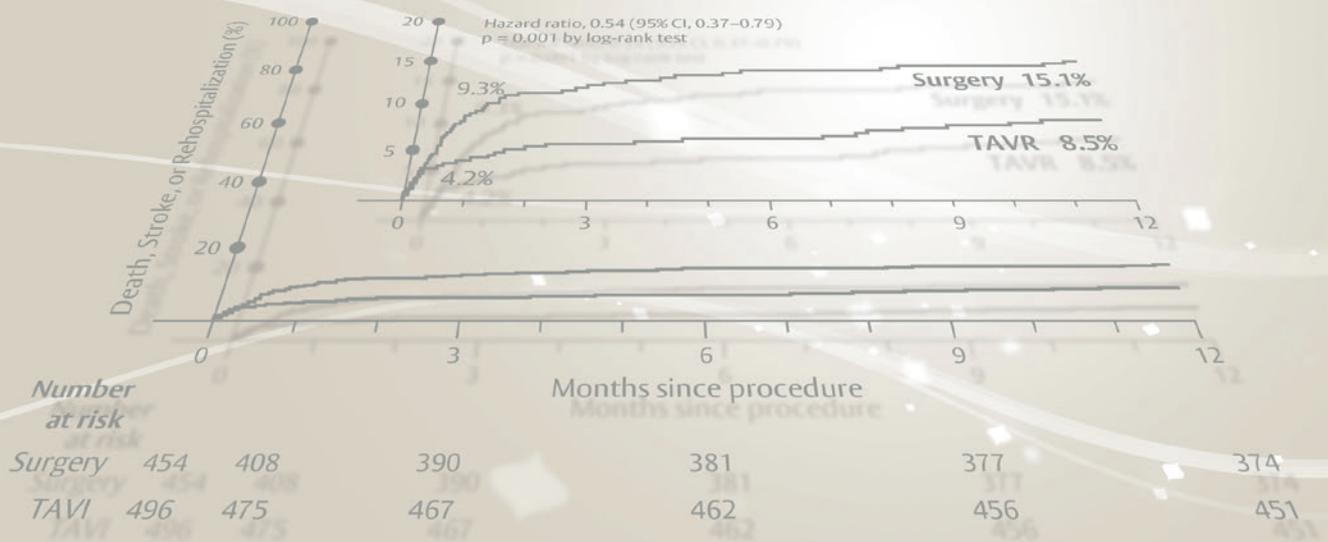
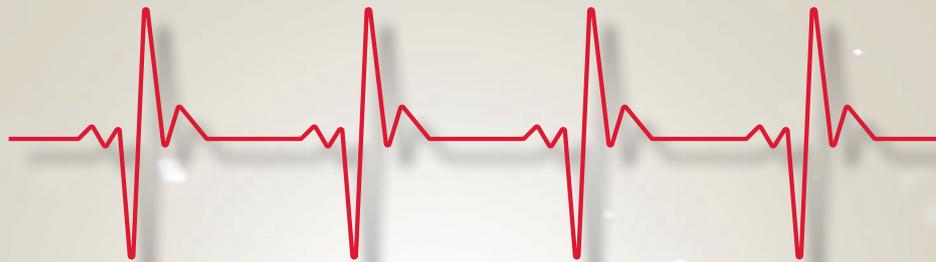


# Edwards Balloon Expandable Study Compendium

Transcatheter  
aortic valve  
implantation (TAVI)



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# Introduction

Dear Reader,

In patients with severe symptomatic aortic valve stenosis, aortic valve replacement is the only therapeutic option with a good long-term prognosis. For many decades, this necessitated open heart surgery. However, about one-third of patients were ineligible for this type of operation due to advanced age, multiple comorbidities, or an unjustifiably high surgical risk.<sup>(1)</sup> The development of transcatheter aortic valve implantation (TAVI) has, for the first time, made it possible to offer this group of patients an effective treatment. With the 2017 update of the European guidelines on the treatment of Valvular Heart Disease, TAVI has become a possible therapeutic option for severe symptomatic aortic stenosis patients at increased surgical risk (STS > 4 %).<sup>(2)</sup>

The PARTNER 3 study, presented at the ACC congress in 2019, now shows superiority of TAVI over surgical aortic valve replacement (sAVR) for low risk patients for the combined endpoint of all cause mortality, all stroke and rehospitalization.<sup>(19,20)</sup>

Aortic valve stenosis is mainly caused by degenerative changes of the valve and is therefore a problem found mostly in older people. An estimated 2 % of people over 65 and 4 % of people over 75 are affected.<sup>(3)</sup>

Due to the demographic development in our societies, we must therefore assume that the prevalence of aortic valve stenosis will further increase in the future. Without aortic valve replacement, the prognosis of patients with this disease would be poor.

In 2002, Professor Alain Cribier performed the first successful TAVI on an inoperable patient. Shortly afterwards, the companies Edwards Lifesciences and Medtronic developed improved TAVI valves and access routes, with convincing results in proof-of-concept studies. The Edwards SAPIEN valve and the CoreValve were approved in 2007. After the publication of positive outcomes in not only inoperable patients but also operable patients at high surgical risk<sup>(4,5)</sup>, TAVI was included in the 2012 ESC/EACTS guidelines for the first time. These guidelines specifically recommend TAVI for inoperable patients with severe symptomatic aortic valve stenosis<sup>(6)</sup>.

Further studies have shown TAVI to be at least as successful as surgery even in patients at intermediate risk<sup>(7)</sup>. Furthermore, the technique has been continually improved meaning that many initial issues such as increased rates of paravalvular regurgitation have now been almost completely resolved. First long-term (five-year) data does not show any signs of premature structural damage of TAVI valves resulting in loss of function<sup>(8,11)</sup>. The increased body of evidence over the past years led to the update of the 2017 ESC/EACTS guidelines and subsequent availability of TAVI for patients at increased surgical risk.

This compendium offers an overview of studies conducted with balloon expandable TAVI valves manufactured by Edwards Lifesciences – starting with the first generation SAPIEN valve leading up to the third generation SAPIEN 3 valve. It takes just one glance to see whether the patients were inoperable or operable at either high, intermediate or low surgical risk.

## TAVI milestones

- 
- 2019 • PARTNER 3 study one-year data
  - 2018 • Approval of the Edwards CENTERA valve in Europe  
• Approval of the Edwards SAPIEN 3 Ultra valve in Europe
  - 2017 • Updated ESC/EACTS Guidelines on the management of VHD  
• SOURCE 3 registry one-year data  
• SOURCE 3 registry 30-days data
  - 2016 • One-year data PARTNER II S3 study (intermediate risk)  
• One-year data SAPIEN 3 CE study (intermediate risk)  
• Two-year data PARTNER II study (Cohort A – intermediate risk)
  - 2015 • One-year data PARTNER II S3 study (high risk/inoperable)  
• One-year data PARTNER II study (Cohort B – inoperable)  
• Five-year data PARTNER study (Cohort A – high risk)
  - 2014 • Five-year data PARTNER study (Cohort B – inoperable)  
• Approval of the Edwards SAPIEN 3 valve in Europe
  - 2013 • 30-day data of the PARTNER II study (Cohort B – inoperable)
  - 2012 • First reference to TAVI in the European guidelines (ESC/EACTS)
  - 2011 • One-year data PARTNER study (Cohort A – high risk)
  - 2010 • One-year data PARTNER study (Cohort B – inoperable)  
• Approval of the Edwards SAPIEN XT valve in Europe
  - 2007 • Approval of the Edwards SAPIEN valve in Europe
  - 2004 • First TAVI valve from Edwards (SAPIEN) in clinical testing
  - 2002 • First ever successful TAVI in a human being (Prof. Alain Cribier)
  - 1992 • First TAVI valve in an animal experiment (Henning Rud Andersen)

## Guidelines

# TAVI or surgical aortic valve replacement - What do the guidelines recommend?<sup>(2)</sup>

According to the 2017 guidelines of ESC/EACTS (European Society of Cardiology/European Association for Cardio-Thoracic Surgery) the following categories of aortic stenosis can be defined:

- High-gradient severe aortic stenosis is defined as a mean gradient  $\geq 40$  mm Hg and jet velocity  $\geq 4$  m/s, where high flow status is excluded. Irreversible high flow indicates severe aortic stenosis
- Low-gradient severe aortic stenosis is defined as a valve area  $\leq 1.0$  cm<sup>2</sup>, mean gradient  $< 40$  mm Hg or stroke volume index  $\leq 35$  ml/m<sup>2</sup>
- Pseudosevere aortic stenosis is defined as left ventricular ejection fraction (LVEF)  $< 50\%$  and an increase in valve area to  $>1.0$  cm<sup>2</sup> with flow normalization. These patients should be treated for heart failure only

Intervention is indicated in:

- Symptomatic patients with severe, high-gradient aortic stenosis (mean gradient  $\geq 40$  mm Hg or peak velocity  $\geq 4.0$  m/s)
- Symptomatic patients with severe low-flow, low-gradient ( $< 40$  mm Hg) aortic stenosis with reduced ejection fraction and evidence of flow (contractile) reserve excluding pseudo-severe aortic stenosis

Intervention should be considered in:

- Symptomatic patients with low-flow, low-gradient ( $< 40$  mm Hg) aortic stenosis with normal ejection fraction after careful confirmation of severe aortic stenosis
- Symptomatic patients with low-flow, low-gradient aortic stenosis and reduced ejection fraction without flow (contractile) reserve, particularly when CT calcium scoring confirms severe aortic stenosis

Intervention should not be performed in patients with severe comorbidities when the intervention is unlikely to improve quality of life or survival.

Aortic valve interventions should only be performed in centers with both departments of cardiology

and cardiac surgery on site and with structured collaboration between the two teams, including a Heart Team (heart centers).

The choice for surgical or interventional treatment must be based on careful individual evaluation of technical suitability and weighing of risks and benefits of each treatment modality.<sup>(2)</sup>

According to surgical mortality risk, the 2017 guidelines recommend the following when selecting a treatment option for patients with severe symptomatic aortic stenosis:

- 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 (Class IB indication))
- TAVI is recommended in patients who are not suitable for sAVR as assessed by the Heart Team (Class IB indication)
- In patients who are at increased surgical risk (STS or EuroSCORE II  $\geq 4\%$  or logistic EuroSCORE I  $\geq 10\%$  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 being favoured in elderly patients suitable for transfemoral access (Class IB indication; see guidelines for more details)

The 2017 updated ESC/EACTS guidelines has allowed for more patients to benefit from TAVI.

Based on the positive outcomes of current studies on low risk patients, a discussion on how to include these findings into the next guideline update has started.

# PARTNER Study (Cohort B)

## Background

For a long time, surgical aortic valve replacement was the only effective therapeutic option in severe symptomatic aortic valve stenosis. If the patient was inoperable, their remaining life expectancy was significantly limited. Transcatheter aortic valve implantation (or TAVI) offered this group of patients the opportunity to benefit from aortic valve replacement for the first time.

## Research question

The **PARTNER study (Cohort B)** was designed to investigate whether patients with severe symptomatic aortic stenosis who were inoperable due to high surgical risk would benefit from TAVI as compared to optimized medical therapy (including balloon valvuloplasty).

## Methods

358 inoperable patients from 21 sites underwent 1:1 randomization with transfemoral (TF) TAVI vs standard treatment.

