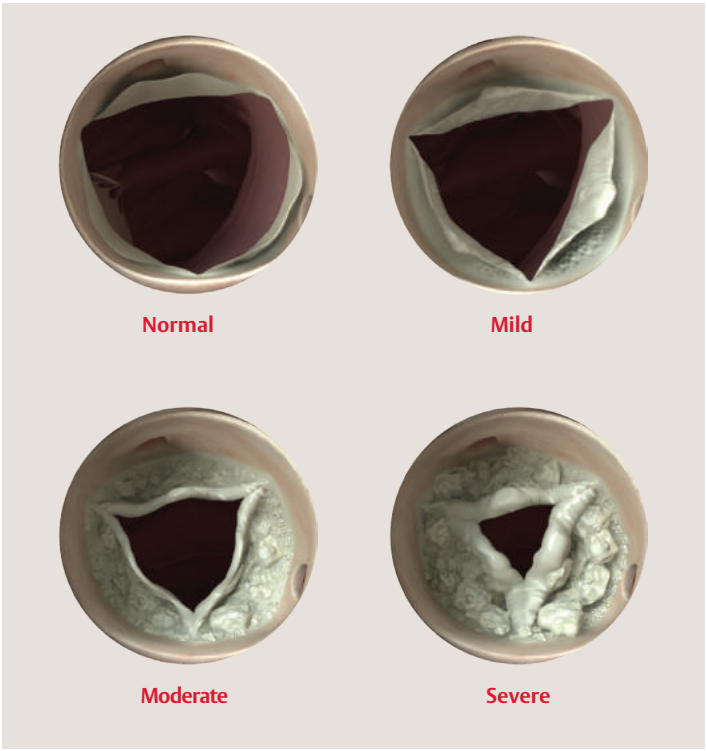
Aortic Stenosis

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]

Prevalence of AS by Age[1]





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.[2]

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.[3]

Diagnosis of Aortic Stenosis

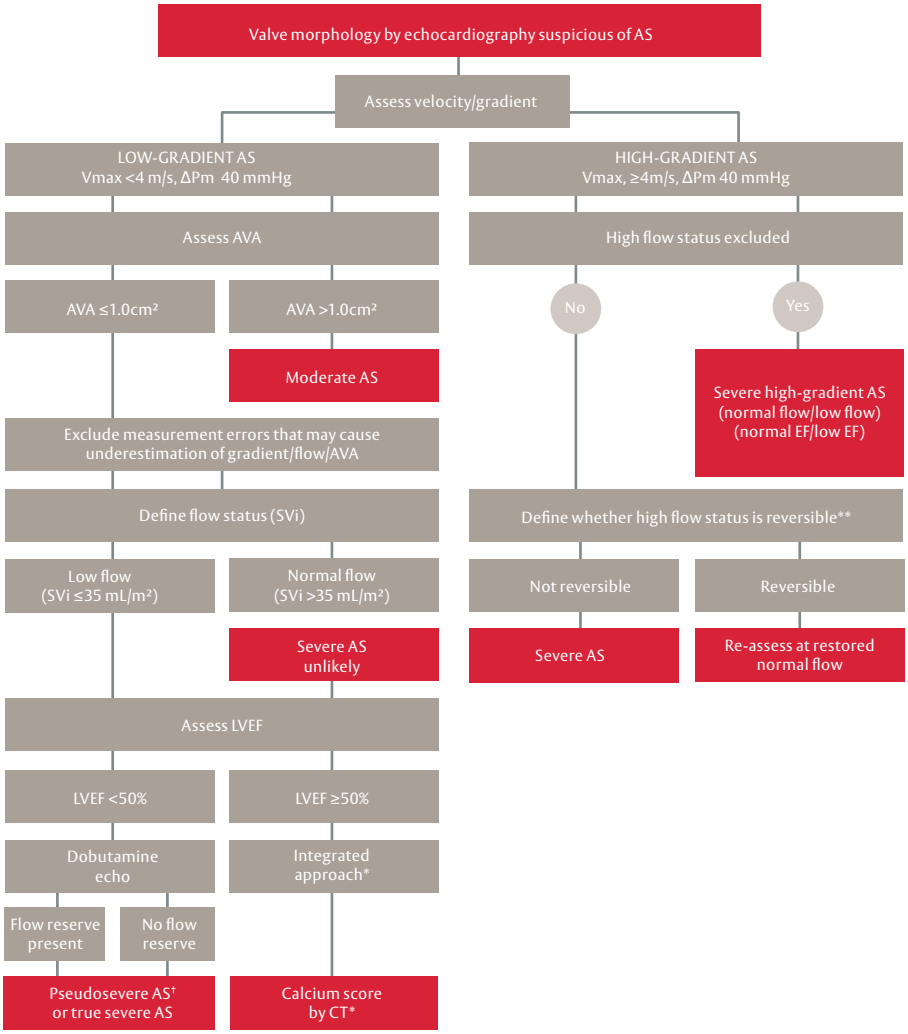
Timely and accurate diagnosis of AS is essential. After onset of symptoms, average survival in patients with severe AS is 50% at 2 years, and 20% at 5 years.[4]

