

# Aortic Stenosis: an Overview

Clinical Evaluation, 2021 ESC/EACTS  
Guidelines and Treatment: from  
Surgery to current Indications for TAVI



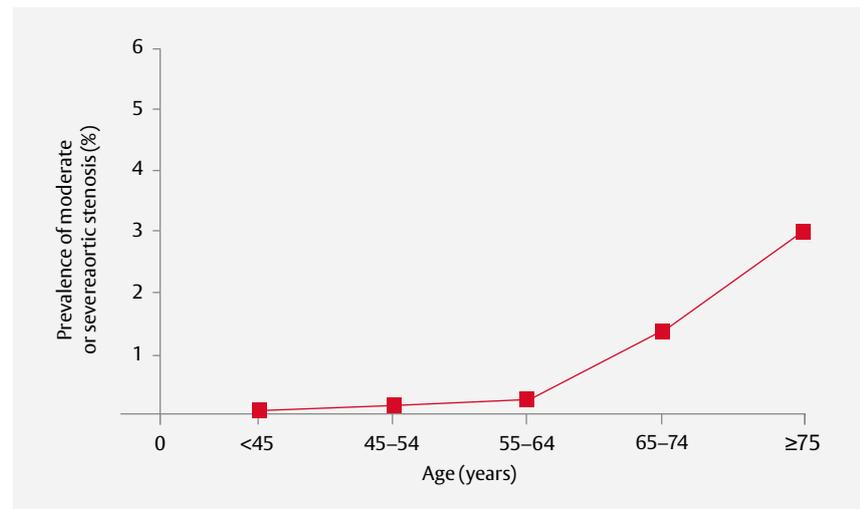
Edwards

## Aortic Stenosis

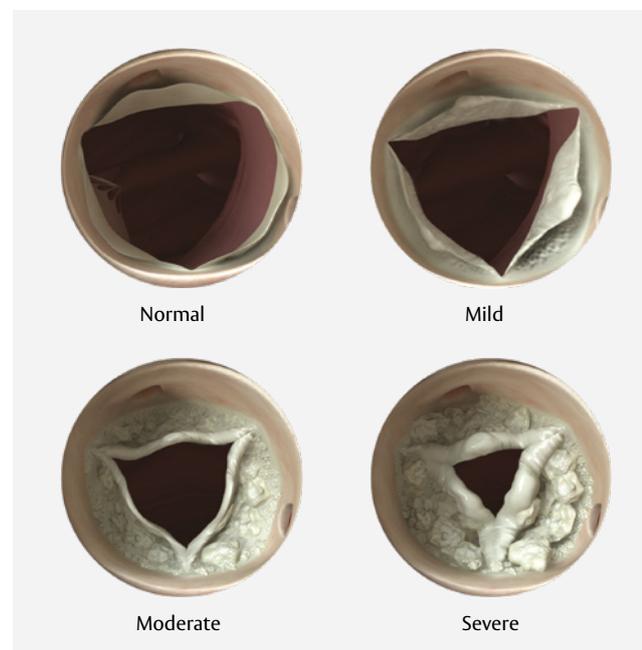
Aortic stenosis (AS) is potentially a life-threatening valvular heart disease, most commonly occurring in elderly patients due to age-related aortic valve calcification.

