Edwards Balloon Expandable Study Compendium

Transcatheter aortic valve implantation (TAVI)
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Introduction

Dear Reader,

In patients with symptomatic severe aortic 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. 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 2021 update of the European guidelines on valvular heart disease (VHD), transfemoral- (TF-) TAVI has become a therapeutic option for patients with symptomatic severe aortic stenosis who are ≥ 75 years of age or at increased surgical risk.

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.

Aortic valve stenosis is mainly caused by degenerative changes of the valve and is therefore a problem found mostly in older patients. An estimated 2% of people over 65 and 4% of people over 75 are affected. 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, TAVI was included in the 2012 ESC/EACTS (European Society of Cardiology/European Association for Cardio-Thoracic Surgery) guidelines for the first time. These guidelines specifically recommend TAVI for inoperable patients with severe symptomatic aortic valve stenosis.

Further studies have shown TAVI to be at least as successful as surgery even in patients at intermediate risk. 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. The increased body of evidence over the past years led to the update of the 2021 ESC/EACTS VHD guidelines and subsequent availability of TF-TAVI for patients who are 75 years of age or older, or 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

2021 • Updated ESC/EACTS VHD Guidelines

2020 • PARTNER II study five-year data
       • PARTNER 3 study two-year data

2019 • PARTNER 3 study one-year data

2018 • Approval of the Edwards SAPIEN 3 Ultra valve in Europe

2017 • Release of 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)
According to the 2021 ESC/EACTS VHD Guidelines the following categories of aortic stenosis can be defined:

- **High-gradient severe aortic stenosis** is defined as a mean gradient ≥ 40 mmHg and jet velocity ≥ 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 ≤ 1.0 cm², mean gradient < 40 mmHg or stroke volume index ≤ 35 ml/m².
- **Pseudosevere aortic stenosis** is defined as left ventricular ejection fraction (LVEF) < 50 % and an increase in valve area to >1.0 cm² 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 ≥ 40 mmHg or peak velocity ≥ 4.0 m/s).
- Symptomatic patients with severe low-flow, low-gradient (< 40 mmHg) 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 mmHg) 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 must be performed in Heart Valve Centres with active interventional cardiology and cardiac surgical programmes on site, and a structured collaborative Heart Team approach.

The choice for surgical or interventional treatment must be based on careful individual evaluation clinical, anatomical and procedural factors by the Heart Team. The Heart Team recommendation should be discussed with the patient who can then make an informed treatment choice.

According to surgical mortality risk, the 2021 guidelines recommend the following when selecting a treatment option for patients with severe symptomatic severe aortic stenosis:

- **SAVR** is recommended in patients aged < 75 years at low surgical risk (STS-PROM/ EuroSCORE II < 4%) or who are unsuitable for TF-TAVI and operable.
- **TAVI** is recommended in patients aged ≥ 75 years, or in those at high surgical risk (STS-PROM/ EuroSCORE II >8%) or who are unsuitable for surgery (Class IA recommendation).
- **TAVI** or **SAVR** are recommended for the remaining patients. Intervention choice is to be made by the Heart Team according to individual clinical, anatomical, and procedural characteristics (Class IB indication; see guidelines for more details).

The updated 2021 ESC/EACTS VHD guidelines provide greater clarity in aortic stenosis management and allows more patients to benefit from TAVI.
PARTNER Study (Cohort B)

Background
For a long time, surgical aortic valve replacement was the only effective therapeutic option in symptomatic severe aortic 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 symptomatic severe aortic stenosis who were inoperable due to high surgical risk would benefit from TAVI as compared with 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 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

PARTNER Study (Cohort B) was designed to investigate whether patients with symptomatic severe aortic stenosis who were inoperable due to high surgical risk would benefit from TAVI as compared with optimized medical therapy (including balloon valvuloplasty).
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 cm² at 5 years, mean gradient 10.6 mm Hg at 5 years)

Conclusion
For inoperable patients with symptomatic severe aortic 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.
PARTNER II Study (Cohort B)

Background

The PARTNER study (Cohort B) had already shown that inoperable patients with aortic 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 symptomatic severe aortic stenosis using the SAPIEN valve with its successor SAPIEN XT.