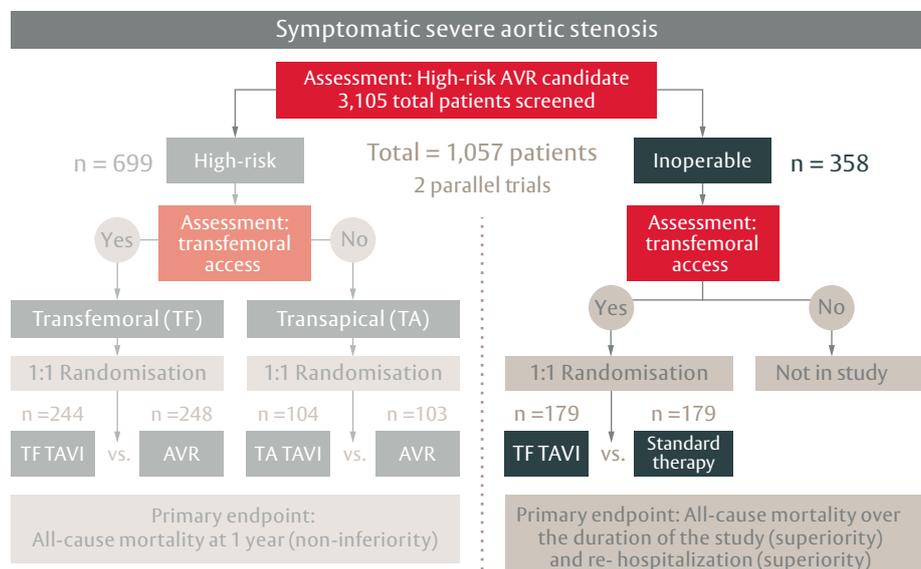
## Criteria for inclusion

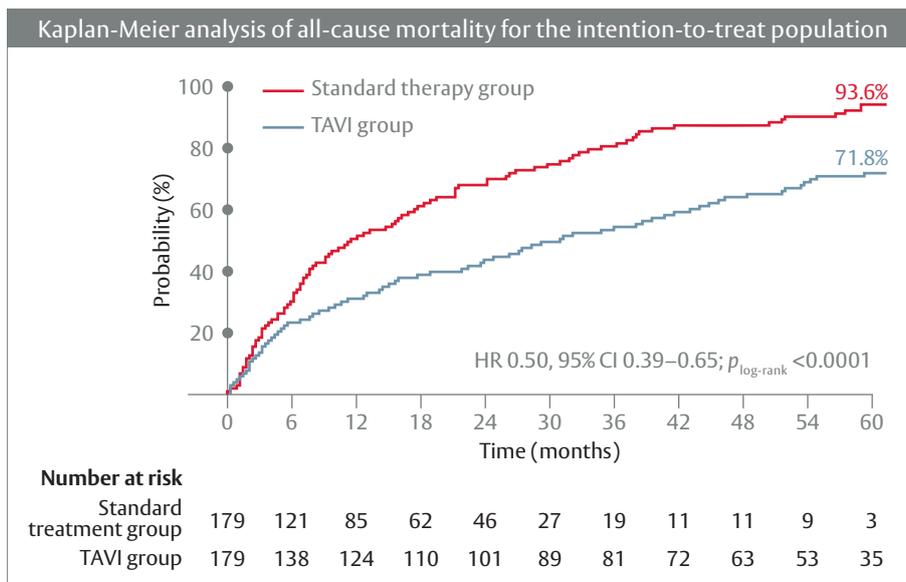
- Severe aortic valve stenosis (aortic valve area < 0.8 cm or mean valve gradient > 40 mm Hg or peak velocity > 4.0 m/s)
- Cardiac symptoms (NYHA class ≥ II)
- Inoperability (risk of death or irreversible severe morbidity of at least 50% according to the assessment of a heart team consisting of one cardiologist and two cardiac surgeons)

## Patient characteristics

179 patients received a TAVI (Edwards SAPIEN valve) and 179 received an optimized medical treatment (including balloon valvuloplasty if appropriate).

## The PARTNER Study Design





### Patient characteristics (continued)

- Mean age: 83.1 years (TAVI) vs. 83.2 years (standard therapy)
- Mean STS score: 11.2 % vs. 12.1 %
- Log. EuroSCORE: 26.4 % vs. 30.4 %
- NYHA class III or IV: 92.9 % vs. 93.9 %

### Primary endpoints

- All-cause mortality at one year, up to five years follow-up (superiority)
- Co-primary end-point: Hierarchical composite of the time to death from any cause or the time to the first occurrence of repeat hospitalization due to valve-related or procedure related clinical deterioration

### Results

At one year:

- All-cause mortality: 30.7 % TAVI vs. 50.7 % standard therapy (absolute reduction by 20 %,  $p < 0.001$ )
- Combined endpoint of death and hospitalization: 42.5 % TAVI vs. 70.4 % standard therapy ( $p < 0.001$ )
- Cardiovascular mortality: 20.5 % vs. 44.6 % ( $p < 0.001$ )
- Combined endpoint of severe stroke and mortality: 33.0 % TAVI vs. 51.3 % standard therapy ( $p < 0.001$ )
- NYHA class I or II: 74.8 % TAVI vs. 42 % standard therapy ( $p < 0.001$ )

At five years:

- All-cause mortality: 71.8 % TAVI vs. 93.6 % standard therapy ( $p < 0.0001$ )
- Sustained improvement of hemodynamic valve function without any signs of structural damage of the TAVI valves (AVA 1.52 cm<sup>2</sup> at 5 years, mean gradient 10.6 mm Hg at 5 years)

### Conclusion

For inoperable patients with severe symptomatic aortic valve stenosis, TAVI offers markedly better chances of survival and a more effective reduction of symptoms than conventional standard therapy with optimized medical treatment. In this severely ill patient group, a survival benefit is still evident even after five years. Severely abnormal hemodynamics on echocardiograms were also infrequent and not associated with excess death or reintervention for either TAVI or sAVR at 5 year follow-up<sup>(4,8)</sup>.

# PARTNER II Study (Cohort B)

## Background

The PARTNER study (Cohort B) had already shown that inoperable patients with aortic valve stenosis benefit from TAVI. Meanwhile, the Edwards SAPIEN valve used in that study was technically improved (SAPIEN XT).

## Research question

The **PARTNER II study (Cohort B)** was designed to compare transfemoral (TF) aortic valve implantation in inoperable patients with severe symptomatic aortic valve stenosis using the SAPIEN valve with its successor SAPIEN XT.

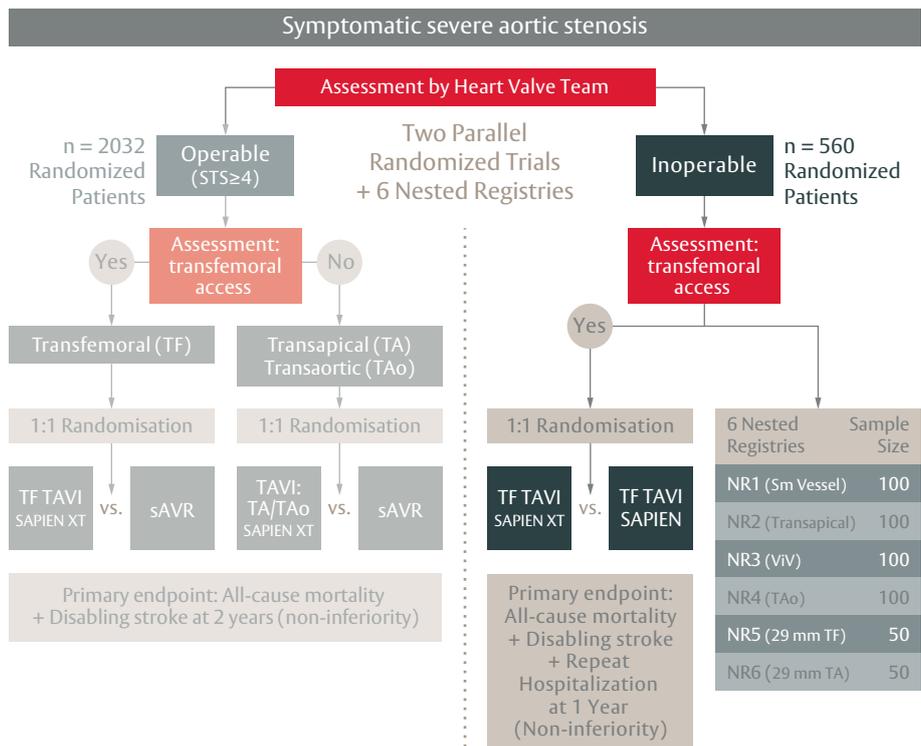
## Methods

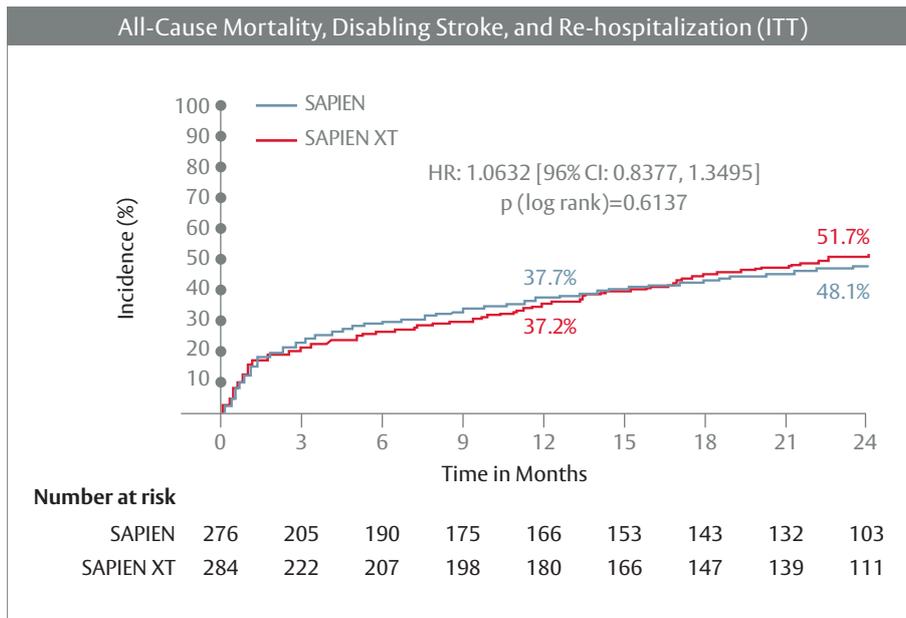
560 inoperable patients with severe symptomatic aortic valve stenosis from 28 sites in the US were included in the study. Patients were randomized to receive TF TAVI with SAPIEN or SAPIEN XT systems.

## Criteria for inclusion

- Severe aortic valve stenosis (aortic valve area < 0.8 cm or AVA index < 0.5 cm<sup>2</sup>/m<sup>2</sup> )
- Cardiac symptoms (NYHA class ≥ II)
- Inoperability (risk of death or irreversible severe morbidity of at least 50 % according to the assessment of a heart team consisting of one cardiologist and two cardiac surgeons)

## The PARTNER II Study Design





### Patient characteristics

270 patients received TAVI with the SAPIEN valve and 282 with the SAPIEN XT valve.

- Mean age: 84.6 years (SAPIEN valve) vs. 84.1 years (SAPIEN XT valve)
- Mean STS score: 11.0 % vs. 10.3 %
- NYHA class III or IV: 96.0 % vs. 96.8 %

### Primary endpoint

Composite of all-cause mortality, disabling stroke or re-hospitalization at 1 year due to symptoms of aortic valve stenosis or TAVI complications (non-inferiority).

### Results

At 30 days:

- Fewer vascular complications with SAPIEN XT valve (22.1 % vs. 15.5 %;  $p = 0.04$ ) and fewer bleeding complications necessitating transfusion with the SAPIEN XT valve 10.6 % vs. 5.3 %; ( $p=0.02$ )

At one year:

- Non-inferiority regarding the combined clinical end-point (SAPIEN valve 37.7 % vs. SAPIEN XT valve 37.2 %,  $p < 0.002$  as regards non-inferiority)
- Comparable results regarding clinical improvement (NYHA class)
- Comparable results regarding echocardiography parameters

### Conclusion

The SAPIEN XT valve was not inferior to the SAPIEN valve used in the PARTNER study in regards to the combined endpoint and there were fewer vascular complications and less severe bleeding with the new valve<sup>(9)</sup>.