Clinical Evaluation and Auscultation: typical symptoms of AS (i.e. signs of heart failure) alongside the use of auscultation[5] and identification of a systolic murmur.[2]

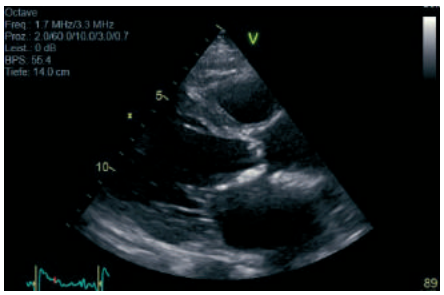
Echocardiography: the key diagnostic tool. It confirms the presence of AS, assesses the degree of valve calcification, left ventricular (LV) function and wall thickness, and provides prognostic information.[5] Doppler echocardiography is preferred when assessing AS severity. A stepwise integrated approach 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.[5]

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.[5]

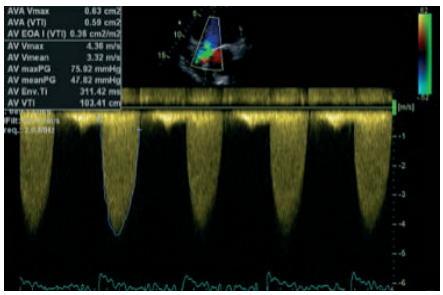
Echocardiographic criteria for the definition of severe AS according to the ESC/EACTS guidelines[5]



*Please refer to Table 6 in the ESC/EACTS guidelines for further detail. **High flow may be reversible in settings such as anaemia, hyperthyroidism, arteriovenous shunts. †Pseudosevere AS is defined by an increase to an AVA >1.0cm² with flow normalisation.
ΔPm, mean transvalvular pressure gradient; AS, aortic stenosis; AVA, aortic valve area; CT, computed tomography; EF, ejection fraction; LVEF, left ventricular ejection fraction; SVi, stroke volume index; Vmax, peak transvalvular velocity.



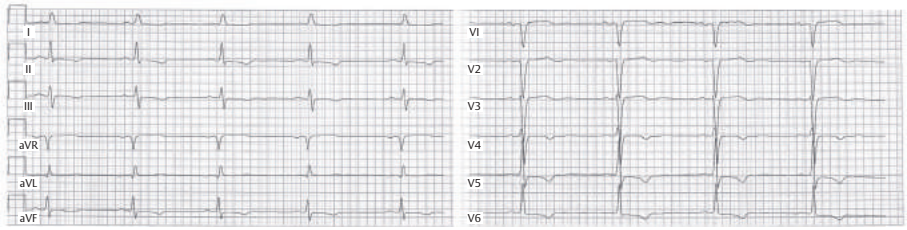
Echocardiographic depiction of severe aortic stenosis with subsequent reduction of valve orifice in the parasternal long axis view.



