PVL Assessment.

Is paravalvular regurgitation after TAVR still an important consideration in 2018?

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Attending, Department of Transcatheter Heart Valves
Paravalvular leak (PVL) after TAVR: Still with us...
Basics

- PVL refers to regurgitant flow between aorta and left ventricle, in diastole due to incomplete annulus/stent frame apposition
- Differs from *transvalvular* regurgitation that signifies structural failure of the prosthesis
- Incidence of ≥moderate PVL with *1st generation* devices 7.4%
- Association with adverse outcomes
  - Readmissions
  - Heart failure
  - 1-year mortality
Moderate / Severe PVL post TAVR: Risk of Mortality

<table>
<thead>
<tr>
<th>Study name</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lemos*</td>
<td>4.900</td>
<td>1.367</td>
<td>17.570</td>
<td>2.439</td>
<td>0.015</td>
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<tr>
<td>Hayashida</td>
<td>1.970</td>
<td>1.187</td>
<td>3.271</td>
<td>2.621</td>
<td>0.009</td>
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<tr>
<td>Amabile</td>
<td>1.500</td>
<td>0.329</td>
<td>6.829</td>
<td>0.524</td>
<td>0.600</td>
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<tr>
<td>Sinning</td>
<td>3.890</td>
<td>2.020</td>
<td>7.491</td>
<td>4.063</td>
<td>0.000</td>
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<tr>
<td>Tamburino</td>
<td>3.785</td>
<td>1.572</td>
<td>9.112</td>
<td>2.969</td>
<td>0.003</td>
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<tr>
<td>Fraccaro</td>
<td>2.190</td>
<td>1.023</td>
<td>4.686</td>
<td>2.020</td>
<td>0.043</td>
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<td>Kodali</td>
<td>2.110</td>
<td>1.433</td>
<td>3.107</td>
<td>3.783</td>
<td>0.000</td>
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<tr>
<td>Moat</td>
<td>1.490</td>
<td>1.002</td>
<td>2.215</td>
<td>1.971</td>
<td>0.049</td>
</tr>
<tr>
<td>Gilard</td>
<td>2.490</td>
<td>1.909</td>
<td>3.248</td>
<td>6.728</td>
<td>0.000</td>
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<tr>
<td>All (N=4791)</td>
<td>2.273</td>
<td>1.840</td>
<td>2.808</td>
<td>7.609</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Hazard ratio and 95% CI

J Am Coll Cardiol 2013;61:1585–95
Basics (2)

• PVL to some degree acceptable in high risk or inoperable patients given limited surgical options

• If TAVR is to expand to *low-intermediate* and biologically less comorbid patients, need to have results similar to surgical AVR in terms of PVL rates

• Goal should be PVL rates ≤mild in all patients across diverse anatomies, degrees of calcification, anatomic orientation
VARC-2 Definition of Device Success

• Absence of procedural mortality AND

• Correct positioning of a single prosthetic heart valve into the proper anatomical location AND

• Intended performance of the prosthetic heart valve (no prosthesis–patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s,

• AND no moderate or severe prosthetic valve regurgitation
• Valve undersizing

• Aortic valve calcification:
  - Affects uniform valve expansion and annular sealing

• Implantation depth

J Am Coll Cardiol 2013;61:1585–95
Mechanisms of Paravalvular Regurgitation

- Malapposition
- High position
- Low position
- Undersizing
Mechanism of Paravalvular Regurgitation (II)

- Prosthesis too small
- Position too high or to low
- Malapposition due to calcified annulus
Paravalvular regurgitation post TAVR

- None/trace, mild
- Moderate/severe

- **Acute**, worsening of AR by at least 1 grade and to ≥moderate (no or mild AR before but moderate to severe AR after TAVR)
- **Chronic**, moderate/severe AR, but not worse compared to before TAVR
PVL after TAVR: Not all the same