Methods

560 inoperable patients with symptomatic severe aortic 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 stenosis (aortic valve area < 0.8 cm² or AVA index < 0.5 cm²/m²)
- 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

Symptomatic severe aortic stenosis

<table>
<thead>
<tr>
<th>Assessment by Heart Valve Team</th>
<th>Operable (STS≥4)</th>
<th>Two Parallel Randomized Trials + 6 Nested Registries</th>
<th>Inoperable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfemoral (TF)</td>
<td>1:1 Randomisation</td>
<td>TF TAVI SAPIEN XT vs. SAVR</td>
<td>Primary endpoint: All-cause mortality + Disabling stroke at 2 years (non-inferiority)</td>
</tr>
<tr>
<td>Transapical (TA)</td>
<td>1:1 Randomisation</td>
<td>TAVI TA/TAo SAPIEN XT vs. SAVR</td>
<td>Primary endpoint: All-cause mortality + Disabling stroke + Repeat Hospitalization at 1 Year (Non-inferiority)</td>
</tr>
<tr>
<td>Transaortic (TAo)</td>
<td>1:1 Randomisation</td>
<td>TF TAVI SAPIEN vs. SAVR</td>
<td></td>
</tr>
</tbody>
</table>

Assessment: transfemoral access

Yes

No

NR1 (Sm Vessel) 100
NR2 (Transapical) 100
NR3 (VW) 100
NR4 (TAo) 100
NR5 (29 mm TF) 50
NR6 (29 mm TA) 50

n = 2032 Randomized Patients

n = 560 Randomized Patients

Inoperable

Operable (STS≥4)

6 Nested Registries

Sample Size
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 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 severe bleeding with the newer valve\(^{(2)}\).
PARTNER Study (Cohort A)

Background
The PARTNER study (Cohort B) has shown that TAVI can improve the chances of survival for inoperable patients with symptomatic severe aortic stenosis. However, many patients with aortic 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.

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

Criteria for inclusion
- Severe aortic stenosis (aortic valve area < 0.8 cm² 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

<table>
<thead>
<tr>
<th>Symptomatic severe aortic stenosis</th>
<th>Assessment: High-risk AVR candidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk</td>
<td>Assessment: transfemoral access</td>
</tr>
<tr>
<td>Yes</td>
<td>1:1 Randomisation</td>
</tr>
<tr>
<td>n = 699</td>
<td>TF TAVI vs. AVR</td>
</tr>
<tr>
<td></td>
<td>n = 244</td>
</tr>
<tr>
<td>Inoperable</td>
<td>1:1 Randomisation</td>
</tr>
<tr>
<td>No</td>
<td>Transapical (TA)</td>
</tr>
<tr>
<td>n = 358</td>
<td>TF TAVI vs. Standard therapy</td>
</tr>
<tr>
<td></td>
<td>n = 179</td>
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</tbody>
</table>

Primary endpoint: All-cause mortality at 1 year (non-inferiority)
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 and 248 received surgical aortic valve replacement. In the transapical access group, 104 patients received TAVI and 103 received surgical 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 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 symptomatic severe aortic stenosis at high surgical risk (STS score ≥ 10), even in the long term. At five years, there were no signs of structural damage or degeneration of the TAVI valves.
PARTNER II S3 Study

Background
The SAPIEN 3 valve was able to solve some technical problems seen with the prior models. 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 severe 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 stenosis (aortic valve area < 0.8 cm², aortic valve index < 0.5 cm²/m² 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

![PARTNER II S3 Trial Study Design Diagram](image-url)
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 or 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/T Ao 5.4 %)
- Disabling stroke rate: 0.9 % (TF 0.8 %; TA/T Ao 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/T Ao subgroup: 74.7 %

Conclusion
TAVI with the SAPIEN 3 valve offers patients with severe aortic 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.
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 high or intermediate surgical risk.