Echocardiographic depiction of a severe transaortic valve gradient (continuous wave Doppler) in the apical 5-chamber view.

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.[5] In such cases, the following tests may be utilised:

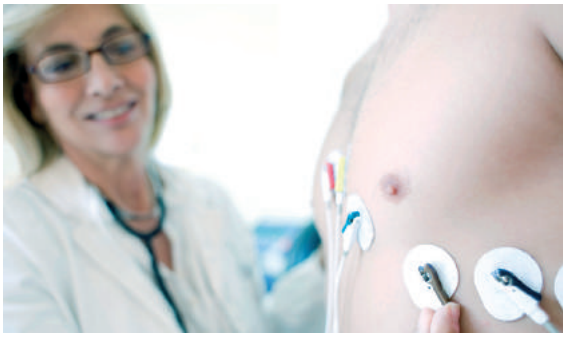
- **Electrocardiogram:** monitor for signs of LV hypertrophy.[6]



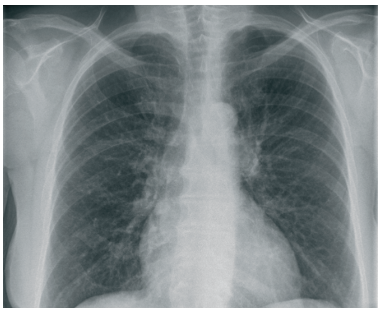
Electrocardiogram of a patient with severe aortic stenosis (Paper speed 50mm/s; 10mm/mV; filter 40Hz). Signs of left ventricular hypertrophy (i.e. positive Sokolow-Lyon index) and T-wave depression in the inferolateral leads can be observed in the presence of normal conduction time intervals.

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.[5]

- **Exercise Testing:** this is recommended as a diagnostic aid for unmasking symptoms in physically active patients and to enable risk stratification in asymptomatic patients who have severe aortic stenosis.[5]



- **Chest X-Ray:** monitor for signs of LV hypertrophy, post-stenotic dilatation of ascending aorta, or potential signs of pulmonary oedema.[6]
- **Multi-slice Computed Tomography:** this is a cornerstone in the peri-interventional work-up of patients considered for transcatheter aortic valve implantation (e.g. evaluation of the severity of aortic disease).[6]



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

- **Invasive Evaluation:** coronary angiography and/or right heart catheterisation, the latter is used for a more accurate assessment of haemodynamics. However it is no longer routinely performed and its use is restricted to when non-invasive tests are inconclusive.[5,6]

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.[1,7]

Key Considerations During Patient Examination[5]

- 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, comorbidities and country-specific life expectancy.

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.[5,8]

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.[9]

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.[5,9]

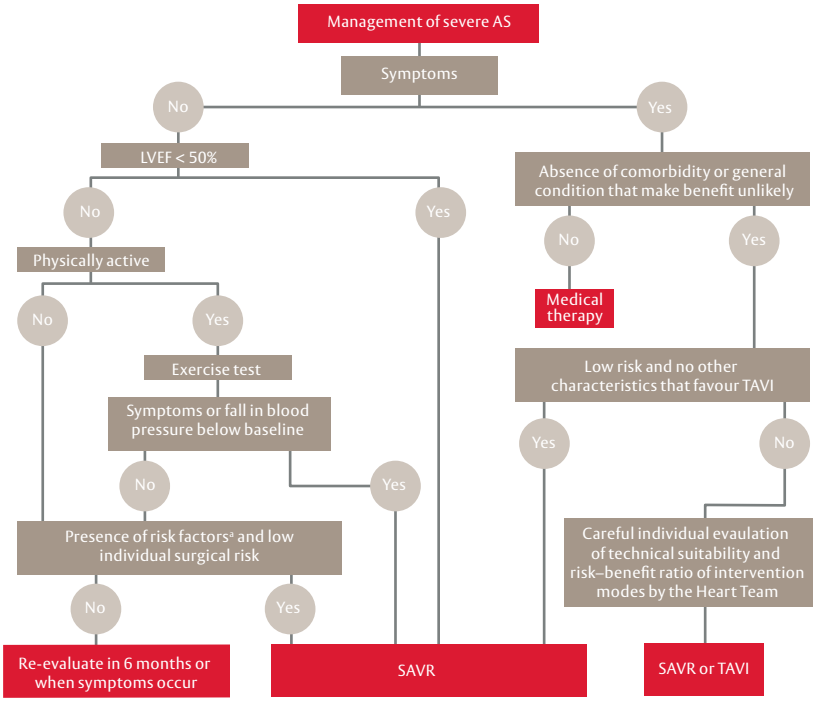
Routine risk assessment should be based on the clinical judgement of the 'Heart Team' with consideration of established scoring systems (logistic EuroSCORE and STS score).[5]