- **Acute** moderate/severe AR carries a worse prognosis
  - Left ventricle unadjusted to increased regurgitant volume
  - Imperative to ameliorate with postdilatation, valve in valve, plug device or cardiac surgery
  - Pacing may decrease diastolic time

- **Chronic** moderate/severe AR better tolerated as compensatory mechanisms in place

J Am Coll Cardiol Intv 2014;7:1022–32
PVL Assessment

- Cine-angiography
- Hemodynamics
- Echocardiography

Examples from different patients
Cine-Angiography for PVL assessment

• Injection of dye in the aorta with 15-20ml/s for 2 sec
  • Await 5-10min with self-expandable valves for nitinol to expand

• LV opacification \(\rightarrow\) grade 1-4

• Grade 1 (Mild): Small amount of contrast entering LV without filling the entire cavity and clearing with each cardiac cycle

• Grade 4 (Severe): Contrast filling entire LV on the first beat with greater density compared to contrast in ascending aorta
Cine-angiography for PVL assessment

• Quick and immediately available

• Interpretation subjective

• Is flow paravalvular or transvalvular (e.g. due to wire)?

• Contrast load, an issue in some patients
Echocardiography for PVL assessment

Prosthetic aortic valve regurgitation

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent or brief early diastolic</td>
<td>Intermediate = 10–29%</td>
<td>Prominent, holodiastolic ≥30%</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>30–59 ml</td>
<td>≥60 ml</td>
</tr>
<tr>
<td>&lt;30 ml</td>
<td>30–49%</td>
<td>≥50%</td>
</tr>
<tr>
<td>&lt;30%</td>
<td>0.10–0.29 cm²</td>
<td>≥0.30 cm²</td>
</tr>
</tbody>
</table>

Semi-quantitative parameters
- Diastolic flow reversal in the descending aorta—PW
- Circumferential extent of prosthetic valve paravalvular regurgitation (%)h

Quantitative parameters
- Regurgitant volume (ml/beat)
- Regurgitant fraction (%)
- EROA (cm²)
PVL: Grading schemes

• Native Valves: Grade 1, 2, 3 and 4

• Traditional for TAVR valve: Mild-Moderate-Severe (VARC-2 definitions)

• Limitations: Wide variability in how different physicians / institutions / studies grade PVLs → Proposal for a Unified Grading Scheme
Assessment of Paravalvular Regurgitation Following TAVR

A Proposal of Unifying Grading Scheme

Philippe Pibarot, DVM, PhD,* Rebecca T. Hahn, MD,† Neil J. Weissman, MD,† Mark J. Monaghan, PhD†

• Trace (grade 1)
• Mild (grade 1)
• Mild to moderate (grade 2)
• Moderate (grade 2)
• Moderate to severe (grade 3)
• Severe (Grade 4)
<table>
<thead>
<tr>
<th>TABLE 1 Scheme, Modalities, Parameters, and Criteria for Grading the Severity of PVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Class Grading Scheme</td>
</tr>
<tr>
<td>4-Class Grading Scheme</td>
</tr>
<tr>
<td>Unifying 5-Class Grading Scheme</td>
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</tbody>
</table>

**Cineangiography**

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 1</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
</table>

**Invasive hemodynamics**

<table>
<thead>
<tr>
<th>Aortic regurgitation index*</th>
<th>&gt;25</th>
<th>&gt;25</th>
<th>&gt;25</th>
<th>10-25</th>
<th>10-25</th>
<th>&lt;10</th>
</tr>
</thead>
</table>

**Doppler echocardiography**

**Structural parameters**

<table>
<thead>
<tr>
<th>Valve stent</th>
<th>Usually normal</th>
<th>Usually normal</th>
<th>Normal/abnormal†</th>
<th>Normal/abnormal†</th>
<th>Usually abnormal†</th>
<th>Usually abnormal†</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV size†</td>
<td>Normal</td>
<td>Normal</td>
<td>Mildly/moderately dilated</td>
<td>Moderately/severely dilated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Doppler parameters (qualitative or semiquantitative)**