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

Criteria for inclusion
- Severe aortic stenosis
- NYHA class ≥ II
- Operability (high or intermediate surgical risk)

SAPIEN 3 valve CE Trial Study Design

Non-randomized, prospective, multicenter study assessing the safety and efficacy of the Edwards SAPIEN 3 Transcatheter Heart Valve (THV) in patients with symptomatic severe aortic stenosis who are eligible for TAVI

<table>
<thead>
<tr>
<th>SAPIEN 3 valve CE</th>
<th>SAPIEN 3 valve CE IR (Extension)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk:</td>
<td>Intermediate Risk:</td>
</tr>
<tr>
<td>STS-score ≥ 8 or log. EuroSCORE ≥ 15</td>
<td>STS-score ≥ 4 or log. EuroSCORE ≥ 10</td>
</tr>
<tr>
<td>Intermediate Risk:</td>
<td></td>
</tr>
<tr>
<td>STS-score ≥ 4 or log. EuroSCORE ≥ 10</td>
<td></td>
</tr>
</tbody>
</table>

150 Patients with procedure
TF=96 TAA=54
142 Patients at 30 Days
99.3% Completed FU
127 Patients at 1 year
100% Completed FU
Primary Endpoint: All cause mortality at 30 days post-index procedure

101 Patients with TF Procedure
Patients at 30 Days
100% Completed FU
Primary Endpoint: All cause mortality at 30 days post-index procedure

Follow Up: 30 Days, 1 Year, Annually to 5 Years

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\(^{16,17}\).
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 symptomatic severe aortic stenosis at intermediate surgical risk from 55 sites in the US and Canada were included in the study.

Criteria for inclusion
- Severe aortic stenosis (aortic valve area < 0.8 cm² or AVA index < 0.5 cm²/m²)
- Signs of heart failure (NYHA class ≥ II)
- Intermediate surgical risk (STS score ≥ 4 % and decision by a heart team)

PARTNER II A Trial Study Design

<table>
<thead>
<tr>
<th>Symptomatic severe aortic stenosis</th>
<th>Assessment by Heart Valve Team</th>
<th>Operable (STS ≥ 4 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized Patients n=2,032</td>
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</tr>
<tr>
<td>Yes</td>
<td>Assessment Transfemoral Access</td>
<td></td>
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<tr>
<td>Transfemoral (TF)</td>
<td>1:1 Randomisation (n=1,550)</td>
<td></td>
</tr>
<tr>
<td>TF TAVI (n=775) vs. SAVR (n=775)</td>
<td></td>
<td></td>
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<tr>
<td>Transapical (TA) / Transaortic (TAo)</td>
<td>1:1 Randomisation (n=482)</td>
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</tr>
<tr>
<td>TF TAVI (n=236) vs. SAVR (n=246)</td>
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</tbody>
</table>

Primary Endpoint: All-Cause Mortality or Disabling Stroke at Two Years
Study design and patient characteristics
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 (SVAR)
- 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% (SVAR) – 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)

At five years:
- No significant difference in all-cause mortality or disabling stroke with TAVI vs. surgery (47.9% and 43.4%, respectively; p=0.21)

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 severe aortic stenosis at intermediate surgical risk. TAVI with transfemoral access may even be a superior choice in these patients.
PARTNER II S3i Study

Background
The development of the SAPIEN 3 valve was able to solve some technical problems seen with preceding models. 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 symptomatic severe aortic stenosis and intermediate surgical risk from 51 US sites were included in the study.

Criteria for inclusion
- Severe aortic stenosis (aortic valve area < 0.8 cm² or aortic valve index < 0.5 cm²/m² 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

![Diagram showing the study design](image)
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/T Ao 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 symptomatic severe aortic 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 (14,19).
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 symptomatic severe aortic 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 stenosis (aortic valve area < 1.0 cm² 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

Non-randomized, prospective, multicenter study assessing the safety and efficacy of the Edwards SAPIEN 3 Transcatheter Heart Valve (THV) in patients with symptomatic, severe aortic stenosis who are eligible for TAVI

**SAPIEN 3 valve CE**

- **High Risk**: STS-score ≥8 or log. EuroSCORE ≥15
- **Intermediate Risk**: STS-score ≥4 or log. EuroSCORE ≥10