# PARTNER Study (Cohort A)

## Background

The PARTNER study (Cohort B) has shown that TAVI can improve the chances of survival for inoperable patients with severe symptomatic aortic valve stenosis. However, many patients with aortic valve stenosis are basically operable, albeit at very high surgical risk. The goal of the trial was to compare TAVI to surgery in this high risk population.

## Research question

**PARTNER study (Cohort A)** was designed to investigate whether TAVI could be as good as sAVR in patients at high surgical risk and if the results could be sustained over a longer period of time.

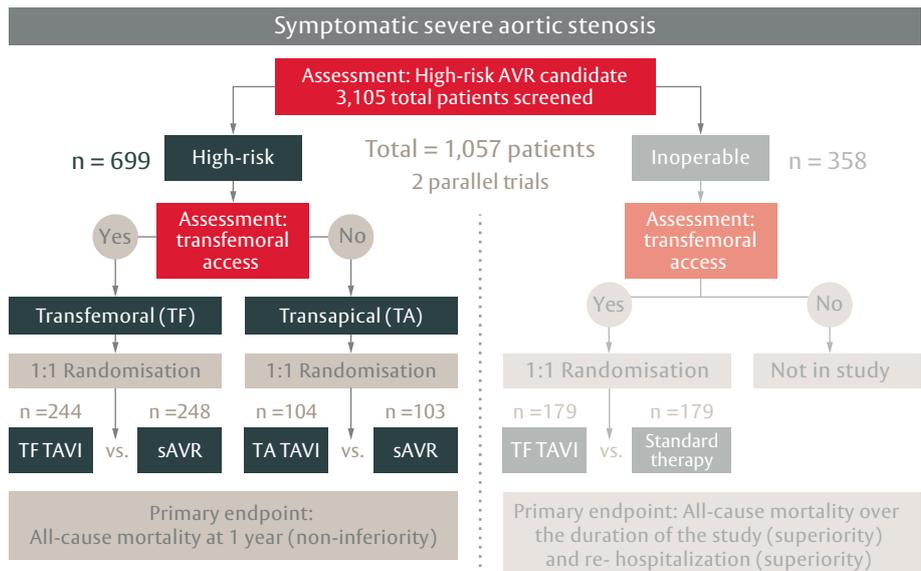
## Methods

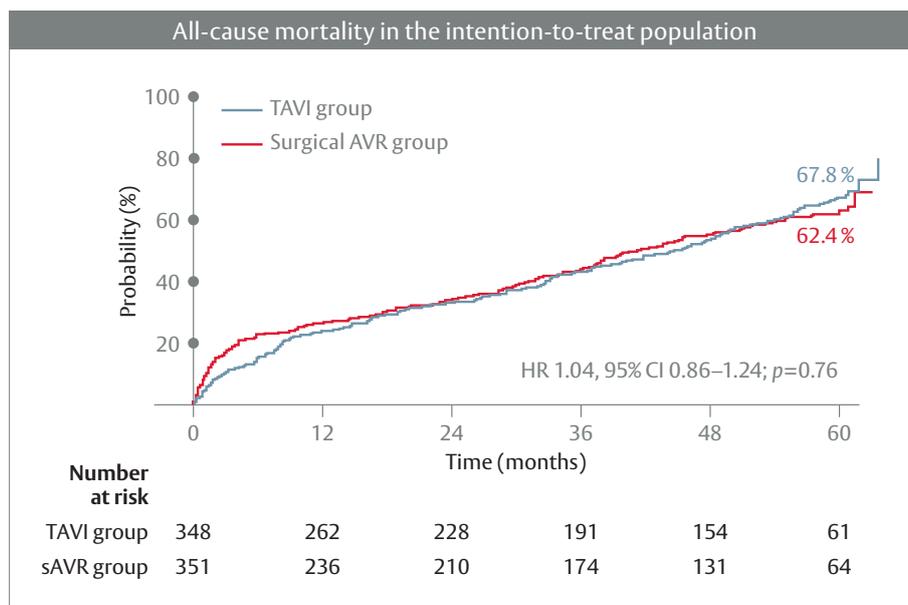
699 patients at high surgical risk from 25 sites were included in the study.

## Criteria for inclusion

- Severe aortic valve stenosis (aortic valve area < 0.8 cm<sup>2</sup> or mean gradient > 40 mm Hg or peak velocity > 4.0 m/s)
- Cardiac symptoms (NYHA class ≥ II)
- High surgical risk (risk of death or irreversible severe morbidity at least 15% according to the assessment of a heart team of cardiologists and cardiac surgeons – STS score ≥ 10)

## The PARTNER Study Design





### Patient characteristics

The patients were randomized separately depending on the best access route – transfemoral or transapical. In the transfemoral access group, 244 patients received TAVI (TF) and 248 received surgical aortic valve replacement. In the transapical access group, 104 patients received TAVI (TA) and 103 received surgical aortic valve replacement.

- Mean age: 83.6 years (TAVI) vs. 84.5 years (surgery)
- Mean STS score: 11.8 % vs. 11.7 %

### Primary endpoint

All-cause mortality at one year (non-inferiority of TAVI compared with surgical aortic valve replacement).

### Results

At one year:

- All-cause mortality: 24.2 % TAVI vs. 26.8 % sAVR ( $p=0.44$ )

At two years:

- All-cause mortality: 33.9 % TAVI vs. 35 % sAVR ( $p=0.78$ )
- No long-term difference in the frequency of strokes after an initial increased rate with TAVI around the time of the procedure ( $p=0.52$ )

At five years:

- All-cause mortality: 67.8 % TAVI vs. 62.4 % sAVR ( $p=0.76$ )
- Sustained improvement of hemodynamic valve function without any signs of structural damage of the TAVI valves

### Conclusion

With a comparable clinical outcome, TAVI constitutes a safe alternative to sAVR for patients with severe symptomatic aortic valve stenosis at high surgical risk (STS score  $\geq 10$ ), even in the long term. At five years, there were no signs of structural damage or degeneration of the TAVI valves<sup>(10, 11)</sup>.

# PARTNER II S3 Study

## Background

The SAPIEN 3 valve was able to solve some technical problems seen with prior generations. For example, the SAPIEN 3 valve has an outer skirt sewn around the outside of the valve frame in order to prevent paravalvular leaks. It was also possible to further reduce the minimum access vessel diameters through improvements to the delivery system. The **PARTNER II S3 study** investigated the third generation of the Edwards SAPIEN valve (SAPIEN 3) in two independent study arms.

## Research question

The study arm PII S3HR/inoperable was designed to investigate the possible benefit of SAPIEN 3 valves in transfemoral, transapical or transaortic TAVI for patients at high surgical risk or contraindications for surgery.

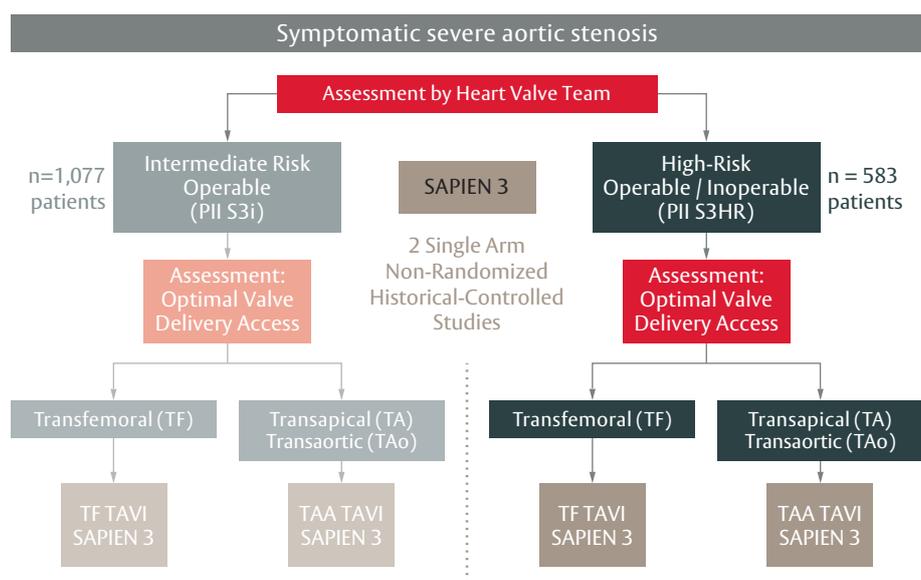
## Methods

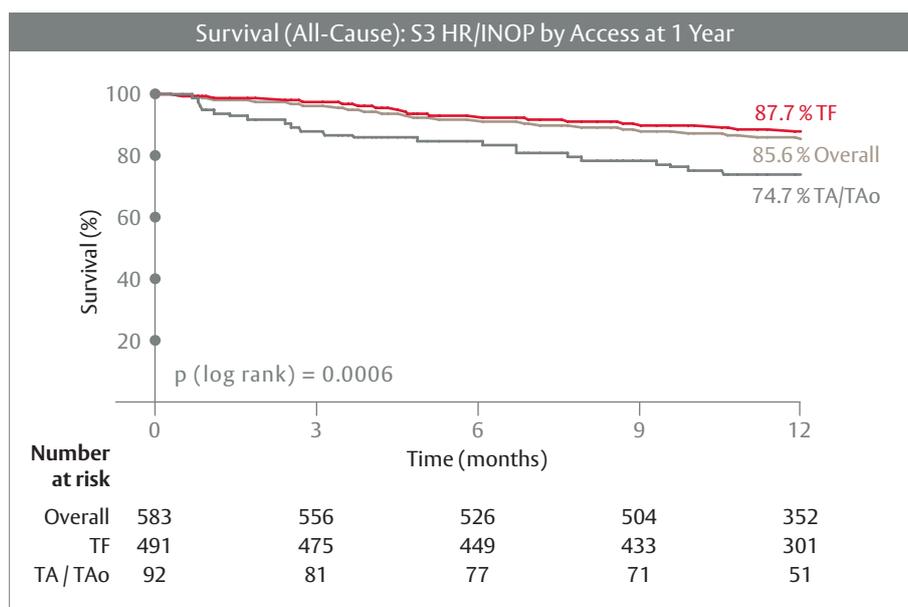
583 patients from 29 US sites with severe symptomatic aortic stenosis who were either inoperable or at high surgical risk were included in the multicenter, single arm non-randomized registry study.

## Criteria for inclusion

- Severe aortic valve stenosis (aortic valve area < 0.8 cm, aortic valve index < 0.5 cm<sup>2</sup>/m<sup>2</sup> and mean gradient > 40 mm Hg or peak velocity > 4.0 m/s)
- High surgical risk or inoperability (STS score > 8 or decision of the heart team)

## The PARTNER II S3 Trial Study Design





### Patient characteristics

The patients received transfemoral TAVI (84 %), transapical TAVI (10 %) or transaortic TAVI (6 %).

- Mean age: 82.7 years
- Mean STS score: 8.7 %
- NYHA class III/IV: 90.1 %
- Significant frailty: 30.9 %

### Primary endpoints

Mortality and disabling stroke at 30 days and overall survival at one year

### Results

At 30 days:

- All-cause mortality: 2.2 % (TF 1.6 %; TA/TAo 5,4 %)
- Disabling stroke rate: 0.9 % (TF 0.8 %; TA/TAo 1.1 %)
- Low rates of paravalvular regurgitation (severe 0 %, moderate 3.7 % combined HR/inop and IR)

At one year:

- Overall survival high risk & inoperable: 85.6 %
- Overall survival in the TF subgroup: 87.7 %
- Overall survival in the TA/TAo subgroup: 74.7 %

### Conclusion

TAVI with the SAPIEN 3 valve offers patients with severe aortic valve stenosis who are inoperable or at high surgical risk very good 30-day outcomes with low rates of mortality and stroke. This is also shown by the one-year results with very high overall survival rates in this geriatric patient cohort. <sup>(12, 13)</sup>

# SAPIEN 3 valve CE Trial

## Background

The SAPIEN 3 valve is the third generation of the Edwards aortic valves for transcatheter implantation. The technical improvements have markedly decreased the rates of paravalvular regurgitation, the access sheath is much smaller, and placing the valve is easier. This may improve TAVI safety even further.