*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%.<sup>1</sup>*

### Prevalence of AS by Age<sup>1</sup>



*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 severe AS.<sup>2</sup>*



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.<sup>3</sup>

# 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.<sup>4</sup>

## Clinical Evaluation and Auscultation:

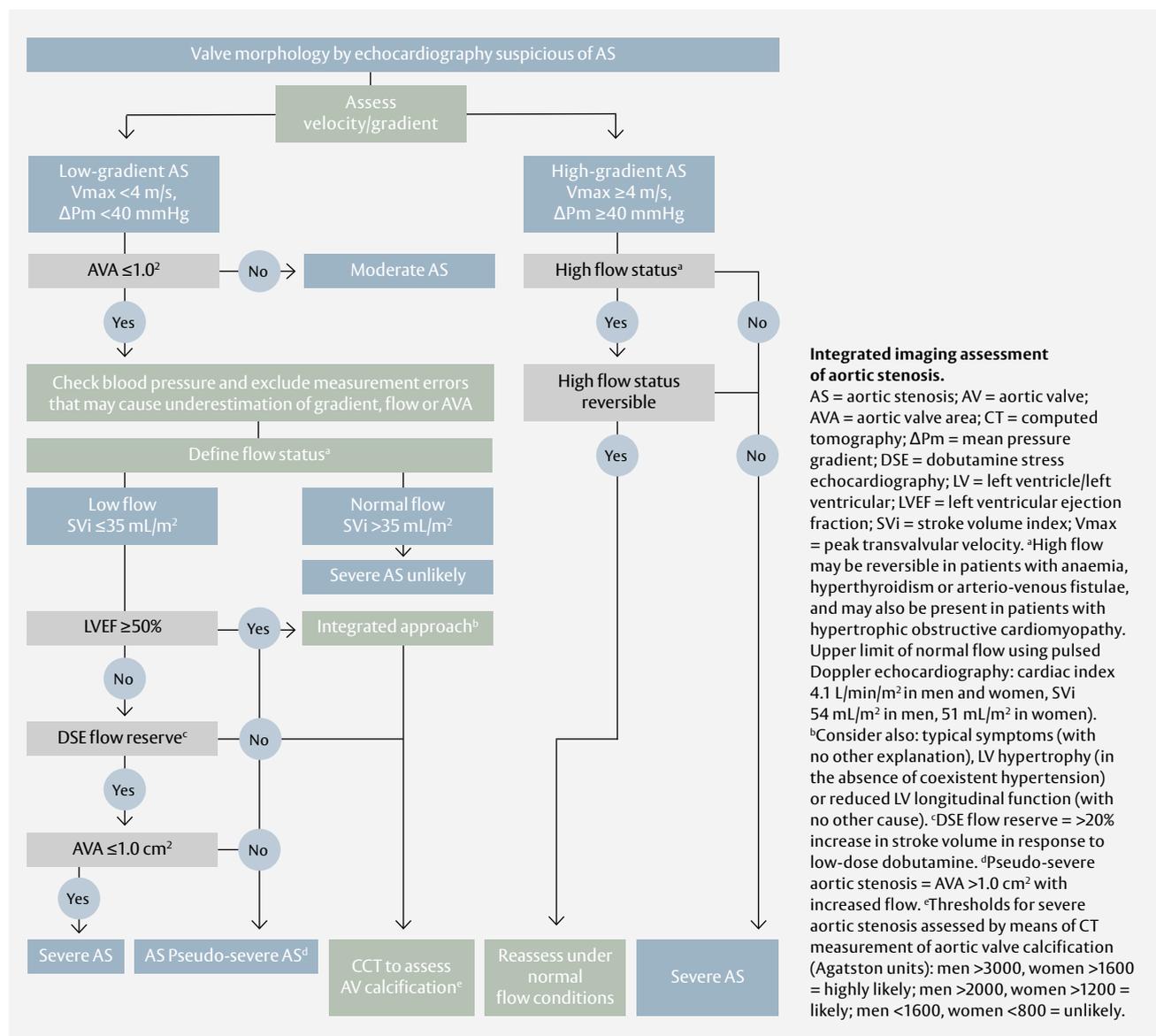
Typical symptoms of AS (i.e. signs of heart failure) alongside the use of auscultation and identification of a systolic murmur.<sup>5</sup>

## 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.<sup>6</sup> 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.<sup>6</sup>

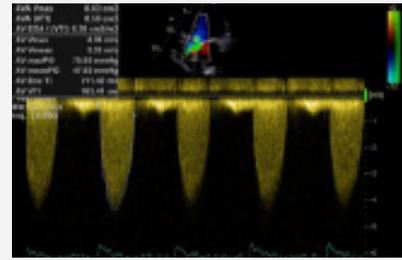
## Echocardiographic criteria for the definition of severe AS according to the ESC/EACTS guidelines



# Key Echocardiographic Measurements



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

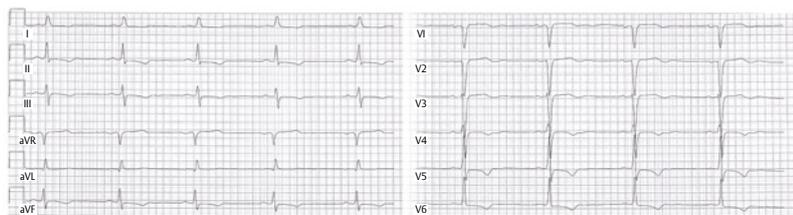


Echocardiographic depiction of a severe transaortic valve gradient (continuous wave Doppler) in the apical 5-chamber view.

