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Medtronic Evolut R: Advantages and Disadvantages

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Physician Name	Company/Relationship
Speaker Bureau/Advisory Board:	Medtronic: C, SB, AB, OF LivaNova: C, SB, AB Highlife: AB, SB Boston Scientific: C, SB, AB Millipede: SB, C Pipeline: SB,C
Equity Interest:	InSeal Medical: E, AB, Valtech: E, SB, Claret: E, AB Shockwave: E, AB Valve Medical: E, AB Mitra/Trialign E, AB, SB

Key

G – Grant and or Research Support E – Equity Interests S – Salary, AB – Advisory Board
C – Consulting fees, Honoraria R – Royalty Income I – Intellectual Property Rights
SB – Speaker's Bureau O – Ownership OF – Other Financial Benefits

Clinical Evidence for Evolut R

Evolut R follows on a foundation provided by 10 years of clinical experience of CoreValve. The goals of this presentation are:

- ✓ To leverage experience gained with CoreValve in various clinical populations and demonstrate the specific utility of the self-expanding platform
- ✓ To show specific instances where the improved features of Evolut R, such as a lower profile delivery system and the ability to recapture the valve, provide further advantages
- ✓ To show specific instances where there is still room for improvement with the Evolut R System and understand the early results from the next generation Evolut PRO System

Evolut R

Design Features

Clinical Trials

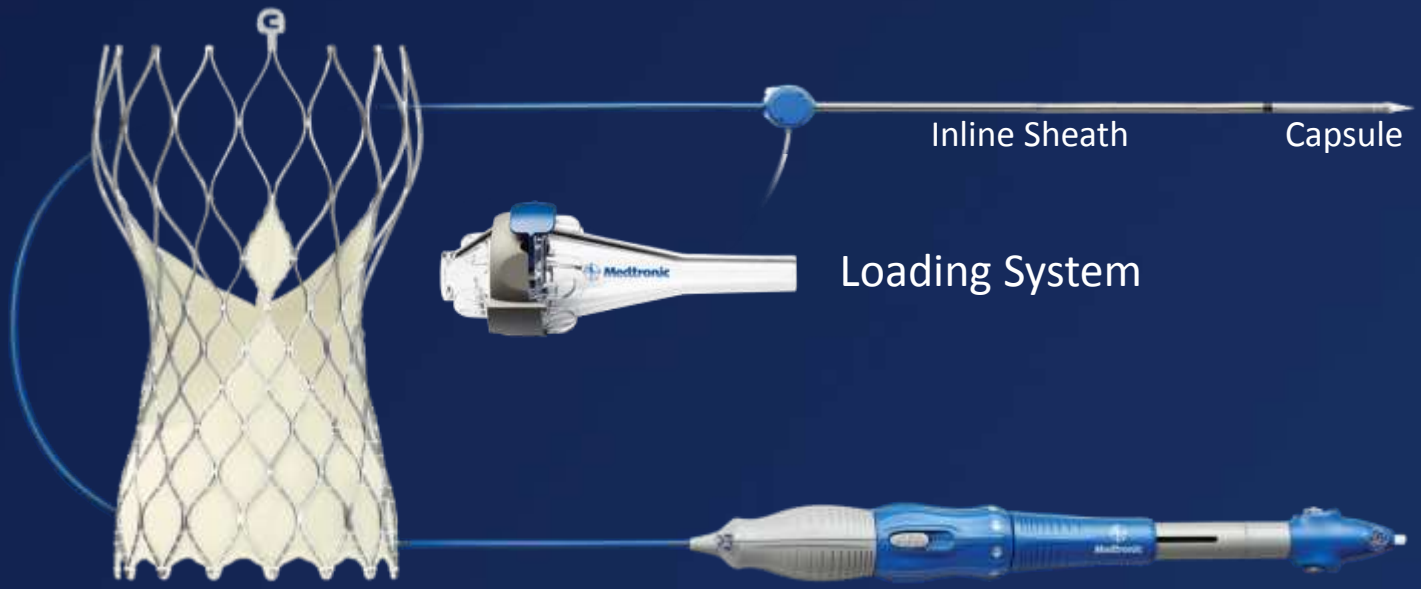
Long Term Follow-Up

Real World Experience

Design Iterations

Clinical Program

- Self-expanding Nitinol frame
- Porcine pericardial supra-annular valve
- Optimized sealing: extended skirt and more conformable frame
- Recapturable
- Annular range: 18 – 30 mm
  - 4 valve sizes: 23, 26, 29, 34 mm
- 14Fr –equivalent profile, vessels ≥ 5.0 mm
  - 34 mm system: 16Fr-equivalent, vessels ≥ 5.5 mm



Evolut R

- Design Features
- Clinical Trials
- Long Term Follow-Up
- Real World Experience
- Design Iterations
- Clinical Program

Evolut R CE Study[1,2,3]

N = 60
STS: 7.0 ± 3.7%
Age: 82.8 ± 6.1 yrs
Female: 66.7%
Enrolled: Oct 2013-July 2014

Follow-up through 2 yrs

Evolut R US IDE Study[4,5]

N = 241
STS: 7.4 ± 3.4%
Age: 83.3 ± 7.2 years
Female: 68.5%
Enrolled: Sept 2014-July 2015

Follow-up through 1 yr

[1]Manoharan, et al., *J Am Coll Cardiol Intv* 2015; 8: 1359-67;[2]Manoharan, et al., presented at TCT 2015; [3]Brecker, et al., presented at TCT 2016; [4]Williams, et al., presented at ACC 2016; [5]Popma, et al., presented at TCT 2016

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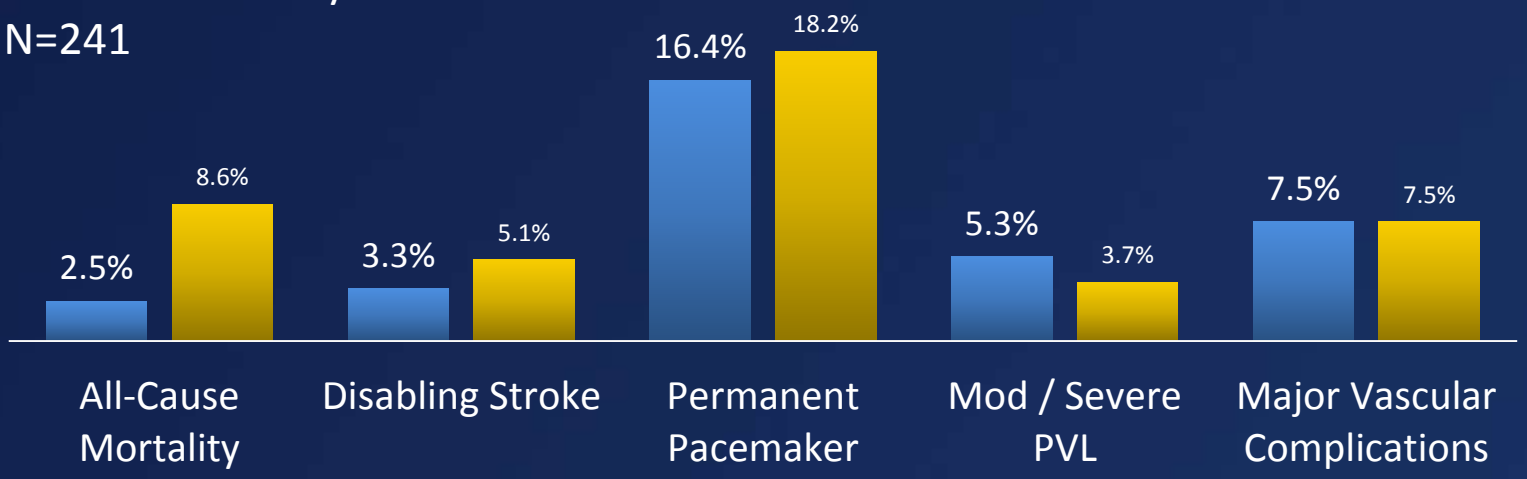

[1]Brecker, et al., presented at TCT 2016; [2]Popma, et al., presented at TCT 2016