150 Patients with procedure
TF=96  TAA=54

142 Patients at 30 Days
99.3% Completed FU

127 Patients at 1 year
100% Completed FU

**Primary Endpoint:** All cause mortality at 30 days post-index procedure

**Follow Up:** 30 Days, 1 Year, Annually to 5 Years

**SAPIEN 3 valve CE IR (Extension)**

- **Intermediate Risk**: STS-score ≥4 ≤8 or log. EuroSCORE ≥10 ≤15

101 Patients with TF Procedure

Patients at 30 Days
100% Completed FU

**Primary Endpoint:** All cause mortality at 30 days post-index procedure


### SAPIEN 3 valve CE IR

**A** All-cause mortality

Freedom from event (%)

Days

<table>
<thead>
<tr>
<th>Days</th>
<th>Patients at risk</th>
<th>Freedom from event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>101</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>100</td>
<td>99.0%</td>
</tr>
<tr>
<td>30</td>
<td>92</td>
<td>99.0%</td>
</tr>
</tbody>
</table>

**B** Stroke

Freedom from event (%)

Days

<table>
<thead>
<tr>
<th>Days</th>
<th>Patients at risk</th>
<th>Freedom from event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>101</td>
<td>100</td>
</tr>
<tr>
<td>15</td>
<td>98</td>
<td>97.0%</td>
</tr>
<tr>
<td>30</td>
<td>90</td>
<td>97.0%</td>
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</tbody>
</table>

**C** All-cause mortality or stroke

Freedom from event (%)

Days

<table>
<thead>
<tr>
<th>Days</th>
<th>Patients at risk</th>
<th>Freedom from event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>101</td>
<td>100</td>
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<tr>
<td>15</td>
<td>98</td>
<td>97.0%</td>
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<tr>
<td>30</td>
<td>90</td>
<td>97.0%</td>
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### Conclusion

Transfemoral TAVI using 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 \(^{(20,21)}\).
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 effectiveness 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 ≤ 1.0 cm² or AVA index ≤ 0.6 cm²/m²
   - Jet velocity ≥ 4.0 m/s or mean gradient ≥ 40 mmHg
   - NYHA Functional Class ≥ 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

<table>
<thead>
<tr>
<th>Symptomatic severe aortic stenosis</th>
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<tbody>
<tr>
<td>Low Risk / TF Assessment by Heart Team (STS&lt;4.9)</td>
</tr>
<tr>
<td>1:1 Randomization</td>
</tr>
<tr>
<td>TAVI (SAPIEN 3 THV)</td>
</tr>
<tr>
<td>Follow up: 30 days, 6 months, and annually through 10 years</td>
</tr>
</tbody>
</table>

Primary Endpoint:
Composite of all-cause mortality, stroke, or CV re-hospitalization at one year post-procedure
Primary endpoints
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.

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% (p=0.21)
- All stroke: 0.6% TAVI vs 2.4% (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% (p=0.09)
- All stroke: 1.2% TAVI vs 3.1% (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)

At two years:
- Outcomes 2 years after transcatheter aortic valve replacement in patients at low surgical risk

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 ≥ 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)
Quality of Life benefits

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 rate of the composite of death, stroke, or re-hospitalization at 1 year was significantly lower with TAVI than with surgery.\(^{(3,4)}\)
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 safety and performance of the SAPIEN 3 aortic 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

1,950 patients with symptomatic severe aortic stenosis (TF: n=1,695 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 ≥8, Logistic EuroSCORE ≥15

PATIENT CHARACTERISTICS

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

## Post-approval multicenter and observational registry using the SAPIEN 3 valve - outcomes of clinical safety and performance in real life practice

<table>
<thead>
<tr>
<th>Symptomatic severe aortic stenosis patients</th>
<th>STS Score ≥8 ; Logistic EuroSCORE ≥15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total of 1,950 patients enrolled</td>
<td></td>
</tr>
<tr>
<td>1,347 patients underwent transcatheter aortic valve implantation using the SAPIEN 3 valve</td>
<td></td>
</tr>
<tr>
<td>Primary Endpoint: All cause mortality at 30 days</td>
<td></td>
</tr>
<tr>
<td>Patients are assessed at discharge, post-discharge (30 days), one year, and annually up to five years post-implantation</td>
<td></td>
</tr>
</tbody>
</table>
Primary end-point
All-cause mortality at 30-days

Results
At 30-days (24):
- 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 (25):
- 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.