<table>
<thead>
<tr>
<th>Jet features§</th>
<th>Absent</th>
<th>Absent</th>
<th>Absent</th>
<th>Present</th>
<th>Present</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive/wide jet origin</td>
<td>Absent</td>
<td>Absent</td>
<td>Often present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Multiple jets</td>
<td>Possible</td>
<td>Possible</td>
<td>Often present</td>
<td>Often present</td>
<td>Often present</td>
<td>Often present</td>
</tr>
<tr>
<td>Jet path visible along the stent</td>
<td>Absent</td>
<td>Absent</td>
<td>Often present</td>
<td>Often present</td>
<td>Often present</td>
<td>Often present</td>
</tr>
<tr>
<td>Proximal flow convergence visible</td>
<td>Absent</td>
<td>Absent</td>
<td>Often present</td>
<td>Often present</td>
<td>Often present</td>
<td>Often present</td>
</tr>
<tr>
<td>Vena contracta width (mm): color Doppler</td>
<td></td>
<td>&lt;2</td>
<td>&lt;2</td>
<td>2-4</td>
<td>4-5</td>
<td>5-6</td>
</tr>
<tr>
<td>Vena contracta area (mm²): 2D/3D color Doppler</td>
<td>&lt;5</td>
<td>5-10</td>
<td>10-20</td>
<td>20-30</td>
<td>30-40</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Jet width at its origin (%LVOT diameter): color Doppler</td>
<td>Narrow (&lt;5)</td>
<td>Narrow (5-15)</td>
<td>Intermediate (15-30)</td>
<td>Intermediate (30-45)</td>
<td>Large (45-60)</td>
<td>Large (&gt;60)</td>
</tr>
<tr>
<td>Jet density: CW Doppler</td>
<td>Incomplete or faint</td>
<td>Incomplete or faint</td>
<td>Variable (500)</td>
<td>Variable (200-500)</td>
<td>Variable (200-500)</td>
<td>Variable (200-500)</td>
</tr>
<tr>
<td>Diastolic flow reversal in the descending aorta: PW Doppler*§</td>
<td>Absent or brief early diastolic</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Circumferential extent of PVR (%): color Doppler</td>
<td></td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>10-20</td>
<td>20-30</td>
<td>30-40</td>
</tr>
</tbody>
</table>

**Doppler parameters (quantitative)**

| Regurgitant volume (mL/beat)§|<15|<15|15-30|30-45|45-60|>60|
| Regurgitant fraction (%)|<5|<5|15-30|30-40|40-50|>50|
| Effective regurgitant orifice area (mm²)**|<5|5-10|10-20|20-30|>30|

**Cardiac magnetic resonance imaging**

| Regurgitant fraction (%)††|<10|<10|10-20|20-30|20-30|>30|
| Regurgitant fraction (%)|<15|<15|15-25|15-25|20-30|>30|
Echocardiography for PVL assessment

• Readily available transthoracic (compatible with minimalist TAVR approach)
• Views somewhat limited while patient on supine position
  • May need transesophageal
• Structural parameters:
  • Stent position and shape
  • Low or high position
  • Irregular shape of stent
  • Visible space between prosthesis and annulus

High position of a Sapien prosthesis
Echocardiography for PVL assessment

• Readily available transthoracic (compatible with minimalist TAVR approach)
• Views somewhat limited while patient on supine position
  • May need transesophageal
• Structural parameters:
  • Stent position and shape
  • Low or high position
  • Irregular shape of stent
  • Visible space between prosthesis and annulus

High position of a Sapien prosthesis
Echocardiography for PVR assessment: Color Doppler

• Color Doppler from multiple views to *scan* the valve thoroughly

• Basic views are the
  • Parasternal short axis
  • Parasternal long axis
  • Apical 5-chamber
  • Apical 3 chamber views