Evolut R

- Design Features
- Clinical Trials
- Long Term Follow-Up
- Real World Experience
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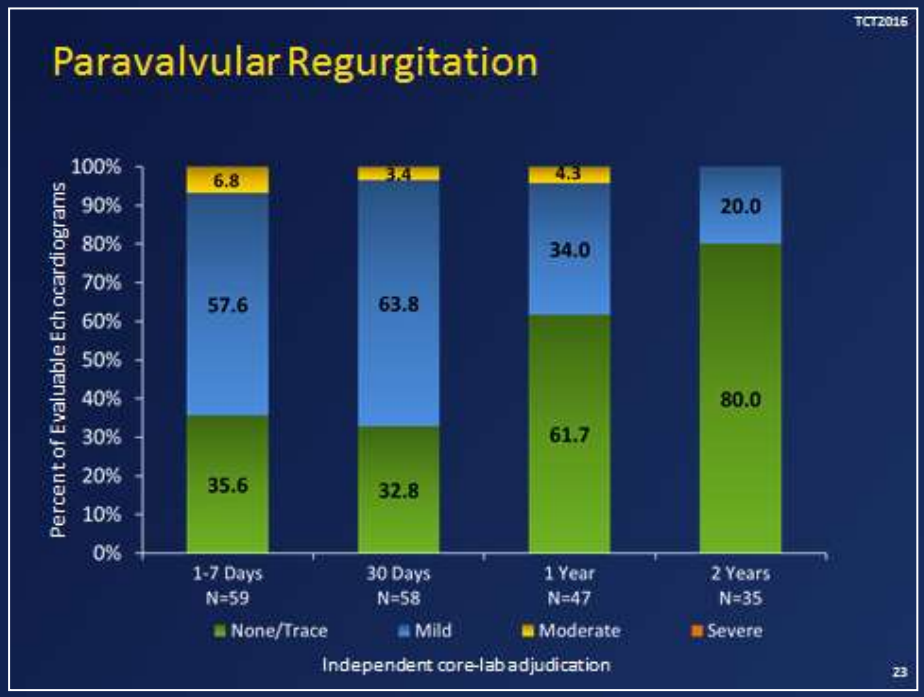
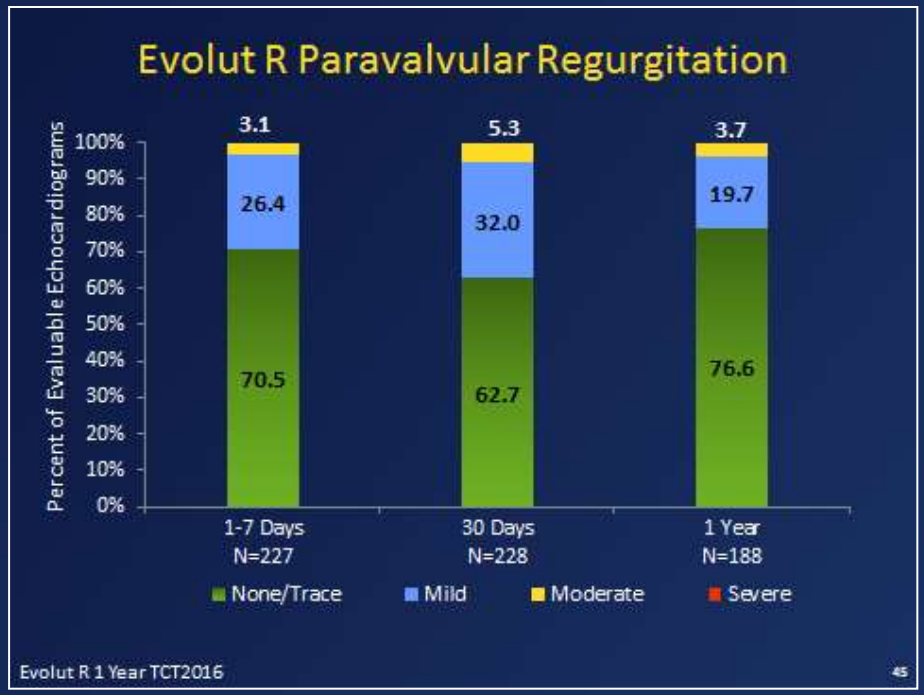
- Clinical Program

Evolut R CE Study
N=60

Both cohorts demonstrate an increase in the % of patients with none/trace PVL over time

Evolut R US Study
N=241





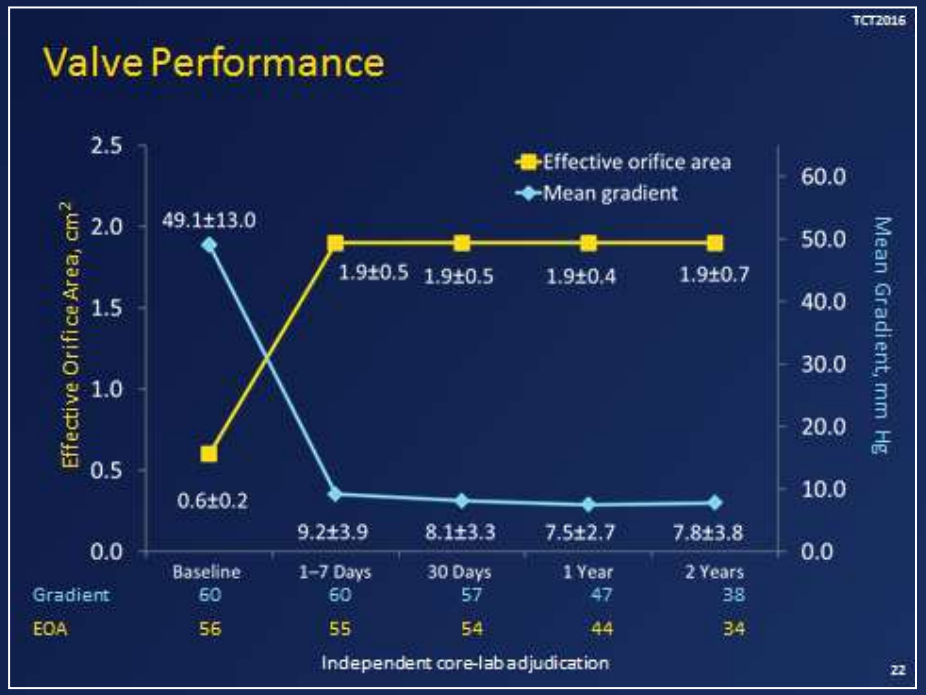
Evolut R

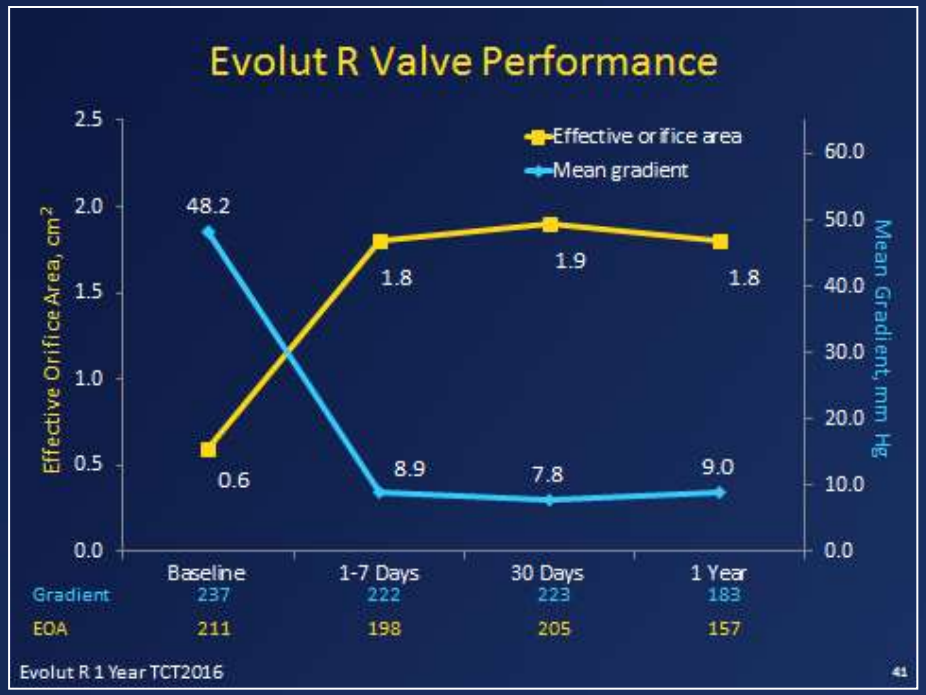
- Design Features
- **Clinical Trials**
- Long Term Follow-Up
- Real World Experience
- Design Iterations
- Clinical Program

Evolut R CE Study
N=60

Very low gradients remained stable to 2 yrs

Evolut R US Study
N=241





Evolut R

Design Features

Clinical Trials

Long Term Follow-Up

Real World Experience

Design Iterations

Clinical Program

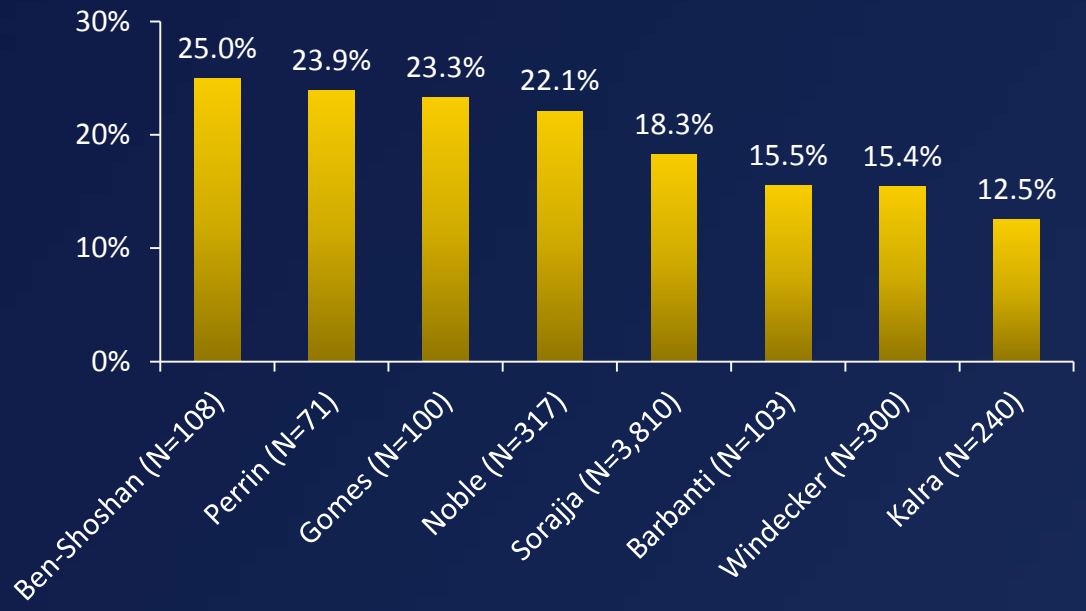
Real-world outcomes in over 5,000 patients have been reported

Study	Type	N	STS (%)	Age (Yrs)
Perrin[1]	Single Center: Geneva	71	4.8 ± 3.5	83.0
Gomes[2]	Single Center: Heidelberg	100	5.4 ± 4.0	82.7
Ben-Shoshan[3]	Single Center: Tel-Aviv	108	4.3 ± 2.7	82.7
Barbanti[4]	REPLACE Registry	103	5.0 ± 3.7	82
Kalra[5]	UK / Ireland Registry	240	6.0 ± 5.6	81.2
Windecker[6]	FORWARD Study	300	5.6 ± 3.8	82.0
Noble[7]	Swiss TAVI Registry	317	4.8 ± 3.4	82.1
Sorajja[8]	STS / TVT Registry	3,810	8.0 ± 5.4	81.2