## 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.<sup>5</sup> In such cases the following tests may be utilised:

- **Electrocardiogram:** Monitor for signs of LV hypertrophy.<sup>7</sup>



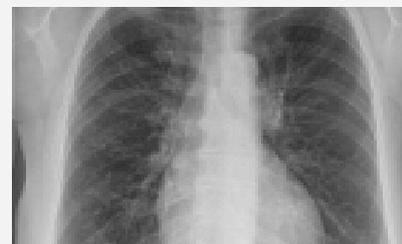
Electrocardiogram of a patient with severe aortic stenosis (Paper speed 50mm/s; 10mm/mV; filter 40Hz). Signs of left ventricular hypertrophy (i.e. positive Sokolow-Lyon index) and T-wave depression in the inferolateral leads can be observed in the presence of normal conduction time intervals.

*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.<sup>6</sup>*

- **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.<sup>6</sup>

- **Chest X-Ray:** Monitor for signs of LV hypertrophy, post-stenotic dilatation of ascending aorta, or potential signs of pulmonary oedema.<sup>7</sup>

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



- **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).<sup>7</sup>
- **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.<sup>6,7</sup>

# Patient evaluation

It is advised that patients in need of treatment are promptly identified and referred to the Heart Team. Once symptoms appear, untreated patients have a poor prognosis.<sup>1,8</sup>

## Key Considerations During Patient Examination<sup>6</sup>

- Does the patient have symptoms?
- Are symptoms most likely related to the present degree of AS?
- Is AS severe?
- What is the patient's age?
- 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?

The 2021 ESC/EACTS VHD Guidelines recommend TF-TAVI as preferred mode of intervention\* in patients† ≥75 years of age, as well as for additional patient groups <75 years of age.

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.<sup>9</sup> Regardless, AVR should be performed promptly due to the mortality risk if such patients are left untreated.<sup>6,10</sup>

## 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 symptomatic severe AS.<sup>11</sup>

## Risk Assessment

Comorbidities place patients with symptomatic severe AS at risk of procedural complications and mortality, and are a key consideration in risk assessment and treatment decisions.<sup>6,11</sup>

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).<sup>6</sup>

Comorbidities	Prevalence in patients with symptomatic severe AS <sup>11</sup>
• Peripheral artery disease	10–30%
• Left ventricular dysfunction	
• Chronic obstructive pulmonary disease	
• Diabetes	
• Cancer	
• Previous coronary artery bypass graft	
• Coronary artery disease	30–50%
• Mitral regurgitation	
• Atrial fibrillation	
• Cerebrovascular disease	
• Pulmonary hypertension	50–70%
• Chronic kidney disease	
• Hypercholesterolaemia	
• Hypertension	>70

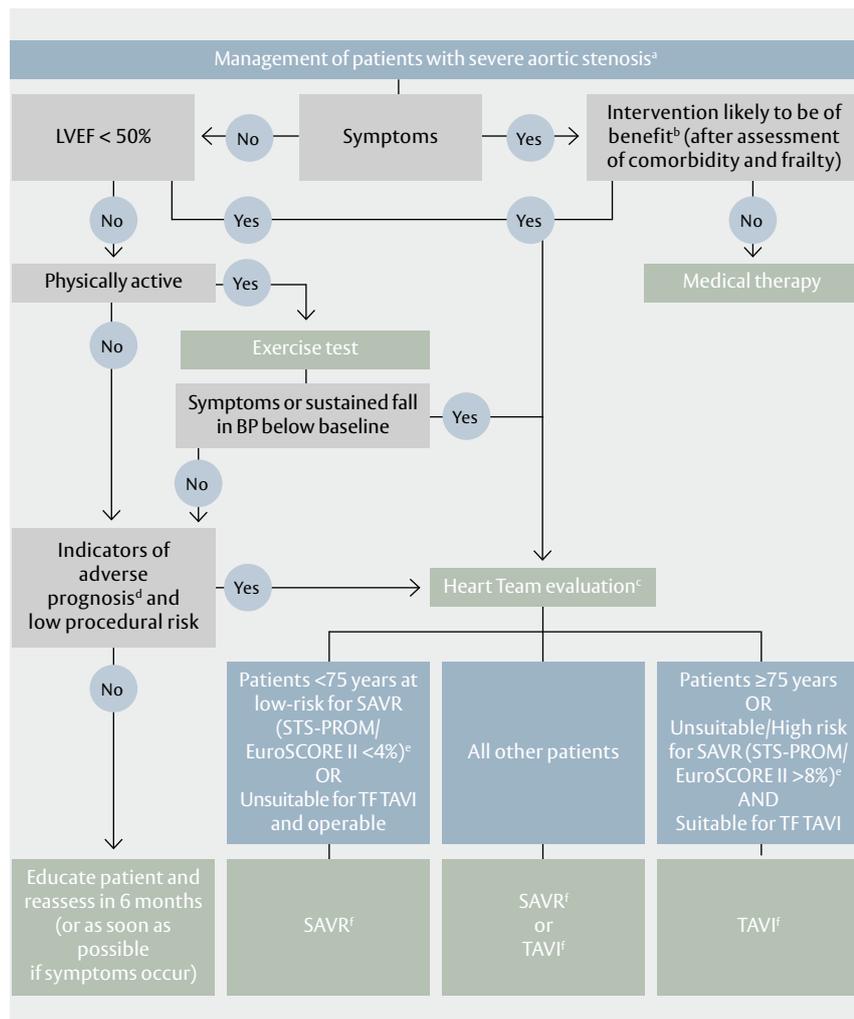
\*Based on evaluation of clinical, anatomical and procedural factors  
†With a treatment indication