Comorbidities	Prevalence in patients with severe symptomatic AS[9]
• Peripheral artery disease • Left ventricular dysfunction • Chronic obstructive pulmonary disease • Diabetes • Cancer • Previous coronary artery bypass graft	10–30%
• Coronary artery disease • Mitral regurgitation • Atrial fibrillation • Cerebrovascular disease	30–50%
• Pulmonary hypertension • Chronic kidney disease • Hypercholesterolaemia	50–70%
• Hypertension	>70%

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]

ESC/EACTS AS Treatment Guidelines[5]



[a]Surgery should be considered if one of the following is present: peak velocity >5.5 m/s; severe valve calcification + peak velocity progression ≥0.3 m/s per year; markedly elevated neurohormones (>threefold age- and sex-corrected normal range) without other explanation; severe pulmonary hypertension (systolic pulmonary artery pressure >60 mmHg).
AS, aortic stenosis; LVEF, left ventricular ejection fraction; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

Aortic valve interventions should only be performed in centres with structured collaboration between cardiology and cardiac surgery departments, including a Heart Team (heart valve centres).[5]

The ESC/EACTS treatment guidelines for AS were updated in 2017[5] following consideration of noteworthy clinical trial data, including those from PARTNER II.[10,11] 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.

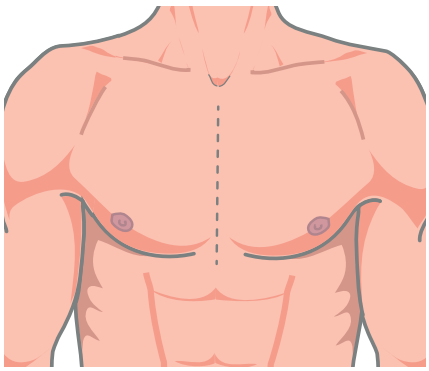
The ESC/EACTS treatment guidelines make the following recommendations when selecting the treatment option for patients with symptomatic aortic stenosis[5]:

- 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% or 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.

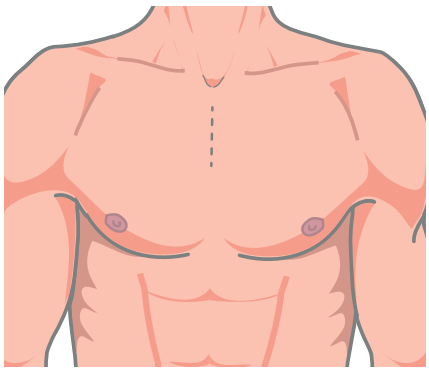
Treatment Options

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.[12]