Evolut R

- Design Features
- Clinical Trials
- Long Term Follow-Up
- **Real World Experience**
- Design Iterations
- Clinical Program

30-Day Permanent Pacemaker

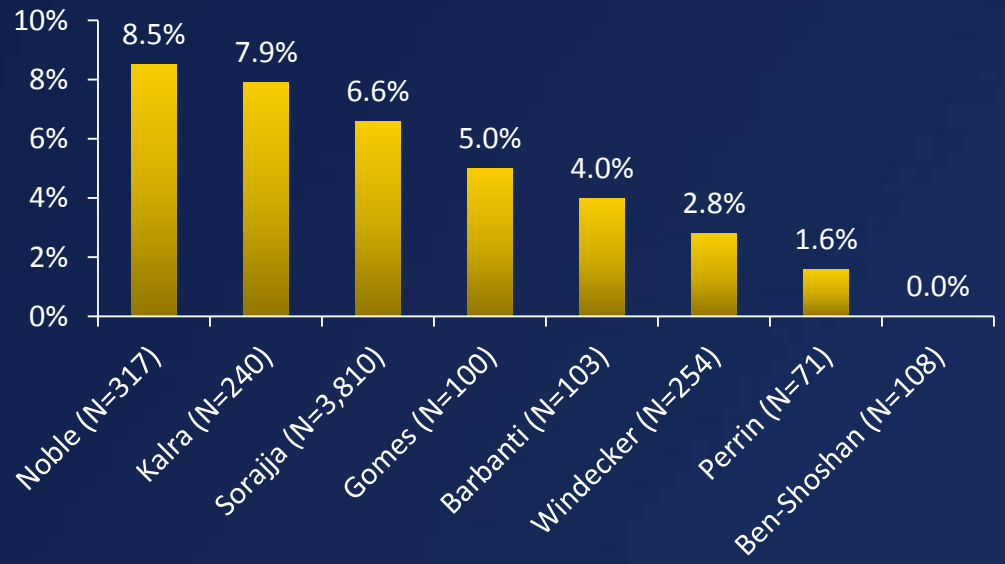


Pacemakers

Weighted Average:

18.3%

Moderate / Severe PVL



PVL

Weighted Average:

6.3%

Evolut R

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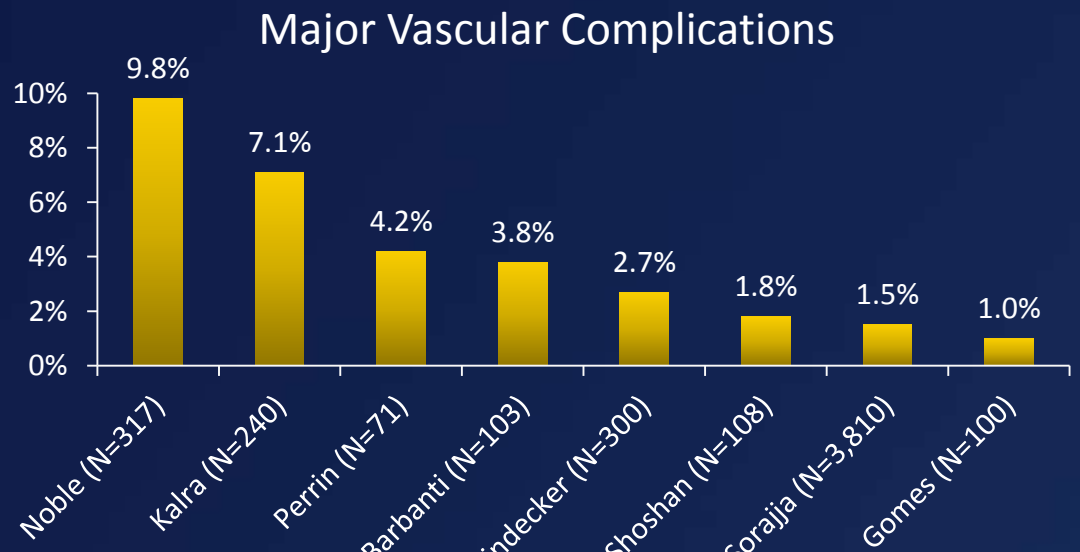
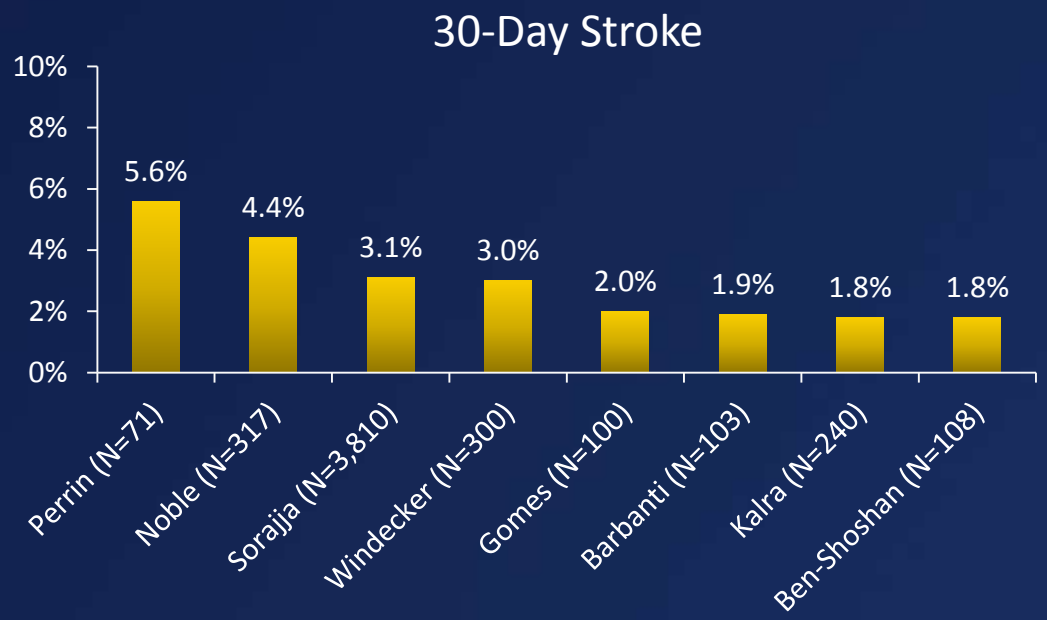


MVCs

Weighted Average:

2.4%



All Stroke

Weighted Average:

3.1%

Small Vasculature

Contemporary Delivery Systems

Indicated Vessel Size

Due to its low profile, the Evolut platform has the potential to reach 17% more patients than SAPIEN XT or CoreValve, and 7% more patients than SAPIEN 3

	 SAPIEN XT			 SAPIEN 3		 Lotus	 CoreValve	 Evolut R	 Evolut PRO
Valve Size (mm)	20, 23	26	29	20, 23, 26	29	23, 25, 27	23, 26, 29, 31	23, 26, 29 34	23, 26, 29
Indicated Vessel Diameter (mm)	6.0	6.5	7.0	5.5	6.0	6.0	6.0	5.0	5.5

*OD of the Gore DrySeal

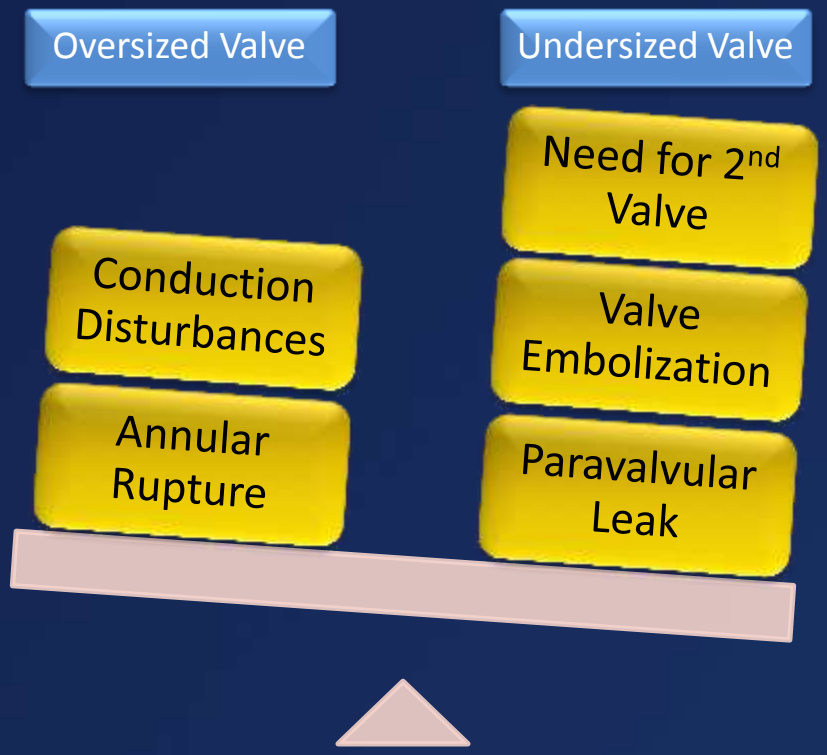
Patients at High Risk for Annular Rupture

Valve Selection

A Patient-Centered Approach

MSCT is the gold-standard tool for pre-TAVI assessment of aortic root anatomy. It should be used in all indicated cases.

