TAVI Summit 2014
Seoul, April 9th, 2014

New transfemoral TAVI Devices

Eberhard Grube MD, FACC, FSCAI
University Hospital, Dept of Medicine II, Bonn, Germany
Stanford University, Palo Alto, California, USA

Eberhard Grube, MD

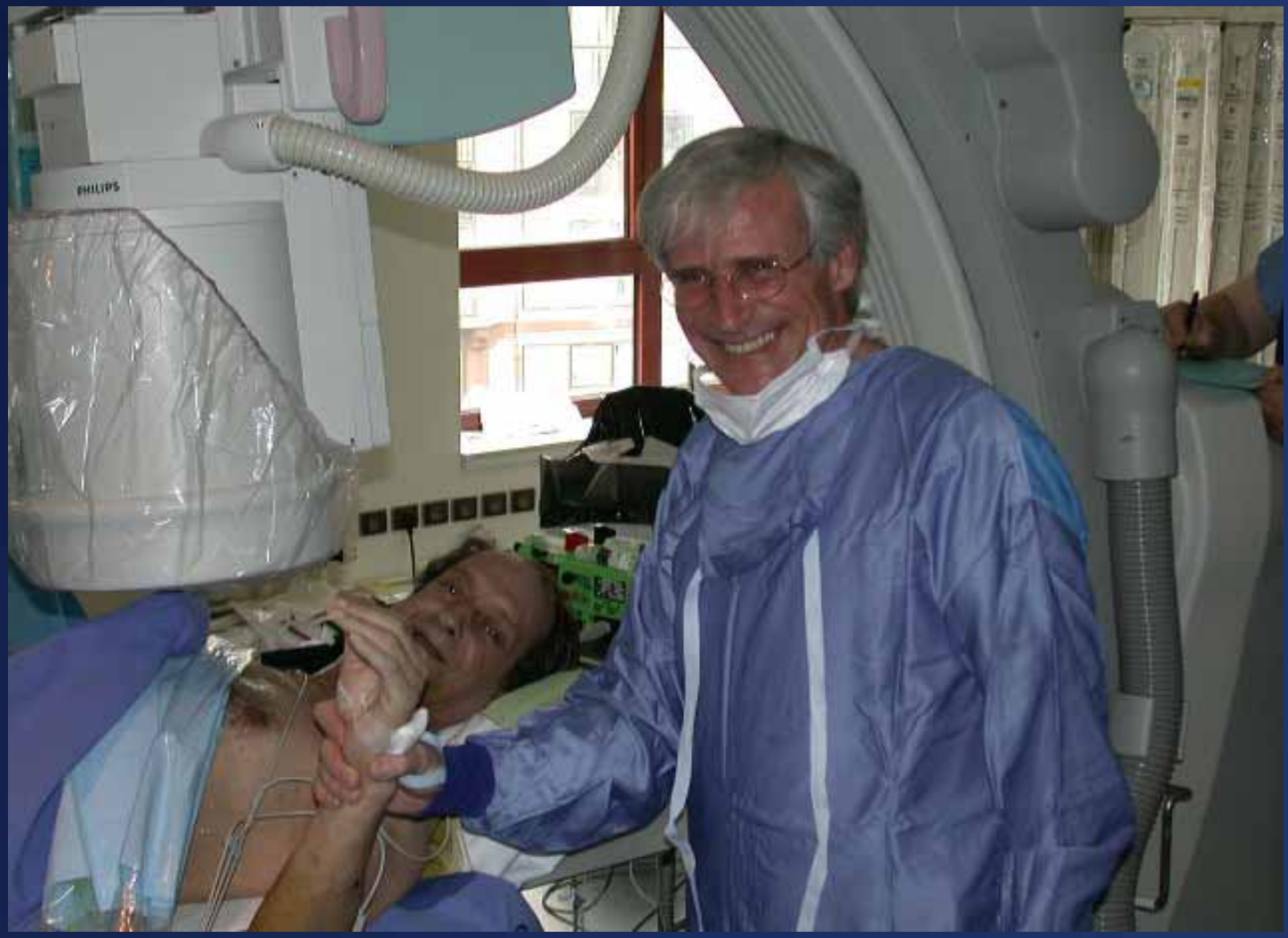
Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Physician Name	Company/Relationship
Eberhard Grube, MD	Medtronic, CoreValve: C, SB, AB, OF Direct Flow: C, SB, AB Mitralign: AB, SB, E Boston Scientific: C, SB, AB Cordis: AB Abbott Vascular: AB Valtech: E, SB, In Seal Medical: SB, E Claret: SB Keystone, 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'