• The most frequent locations of PVR following TAVR are at the commissures of the native aortic valve
  • 1 to 2, 5 to 6, and 9 to 11 o’clock positions
Location of PVR jets in different TTE views

A

B

C

D

J Am Coll Cardiol Img 2015;8:340–60
Aorta to LVOT sweep in short axis views
Translational and rotational sweep from long axis views
Because of the shadowing caused by the native aortic valve calcifications and the THV stent, the PVR jets located posteriorly are often totally or partially masked in the parasternal long-axis or short-axis TTE views
Severe Paravalvular Regurgitation

Valve not well apposed to the annulus
Calcium deposits not allowing stent frame to fully expand
Baseline MDCT

- MDCT

- Severely Calcified Valve
Additional Echo Parameters for PVL assessment

• **Pressure half time**

• **Flow reversal** in descending thoracic aorta; high end-diastolic velocity
  • Limitations due to noncompliant aorta in elderly and diastolic dysfunction → false positives

• **Quantitative measures**
  • Compare RV stroke volume to LV stroke volume
3-D Echocardiography for PVL sizing
Aortic Regurgitation Index is calculated by simultaneous recording of LVEDP and Ao-Diastolic pressure; the difference is then divided by the systolic arterial pressure.

- AoD 65mmHg
- LVEDP 10mmHg
- Systolic 160mmHg
- AR Index = 34.4%

*Patient without PVL

J Am Coll Cardiol 2012;59:1134–41
Aortic Regurgitation Index is calculated by simultaneous recording of LVEDP and Ao-Diastolic pressure; the difference is then divided by the systolic arterial pressure.

- AoD 40mmHg
- LVEDP 20mmHg
- Systolic 130mmHg
- AR Index = 15.4%

*Patient with moderate PVL*
Aortic Regurgitation Index < 25% Independent Prognostic Indicator

J Am Coll Cardiol 2012;59:1134–41
Aortic Regurgitation Index: Advantages

• Allows a precise judgment of paravalvular regurgitation

• Predicts 1-year mortality after TAVR

• Prognostic information complementary to the degree of PAR

• Simple to assess, investigator-independent, immediately performed

J Am Coll Cardiol 2012;59:1134–41
Aortic Regurgitation Index: Limitations

• Left Ventricular End Diastolic Pressure (LVEDP) may be elevated due to:
  – High blood pressure
  – Diastolic dysfunction
  – Myocardial ischemia during BAV and valve deployment
  – Complications from TAVR
• A nonspecific elevation of the LVEDP
  – Low transvalvular end-diastolic gradient
  – False positive AR index
• Complementary value of the AR index, which should be used in addition to other imaging methods
• Best discriminative ability in patients with borderline paravalvular leaks.
Hemodynamic Assessment of PVL:
The Aortic Regurgitation Index Ratio
(after TAVR vs. before TAVR)

• The ratio shows whether diastolic loading and diastolic filling pressures worsened significantly after TAVR compared to prior to the procedure

• A ratio of <0.6 implies clinically significant deterioration in LV diastolic filling pressures

• An indicator of acute AR (i.e. AR worse than prior to TAVR)

J Am Coll Cardiol Intv 2016;9:700–11
Aortic Regurgitation Index Ratio

Before: $\frac{44-31}{111} = 11.7\%$

After: $\frac{51-21}{110} = 27.2\%$

Ratio $\frac{27.2}{11.7} = 2.3$
Hemodynamic Assessment of PVL: The Aortic Regurgitation Index Ratio (after TAVR vs. before TAVR)

ARI ratio = \frac{ARI_{post}}{ARI_{pre}}
AR Index Ratio: Independent Prognostic Indicator for Survival

**A**
- $p$ (log rank-test) $< 0.001$
- HR (95% CI) $= 1.9$ (1.2-3.0); $p = 0.003$
- HR (95% CI) $= 4.4$ (2.9-6.8); $p < 0.001$