## Research question

The prospective, non-randomized study **SAPIEN 3 valve CE trial** was designed to investigate the safety and efficacy of TAVI with the SAPIEN 3 valve in patients with severe symptomatic aortic valve stenosis and at either high or intermediate surgical risk.

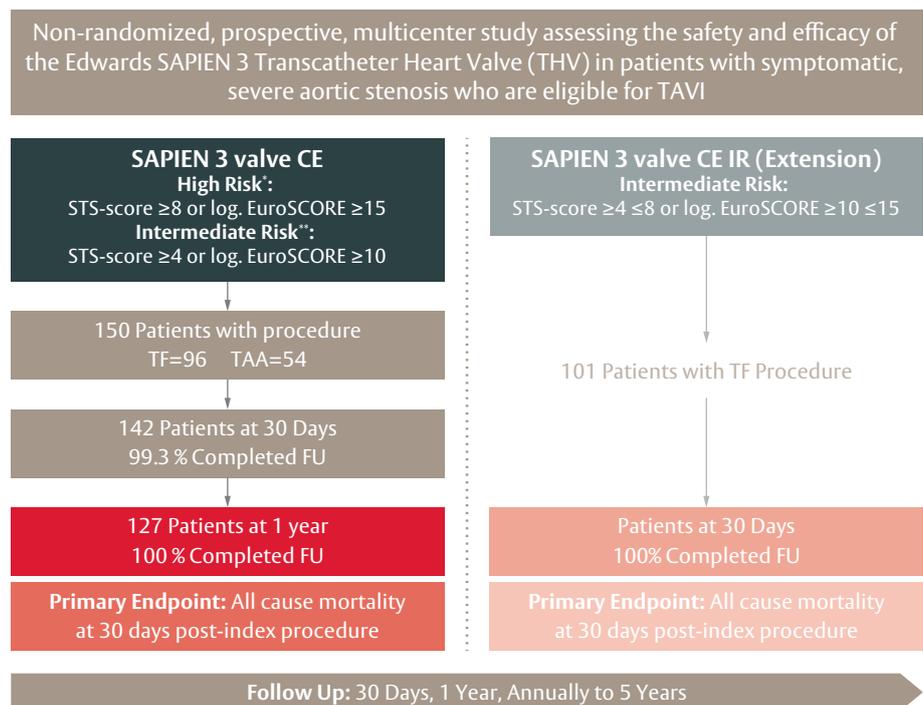
## Methods

Patients at high surgical risk (STS score  $\geq 8$  or log. EuroSCORE  $\geq 15$ ), as well as patients at intermediate surgical risk (STS score  $\geq 4$  or log. EuroSCORE  $\geq 10$ ) from 16 study sites in Europe and Canada were included in the trial.

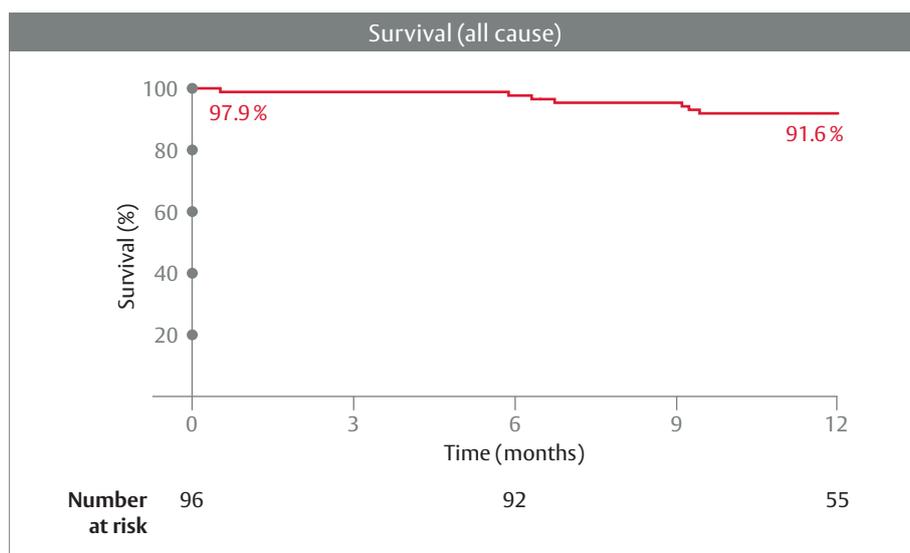
## Criteria for inclusion

- Severe aortic valve stenosis
- NYHA class  $\geq$  II
- Operability (high or intermediate surgical risk)

## SAPIEN 3 valve CE Trial Study Design



\*France STS  $\geq 10$ , EuroSCORE  $\geq 20$ . \*\*Excluding France.



### Patient characteristics

The high risk cohort consisted of 96 patients with TF TAVI and 54 patients with transaortic/transapical TAVI (TAA) performed with the Edwards SAPIEN 3 valve.

- Mean age: 83.6 years
- Mean STS score: 7.4 %
- NYHA class III or IV: 86.7 %

### Primary endpoint

All-cause mortality at 30 days.

### Results

At 30 days:

- All-cause mortality: 4.7 % (1.1 % TF and 11.1 % TAA)
- Stroke rate:
  - TF 1.0 % (disabling stroke 0 %)
  - TAA 5.6 % (disabling stroke 0 %)

At one year:

- All-cause mortality (TF): 8.4 %
- Stroke rate (TF): 2.1 % (disabling strokes 1.1 %)

### Conclusion

For patients at high or intermediate surgical risk, TAVI with the SAPIEN 3 valve is a very safe option with an extremely low 30-day mortality and stroke rate, especially when a transfemoral approach is chosen. Even at one year, there are no signs of an increased rate of complications<sup>(14,15)</sup>.

# PARTNER II Study (Cohort A)

## Background

After the PARTNER study had shown that TAVI can markedly increase the chances of survival for inoperable patients with severe symptomatic aortic valve stenosis and that the intervention is equivalent to surgical aortic valve replacement in patients at high surgical risk, the next question was whether patients at intermediate surgical risk might benefit from TAVI as well.

## Research question

The PARTNER II study (Cohort A) was designed to investigate the efficacy and safety of TAVI using the Edwards SAPIEN XT valve in patients with severe symptomatic aortic valve stenosis at intermediate surgical risk and to compare the results with those of surgical aortic valve replacement (non-inferiority).

## Methods

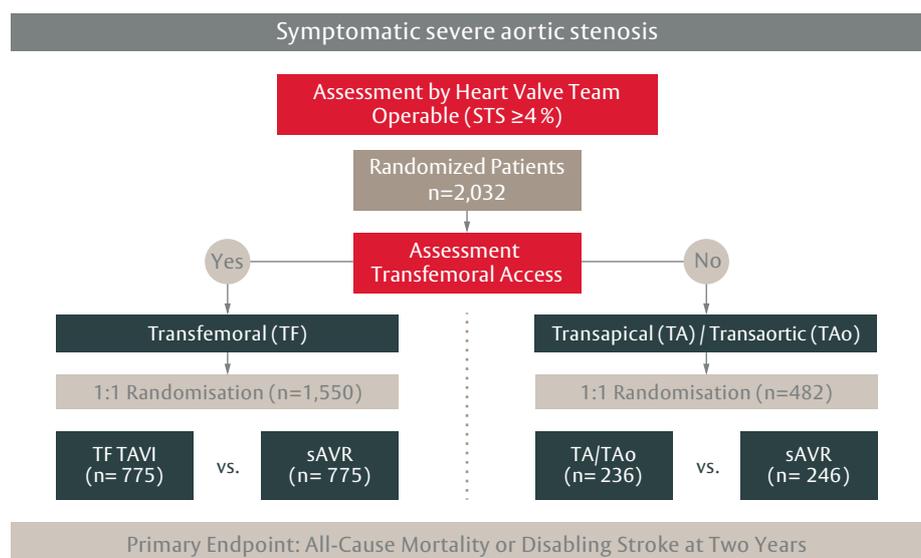
2,032 patients with severe symptomatic aortic valve stenosis at intermediate surgical risk from 55 sites in the US and Canada were included in the study.

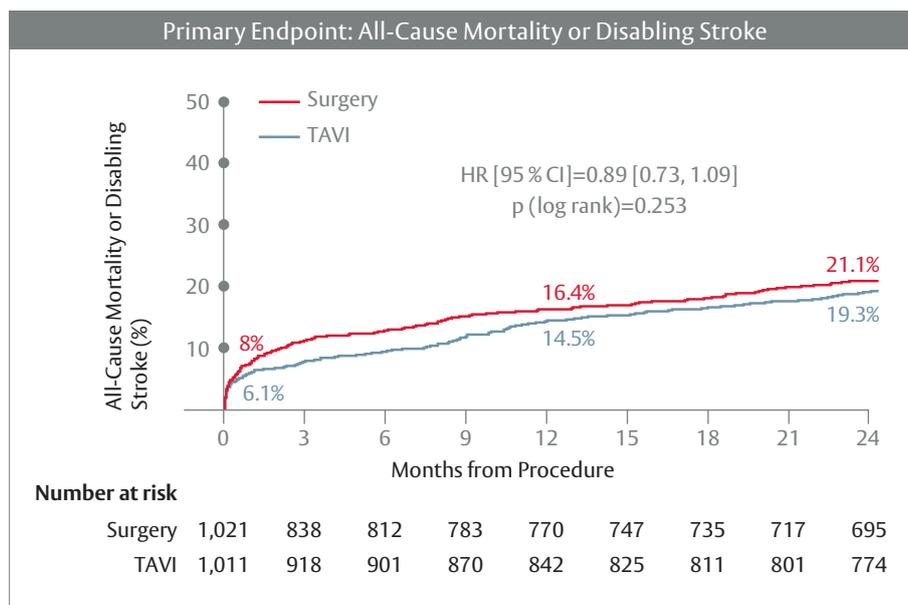
## Criteria for inclusion

- Severe aortic valve stenosis (aortic valve area  $< 0.8$  cm or AVA index  $< 0.5$  cm<sup>2</sup>/m<sup>2</sup>)
- Signs of heart failure (NYHA class  $\geq$  II)
- Intermediate surgical risk (STS score  $\geq 4\%$  and decision by a heart team)

## Study design and patient characteristics

## PARTNER II A Trial Study Design





The first step was stratification according to access possibilities. Transfemoral access was essentially possible in 1,550 patients and not possible in 482. Both groups were randomized 1:1 to receive either TAVI or surgical aortic valve replacement.

775 patients received transfemoral TAVI and 236 transapical/transaortic TAVI with the SAPIEN XT valve, while 1,021 (775 + 246) received surgical aortic valve replacement.

- Mean age: 81.5 years (TAVI) vs. 81.7 years (sAVR)
- Mean STS score: 5.8% vs. 5.8%
- NYHA class III or IV: 77.3% vs. 76.1%

### Primary endpoint

Combination of all-cause mortality or disabling stroke at two years

### Results

At two years:

- All-cause mortality or disabling stroke: 19.3% (TAVI) vs. 21.1% (sAVR) – p=0.253 (non-inferiority of TAVI as compared to surgery p=0.001)
- In the cohort with transfemoral TAVI (76% of patients), TAVI was superior to surgery with regards to the primary endpoint (p=0.04)

### Conclusion

These results support the use of TAVI as an alternative that is on par with surgical aortic valve replacement in patients with severe symptomatic aortic valve stenosis at intermediate surgical risk. TAVI with transfemoral access may even be a superior choice in these patients<sup>(7)</sup>.

# PARTNER II S3i Study

## Background

The development of the SAPIEN 3 valve was able to solve some technical problems seen with preceding generations. For example, the SAPIEN 3 valve has an outer skirt sewn around the outside of the valve frame to prevent paravalvular leaks. It was also possible to further reduce the minimum access vessel diameters. The PARTNER II S3 study investigated the third generation of the Edwards SAPIEN valve (SAPIEN 3) in two independent study arms.