The Past

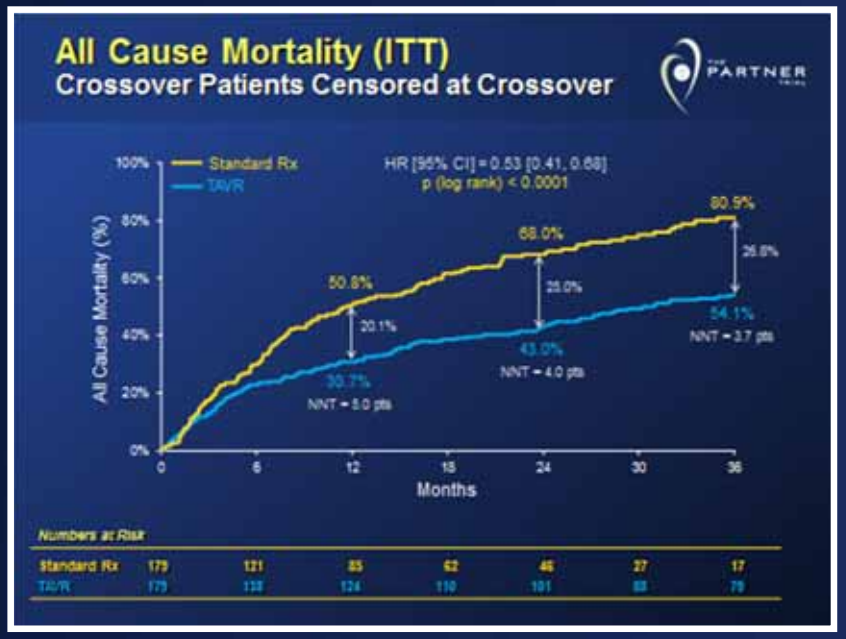
Dr. Alain Cribier
First-in-Man PIONEER

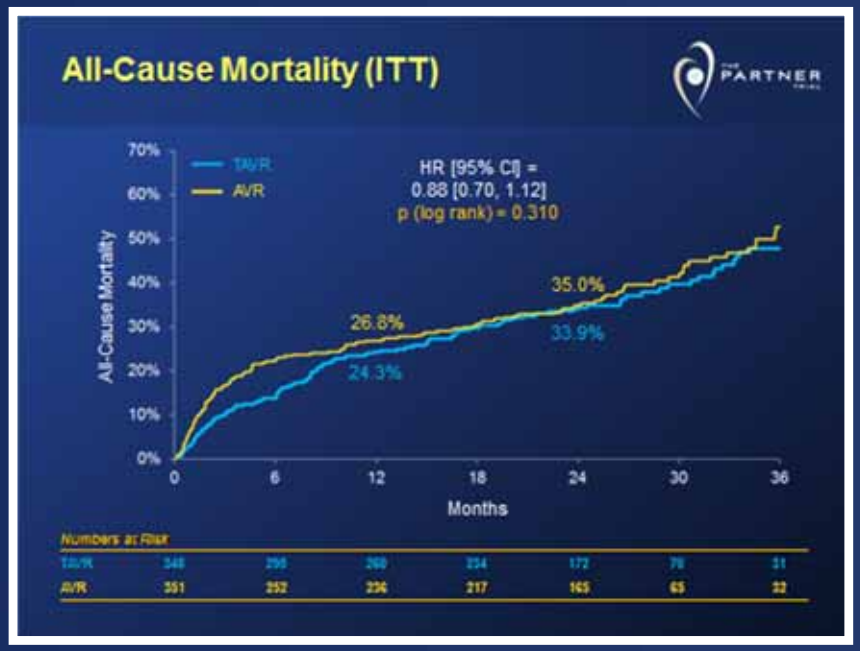


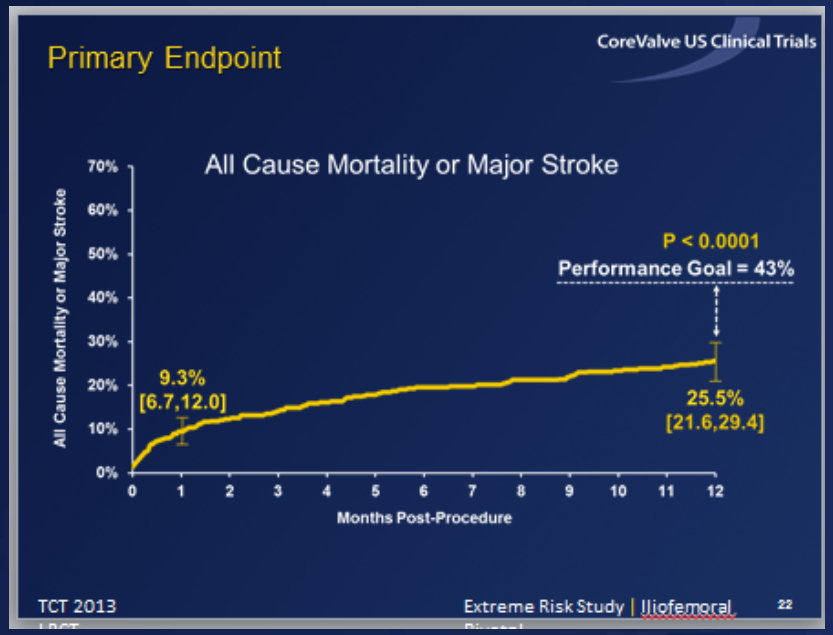
April 16, 2002

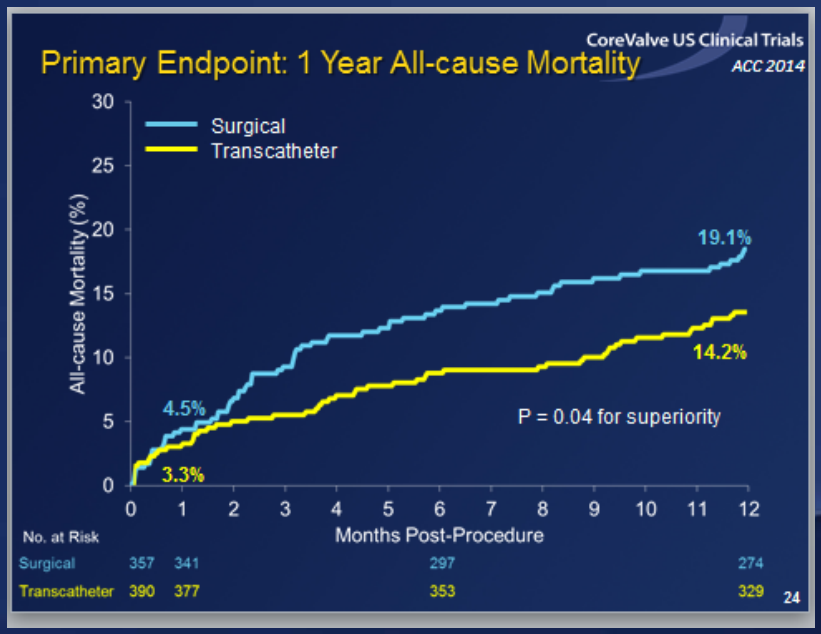
Anatomic “Footprint” of Edwards Sapien Valve vs. MDT CoreValve

Consistent positive Clinical Outcomes







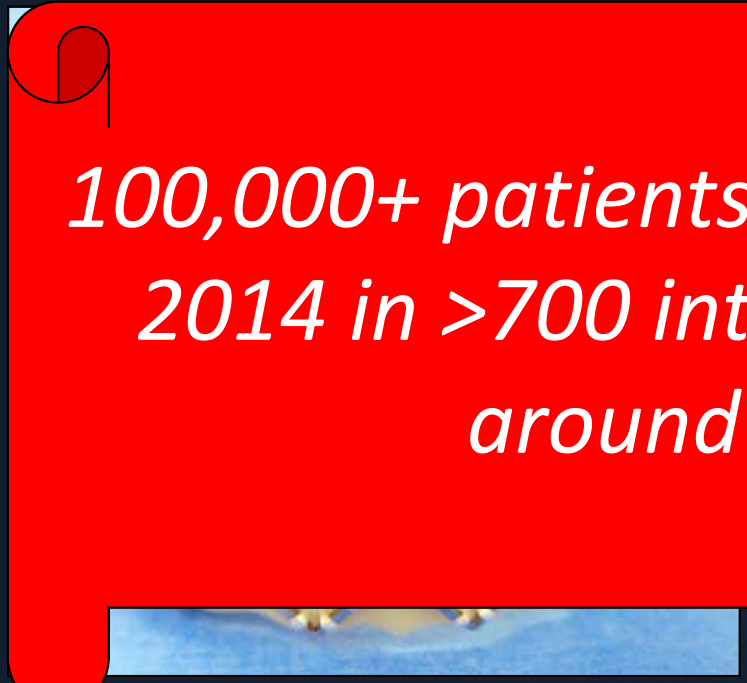


The Present

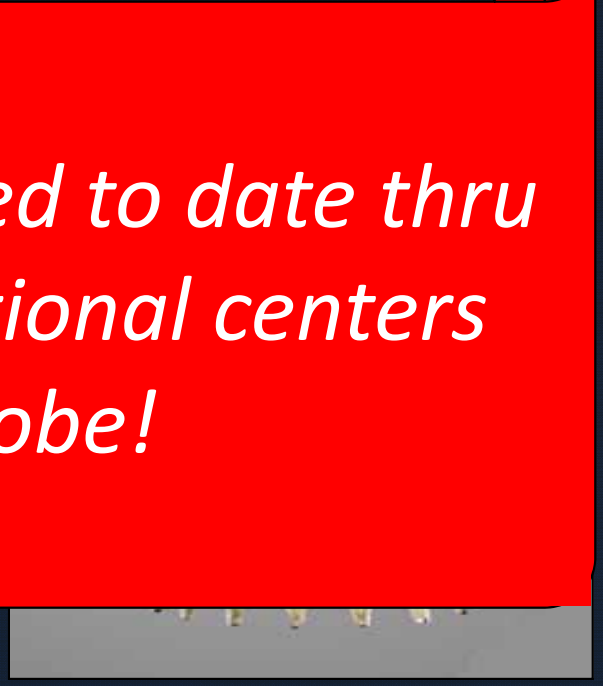
TAVI Arrives….