**B**
- $p$ (log rank test) $< 0.001$
- HR (95% CI) $= 1.7$ (1.2-2.4); $p = 0.003$
- HR (95% CI) $= 3.5$ (2.4-5.1); $p < 0.001$

Cumulative mortality

Follow-up (days)
Aortic Regurgitation index (ARI) and index ratio
Survival stratified by degree and acuity of aortic regurgitation

- **Acute** AR moderate to severe degree was well tolerated if AR index post ≥25
- However, 1-year mortality was significantly increased in patients with ARI post <25 with *acute* moderate to severe AR (35.7%), even more so when the ARI ratio was <0.60 (72.7%)
Post-Dilatation

- Systematic review and meta-analysis of 6 studies
- N=889 PD compared to 4118 pts without PD
- Reduces incidence of mod/sev PVR x15 fold
- Risk of stroke (OR 1.71 p<0.001)

J Interven Cardiol. 2017; 30:204–211
Transcatheter closure of significant PVL with AVP-4

Incidence, Predictors, and Outcomes of Aortic Regurgitation After Transcatheter Aortic Valve Replacement

Meta-Analysis and Systematic Review of Literature

- Valve undersizing
- Aortic valve calcification:
  - Affects uniform valve expansion and annular sealing
- Implantation depth

J Am Coll Cardiol 2013;61:1585–95
3-Dimensional Imaging for TAVR sizing

**Edwards SAPIEN 3 Transcatheter Heart Valve**
with the Edwards Commander System

**ANNULUS SIZING AND VASCULAR ACCESS**

Complete range of valve sizes expands the treatable patient population

<table>
<thead>
<tr>
<th>Annulus Sizing</th>
<th>20 mm</th>
<th>23 mm</th>
<th>26 mm</th>
<th>29 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native Valve Annulus Size (CT)</td>
<td>16.0 - 21 mm</td>
<td>20.7 - 23.4 mm</td>
<td>23.4 - 26.4 mm</td>
<td>26.2 - 29.5 mm</td>
</tr>
<tr>
<td>Area Derived Diameter</td>
<td>16.0 - 21 mm</td>
<td>20.7 - 23.4 mm</td>
<td>23.4 - 26.4 mm</td>
<td>26.2 - 29.5 mm</td>
</tr>
<tr>
<td>Native Valve Annulus Size TEE</td>
<td>16 - 19 mm</td>
<td>18 - 22 mm</td>
<td>21 - 25 mm</td>
<td>24 - 28 mm</td>
</tr>
</tbody>
</table>
3-Dimensional Imaging for TAVR sizing

**Edwards SAPIEN 3 Transcatheter Heart Valve**
with the Edwards Commander System

**Annulus Sizing and Vascular Access**

<table>
<thead>
<tr>
<th>Valve Size Selection</th>
<th>Evolut™ PRO Bioprosthesis</th>
<th>Evolut™ R Bioprosthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>23 mm</td>
<td>26 mm</td>
</tr>
<tr>
<td><strong>Annulus Diameter</strong></td>
<td>18-20 mm</td>
<td>20-23 mm</td>
</tr>
<tr>
<td><strong>Annulus Perimeter</strong>†</td>
<td>56.5-62.8 mm</td>
<td>62.8-72.3 mm</td>
</tr>
<tr>
<td><strong>Sinus of Valsalva Diameter (Mean)</strong></td>
<td>≥ 25 mm</td>
<td>≥ 27 mm</td>
</tr>
<tr>
<td><strong>Sinus of Valsalva Height (Mean)</strong></td>
<td>≥ 15 mm</td>
<td>≥ 15 mm</td>
</tr>
</tbody>
</table>

†Annulus Perimeter = Annulus Diameter x π  
NOTE: Evolut™ PRO valve size selection is identical to Evolut™ R valve size selection criteria
3-Dimensional Imaging for TAVR sizing