Conventional surgery: full sternotomy

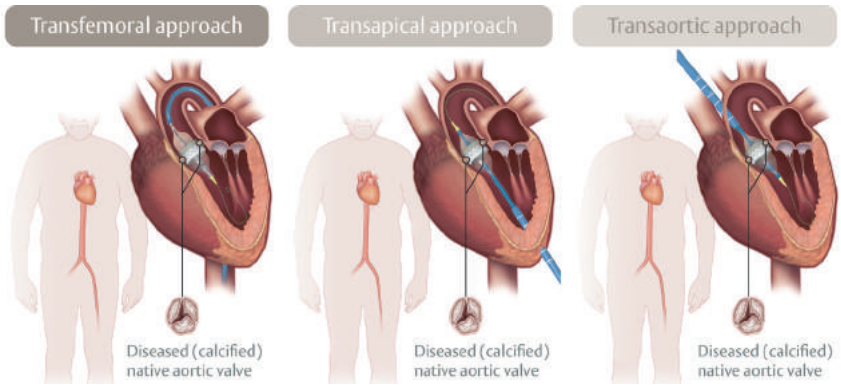


Minimally invasive: mini-sternotomy

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.[10] Two other alternatives, the transapical (TA) or transaortic (TAo) approaches, can be used if TF access is not feasible, due to anatomical contraindications.[13]



TAVI is recommended in patients 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 and frailty.[5]

The PARTNER Trials, large randomised studies using the Edwards SAPIEN valves, evaluated TAVI as a treatment option in symptomatic patients with severe AS.[10-11,14-17]

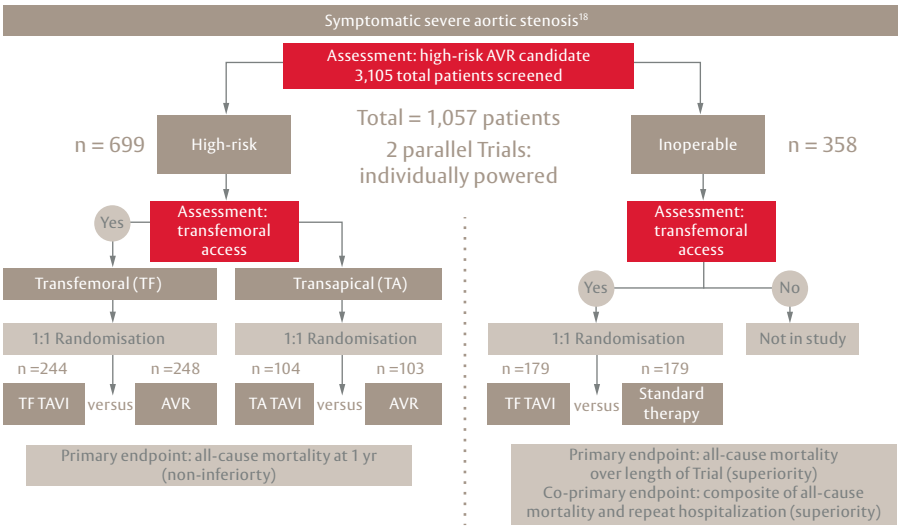
The PARTNER Trials – Placement of AoRtic TraNscathetER Valve

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, 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 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 haemodynamic 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[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**).

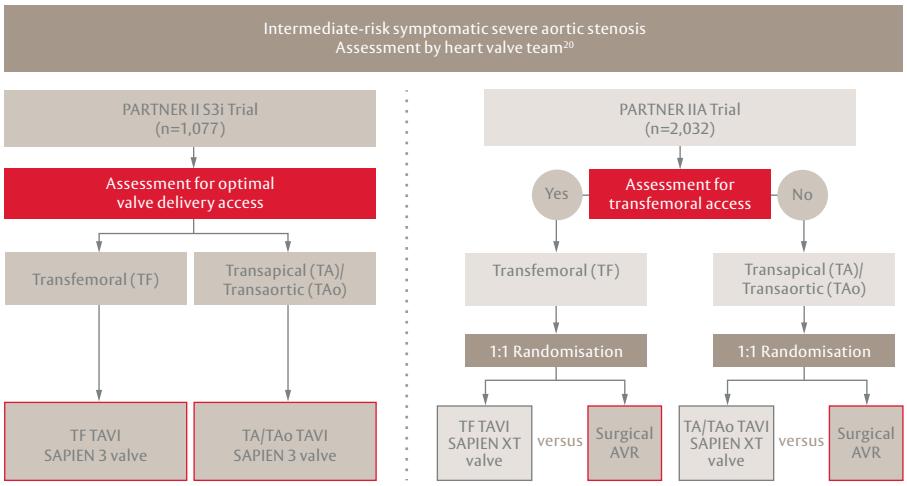
Results at 5 years: all-cause mortality 71.8% (TAVI) vs. 93.6% (sAVR) (***p*<0.0001**).