Current Generation Devices

100,000+ patients treated to date thru 2014 in >700 interventional centers around the globe!



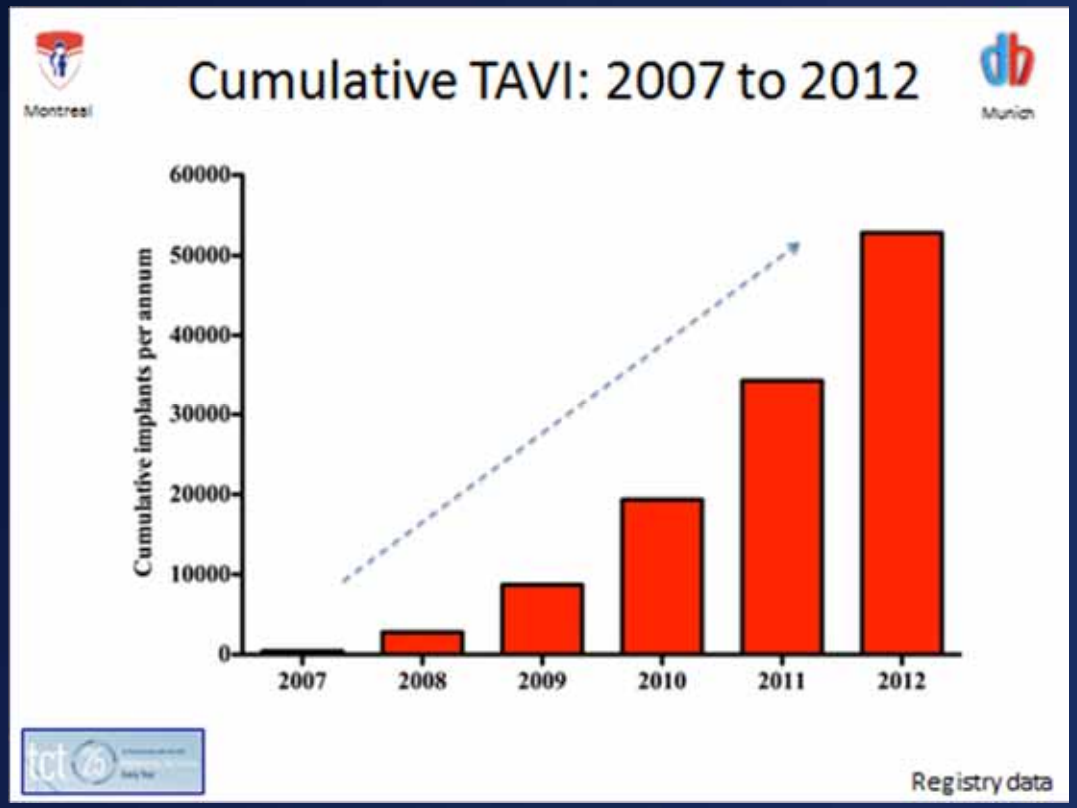
Edwards Lifesciences



Medtronic CoreValve

TAVI Adoption | Background

- Clinical, quality-of-life, and economic evidence demonstrates the value of TAVI as an alternative to open surgery in aortic stenosis patients at high or extreme surgical risk.
- A study looking at how extensively this therapy has been utilized in 11 countries in Western Europe was recently published[1,2].

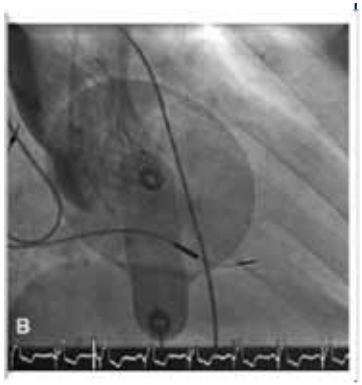


- *Approximately 50,000 patients underwent TAVI between 2007-2012*
- *TAVI procedures more than quadrupled between 2009-2012*

[1]Mylotte, et al., *J Am Coll Cardiol* 2013; 62: 210-9; [2]Piazza, et al., presented at TCT 2013

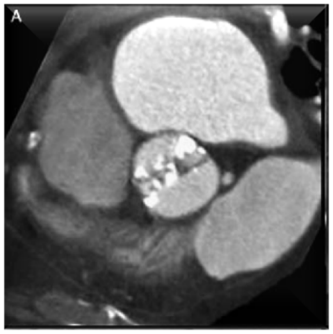
Potential to Expand Indications

New Access Routes
-- Carotid --



Pure Aortic Insufficiency

Bicuspid Valve



Moderate Risk Population

Remaining TAVI Challenges

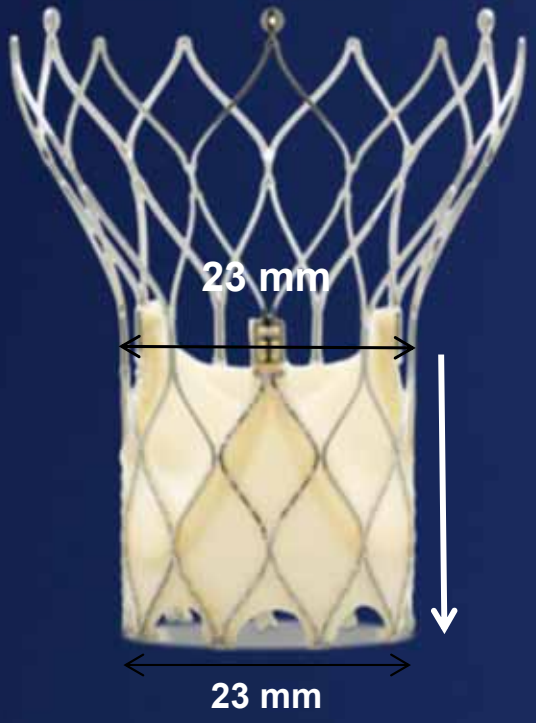
	Procedure/Technique	Technology
Stroke	Balloon strategies Anti-coagulation mgmt	Embolic Protection
AR and PVL	Sizing Post-implant intervention (dilation, snare) Depth of Implant	Frame design Advanced Sealing Positioning, Recapture
Vascular Complications	Alternative Access	Lower profile Access specific delivery Coatings
Conduction Disturbances	Depth of Implant Balloon strategies	Frame design Stable deployment with recapture