# Management of Severe Aortic Stenosis

*SAPIEN 3 TAVI is now approved for severe aortic stenosis patients, independent of their surgical risk.<sup>9</sup>*

According to current 2021 ESC/EACTS VHD Guidelines, operative and interventional treatment options should be carefully considered in all patients with severe AS.<sup>6</sup>

## ESC/EACTS AS Treatment Guidelines<sup>6</sup>



**Management of patients with severe aortic stenosis.** BP= blood pressure; EuroSCORE= European System for Cardiac Operative Risk Evaluation; LVEF= left ventricular ejection fraction; SAVR= surgical aortic valve replacement; STS-PROM= Society of Thoracic Surgeons predicted risk of mortality; TAVI= transcatheter aortic valve implantation; TF= transfemoral. <sup>a</sup>Heart Team assessment based upon careful evaluation of clinical, anatomical, and procedural factors. The Heart Team recommendation should be discussed with the patient who can then make an informed treatment choice. <sup>b</sup>Adverse features according to clinical, imaging (echocardiography/CT), and/or biomarker assessment. <sup>c</sup>STS-PROM: <http://riskcalc.sts.org/stswebriskcalc/#/calculate>, EuroSCORE II: <http://www.euroscore.org/calc.html>. <sup>d</sup>If suitable for procedure according to clinical, anatomical, and procedural factors

The ESC/EACTS VHD Guidelines with treatment recommendations for AS were updated in 2021<sup>6</sup> following consideration of noteworthy clinical trial data, including those from PARTNER 3 Trial.<sup>12</sup>

The 2021 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 2021 ESC/EACTS VHD Guidelines make the following recommendations when selecting the treatment option for patients with symptomatic severe aortic stenosis<sup>6</sup>:

- Surgical AVR (SAVR) is recommended in younger patients (<75 years) at low surgical risk (STS or EuroSCORE II <4% or logistic EuroSCORE I <10%) or unsuitable for TF-TAVI and operable for SAVR
- The guidelines recommend TF-TAVI as preferred mode of intervention\* in patients<sup>†</sup> ≥75 years of age, as well as for additional patient groups <75 years of age
- In all other patients, the decision between SAVR and TAVI should be made by the Heart Team according to the individual patient characteristics
- Patients have their own values and preferences for their AS therapy, which should be part of the decision-making process<sup>6,13</sup>
- The 2021 ESC/EACTS Guidelines emphasise the need for patients to understand and decide on their preferred treatment<sup>6</sup>

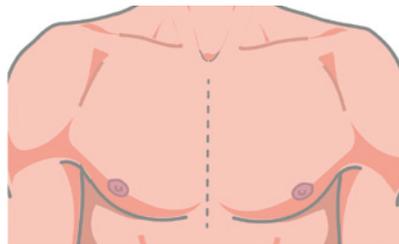
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*TF-TAVI is the preferred mode of intervention\* in patients<sup>†</sup> ≥75 years of age, as well as for additional patient groups <75 years of age*

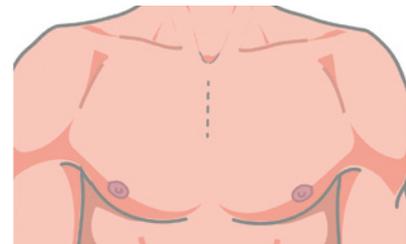
## Treatment Options

### Surgical Aortic Valve Replacement

SAVR has been the established treatment of choice for many years in the treatment of symptomatic patients with severe AS.<sup>14</sup>