- Assess annulus geometry
- Identify adverse features which may precipitate PVL, annular rupture, or coronary occlusion
- Select an appropriate bioprosthesis type and size.
    - In cases where the valve is on the borderline between two sizes, the relative complication risks should be considered for the individual patient

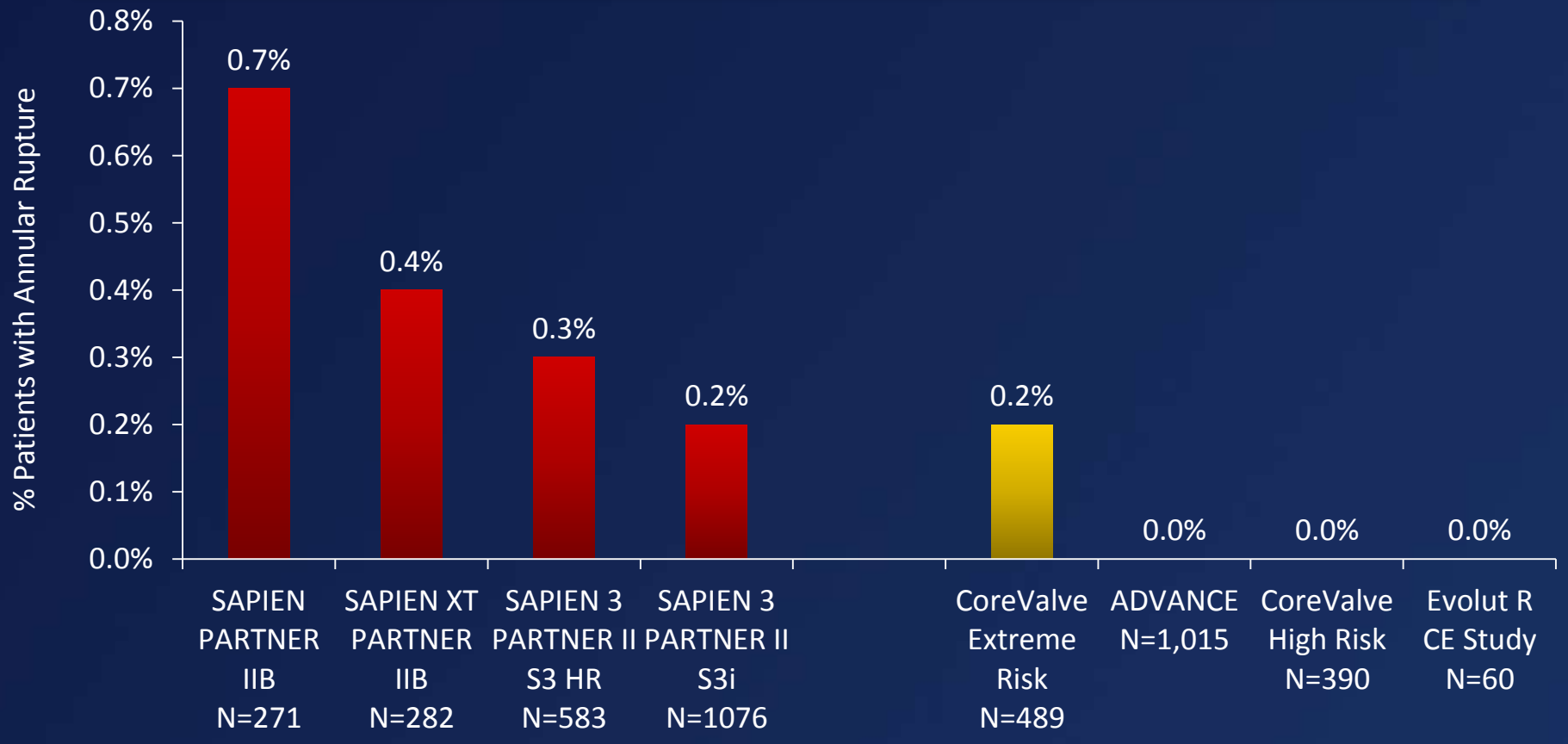


[1]Dvir, et al., *Catheter Cardiovasc Interv* 2015;86:508-15

Annular Rupture

Rare but Catastrophic

- Annular rupture is a rare event, but is associated with a mortality rate of ~50%.
- It is typically associated with balloon expansion, and is therefore very uncommon with self-expanding valves



[1]Leon, et. al. presented at ACC 2013; [2]Kodali, et al., presented at ACC 2015; [3]Popma, et al., *J Am Coll Cardiol* 2014; 63: 1972-81; [4]Linke, et al. , *Eur Heart J* 2014; 35: 2672-84; [5]Adams, et al., *N Engl J Med* 2014; 370: 1790-8; [6]Meredith, et. al. presented at EuroPCR 2015

Failing Surgical Aortic Valve Bioprostheses

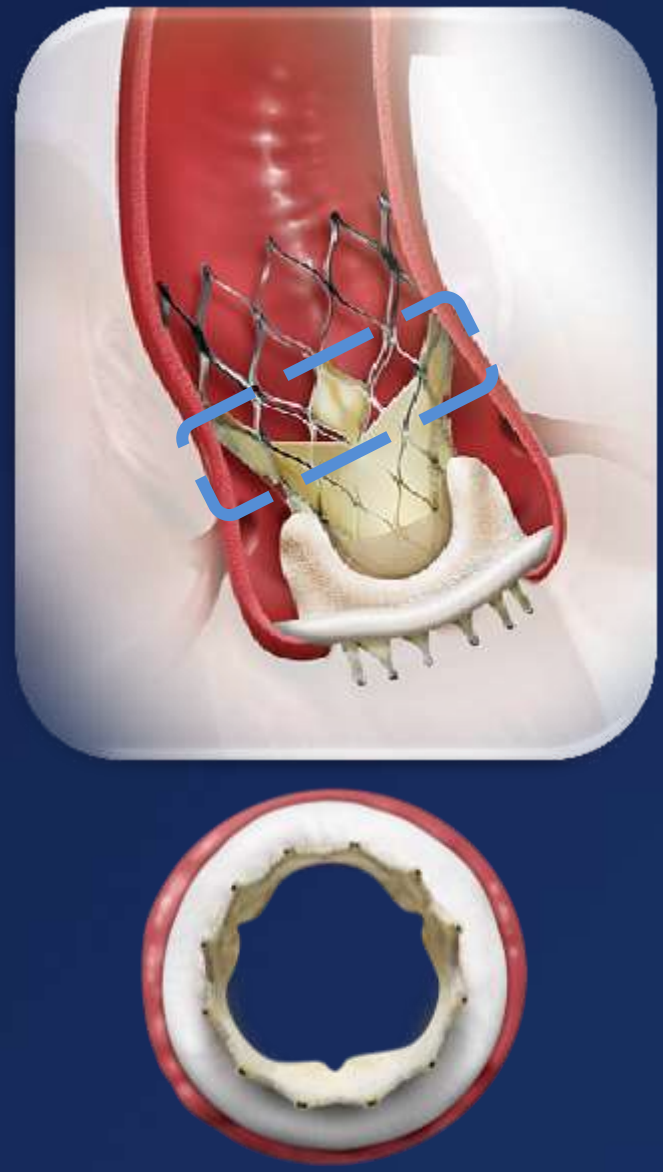
TAV in SAV

Supra-Annular Design Maximizes Forward Flow

Surgical bioprostheses often fail due to stenosis, which reduces the effective orifice area. It can be difficult to "gain back" this space with TAV in SAV, especially in small annuli.

Advantages of a self-expanding valve:

- Supra-annular leaflets optimize forward flow and maximize the potential effective orifice area
- The 23 mm CoreValve bioprosthesis is indicated to treat failed surgical valves with a 17 mm internal diameter



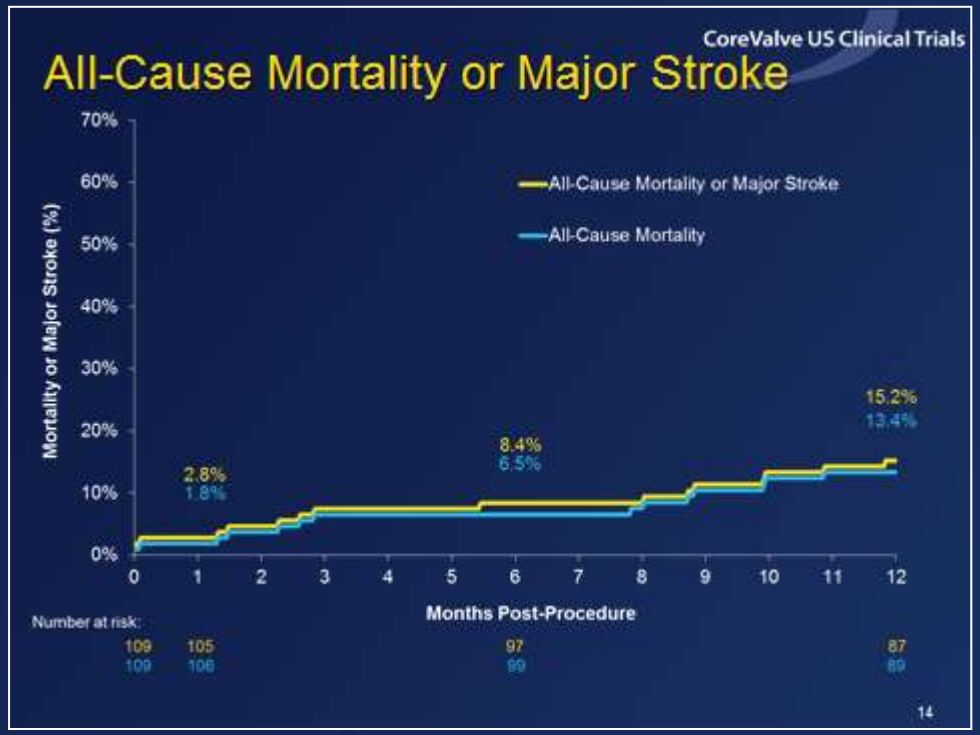
Pivotal Trial Expanded Use Study

TAV in SAV

- TAV in SAV using CoreValve was studied in the US Pivotal Trial Expanded Use Study
- Patients were at high surgical risk with a mean SAV age of 10.0 ± 4.6 years
- 36% of the failed SAVs were small, either 19 or 21 mm