Clinical implication: TAVI should be 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 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.[10,11,19] 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.[10,11,19]



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=1,011, 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**).

(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 (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**).

"TAVI might be the preferred treatment alternative in intermediate-risk patients with symptomatic severe aortic stenosis"[11]

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

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

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.

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.[21]
- **Shorter Length of Hospital Stays versus sAVR**
  Mean hospital stay of 9.76 vs. 12.01 days with sAVR (***p*<0.001**).[22]
  Time in intensive care 2 vs. 4 days with sAVR (***p*<0.001**).[10]
- **Faster Recovery versus sAVR**
  TAVI is a less invasive treatment and shortens the recovery time compared to sAVR.[23]
- **Better Quality of Life (QoL)**
  Significantly more rapid improvements in measures of QoL vs. sAVR.[24]
- **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.[25]

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.[16,26] Registry data investigating outcomes in patients who had undergone successful TAVI reinforced these findings and demonstrated sustained efficacy and excellent haemodynamics at 5 years and beyond.[27]

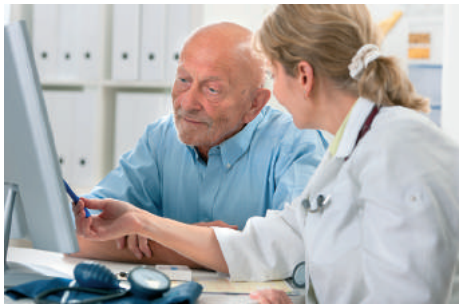
Long-term Benefits to Patients

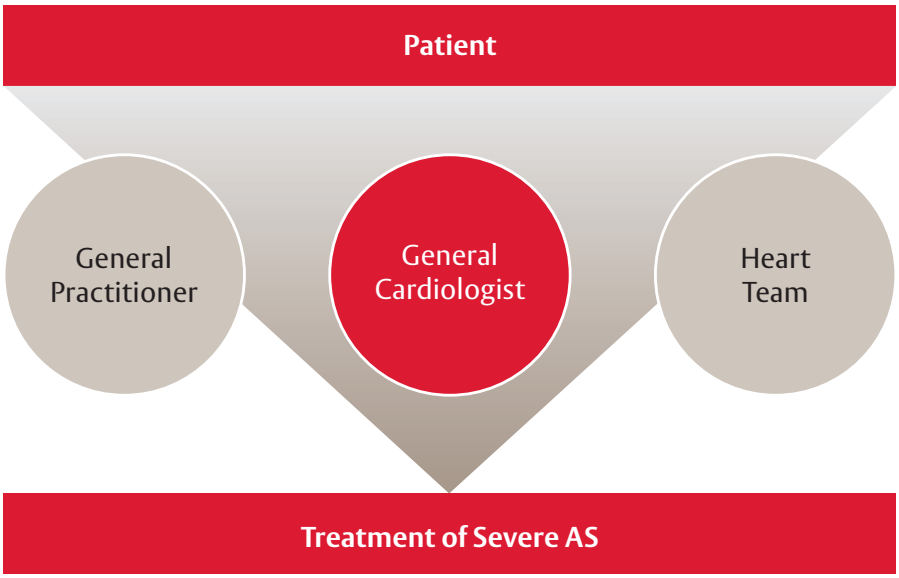
- **Preservation or Improvement in LV function**
  Better ejection fraction (50.2%) vs. sAVR (40.9%) (***p*=0.003**) in those with normal baseline ejection fraction (>50%).[28]
  In those with a low baseline ejection fraction (~34%) TAVI patients had better recovery to normal ejection fraction at the 1-year follow-up (58%) vs. sAVR (20%).[29]
- **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.[30]
- **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**).[17]
  Increased median survival from 1 year without treatment to 2.5 years following TAVI.[17]

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

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