## Research question

The aim of the study arm PII S3i was to investigate to what extent patients at intermediate surgical risk benefit from transfemoral, transapical or transaortic TAVI using a SAPIEN 3 valve. In order to achieve a long-term comparison with surgical aortic valve replacement at one year, a propensity score analysis was undertaken. The one-year results of the surgical patient cohort (n=944) from the randomized PARTNER II study (Cohort A) were used for comparison.

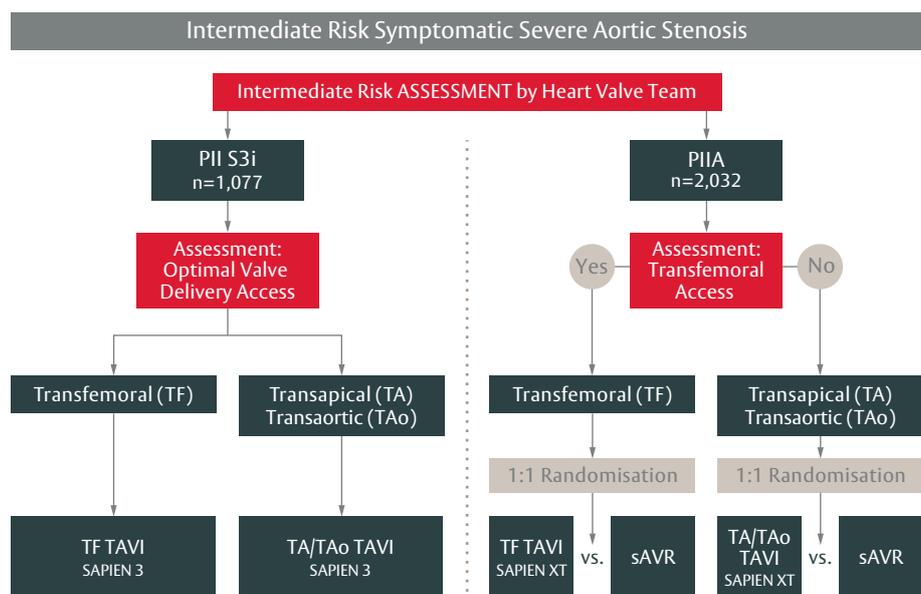
## Methods

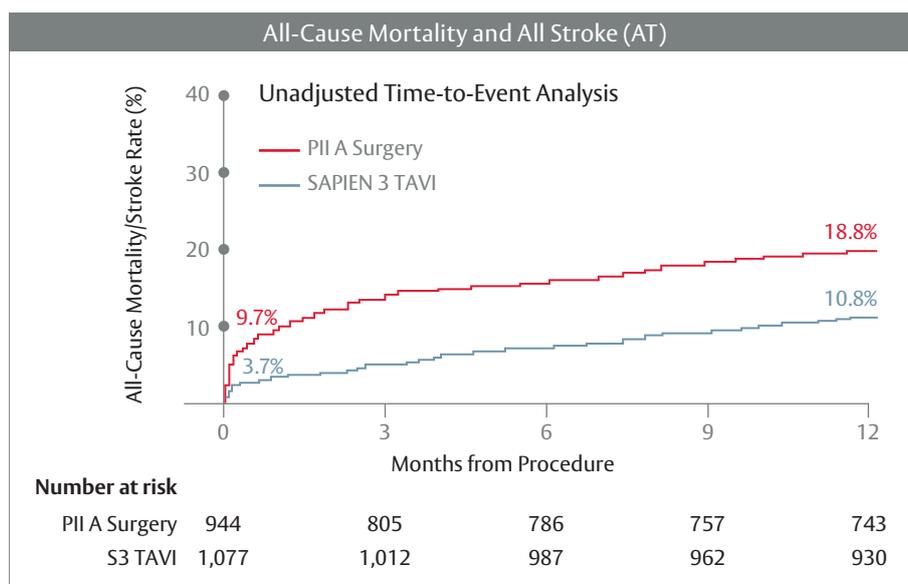
1,077 patients with severe symptomatic aortic stenosis and intermediate surgical risk from 51 US sites were included in the study.

## Criteria for inclusion

- Severe aortic valve stenosis (aortic valve area < 0.8 cm or aortic valve index < 0.5 cm<sup>2</sup>/m<sup>2</sup> and aortic valve gradient > 40 mm Hg or peak velocity > 4.0 m/s)
- Intermediate surgical risk (STS score 4-8 or decision by a heart team)

## The PARTNER IIA and S3i Trials Study Design





Thourani VH, SAPIEN 3 transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Presentation at ACC 2016, Chicago, April 3, 2016

### Patient characteristics

The patients received either transfemoral TAVI (89%), transapical TAVI (7%) or transaortic TAVI (0.4%).

- Mean age: 81.9 years TAVI; 81.6 years sAVR
- Mean STS score: 5.2% TAVI; 5.4% sAVR
- NYHA class III/IV: 72.5% TAVI; 76.1% sAVR

### Primary endpoints

- Mortality and stroke rate at 30 days
- Non-hierarchical composite endpoint of overall survival, stroke rate and severe/moderate paravalvular regurgitation at one year (non-inferiority in the propensity score analysis)

### Results

At 30 days:

- All-cause mortality: 1.1% (TF 1.1%; TA/TAo 1.6%)
- Stroke rate: 2.7% (disabling stroke 1.0%)
- Low rate of paravalvular regurgitation (PII S3HR and PII S3i: severe 0%, moderate 3.7%)

Propensity score analysis at one year:

- Non-inferiority as compared to the surgical cohort ( $p < 0.001$ ) for the combined primary end-point
- Superiority analysis showed superiority of TAVI with regards to the combined endpoint ( $p < 0.001$ ) and individually for:
  - All-cause mortality 7.4% (TAVI) vs. 13% (surgery)
  - Disabling stroke 2.3% vs. 5.9%

### Conclusion

In patients with severe symptomatic aortic valve stenosis at intermediate surgical risk, TAVI with the SAPIEN 3 valve achieves very good 30-day results with low mortality and stroke rates. At one year, TAVI proves to be superior to surgical aortic valve replacement in this cohort as shown by propensity score analysis regarding the combined endpoint of mortality, stroke rate and paravalvular regurgitation<sup>(12, 16)</sup>.

# SAPIEN 3 valve CE Trial (Extension)

## Background

The SAPIEN 3 valve is the third generation of the Edwards aortic valves for transcatheter implantation. The technical improvements have markedly decreased the rates of paravalvular regurgitation, the diameter of the access sheath is much smaller and the placing of the valve is easier. This may improve TAVI safety even further and in the future this may also prove beneficial for patients with intermediate surgical risk.

## Research question

In an additional arm of the prospective, non-randomized SAPIEN 3 valve CE trial, the safety and efficacy of transfemoral TAVI with the SAPIEN 3 valve was investigated in patients with severe symptomatic aortic valve stenosis at intermediate surgical risk.

## Methods

101 patients with transfemoral access option at intermediate surgical risk from 13 sites in Europe and Canada were included in the study.

## Criteria for inclusion

- Severe aortic valve stenosis (aortic valve area < 1.0 cm<sup>2</sup> and mean gradient > 40 mm Hg)
- NYHA class: ≥ II
- STS score: ≥ 4 % to ≤ 8 % or log. EuroSCORE ≥ 10 % to ≤ 15 %
- Age: > 75 years

## Patient characteristics

All patients received transfemoral TAVI with the Edwards SAPIEN 3 valve.

- Mean age: 84.4 years
- Mean STS PROM score: 5.2 % and mean log. EuroSCORE 13.2 %
- NYHA class III or IV: 64.4 %

## Primary endpoint

All-cause mortality at 30 days post index procedure

## Secondary endpoints

- Safety, clinical efficacy and echocardiographic valve performance

## Results

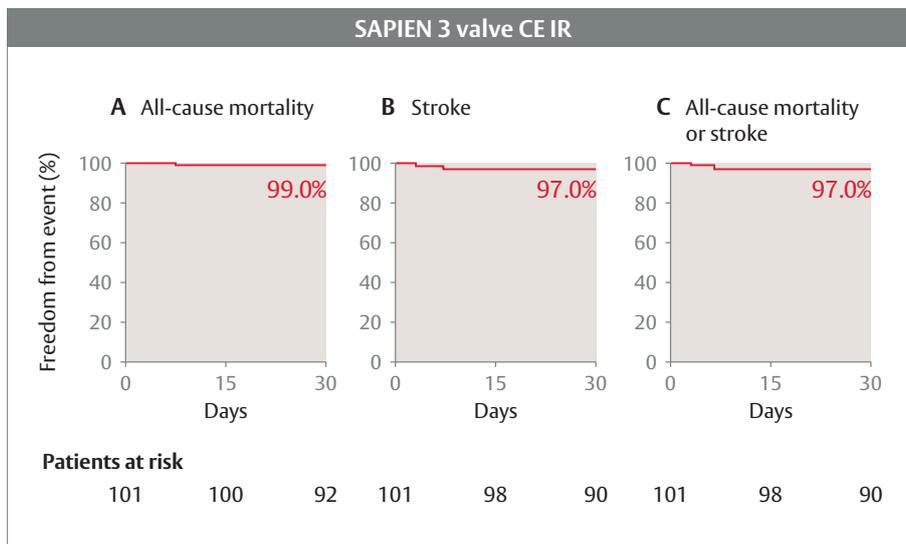
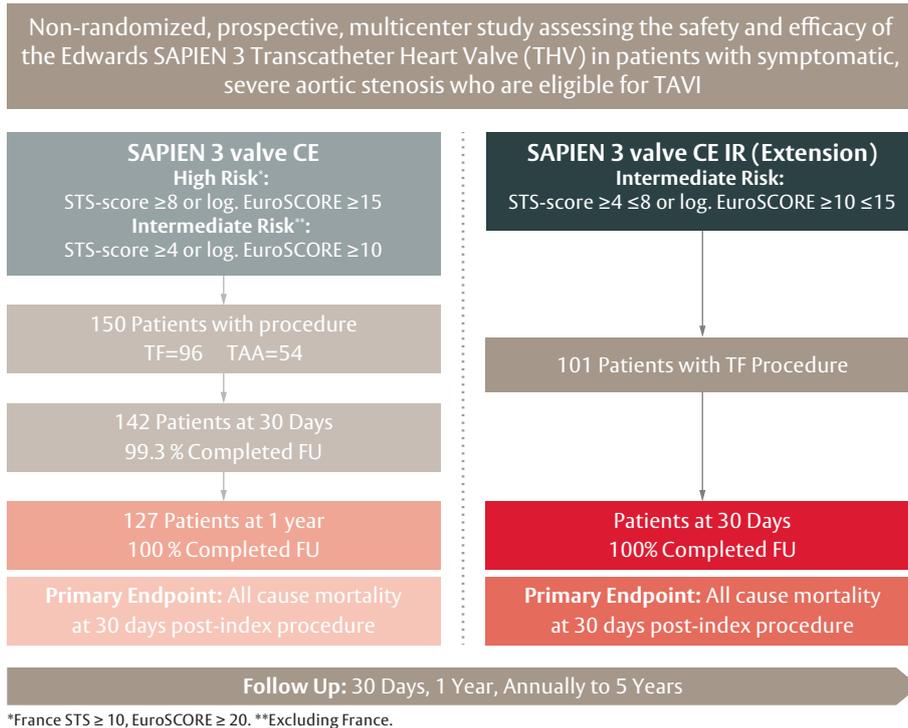
At 30 days:

- All-cause mortality: 1 %
- Stroke rate: 3 % (disabling stroke 2 %)
- Paravalvular regurgitation: moderate 2.3 %; severe 0 %

At one year:

- All-cause mortality: 7.9 %
- Stroke rate: 6 % (disabling stroke 5 %)

## SAPIEN 3 valve CE Mark Trial Study Design



### Conclusion

Transfemoral TAVI with the SAPIEN 3 valve is a very safe method for patients with a transfemoral access option with very low 30-day mortality, a low risk of stroke and a markedly reduced rate of paravalvular regurgitation<sup>(17, 18)</sup>.