Many New CE Mark Valves during last months

Several new TF and TA valves received CE Mark in last 6-12 months

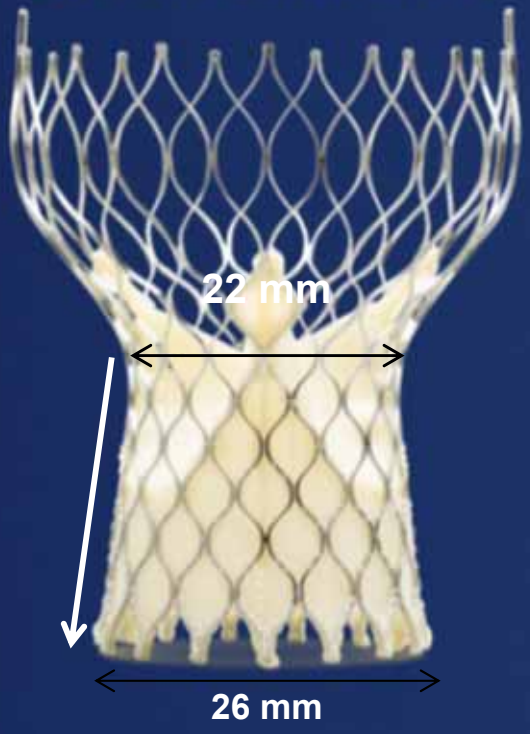
Portico and CoreValve Design Comparison

23 mm Portico[1]



Non-flared annulus design

26 mm CoreValve[2]



Flared annulus design

The annulus section of the Portico stent is not flared when compared to the flared annulus section of the CoreValve. Designed to minimize the risk of interfering with the conduction system and mitral valve apparatus.

1. St. Jude Medical Data on File.
2. Medtronic, CoreValve brochure, PN090401 V1 April 2007

Lotus™ Valve System
Components and Function

Locking Mechanism

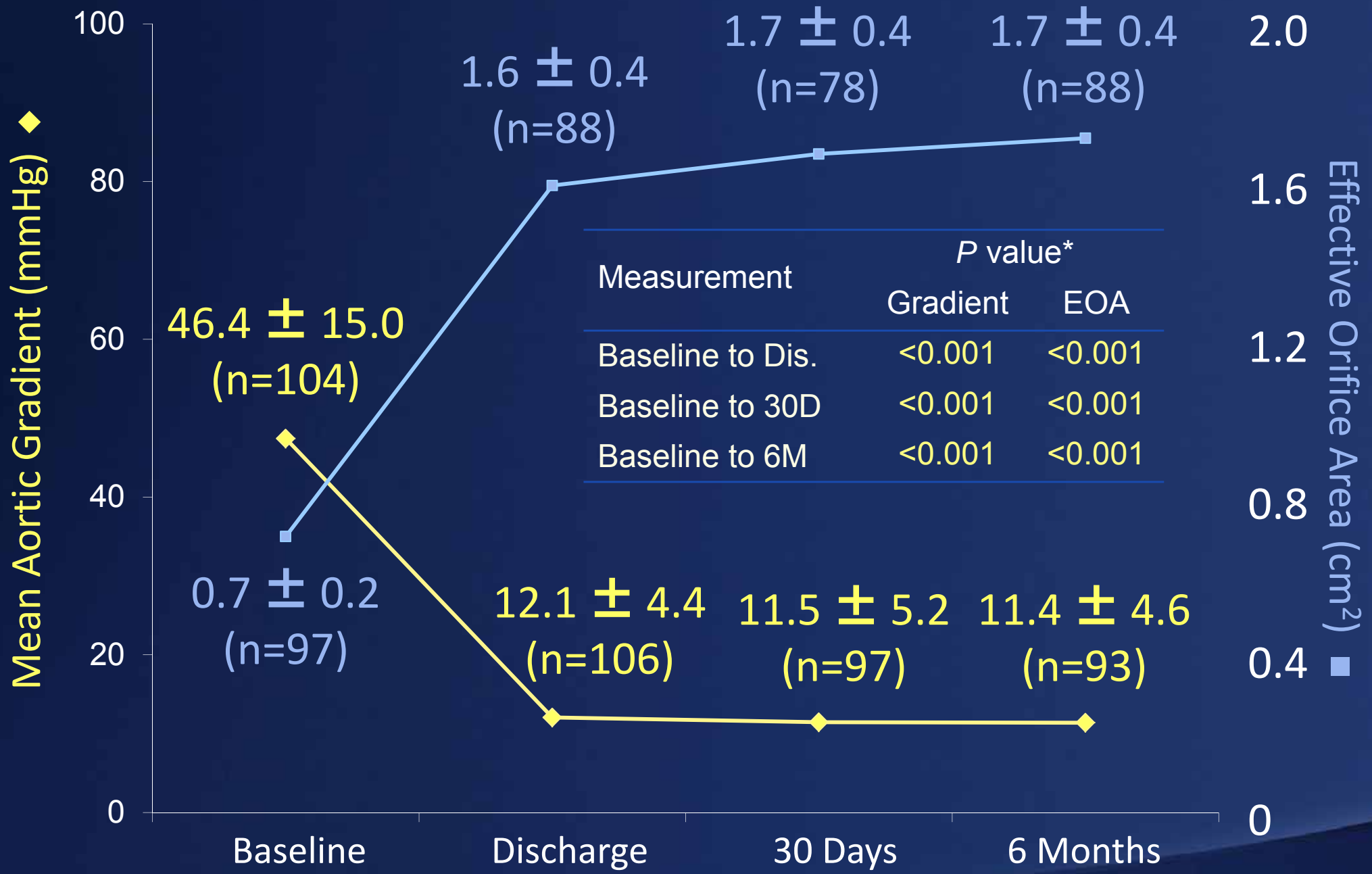
Nitinol Frame
designed for strength, flexibility, repositioning and retrieval

Bovine Pericardium
proven long-term material

Center Marker
Aids precise positioning

Adaptive Seal
Conforms to irregular anatomical surfaces and minimizes paravalvular leaks

REPRISE II Mean Aortic Gradient & EOA



Measurement	*P* value*	
	Gradient	EOA
Baseline to Dis.	<0.001	<0.001
Baseline to 30D	<0.001	<0.001
Baseline to 6M	<0.001	<0.001