<table>
<thead>
<tr>
<th>Portico™ Valve Labeled Size</th>
<th>Labeled Use Range – Mean Diameter (mm)</th>
<th>Use Range - Area (mm²)*</th>
<th>Use Range - Perimeter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 mm</td>
<td>19 – 21</td>
<td>277 – 346</td>
<td>60 – 66</td>
</tr>
<tr>
<td>25 mm</td>
<td>21 – 23</td>
<td>338 – 415</td>
<td>66 – 73</td>
</tr>
<tr>
<td>27 mm</td>
<td>23 – 25</td>
<td>405 – 491</td>
<td>72 – 79</td>
</tr>
<tr>
<td>29 mm</td>
<td>25 – 27</td>
<td>479 – 573</td>
<td>79 – 85</td>
</tr>
</tbody>
</table>

* Recommendation driven by circular or elliptical geometry (≥ 0.73 ratio)
3-Dimensional Imaging for TAVR sizing

Edwards SAPIEN 3 Transcatheter Heart Valve
with the Edwards Commander System

ANNULUS SIZE

Valve Size Selection

ACURATE neo™
Aortic Valve

VALVE SIZING
GUIDELINES

<table>
<thead>
<tr>
<th>Valve Size</th>
<th>S – 23 mm</th>
<th>M – 25 mm</th>
<th>L – 27 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic annulus diameter*</td>
<td>21 mm ≤ annulus ø ≤ 23 mm</td>
<td>23 mm &lt; annulus ø ≤ 25 mm</td>
<td>25 mm &lt; annulus ø ≤ 27 mm</td>
</tr>
<tr>
<td>Aortic annulus perimeter</td>
<td>66 mm ≤ annulus ≤ 72 mm</td>
<td>72 mm &lt; annulus ≤ 79 mm</td>
<td>79 mm &lt; annulus ≤ 85 mm</td>
</tr>
</tbody>
</table>

†Annulus Perimeter = Annulus ø

NOTE: Evolut™ PRO valve
3-Dimensional Imaging for TAVR sizing
**Sapien 3**

**Frame Design**
- Enhanced frame geometry for ultra-low delivery profile
- High radial strength for circularity and optimal haemodynamics

**Low Frame Height**
- Respects the cardiac anatomy

**Outer Skirt**
- Designed to minimise paravalvular leak

**Bovine Pericardial Tissue**
- Optimised leaflet shape
- Carpentier-Edwards ThermaFix* process for anti-calcification
SOURCE 3 Registry

N=1947 patients, Sapien-3 TAVR
Transfemoral 87%
Direct (w/o pre-dilatation) 50%
Post-dilatation 10.4% TF cases
Pacemaker 12%
30-day mortality 2.2%
PVL ≤ mild in 96.9%

Circulation. 2017;135:1123–1132
Association of PVR With 1-Year Outcomes After TAVR With Sapien 3 Valve

1,592 patients, of whom 3.5% had moderate or worse paravalvular regurgitation at 30 days.

<table>
<thead>
<tr>
<th>1-Year Outcome</th>
<th>Hazard Ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Mortality</td>
<td>2.59 (1.39-4.85)</td>
</tr>
<tr>
<td>Cardiovascular Mortality</td>
<td>2.87 (1.30-6.30)</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>2.27 (1.31-3.94)</td>
</tr>
</tbody>
</table>

* Moderate or worse PVR vs none/trace

Conclusion: Moderate or worse PVR at 30 days is rare in patients treated with Sapien 3 but is associated with worse clinical outcomes at 1 year.