# PARTNER 3 Study

(TAVI with SAPIEN 3 valve in low risk patients)

## Background

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 is insufficient evidence regarding the comparison of the two procedures in patients who are at low risk.

## Research question

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

## Methods

Randomized controlled trial including 1,000 patients at low surgical risk from 71 sites (496 TAVI vs 454 sAVR). Follow-up at 30 days, 6 months, 1 year, and will continue annually for 10 years.

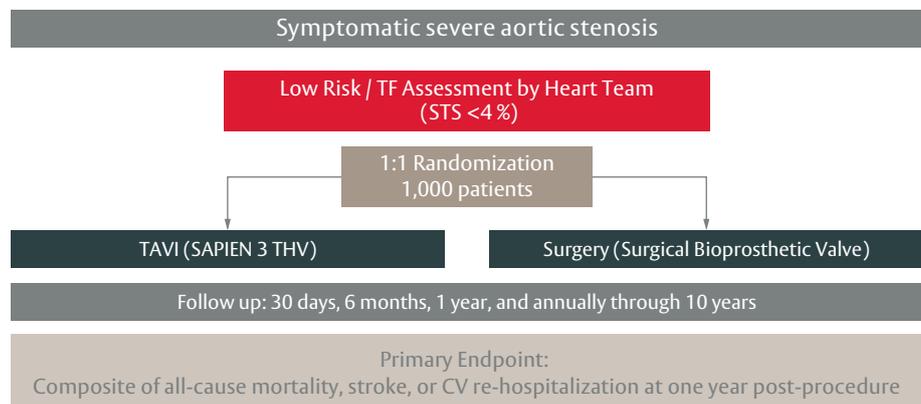
## Patient characteristics

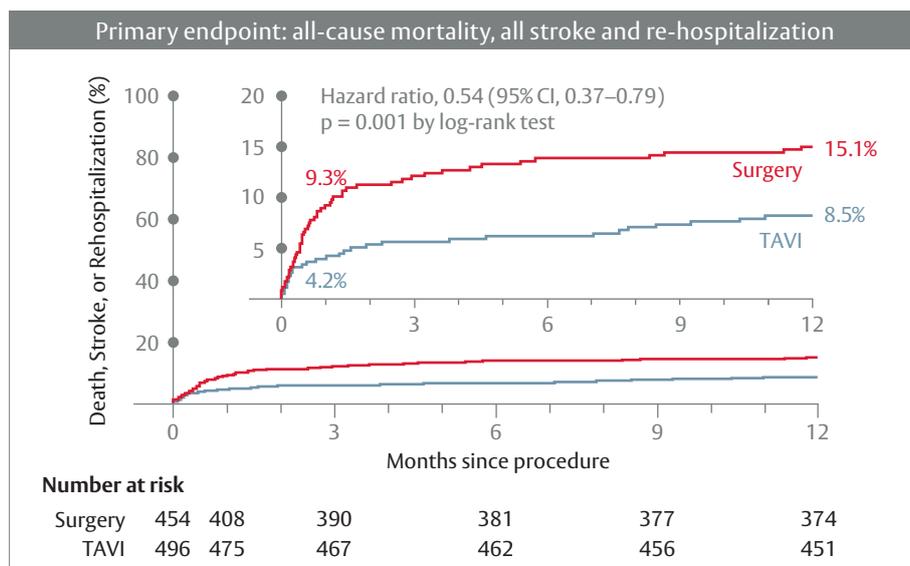
- Mean age: 73 years
- STS score: 1.9%
- NYHA class III or IV: 31.2% TAVI; 23.8% sAVR

## Criteria for inclusion

1. Severe calcific aortic stenosis:
  - AVA  $\leq 1.0 \text{ cm}^2$  or AVA index  $\leq 0.6 \text{ cm}^2/\text{m}^2$
  - Jet velocity  $\geq 4.0 \text{ m/s}$  or mean gradient  $\geq 40 \text{ mmHg}$
  - NYHA Functional Class  $\geq 2$  OR exercise tolerance test that demonstrates a limited exercise capacity, abnormal BP response, or arrhythmia OR asymptomatic with LVEF  $< 50\%$
2. Heart team agrees the patient has a low-risk of operative mortality and STS Score  $< 4$
3. Patient agrees to IRB approved informed consenting process.

## The PARTNER 3 Study Design





### Primary endpoints

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

### Results

Primary endpoint:

The PARTNER 3 Trial demonstrated that TAVI with the SAPIEN 3 valve in low-risk patients was superior to surgery, with a 46% reduction in the composite primary endpoint, from 15.1% in the surgical group to 8.5% with TAVI, of all-cause mortality, all stroke and re-hospitalization (p=0.001).

At 30 days:

- All cause death: 0.4% TAVI vs 1.1% sAVR (p=0.21)
- All stroke: 0.6% TAVI vs 2.4% sAVR (p=0.02)
- Death or disabling stroke: 0.4% TAVI vs 1.3% sAVR (p=0.12)
- Re-hospitalization: 3.4% TAVI vs 6.5% sAVR (p=0.04)

At one year:

- All cause death: 1% TAVI vs 2.5% sAVR (p=0.09)
- All stroke: 1.2% TAVI vs 3.1% sAVR (p=0.04)
- Death or disabling stroke: 1% TAVI vs 2.9% sAVR (p=0.03)
- Re-hospitalization: 7.3% TAVI vs 11% sAVR (p<0.05)

Key secondary end-points:

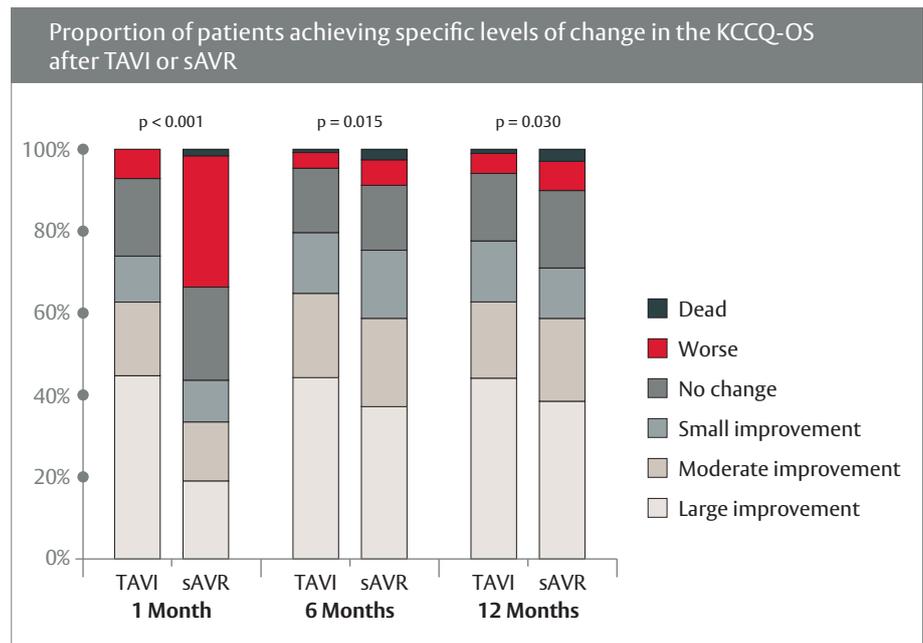
- New-onset atrial fibrillation 30-days: 5% TAVI vs 39.5% sAVR (p<0.0001)
- Index hospitalization days: 3.0 days TAVI vs 7.0 days sAVR (p<0.0001)
- Measure of poor treatment outcome (Death, KCCQ < 45 or KCCQ decrease from baseline  $\geq$  10 points at 30 days): 3.9% TAVI vs 30.6% sAVR (p<0.0001)
- Death or stroke at 30 days: 1.0% TAVI vs 3.3% sAVR (p=0.01)

### Echocardiographic results:

At 30-days: mean gradients were 12.8 mmHg in the TAVI group and 11.2 mmHg in the surgery group  $\rightarrow$  AVA was 1.7 cm<sup>2</sup> and 1.8 cm<sup>2</sup> respectively  
PVL: moderate/severe 0.8% TAVI vs 0% sAVR at 30-days and 0.6% and 0.5% at 1 year; mild PVL at 1 years was 29.4% with TAVI vs 2.1% sAVR.

### Quality of Life benefits<sup>(27)</sup>

Using data from the PARTNER 3 trial, the purpose was to compare health status outcomes after TAVI vs. sAVR in low-risk patients at 1, 6 and 12 months. Consistent with previous studies of transfemoral TAVI, TAVI was associated with significantly better early health status compared with sAVR. However, in contrast to findings in higher risk populations, TAVI was also associated with late health status benefits at 12 months compared with sAVR in this low-risk population.



### Conclusions

Among patients with severe aortic stenosis who were at low surgical risk, the composite rate of death, stroke or re-hospitalization at 1 year was significantly lower with TAVI than with surgery.<sup>(19,20)</sup>

# SOURCE 3 Registry

## Background

While randomized trials are excellent in assessing the value of a new technology in a selected cohort suitable for direct comparison with the gold-standard treatment, they do not provide information on the results using a new technology in larger patient populations in daily practices. This registry was initiated to observe the safety and performance of the SAPIEN 3 valve under 'real world' conditions.

## Research question

The purpose of the SOURCE 3 registry was to document outcomes of clinical safety and performance after European approval.

## Methods

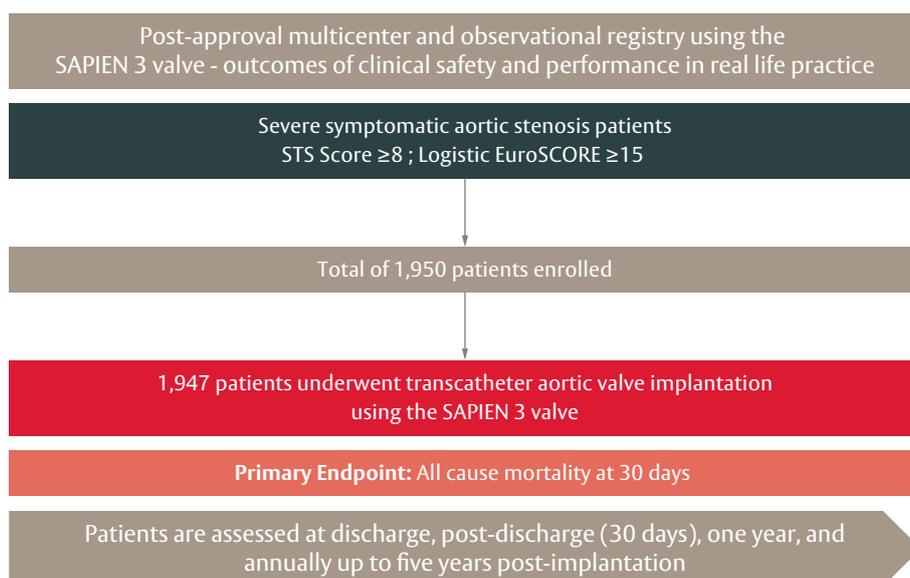
1950 patients with severe, symptomatic aortic stenosis (TF: n=1695 and Non-TF: n=252) from 80 centers in 10 countries were enrolled between July 2014 and October 2015. All study endpoints were defined using VARC-2 criteria. Review and adjudication of key clinical events were performed by an independent clinical events committee. All data is self-reported.