Meredith et al. *JACC* 2014 (In press) & Meredith EuroPCR 2014

*Repeated measures and random effects ANOVA

REPRISE II Trial

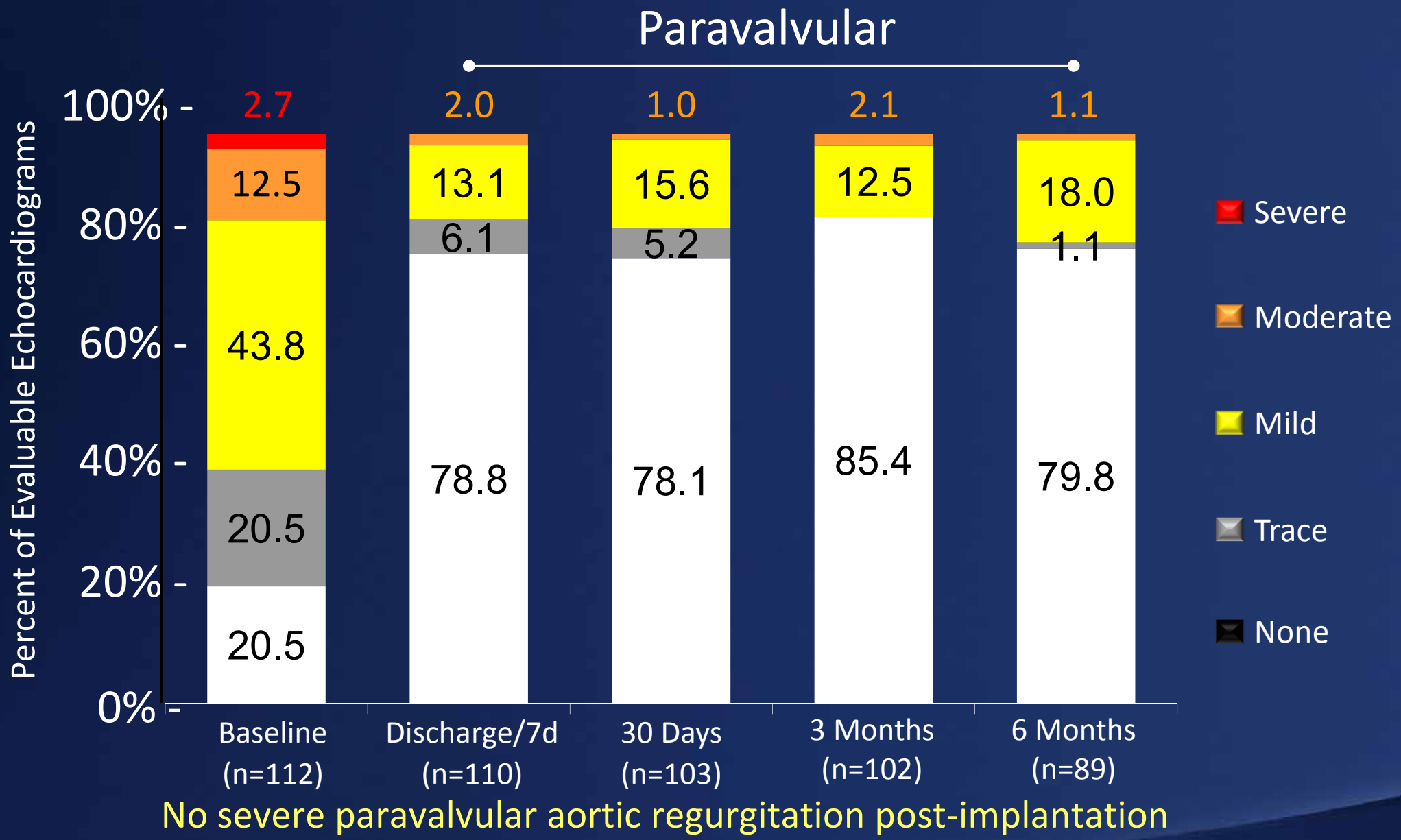
6-Month Safety Results

	Patients (N=119*)
All-cause mortality (Primary Safety Endpoint at 30 days)	8.4% (10/119)
Disabling stroke†	3.4% (4/119)
Myocardial infarction	3.4% (4/119)
Life-threatening or disabling bleeding	5.0% (6/119)
Major vascular complication	2.5% (3/119)
New permanent pacemaker	29.4% (35/119)
LVOT overstretch ≥10%	57.1% (20/35)
Annulus overstretch ≥10%	40.0% (14/35)