Baseline		
Age (years)	STS (%)	% SAVs 19 or 21 mm
77.1 ± 10.5	9.5 ± 5.6	36.3

- Clinical outcomes were excellent, with an all-cause mortality rate of 13.4% at 1 year



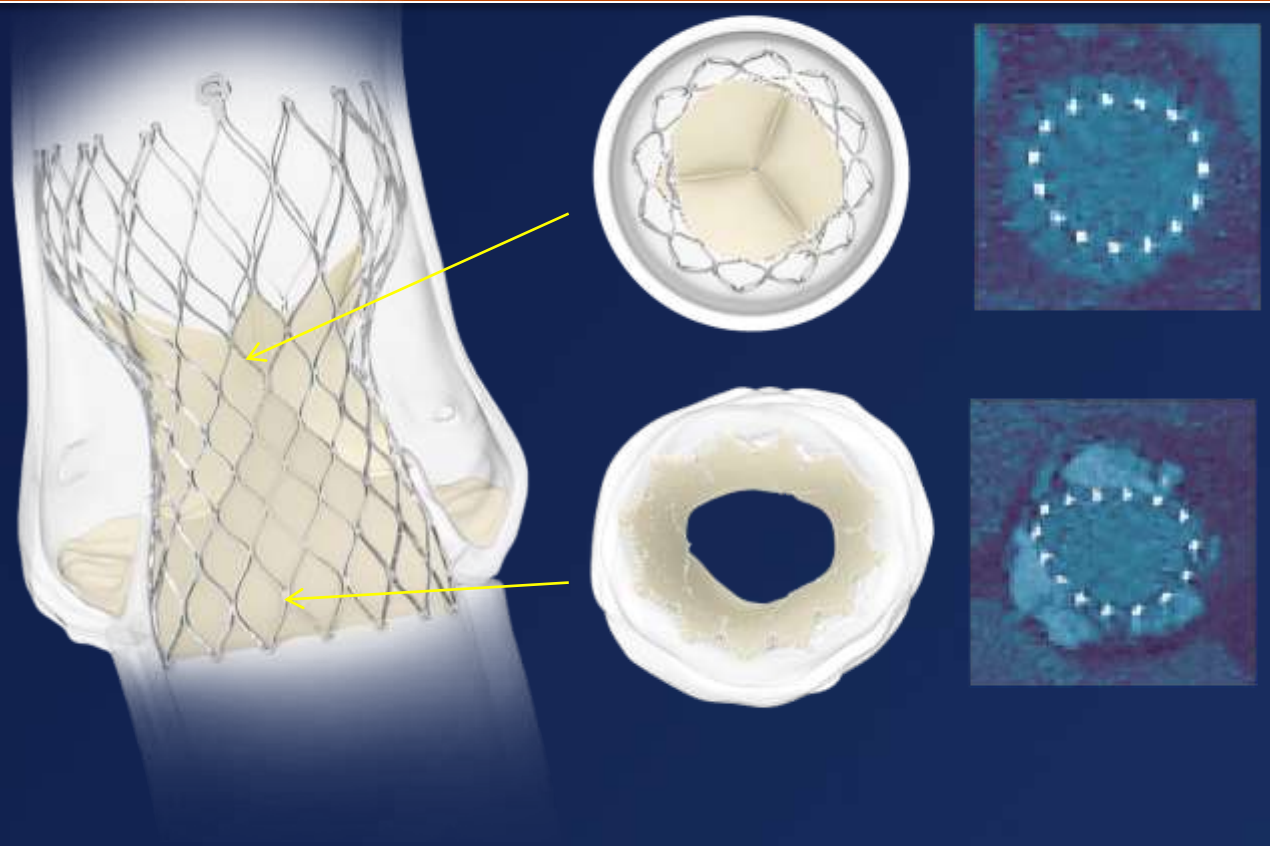
[1]Deeb, et al., presented at TCT 2015

Lifetime Management: Durability

Supra-annular Valve Function

Coaptation in non-circular anatomy

- Supra-annular valve design decouples the new leaflets from the native annulus— minimizing the impact of calcium and annular ellipticity on leaflet motion and coaptation.
- Provides unsurpassed hemodynamics and may increase durability



Images courtesy of Drs. DeJaegere and Schultz, Erasmus MC, Rotterdam, The Netherlands

High Risk | Valve Hemodynamics*

- TAVR had significantly better valve performance vs SAVR at all follow-ups (P<0.001)
- Stable hemodynamics over time suggests the absence of leaflet degeneration

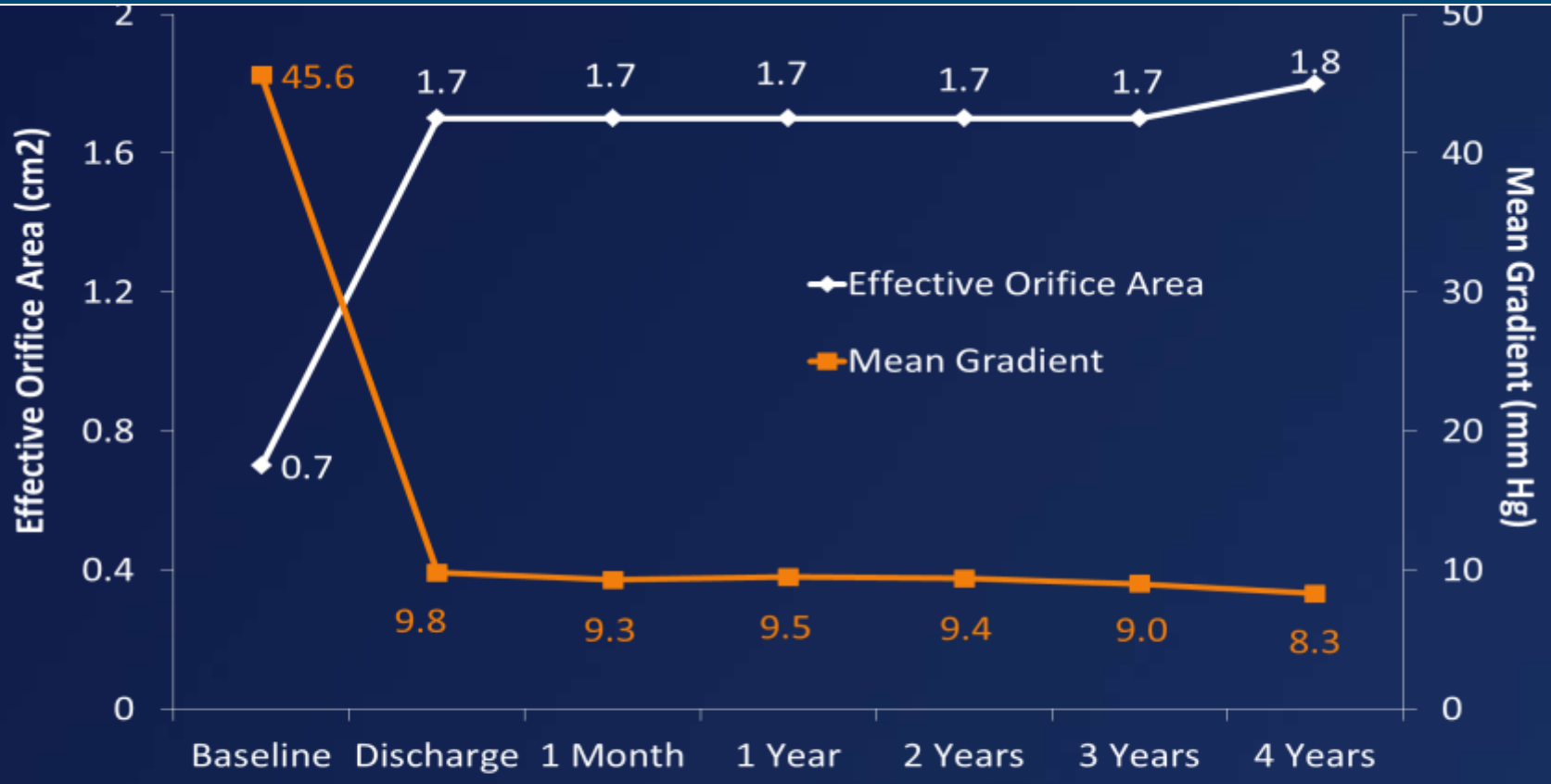
*Site-reported

	Baseline	Discharge	1 Month	1 Year	2 Years	3 Years
Gradient - TAVR	174	174	174	174	174	174
Gradient – SAVR	113	113	113	113	113	113
EOA – TAVR	126	126	126	126	126	126
EOA - SAVR	85	85	85	85	85	85

Deeb GM, et. al. "3-Year Results From the US Pivotal High Risk Randomized Trial Comparing Self-Expanding Transcatheter and Surgical Aortic Valves." ACC 2016.

ADVANCE | Valve Hemodynamics

- Hemodynamics remain stable at 4 years, suggesting the absence of leaflet degeneration



Number of Echos							
EOA:	795	514	389	394	351	253	210
Mean Gradient	885	807	610	576	488	356	310

Data in this figure represent the mean value at each timepoint.