## Criteria for inclusion

Patients suffering from severe, symptomatic, calcific aortic stenosis, STS Score  $\geq 8$ , Logistic EuroSCORE  $\geq 15$

## Patient characteristics

- Mean age:  $81.6 \pm 6.6$  years
- Mean log. EuroSCORE I:  $18.3 \pm 13.2$  %.
- NYHA class IV: 9.3% TF TAVI; 6.9% non-TF TAVI



**Primary end-point**

All-cause mortality at 30-days

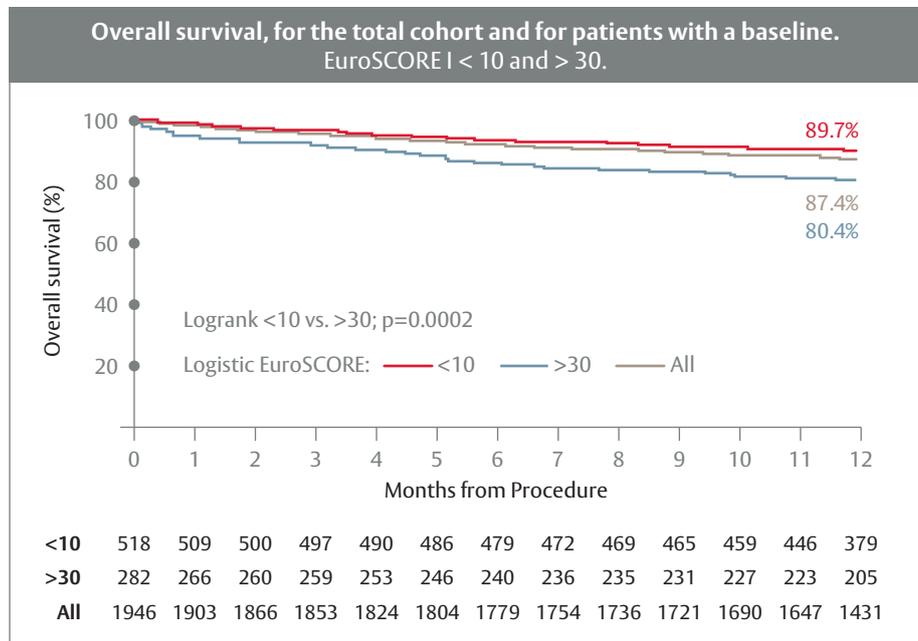
**Results**

At 30-days <sup>(21)</sup>:

- All-cause mortality: 2.2 % (1.9 % TF vs 4.0 % non-TF (p=0.0023))
- Cardiovascular mortality: 1.1 % (1 % TF vs 1.2 % non-TF (p=0.47))
- All stroke: 1.4 % (1.3 % TF vs 2.8 % non-TF (p=0.47))
- Disabling stroke: 0.5 % (0.5 % TF vs 0.8 % non-TF (p=0.58))
- New permanent pacemaker: 12 % (12.3 % TF vs 10 % non-TF (p=0.15))

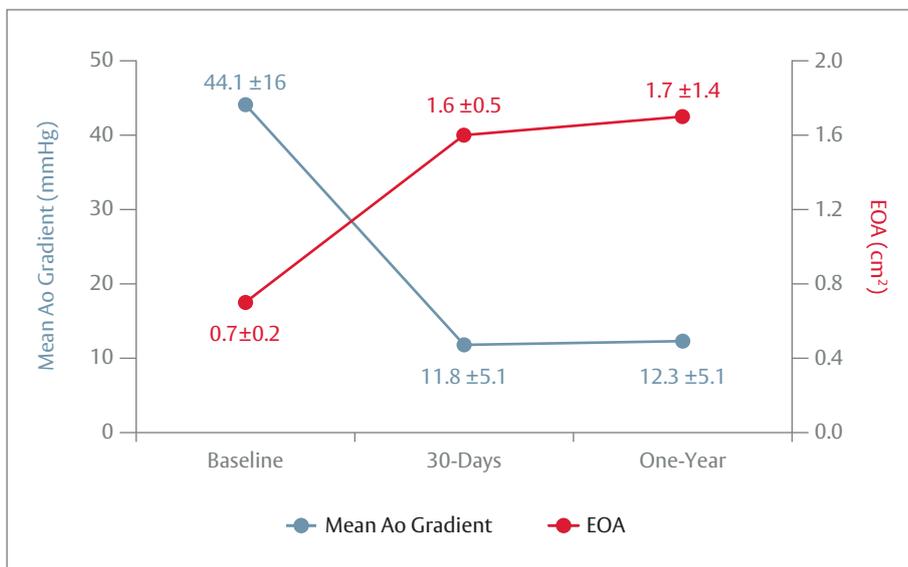
At one year <sup>(22)</sup>:

- All-cause mortality: 12.6 % (11.8 % TF vs 18.5 % non-TF)
- Cardiovascular mortality: 8 % (7.5 % TF vs non-TF 11.3 %)
- All stroke: 3.1 % (2.7 % TF vs 5.6 % non-TF)
- Disabling stroke: 1.4 % (1.1 % TF vs 3.6 % non-TF)
- New permanent pacemaker: 13.2 % (13.6 % TF vs 10.4 % non-TF)
- Causes of death: 62.0% cardiovascular and 38.0% non-cardiovascular
- Predictors of all-cause 1-year mortality: NYHA Class IV and renal insufficiency.

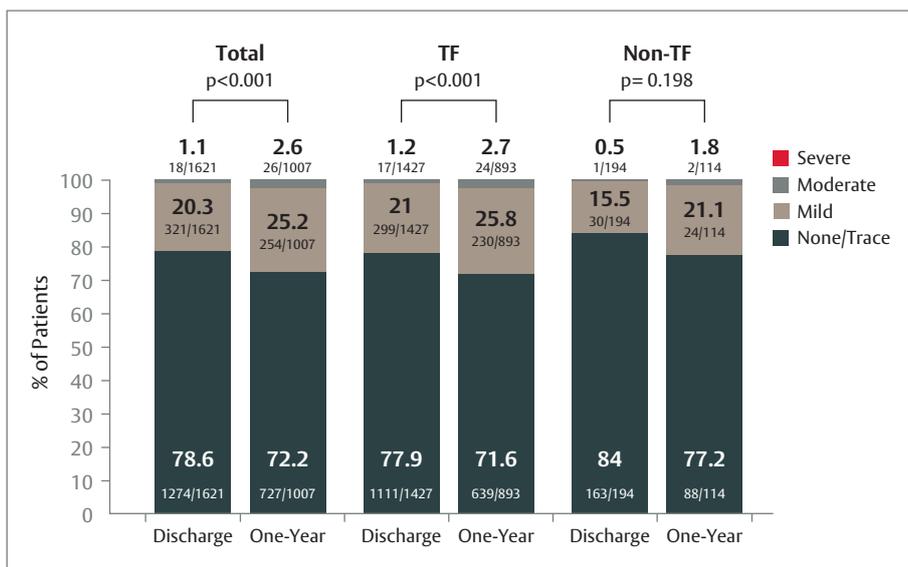


**Hemodynamics:**

Mean transaortic gradients significantly decreased and mean effective orifice areas significantly increased after the index procedure. Both parameters remained stable up to 1-year, as did the left-ventricular ejection fraction.



At 1-year, PVL was classified at none/trace degree in 72.2% of patients and 25.2% were classified with mild PVL, while moderate PVL was rare (2.6%) and no patient experienced severe PVL.



**Conclusion**

At one year, SOURCE 3 demonstrated a low complication rate and mortality in real world data. Given the low incidence of higher degree paravalvular leakages, this variable no longer affects outcomes.

## Summary and Outlook

# TAVI: From an experimental procedure towards a standard method with an exciting future

Age-associated diseases like aortic valve stenosis will become ever more significant in the future, simply due to demographic development. This also applies to the treatment methods used, such as transcatheter aortic valve implantation (TAVI). The procedure offers a safe and effective treatment and is now available for patients, independent of surgical risk. Acceptance of TAVI has increased steadily over the last few years due to the continual advancements in available study data as well as technical innovations in the design of the transcatheter aortic valves and delivery systems. For these reasons, TAVI as a treatment option has progressed from its earlier days as an experimental procedure in patients with no alternatives to a proven therapeutic choice as a routine procedure in severe aortic stenosis patients.

As soon as aortic valve stenosis becomes symptomatic, with exertional dyspnoea, cardiac syncope, and angina pectoris, the patient's life expectancy is severely limited and in fact worse than with many forms of cancers. For many decades surgical aortic valve replacement has been the method of choice in clinical practice. However for about one-third of the mostly elderly patients, the strain of this operation requiring life support machines made the procedure out of the question<sup>(1)</sup>. This created the unsatisfactory situation of being unable to offer these patients any effective therapy. Balloon valvuloplasty of the aortic valve, introduced in the 1980s, led to short-term relief of the symptoms in some cases, but the rate of re-stenosis is very high<sup>(23)</sup>.

The development of TAVI offered a solution to this dilemma, providing inoperable patients an effective therapeutic option for the first time. In addition, it enabled doctors to spare patients at high surgical risk an operation that would require opening of the thorax and a longer recovery period, while still replacing the stenosed valve with a functional implant.

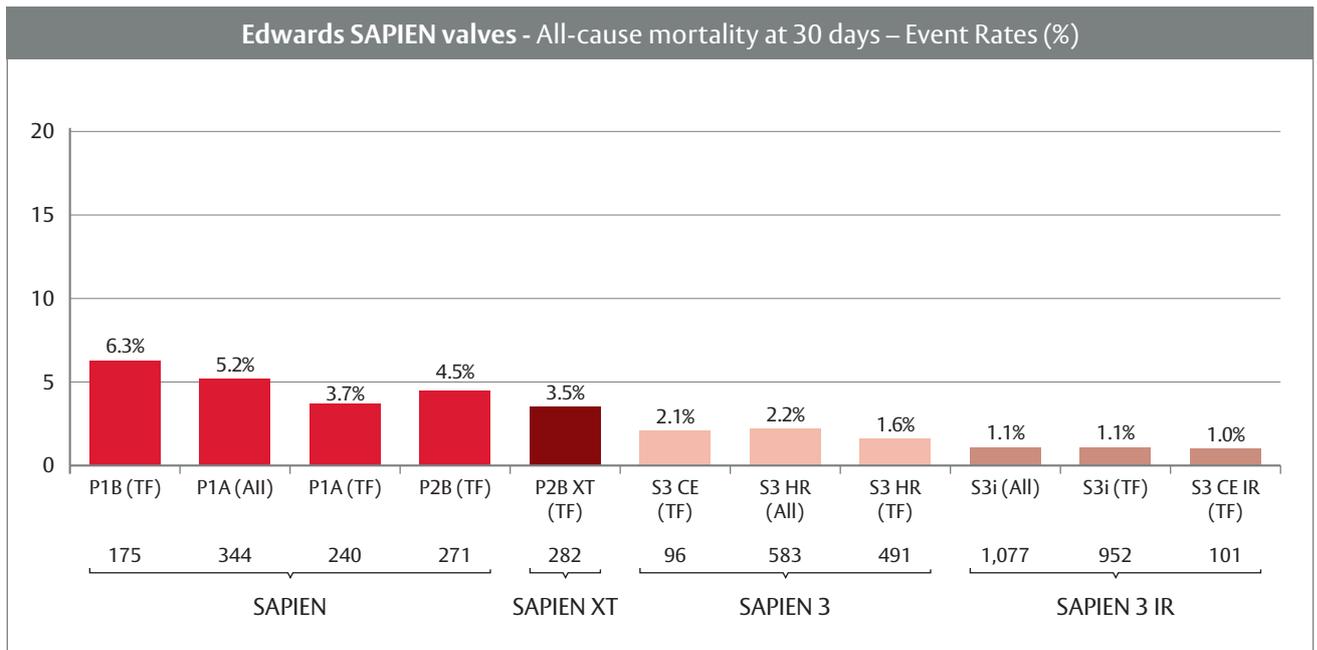
### **TAVI offers an effective therapeutic option to inoperable patients for the first time**

After the pioneering TAVI procedure was first performed by Professor Alain Cribier in 2002, the companies Edwards Lifesciences and Medtronic very quickly developed improved transcatheter aortic valves and delivery systems. The ground breaking PARTNER study (Cohort B) showed a marked survival

benefit for TAVI in inoperable patients as compared with conservative standard therapy (with or without balloon valvuloplasty<sup>(4)</sup>), and this benefit was maintained over five years<sup>(8)</sup>. As a result, TAVI was recommended in the 2012 ESC/EACTS guidelines as a first line therapy (recommendation grade I, evidence level B) for patients with symptomatic, severe aortic valve stenosis and contraindications for surgery whose life expectancy is more than one year<sup>(6)</sup>. These positive results in inoperable patients (Cohort B) of the PARTNER II study have been confirmed for the second generation SAPIEN XT valve as well<sup>(9)</sup>.