Overall survival, for the total cohort and for patients with a baseline.
EuroSCORE I < 10 and > 30.
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 stenosis will become ever more significant in the future, simply due to demographic development. This also applies to the treatment methods used, such as TAVI. The procedure offers a safe and effective treatment and is now available for patients at all risk levels. Acceptance for 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 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 (1). 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 (26).

The development of TAVI offered a solution to this dilemma, providing to 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 Lifescience 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 (6)), and this benefit was maintained over five years (9). As a result, TAVI was recommended in the 2012 ESC/EACTS guidelines as a first line therapy (recommendation grade IIa, evidence level B) for patients with symptomatic severe aortic stenosis and contraindications for surgery whose life expectancy is more than one year (6). These positive results in inoperable patients (Cohort B) of the PARTNER II study have been confirmed for the newer valve SAPIEN XT as well (9).

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 with SAVR (randomization 1:1) in a group of patients at high surgical risk (mortality risk ≥ 15 %, STS score ≥ 10). No differences in mortality were evident at one year (7) or up to five years (11) 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, there would seem to be no substantial advantages in subjecting these patients to a stressful operation. The European guidelines made allowance for this, recommending TAVI in patients at high surgical risk.
Edwards SAPIEN valves - All-cause mortality at 30 days – Event Rates (%)

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>Event Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1B (TF)</td>
<td>6.3%</td>
</tr>
<tr>
<td>P1A (AII)</td>
<td>5.2%</td>
</tr>
<tr>
<td>P1A (TF)</td>
<td>3.7%</td>
</tr>
<tr>
<td>P2B (TF)</td>
<td>4.5%</td>
</tr>
<tr>
<td>P2B XT (TF)</td>
<td>3.5%</td>
</tr>
<tr>
<td>S3 CE (TF)</td>
<td>2.1%</td>
</tr>
<tr>
<td>S3 HR (AII)</td>
<td>2.2%</td>
</tr>
<tr>
<td>S3 HR (TF)</td>
<td>1.6%</td>
</tr>
<tr>
<td>S3i (AII)</td>
<td>1.1%</td>
</tr>
<tr>
<td>S3i (TF)</td>
<td>1.1%</td>
</tr>
<tr>
<td>S3 CE IR (TF)</td>
<td>1.0%</td>
</tr>
</tbody>
</table>


risk if decided upon by an interdisciplinary heart valve team (previously class IIa recommendation, evidence level B[6]; now class I, evidence level A[7])

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 symptomatic severe aortic stenosis at intermediate surgical risk (STS score 4-8), while the second arm included patients at high surgical risk (STS score > 8) or contra indications 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[14].

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[16].

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 PARNER 3 trial shows that TAVI with the Sapien 3 valve is superior to surgery, at least with the transfemoral approach[3].

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 is 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 are 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)(27).

The SOURCE 3 registry is a post approval multicenter, observational registry of the latest generation of transcatheter heart valve, the SAPIEN 3. A total of 1,950 patients from 80 sites in 10 countries were enrolled between July 2014 and October 2015. Of those 1,947 patients underwent TAVI using 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=1,695), 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(24).
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% (25).

**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 study 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 (3). 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.
References

1. Lung B et al; Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? European Heart Journal (2005); 26: 2714-2720.


17. Webb J; One-Year Outcomes from the SAPIEN 3 Trial; PCR Paris (2015).


23. Baron SJ et al, Health Status after Transcatheter vs. Surgical Aortic Valve Replacement in Low-Risk Patients with Aortic Stenosis, J Am Coll Cardiol. 2019 Sep 18. pii: S0735-1097(19)37633-8


27. Walther T et al; Perioperative Results and Complications in 15,964 Transcatheter Aortic Valve Replacements – Prospective Data From the GARY Registry; J Am Coll Cardiol. (2015); 65(20):2173-2180.
This is TAVI Today

With more than a decade of evidence in randomised clinical trials, TAVI with the SAPIEN 3 valve 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 an online resource on aortic stenosis and TAVI exclusively for cardiologists.