Brecker S et. Al. "Four-Year Clinical and Echocardiographic Follow-Up of Aortic Stenosis Patients Implanted with a Self-Expanding Bioprosthesis." EuroPCR 2016

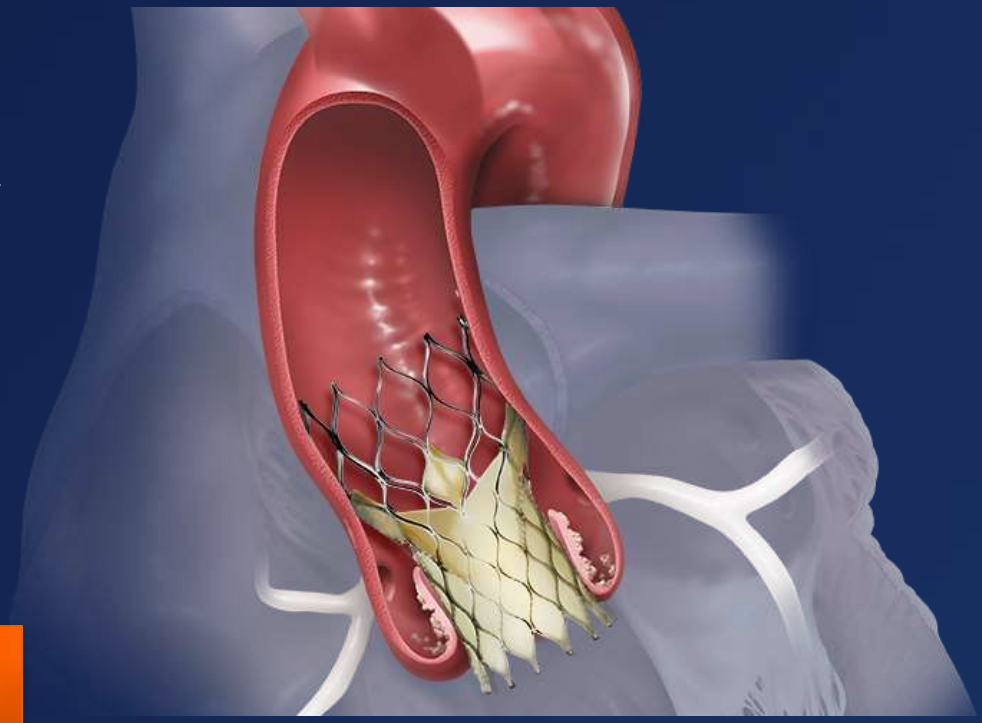
Patients at High Risk for Coronary Obstruction

Special Anatomy

Patients at High Risk for Coronary Obstruction

Medtronic recommends implantation in patients with coronary ostia height ≥ 14 mm, however the self-expanding valve may still be a better choice in patients at high risk for obstruction:

- Tapered shape of the frame diminishes the risk
- If needed, coronary access can be achieved through the struts of the frame
- Evolut R can be completely recaptured in an emergency situation

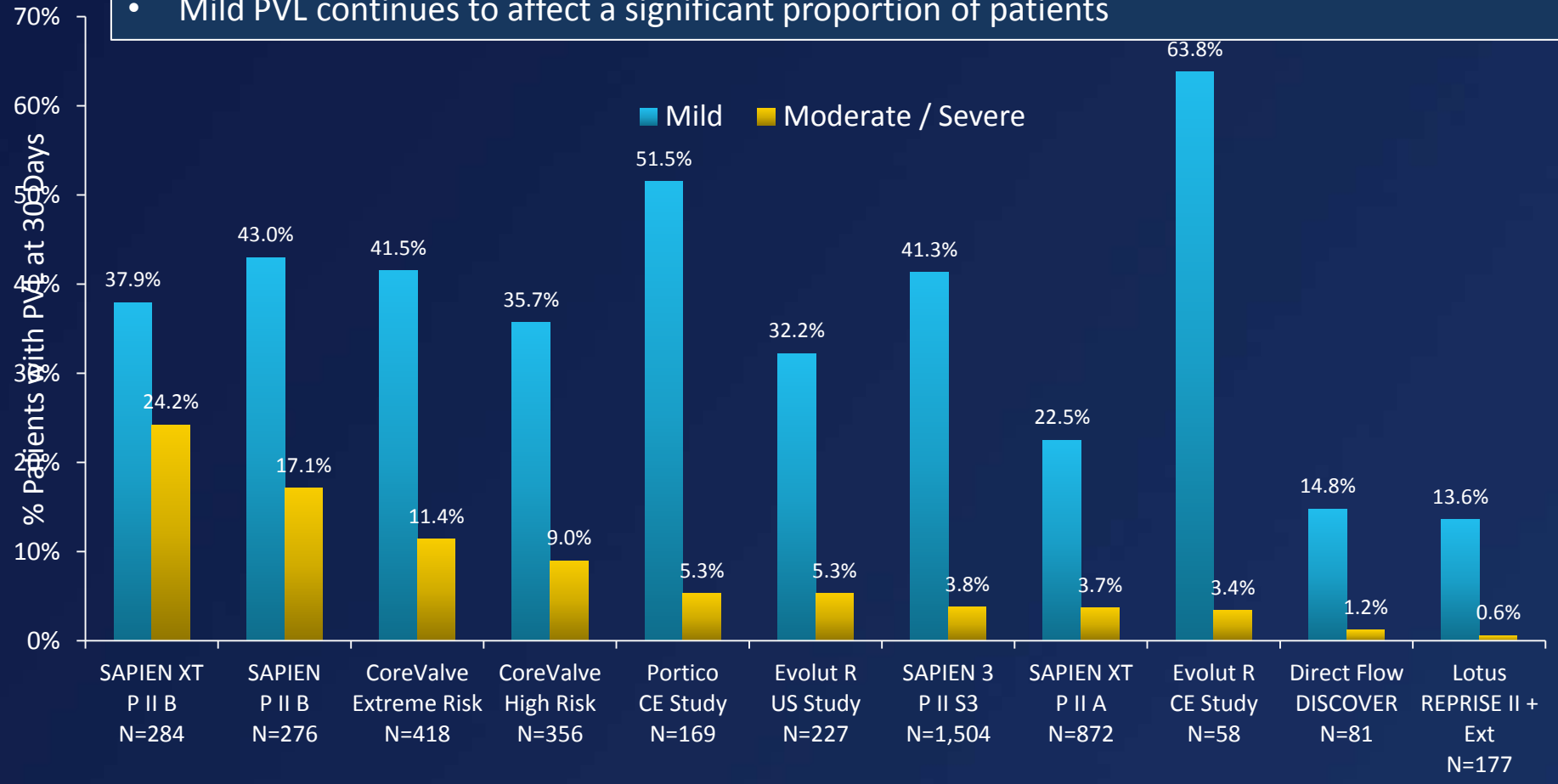


Paravalvular Leak

Paravalvular Leak

Rates at 30 Days

- The rates of moderate and severe PVL in contemporary practice are low due to sealing skirts and careful sizing practices using MSCT
- Mild PVL continues to affect a significant proportion of patients

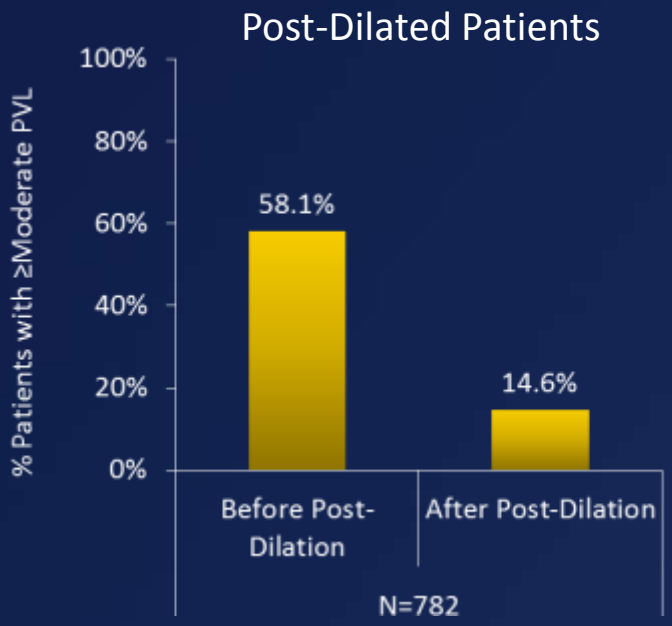


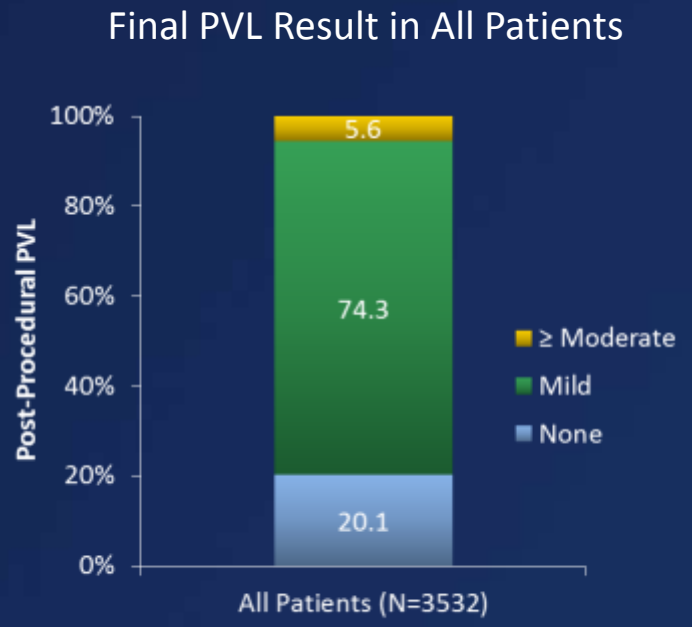
[1]Webb, et. al. *J Am Coll Cardiol Intv* 2015; 8: 1797-806; [2]Popma, et al., *J Am Coll Cardiol* 2014; 63: 1972-81; [3]Adams, et al., *N Engl J Med* 2014; 370: 1790-8; [4]Linke, et. al. presented at PCR London Valves 2015; [5]Williams, et al., presented at ACC 2016; [6]Kodali, et al., *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw112; [7]Manoharan, et al., *J Am Coll Cardiol Intv* 2015; 8: 1359-67; [8]Lefevre, et al., *J Am Coll Cardiol Intv* 2016; 9: 68-75; [9]Meredith, et al., presented at PCR London Valves 2014