Ian Meredith AM, MBBS, PhD at EuroPCR 2014

REPRISE II Aortic Regurgitation

Paravalvular Aortic Regurgitation Over Time



No severe paravalvular aortic regurgitation post-implantation

Ian Meredith AM, MBBS, PhD at EuroPCR 2014

Lotus Valve System: Fully Deployed

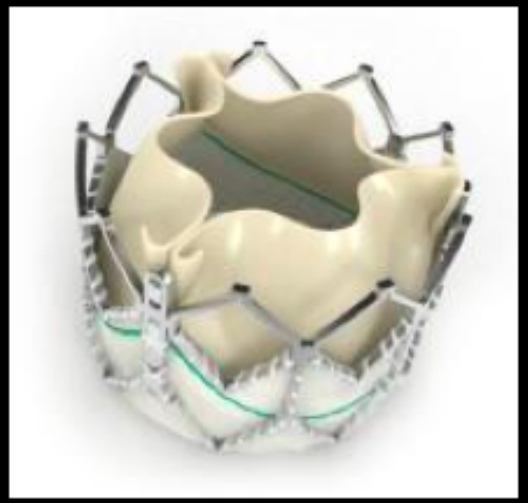
Edwards – SAPIEN Evolution

2002

Cribier-Edwards THV

2006

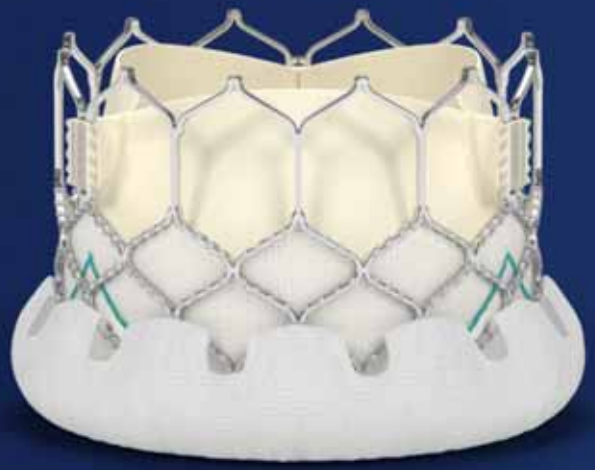
Edwards SAPIEN THV

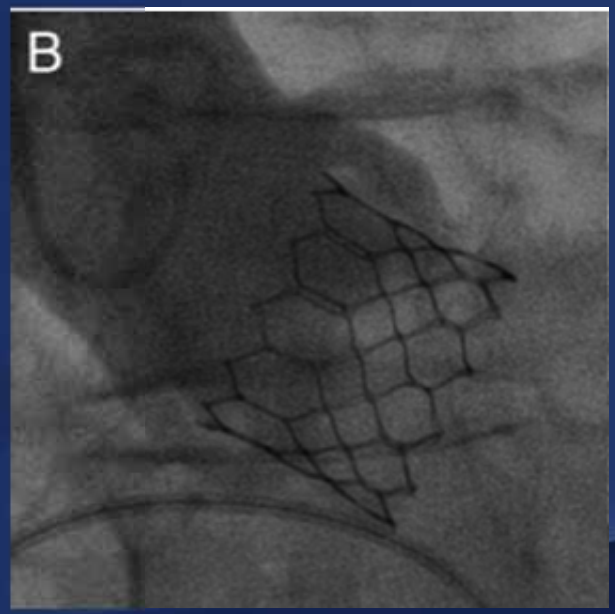


2010

Edwards SAPIEN XT* THV

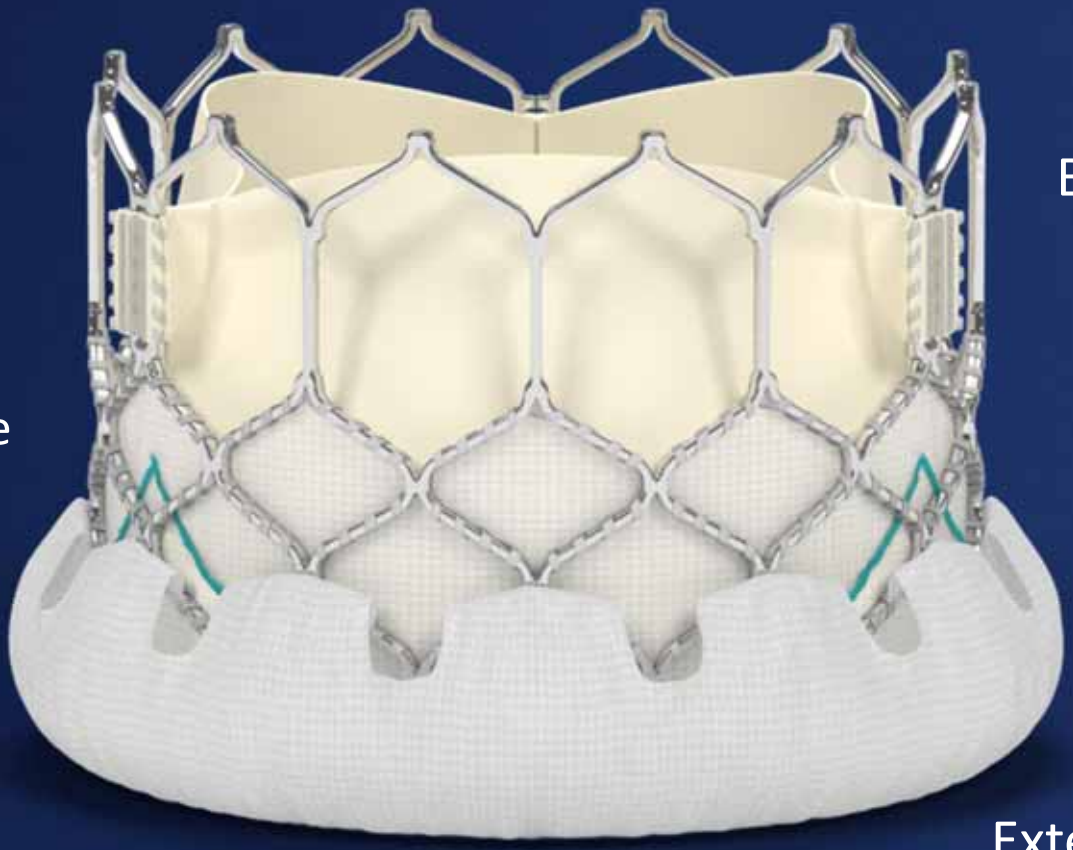
2014
SAPIEN 3





Edwards SAPIEN 3 (balloon-expandable THV)

20, 23, 26 and 29 mm sizes



Balloon-expandable Cobalt Chromium Frame

Bovine Pericardial Tissue Leaflets

External Sealing Ring

The Direct Flow Medical® Transcatheter Aortic Valve

Minimize Risk of Aortic Regurgitation

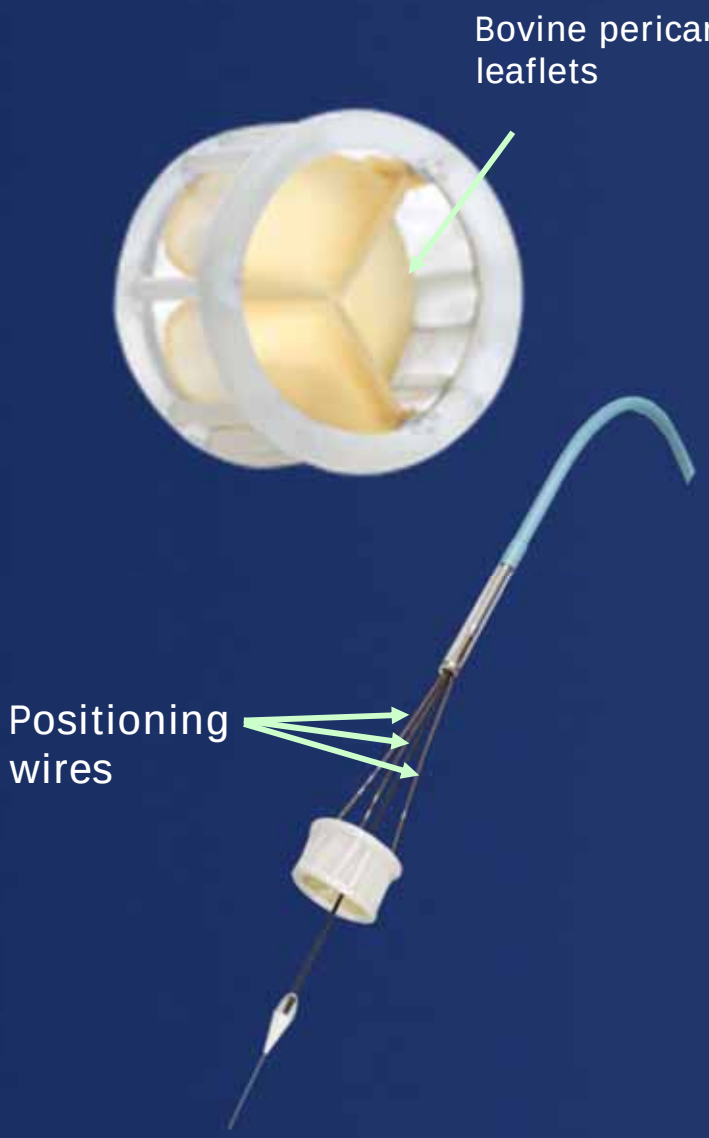
- Double-ring design conforms to anatomy for a better seal

Optimization of Positioning

- Full hemodynamic assessment before final detachment
- Repositionable
- Fully retrievable

Improved TAVR Procedure

- Flexible, low profile delivery system
- Fully competent during positioning
- No post dilatation or rapid pacing



DFM Procedure Summary

Delivery - Valve delivered through flexible 18F sheath (all valve sizes)

Deployment - After initial expansion in the ventricle, the valve remains fully competent throughout the procedure