Conventional surgery: full sternotomy



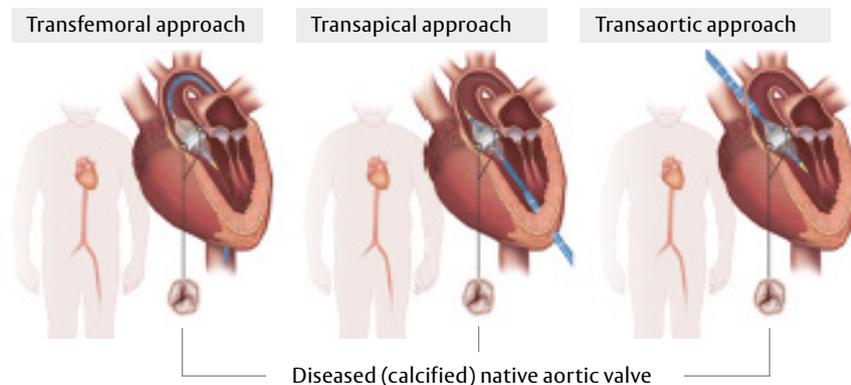
Minimally invasive: mini-sternotomy

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.

*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.<sup>9,12,15,16,18,21</sup>*

### Transcatheter Aortic Valve Implantation

This less-invasive, beating heart procedure is commonly performed via TF access, which reduces patient time in intensive care.<sup>15</sup> Other alternatives, for example, the transapical (TA) or transaortic (TAo) approaches, can be used if TF access is not feasible, due to anatomical contraindications.<sup>17</sup>



TF-TAVI is recommended as the preferred mode of intervention\* in patients<sup>†</sup>  $\geq 75$  years of age, as well as for additional patient groups  $< 75$  years of age.

Both SAVR and TAVI are recommended for the treatment of patients at increased surgical risk (STS $\geq 4\%$ ). 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.<sup>6</sup>

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.<sup>9,12,15,16,18,21</sup>

\*Based on evaluation of clinical, anatomical and procedural factors  
†With a treatment indication

# The PARTNER Trials – Placement of AoRtic TraNscathetER Valve

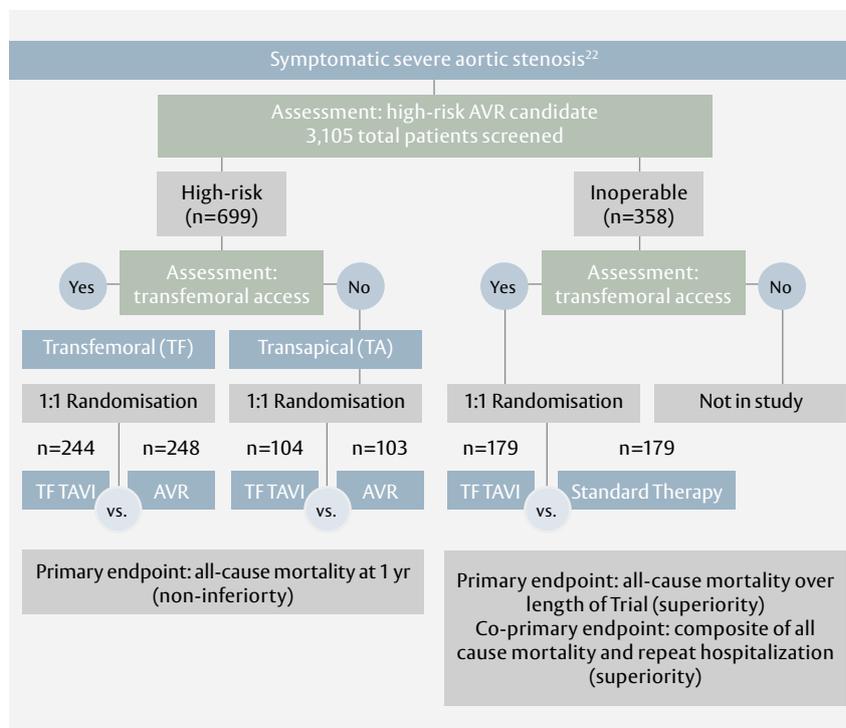
## The PARTNER Trial

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<sup>19,20</sup>
- Cohort B: standard therapy versus TAVI in inoperable patients<sup>18,21</sup>