Management of Paravalvular Leak

Post-Dilation

- Balloon post-dilation can be used to reduce paravalvular leak if the frame does not fully expand
- Data from the CoreValve US Pivotal Trial confirmed the effectiveness of this technique
  - 782 patients out of 3,532 (22%) underwent post-dilatation, reducing the rate of moderate / severe PVL by 75% in those patients
- In the total cohort of patients, the rate of moderate / severe PVL was 5.6%





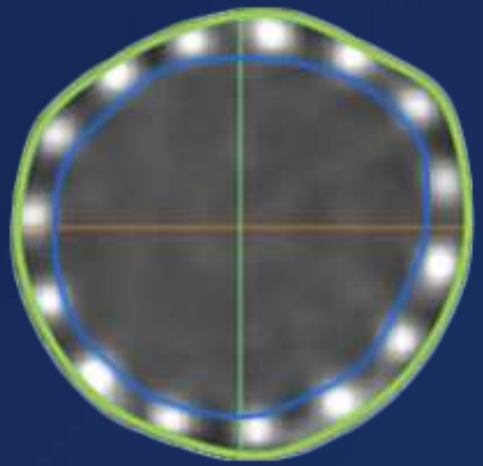
[1]Harrison, et al., presented at TCT 2015

Evolut PRO

- Design Features
- Clinical Trials
- Long Term Follow-Up
- Real World Experience
- **Design Iterations**
- Clinical Program

Evolut PRO

- Evolut R with an added pericardial tissue wrap
- Provides greater surface area contact with native annulus
- Reduces “open spaces” between frame struts
- Enhances healing response due to pericardial tissue properties and increased surface contact



Evolut PRO

- Design Features
- Clinical Trials
- Long Term Follow-Up
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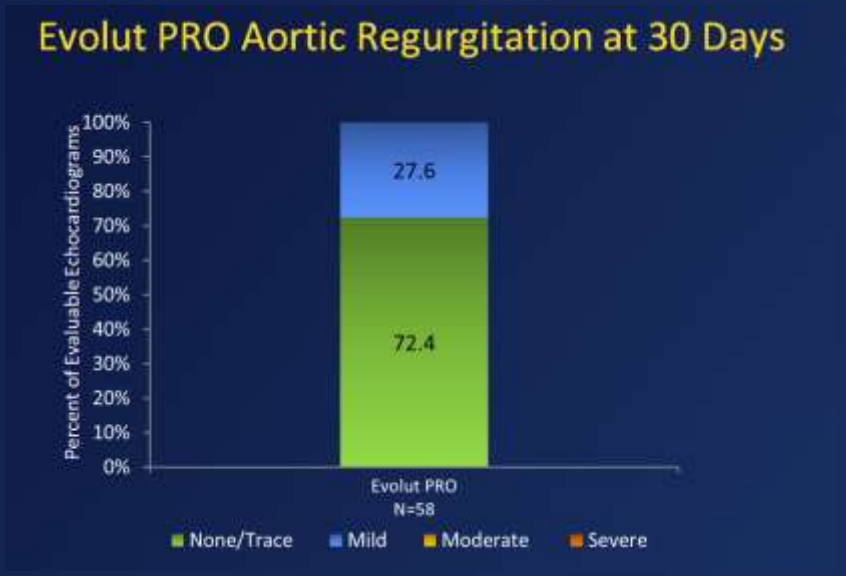
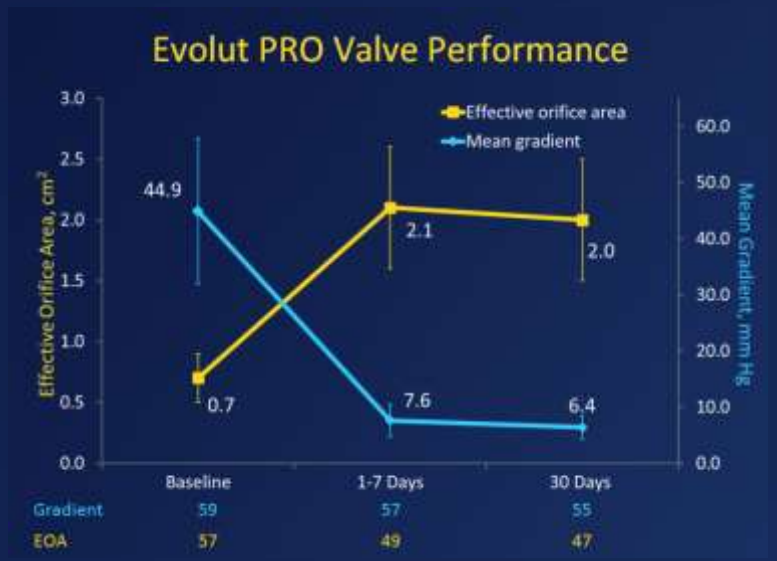
- **Clinical Program**

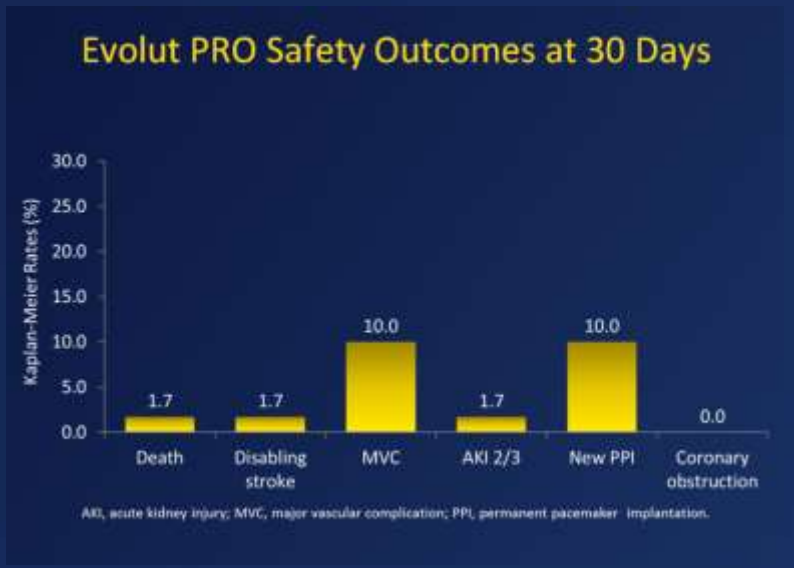
Evolut PRO US Study
N=60

There were no patients with more than mild PVL at 30 days.

The valve demonstrated excellent hemodynamics with a new PPI rate of 10% at 30 days.







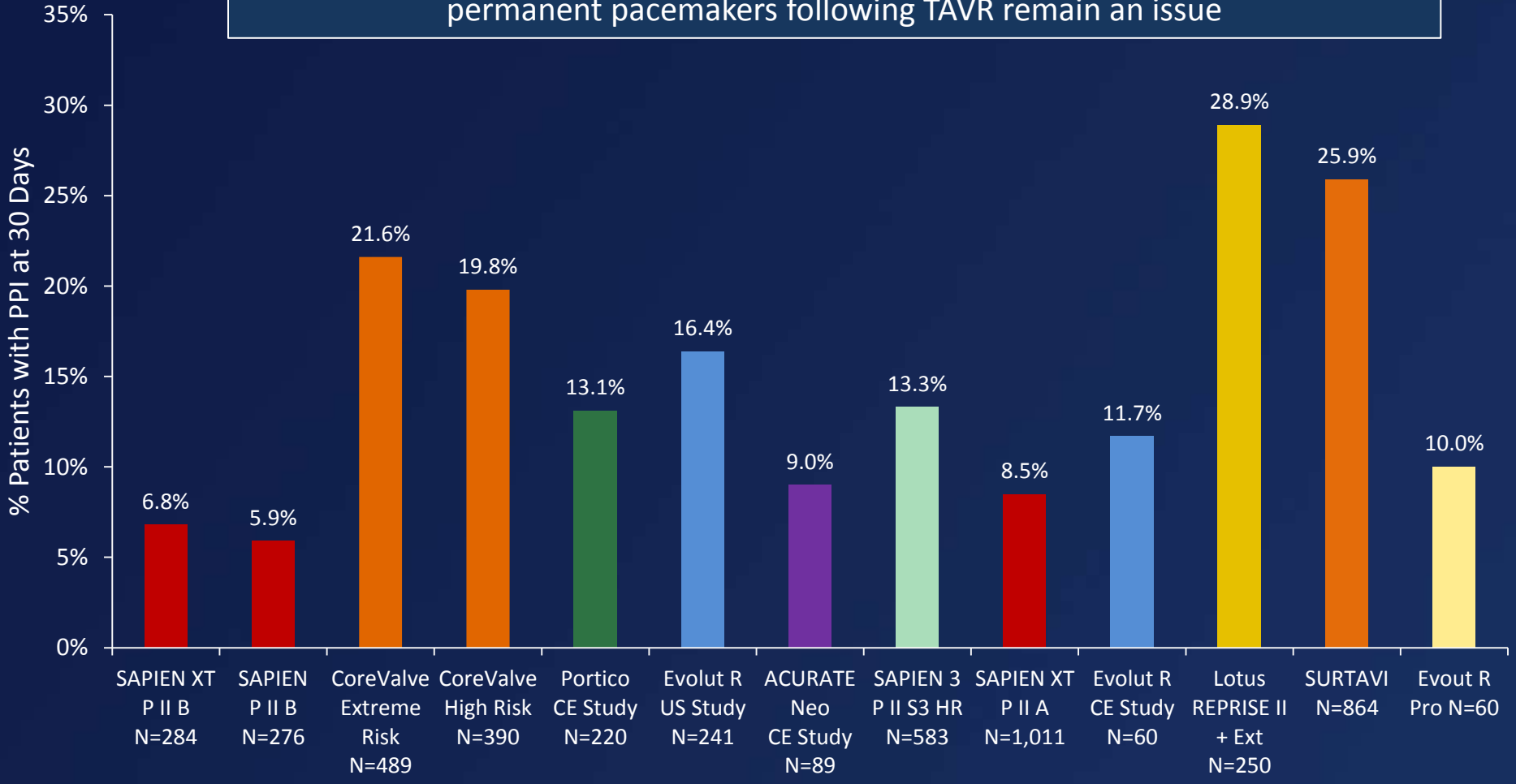
Forrest, et al., presented at ACC 2017

Conduction Disturbances

Permanent Pacemakers

Rates at 30 Days

Despite new technological advances, new conduction disturbances and the need for permanent pacemakers following TAVR remain an issue