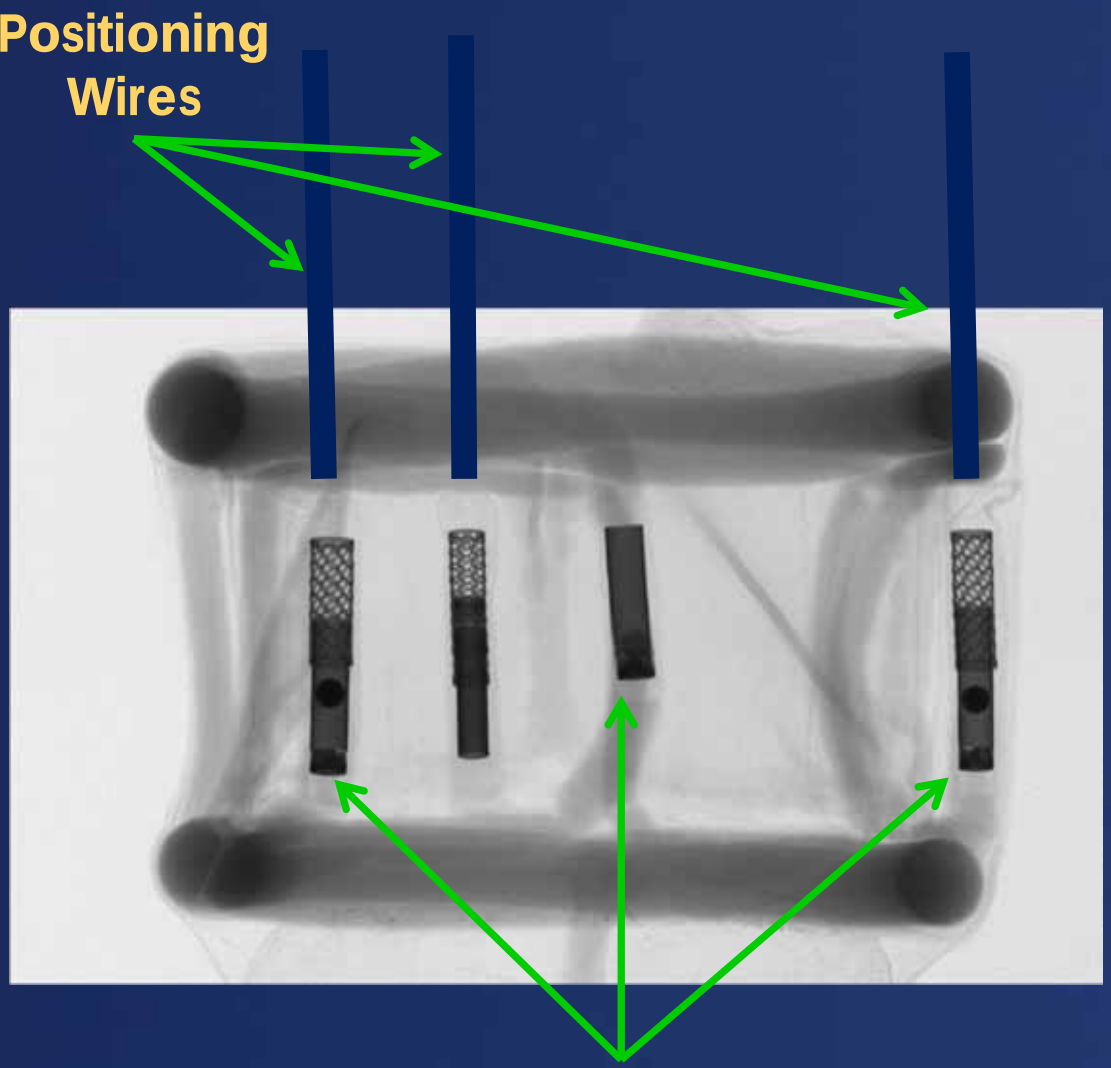
Positioning - To begin positioning, the valve is partially deflated and then placed into the native annulus

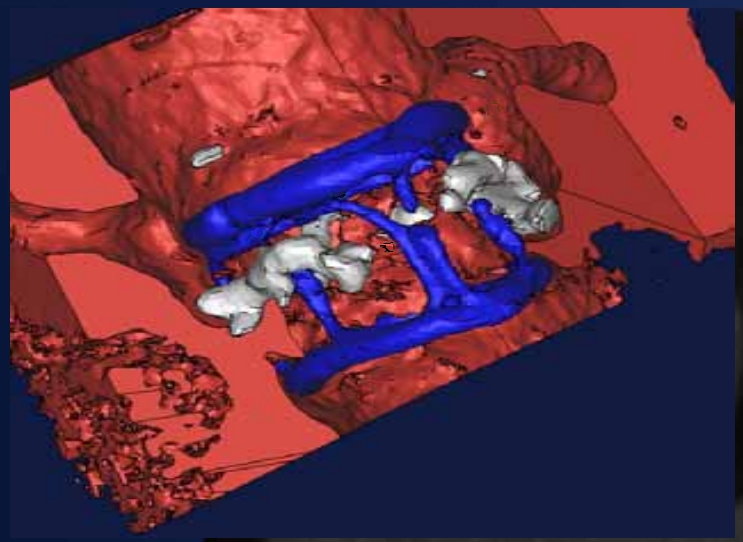
Assessment - Once the valve is positioned and fully deployed, a complete assessment of hemodynamic performance is done

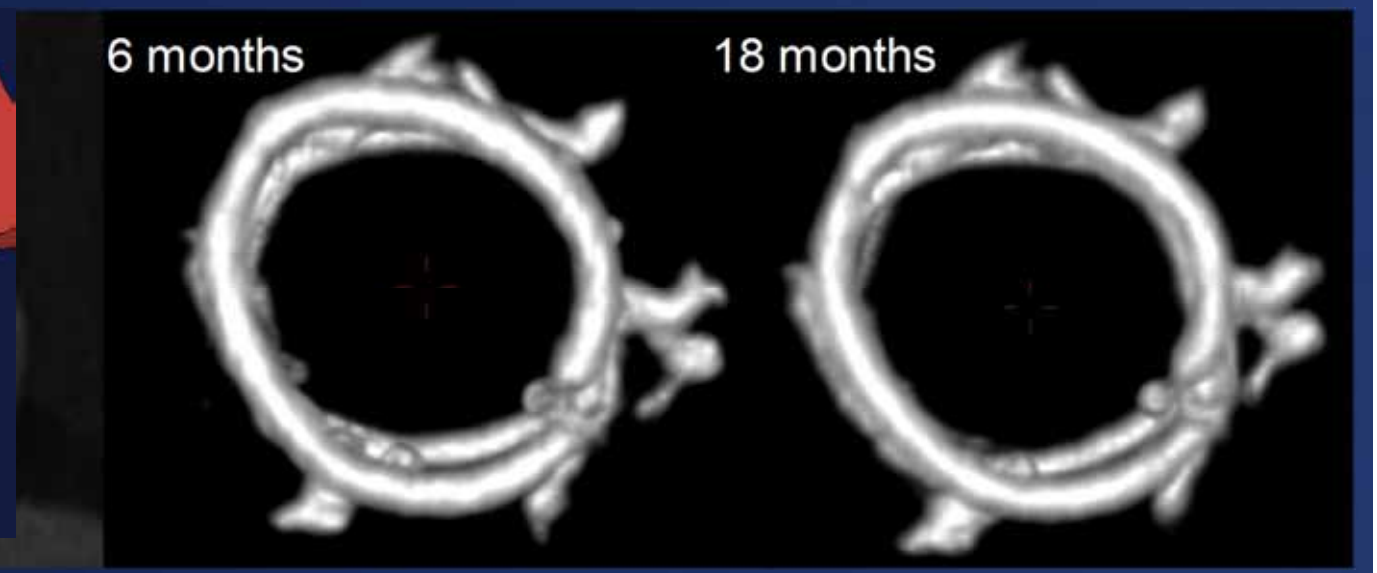
Repositioning - Unlimited repositioning of the valve is possible by simply deflating either ring and manipulating the positioning wires