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



## Cohort A – High-risk<sup>19,20</sup>

**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.

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*Conclusion: TAVI has demonstrated benefits compared to standard medical therapy in inoperable patients.<sup>18,21</sup>*

#### **Cohort B – Inoperable<sup>18,21</sup>**

**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.

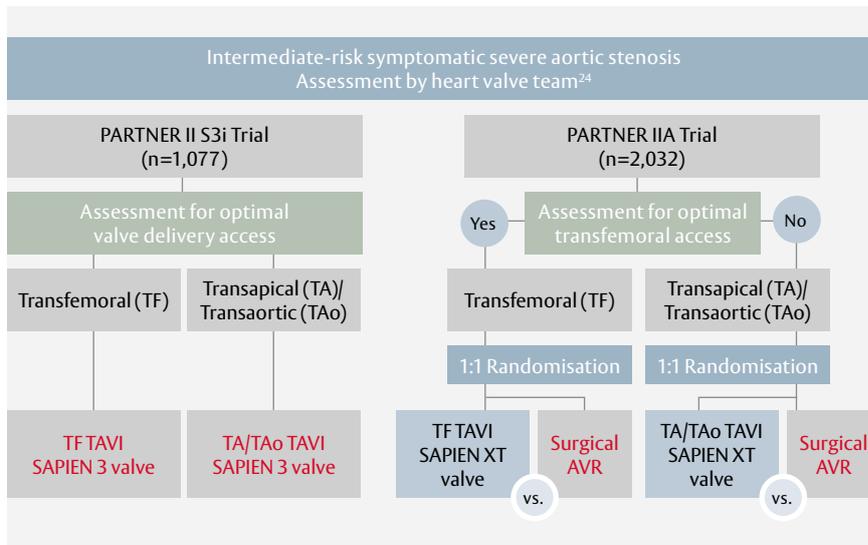
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*“TAVI might be the preferred treatment alternative in intermediate-risk patients with symptomatic severe aortic stenosis.”<sup>16</sup>*

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

## **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.<sup>15,16,23</sup> 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.<sup>16</sup> This registry was used to compare the outcomes of patients treated with TAVI (from PARTNER II S3i) and SAVR (from PARTNER IIA), using a propensity score analysis.<sup>16,23</sup>



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

### TAVI versus SAVR in Patients at Intermediate-risk (PII A)<sup>15</sup>

**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 with 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)<sup>16,23</sup>

**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 (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 ( $p < 0.0001$ ) and superiority of TAVI compared with 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.*

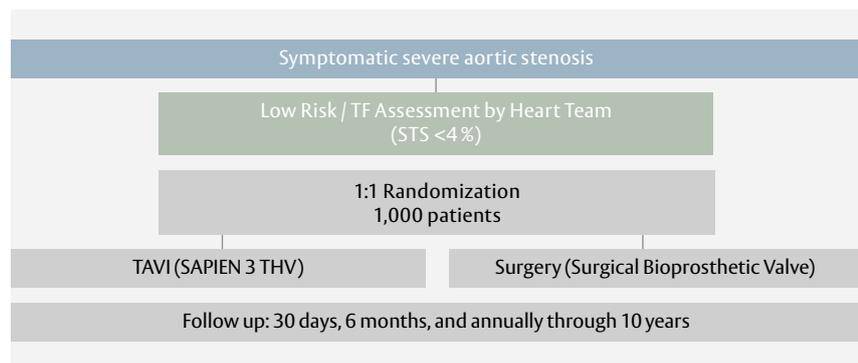
## The PARTNER 3 Trial (SAPIEN 3 TAVI in low risk patients)