[1]Webb, et. al. *J Am Coll Cardiol Intv* 2015; 8: 1797-806; [2]Popma, et al., *J Am Coll Cardiol* 2014; 63: 1972-81; [3]Adams, et al., *N Engl J Med* 2014; 370: 1790-8; [4]Linke, et. al. presented at PCR London Valves 2015; [5]Williams, et al., presented at ACC 2016; [6]Abizaid, et al., presented at CRT 2015; [7]Kodali, et al., *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw112; [8]Leon, et al., *N Engl J Med* 2016 Apr 2 [E-pub ahead of print]; [9]Manoharan, et al., *J Am Coll Cardiol Intv* 2015; 8: 1359-67; [10]Lefevre, et al., *J Am Coll Cardiol Intv* 2016; 9: 68-75; [11]Meredith, et al., presented at PCR London Valves 2014; [12]Reardon et al. presented at ACC 2017; [13]Forrest et al. presented at ACC 2017

Permanent Pacemakers

Clinical Impact

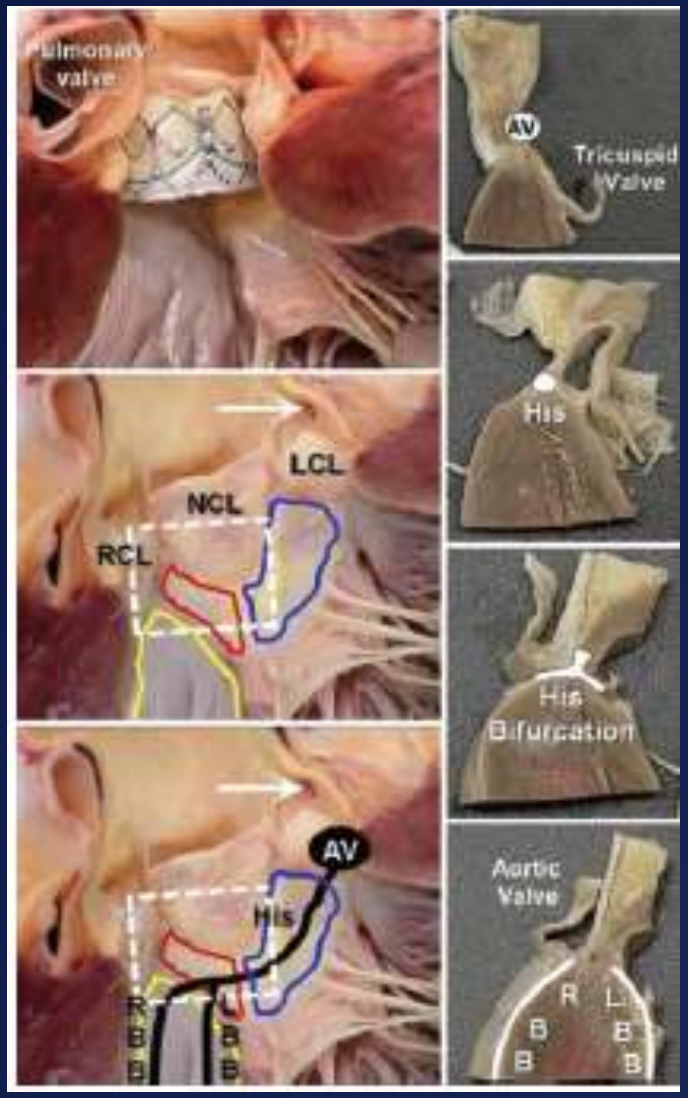
Studies out to 3 years have demonstrated no impact of pacemakers on mortality, but this needs to be monitored over the long term, especially in patients with fewer competing comorbidities

Study	Valve Type (n)	30 Day PPM Rate	Follow-Up	Mortality Impact
De Carlo[1]	CoreValve (n=275)	25.5%	1 year	None (p=0.90)
Buellesfeld[2]	CoreValve (n=319) Edwards (n=34)	27.8%	1 year	None (p=0.77)
Pereira[3]	CoreValve (n=65)	32.8%	1 year	None (p=0.11)
Nazif[8]	SAPIEN (n=1973)	8.8%	1 year	None (p=0.08)
SURTAVI[9]	CoreValve (n=864)	25.9%	2 years	None (p=0.32)
CoreValve ANZ[4]	CoreValve (n=476)	31.1%	2 years	None (p=0.32)
Extreme Risk US Trial[5]	CoreValve (n=489)	21.6%	3 years	None (p=0.62)
ADVANCE[7]	CoreValve (n=1015)	26.3%	3 years	None (p=0.70)
Urena[6]	CoreValve (n=698) Edwards (n=858)	15.4%	3 years	None (p=0.15)

[1]De Carlo M, et al., *Am Heart J* 2012; 163: 492-9; [2]Buellesfeld L, et al., *J Am Coll Cardiol* 2012; 60(6): 493-501; [3]Pereira E, et al., *PACE* 2013; 36(5): 559-69; [4]Muller D, et al., presented at EuroPCR 2013; [5]Popma J, et al., *J Am Coll Cardiol* 2014; 63(10): 1972-81; [6]Urena M, et al., *Circulation* 2014; 129: 1233-1243; [7]Piazza N, et al., presented at TVT 2015; 8Nazif T, et al., *J Am Coll Cardiol Intv* 2015; 8: 60-9; [9]Reardon et al. presented at ACC 2017

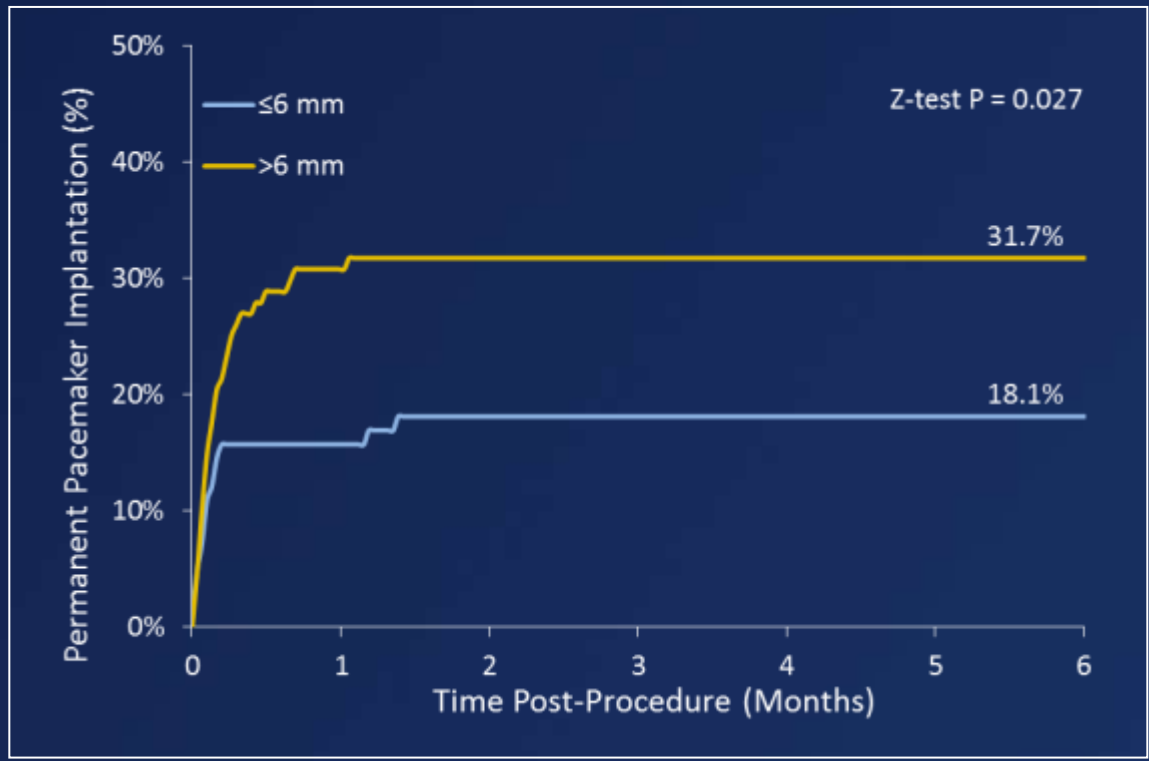
Permanent Pacemakers

Why Do They Happen?



White box represents location of the valve

- Problems arise when the TAV comes in contact with conductive tissue.
- Studies with all contemporary valves have shown that new conduction disturbances are more likely with deeper implants. Control of implant depth to ≤ 5 mm is the best way to minimize risk.



[1]Bax, et al., *Eur Heart J* 2014; 35:2639-54; [2]Petronio, et al., presented at EuroPCR 2014

Final Thoughts

The self-expanding platform offers the following specific advantages:

- ✓ Slow, steady deployment
- ✓ A frame that conforms to the annulus
- ✓ Avoids rapid pacing
- ✓ Can completely eliminate the need for a balloon
- ✓ Offers the smallest available delivery system
- ✓ Has supra-annular function
- ✓ Cautionary labeling has been removed for TAV in SAV, End Stage Renal, and Low Gradient Low Output patients

Potential Problems are:

- ✓ Moderate PVL and Pacemaker Rates

The newest generation Evolut PRO valve shows promising PVL and pacemaker rates without compromising valve performance