### **No advantages in conventional surgery for patients at high surgical risk**

The logical next step was to consider whether patients who were essentially operable but were at markedly increased surgical risk could also benefit from TAVI. In parallel to cohort B, an independent arm of the PARTNER study compared TAVI to SAVR (randomization 1:1) in a group of patients at high surgical risk (mortality risk  $\geq 15\%$ , STS score  $\geq 10$ ). No differences in mortality were evident at one year<sup>(5)</sup> or up to five years<sup>(11)</sup> leading to the conclusion that TAVI, even with first-generation valves that are by now considered outdated, is on par with surgery. In subgroup analyses, TAVI seems to be more favourable than surgery in patients who are female or patients with moderate/severe mitral regurgitation, pulmonary hypertension, diabetes, small aortic annulus and an existing pacemaker. As long-term data do not indicate any premature degeneration or loss of function of the TAVI valves,



Adapted according to Vahl TP et al, Transcatheter Aortic Valve Replacement 2016, A Modern-Day “Through the Looking-Glass” Adventure, Journal of the American College of Cardiology 2016 67(12):1472-1487.

there would seem to be no substantial advantages in subjecting these patients to a stressful operation. The European guidelines have already made allowance for this, stating that TAVI may be used as an alternative therapeutic option in patients at high surgical risk if decided upon by an interdisciplinary heart valve team (recommendation grade IIa, evidence level B)<sup>(6)</sup>.

**Modern valves also prove their value in patients at intermediate risk**

In keeping with this recommendation, the PARTNER II study also included patients at intermediate surgical risk. This was also the first time that the SAPIEN 3 valve was used, which had undergone important technical improvements. The fabric skirt sewn around the outside of the valve frame acts as a seal and reduces paravalvular regurgitation, a frequent issue with first generation valves that often had a significant clinical effect on the individual prognosis of the patients. In addition, the necessary size of the sheath could be further reduced in comparison to the SAPIEN XT valve, reducing the risk of vascular complications and allowing for a transfemoral approach.

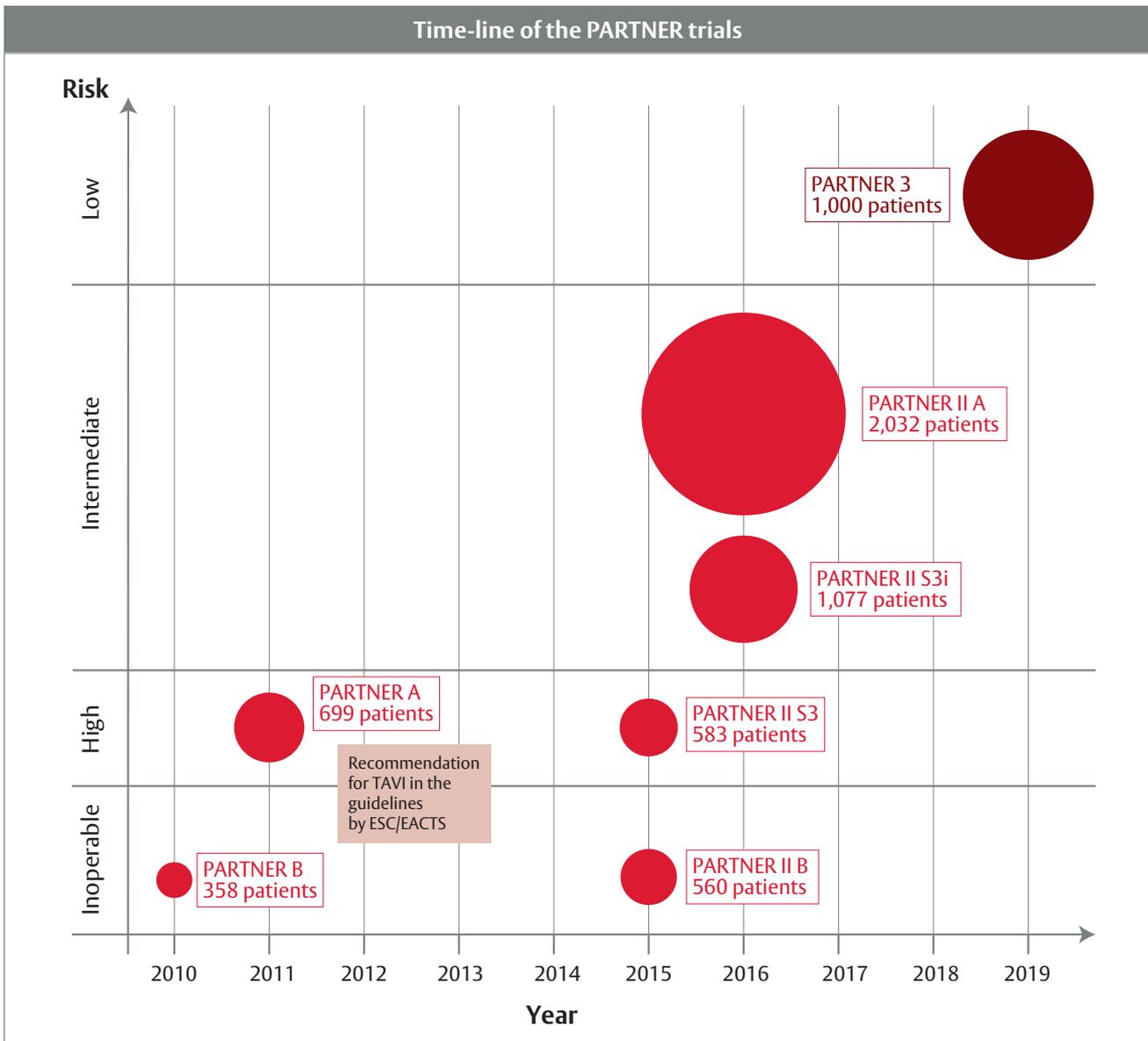
The first study arm (PII S3i) included patients with severe symptomatic aortic stenosis at intermediate surgical risk (STS score 4-8), while the second arm

included patients at high surgical risk (STS score > 8) or contraindications for surgery. The data showed that TAVI is also safe and effective in patients at intermediate risk. When the SAPIEN 3 valve was used, these patients had a very low mortality and stroke rate at 30 days and the rate of paravalvular regurgitations was markedly lower than in the studies investigating earlier valve generations<sup>(12)</sup>.

In a propensity score analysis using the surgical cohort of the randomized PARTNER II A study for comparative purposes, transfemoral TAVI with the SAPIEN 3 valve actually proved to be superior to surgical aortic valve replacement with regards to the combined endpoint of mortality, stroke rate and paravalvular regurgitation<sup>(16)</sup>.

**Superiority over sAVR for low risk patients shown in the PARTNER 3 study**

A trend is apparent: The first studies comparing TAVI with surgical aortic valve replacement were designed to show non-inferiority to the former gold standard (surgical aortic valve replacement). However, the PARTNER 3 Trial shows that TAVI with the SAPIEN 3 valve is superior to surgery, at least with the transfemoral approach<sup>(19)</sup>.



### Registry data confirm decrease in complications

Clinical reality is mainly reflected in registry data. One of these registries is the German Aortic Valve Registry or GARY, founded in 2011 with the support of the DGTHG (Deutsche Gesellschaft für Thorax-, Herz- und Gefäßchirurgie, German Society for Thoracic and Cardiovascular Surgery) and the DGK (Deutsche Gesellschaft für Kardiologie – Herz- und Kreislaufforschung, German Cardiac Society). The aim of GARY is to improve the safety of patients with an aortic valve replacement. This is achieved by analyzing the structural, procedural and outcome quality of the different techniques of aortic valve treatments as well as the criteria for deciding on the intervention. The quality and safety of the medical products are recorded and the quality of

care in the participating centers evaluated. Technical advancements in the development of TAVI valves and the increasing experience of the users is reflected in the one year data recorded for nearly 16,000 TAVI patients. The rate of severe vital complications decreased from 6.8% in 2011 to 3.9% in 2013 ( $p < 0.001$ ), and the rate of technical complications from 5.5% to 1.1% ( $p=0.003$ )<sup>(26)</sup>.

The SOURCE 3 registry is a post approval multicenter, observational registry of the latest generation of transcatheter heart valve, the SAPIEN 3 valve. A total of 1950 patients from 80 sites in 10 countries were enrolled between July 2014 and October 2015. Of those 1,947 patients underwent TAVI with the SAPIEN 3 valve (mean age 81.6, 48.1% female) with a mean log. EuroSCORE of 18.3%. Transfemoral access

was used in 87.1 % (n=1695), conscious sedation was employed in 59.9% of the transfemoral procedures. The procedural success was 98.3%. Adverse events were low with site reported 30-day all-cause mortality at 2.2%, cardiovascular mortality 1.1%, stroke 1.4%, major vascular complication 4.1%, life-threatening bleeding 5% and post TAVI pacemaker 12%. Moderate or greater paravalvular regurgitation was observed in 3.1% of reporting patients<sup>(21)</sup>. Further, the one year results showed low complication rates and mortality, with all-cause mortality at 12.6%, cardiovascular mortality 8.0%, stroke 3.1%, disabling stroke 1.4%, and rate of new pacemakers at 13.2%. Causes of death were 62.0% cardiovascular and 38.0% non-cardiovascular. NYHA Class IV and renal insufficiency were identified as predictors of mortality, while a higher BMI was a predictor for improved survival. Severe paravalvular leakage was 0% and moderate paravalvular leakage 2.6%<sup>(22)</sup>.

### **What about surgery?**

Surgical aortic valve replacement has a long-standing history of more than 40 years on lower risk-patients. The long-term data for TAVI, now increasingly available, as well as the first indications of superiority in overall survival for patient cohorts at high and intermediate surgical risk indicates that TAVI may

become the preferred treatment choice for these patients. This would especially be the case if further controlled studies also confirm the superiority of TAVI compared to surgery. The crucial advantage of TAVI is that the patient is spared the strain of open-heart surgery resulting in shorter recovery time, faster return to mobility and return home, allowing patients to resume their everyday lives rapidly post-procedure.

### **TAVI, the new standard procedure of the future?**

The PARTNER 3 Trial has shown superiority of TAVI with SAPIEN 3 over SAVR in low risk patients for the combined endpoint of all-cause mortality, all stroke and rehospitalization. With the Medtronic low risk study showing non-inferiority against surgery for the combined endpoint of all-cause mortality and all-stroke, there are current discussions about whether or not TAVI should become the standard procedure for the majority of symptomatic patients with severe aortic valve stenosis<sup>(19)</sup>. Registries as well as further randomized, controlled studies may contribute to generating more long-term data and defining sub-groups for differentiated treatment. Until such data are available, a decision for or against TAVI should be reached by an interdisciplinary heart valve team in consultation with the patient and taking into account his or her individual risk profile.

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Transcatheter Aortic Valve Implantation (TAVI)

# This is TAVI Today

With more than a decade of evidence in randomised clinical trials, TAVI with the SAPIEN 3 System is now approved for use in patients with native calcific aortic stenosis, independent of surgical risk.

**Give your low-risk patients the lowest risk procedure**

Find out how TAVI can help more patients than ever at [www.TAVI.today](http://www.TAVI.today)  
an online resource on aortic stenosis and TAVI exclusively for cardiologists.

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