THE EVOLUT PRO VALVE

- Supra-Annular Valve
- Self-expanding nitinol frame
- Porcine Pericardial Tissue
- Cell Size Enables Coronary Access
- Pericardial wrap increases surface contact with native anatomy

Skirt Height 13 mm
Clinical Outcomes With a Repositionable Self-Expanding Transcatheter Aortic Valve Prosthesis

The International FORWARD Study

**CENTRAL ILLUSTRATION:** Real-World Experience With a Self-Expanding Transcatheter Aortic Valve Implantation and Outcomes

![Graph showing changes in effective orifice area and mean AV gradient from baseline to discharge](image-url)
EVOLUT PRO PARAVALLULAR LEAK – MATCHED DATA

<table>
<thead>
<tr>
<th>Time</th>
<th>None/Trace</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7 Days N=45</td>
<td>75.6%</td>
<td>22.2%</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>30 Days N=45</td>
<td>80.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Months N=45</td>
<td>84.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Year N=45</td>
<td>88.9%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Core Laboratory Assessments
Portico Valve Design: Mitigating PV Leak

- Large cell geometry
- High tissue-to-stent ratio
- Allows valve tissue to conform around calcific nodules

Calcific Nodules Simulation

Portico™ valve

Calcific Nodules
Portico Valve Design: Mitigating PV Leak

- Large cell geometry
- High tissue-to-stent ratio
- Allows valve tissue to conform around calcific nodules

Low Rates of Paravalvular Leak

Echo data evaluated by an independent core lab.

<table>
<thead>
<tr>
<th></th>
<th>Discharge N = 198</th>
<th>30 Day N = 175</th>
<th>12 Month N = 147</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>5.0%</td>
<td>5.7%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Moderate</td>
<td>50.5%</td>
<td>50.3%</td>
<td>44.2%</td>
</tr>
<tr>
<td>Mild</td>
<td>44.5%</td>
<td>44.0%</td>
<td>48.3%</td>
</tr>
<tr>
<td>None/Trace</td>
<td>0.5%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Calcific Nodules Simulation
LOTUS Edge™ Aortic Valve System

**Design**

**Adaptive Seal™**
Designed to minimize paravalvular leak by conforming to irregular anatomical surfaces

**Bovine Pericardium Leaflets**
Proven long-term material

**Depth Guard™**
Minimizes LVOT interaction to reduce PPM

**One View Locking**
Additional radiopaque markers enable operator to confirm locking in 1 view

**Braided Nitinol Frame**
Designed for strength, flexibility, and ability to retrieve, reposition, and redeploy

**Flexible Catheter**
Reduced proximal profile and more flexibility improves trackability

The LOTUS Edge Valve may only be used in countries where they are approved for use. The LOTUS Edge is investigational devices and is not available for sale in the United States. The LOTUS Edge Valve is not available for sale in the European Economic Area. For education purposes only.
Surgical like PVL Rates in RESPOND & RESPOND EXT Studies\(^1\)

- **RESPOND 1-Year**
  - 94.5% None /Trace PVL
  - 0.4% Moderate / Severe PVL
  - LOTUS\(^\text{TM}\) Valve
  - N=988

- **RESPOND Extension 30-Days**
  - 86.5% None /Trace PVL
  - 0.0% Moderate / Severe PVL
  - LOTUS Valve w/ Depth Guard\(^\text{TM}\) Technology
  - N=50

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\(^1\) RESPOND, N. Van Mieghem PCR 2017, RESPOND Ext, Dan Blackman PCR 2017. PPM Among patients who did not have a pacemaker at baseline rate is 36.8% in RESPOND and 20.0% in RESPOND Extension.

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Symetis Acurate Neo

<table>
<thead>
<tr>
<th>Performance</th>
<th>7 DAYS n=999*</th>
<th>12 MONTHS n=604*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean δp gradient [mmHg, mean ± SD]</td>
<td>8.3 ± 4.0</td>
<td>7.3 ± 3.7 (484)</td>
</tr>
<tr>
<td>Mean EOA [cm², mean ± SD]</td>
<td>1.81 ± 0.5</td>
<td>1.8 ± 0.4 (257)</td>
</tr>
<tr>
<td>PVL Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ Grade 1 (none to mild) [n/%]</td>
<td>926 / 95.9</td>
<td>566 / 96.4</td>
</tr>
<tr>
<td>Grade 2 (moderate) [n/%)</td>
<td>39 / 4.0</td>
<td>20 / 3.4</td>
</tr>
<tr>
<td>&gt; Grade 2 [n/%)</td>
<td>1 / 0.1</td>
<td>1 / 0.2</td>
</tr>
</tbody>
</table>
Outcomes with new-generation TAVR devices

Transcatheter aortic valve replacement with new-generation devices: A systematic review and meta-analysis.