*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.<sup>9,12</sup>*

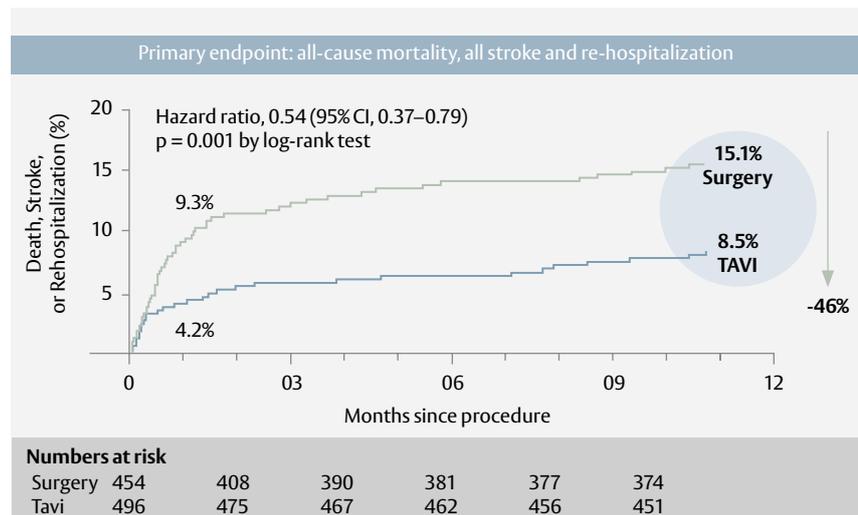
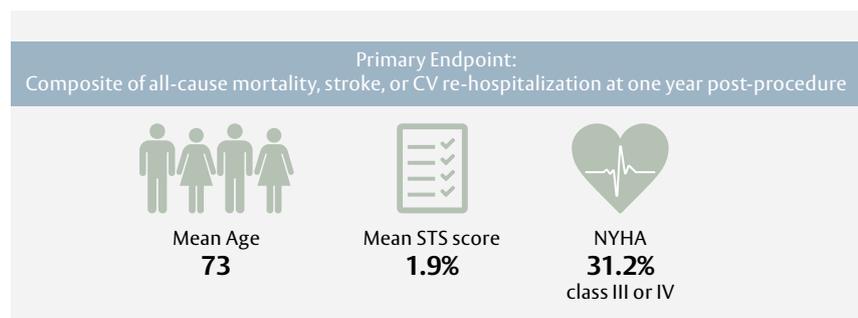
Previous TAVI RCTs showed that, in patients who were at intermediate or high risk for death with surgery, TAVI was either superior or non-inferior to standard therapies, including SAVR. There was insufficient evidence regarding the comparison of the two procedures in patients who are at low risk.

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 is superior to surgery in patients with severe aortic stenosis at low-risk for surgery.<sup>9</sup>*



### 2-year follow-up<sup>25</sup>

The prolonged follow-up, to 2 years, continues to show a statistical benefit in favour of SAPIEN 3 TAVI compared with SAVR

– 17.4% vs 11.5% (absolute difference 5.9%; HR 0.63 [95% CI, 0.45 to 0.88]; p=0.007)

### TAVI versus SAVR in Patients at Low-risk (PIII)<sup>25</sup>

**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).

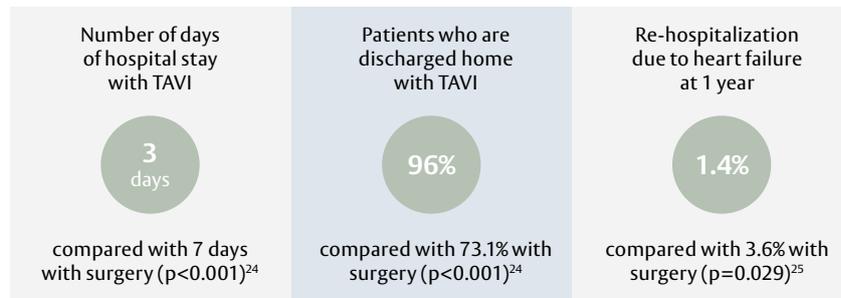
### Superior to surgery for the outcomes that matter most

	30 days <sup>12</sup>		1 year <sup>12</sup>		2 years <sup>24+</sup>	
	SAPIEN 3 TAVI	SAVR	SAPIEN 3 TAVI	SAVR	SAPIEN 3 TAVI	SAVR
Stroke	0.6%	2.4%	1.2%	3.1%	2.4%	3.6%
HR (95% CI)	0.25 (0.07 to 0.88)		0.38 (0.15 to 1.00)		0.66 (0.31 to 1.40)	
Death or disabling stroke	0.4%	1.3%	1.0%	2.9%	3.0%	3.8%
HR (95% CI)	0.30 (0.06 to 1.51)		0.34 (0.12 to 0.97)		0.77 (0.39 to 1.55)	
New AF	5.0%	39.5%	7.0%	40.9%	7.9%	41.8%
HR (95% CI)	0.10 (0.06 to 0.16)		0.13 (0.09 to 0.20)		-	

‡ Prolonged follow-up  
Length of the index hospitalisation was 3 days for TAVI and 7 days for SAVR (p<0.001). Composite of death or a low KCCQ overall summary score at 30 days was 3.9% for TAVI compared with 30.6% for SAVR (p<0.001), this result was confirmed using multiple imputation for missing data.

### Quality of Life improvements

With the SAPIEN 3 valve, low-risk patients can expect to resume their everyday lives rapidly post-procedure.<sup>9,12,26</sup>



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*Early diagnosis of severe AS and timely referral to a Heart Team is essential to direct each patient toward their best treatment option*

## 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.<sup>26,27</sup>
- **Shorter Length of Hospital Stays versus SAVR**  
Median hospital stay of 4 vs. 9 days with SAVR.<sup>16</sup> Time in intensive care 2 vs. 4 days with SAVR ( $p < 0.001$ ).<sup>15</sup>
- **Faster Recovery versus SAVR**  
TAVI is a less invasive treatment and shortens the recovery time compared with SAVR.<sup>28</sup>
- **Better Quality of Life (QoL)**  
Significantly more rapid improvements in measures of QoL vs. SAVR.<sup>29</sup>
- **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.<sup>30</sup>

### 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.<sup>20,31</sup> Registry data investigating outcomes in patients who had undergone successful TAVI reinforced these findings and demonstrated sustained efficacy and excellent haemodynamics at 5 years.<sup>32</sup>

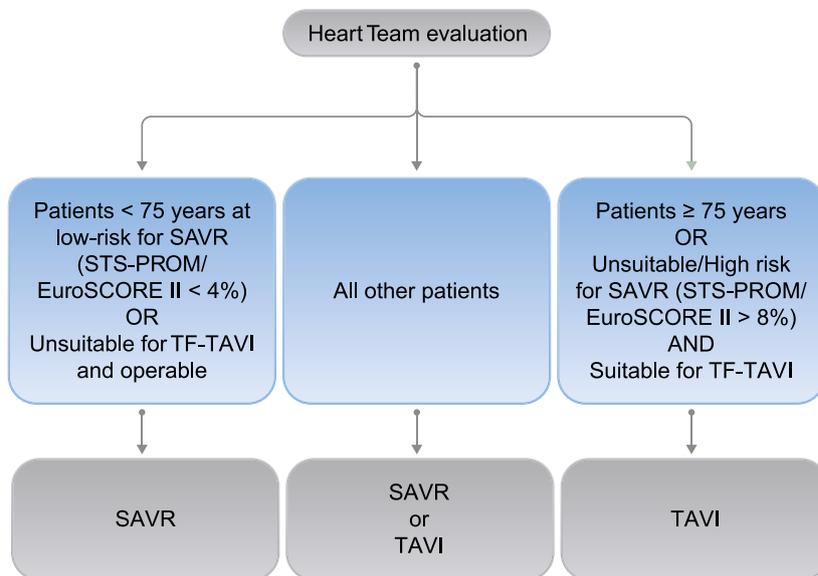
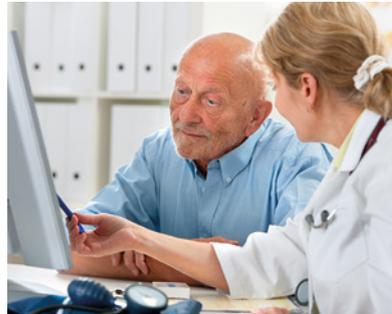
### Long-term Benefits to Patients

- **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 ( $> 50\%$ ).<sup>33</sup> In those with a low baseline ejection fraction ( $\sim 34\%$ ) TAVI patients had better recovery to normal ejection fraction at the 1-year follow-up (58%) vs. SAVR (20%).<sup>34</sup>
- **Alleviation of Symptoms**  
Patients previously symptomatic at rest and unable to exercise (95.3% 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.<sup>35</sup>
- **Extended Life Expectancy**  
Higher rates of survival in inoperable patients with TAVI versus standard treatment at 5 years (28.2% vs. 6.4%,  $p < 0.0001$ ).<sup>21</sup> Increased median survival from 1 year without treatment to 2.5 years following TAVI.<sup>21</sup>
- **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 KCCQ score, not only at 1 month but also at 6 and 12 months.<sup>36</sup>

# 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.



*TAVI has both short- and long-term benefits for patient symptoms, recovery and quality of life*

## 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](http://www.findatavicenter.com/eu)

## Want to know more?

For information about aortic stenosis visit [www.TAVI.today](http://www.TAVI.today)  
Further material on aortic stenosis can be ordered free of charge via this website.

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