Int J Cardiol. 2017 Jul 25
30-day outcomes of early vs. new-generation TAVR devices

![Bar chart showing outcomes of early vs. new-generation TAVR devices](image)

Early-generation THV (Corevalve, Sapien, Sapien XT)

New-generation THV (Evolut R, Sapien3, Portico, Acurate/Neo, Lotus)

- All-cause death: Early 7.8%, New 2.2%
- CV death: Early 5.6%, New 1.6%
- All stroke: Early 5.7%, New 2.5%
- Disabling stroke: Early 3.2%, New 1.1%
- LT bleeding: Early 15.6%, New 3.9%
- Major vascular complications: Early 11.9%, New 4.5%
- PM implantation: Early 13.9%, New 16.2%
- More than mild AR: Early 7.4%, New 1.6%

EuroIntervention 2017;13:AA11-AA21
Transcatheter aortic valve implantation in 2017: state of the art
Procedural outcomes in bicuspid vs. tricuspid
First generation devices

(J Am Coll Cardiol 2017;69:2579–89)
Procedural outcomes in bicuspid vs. tricuspid
Second generation devices

(J Am Coll Cardiol 2017;69:2579–89)
Prediction of paravalvular leakage after transcatheter aortic valve implantation

Agatston score predictive of significant PVL

<table>
<thead>
<tr>
<th>Predictor</th>
<th>VARC-2 score</th>
<th>Angiography score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ρ value</td>
<td>p value</td>
</tr>
<tr>
<td>Maximal annulus diameter</td>
<td>0.210</td>
<td>0.003</td>
</tr>
<tr>
<td>Cover index</td>
<td>-0.134</td>
<td>0.043</td>
</tr>
<tr>
<td>Eccentricity index</td>
<td>0.030</td>
<td>0.350</td>
</tr>
<tr>
<td>Agatston score</td>
<td>0.305</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Severe calcifications:
Major Challenge for all TAVR prostheses
Extension of calcifications to LVOT

- Increased risk for landing zone complications

*Barbanti M et al Circulation 2013; 128: 244-253*
PVL testing will drive TAVR innovation

- Paravalvular leak (PVL) after TAVR adversely affects patient outcomes
- Mild PVL was acceptable in Extreme Risk group
  - TAVR performance must approach SAVR performance for lower risk populations
- Newer devices aim to reduce PVL
  - Need to demonstrate functional improvement pre-clinically
- A standardized, clinically relevant *in vitro* PVL test method is needed

Pibarot et al. *J Am Coll Cardiol Img* 2015;8:340–60
Attribute based approach

Aorta
- Aortic diameter
- Compliance
- Curvature

Annulus
- Diameter
- Height
- Eccentricity
- Compliance
- Calcification

Leaflets
- Length
- Thickness
- Compliance/material
- Calcification

Paravalvular Leakage

Sinus
- STJ diameter
- STJ height
- Maximum diameter
- Max. dia. location

Pulse duplicator
- Stroke volume
- Beat rate
- Mean Aortic Pressure
dP/dt

TAVR
- Implant depth
- Radial positioning
- Sizing
Is paravalvular regurgitation still an important consideration in 2018?

• Much progress in prevention, grading and treatment
• Degree of calcification will continue to pose challenge for TAVR devices
• Sizing still not always straightforward
  – Occasionally BAV to assess choice of prosthesis size
• For balloon expandable, risk of annular rupture always balanced against risk of significant PVL
• Further refinements in accuracy of delivery, landing zone identification, and enhanced stent to annulus contact will further decrease rates of PVL to “surgical” levels