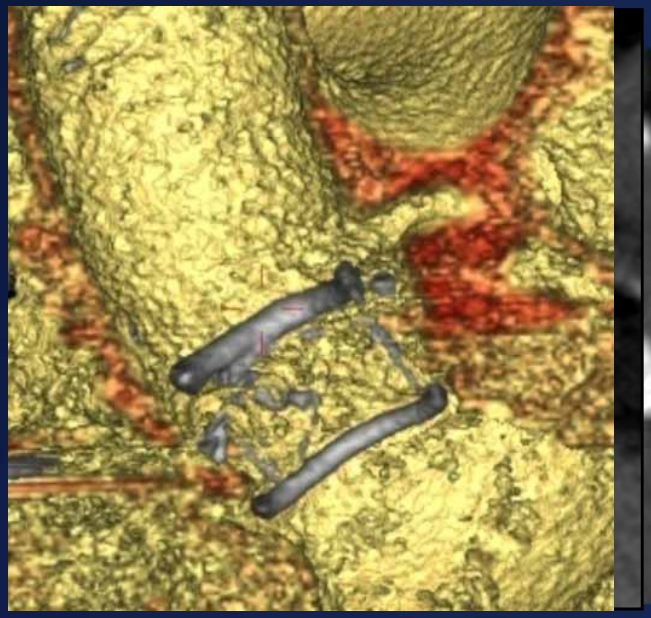
Implantation - After the valve placement is optimized, final implantation is done

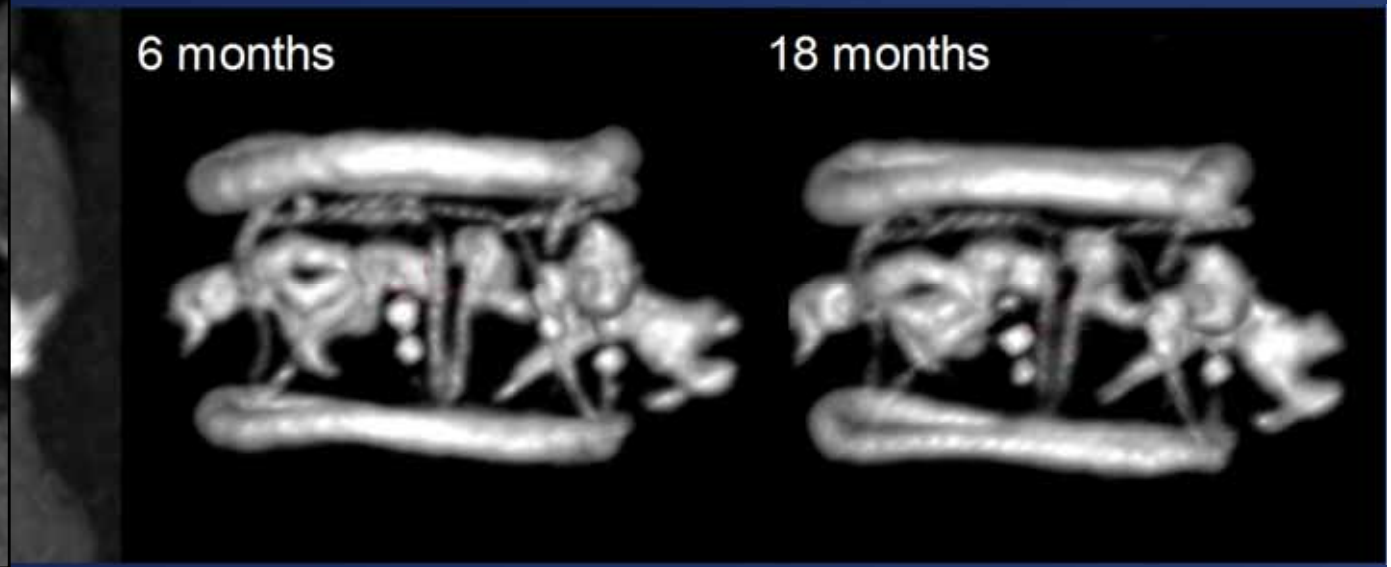
Direct Flow Medical: Valve Concept





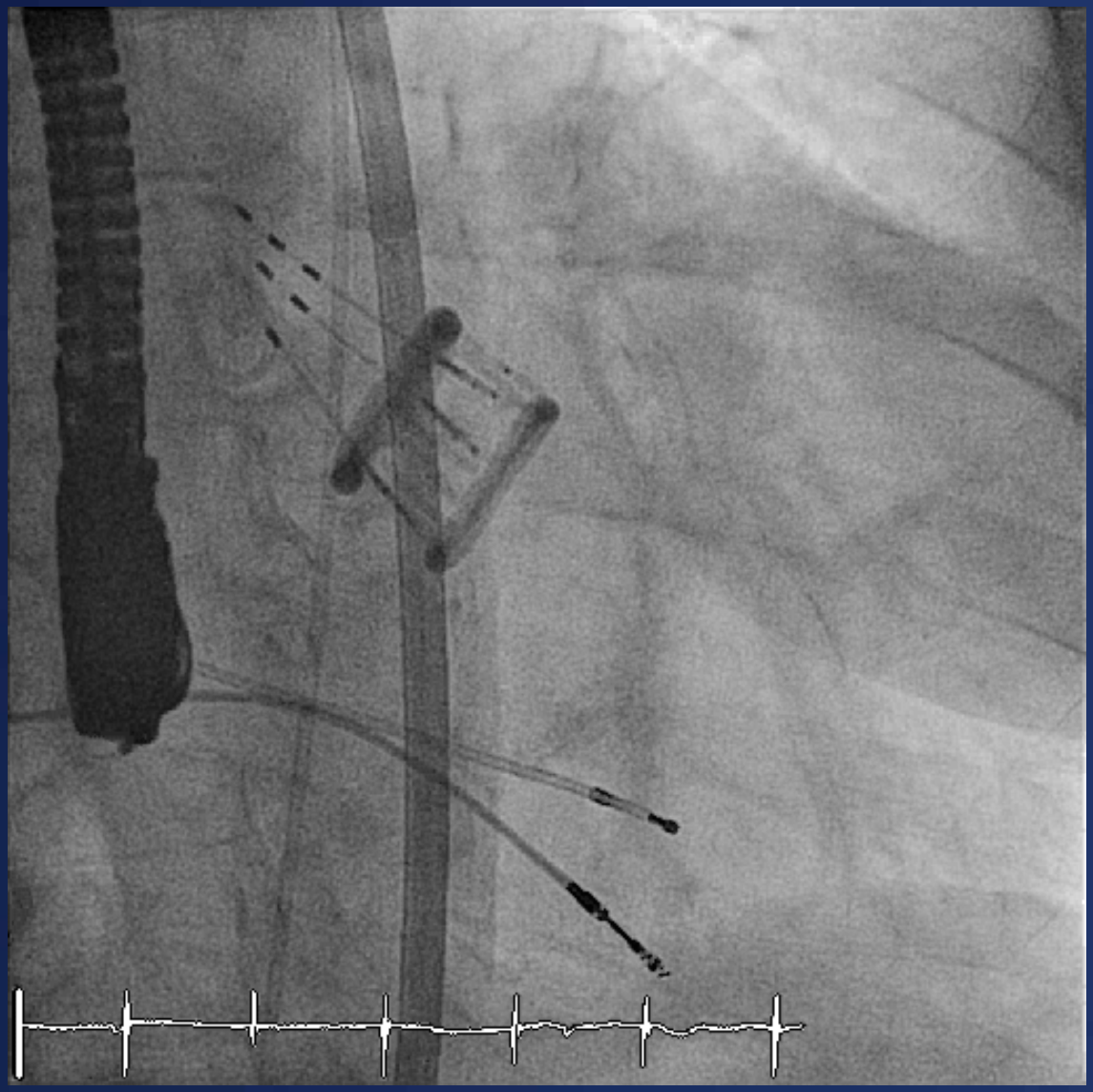






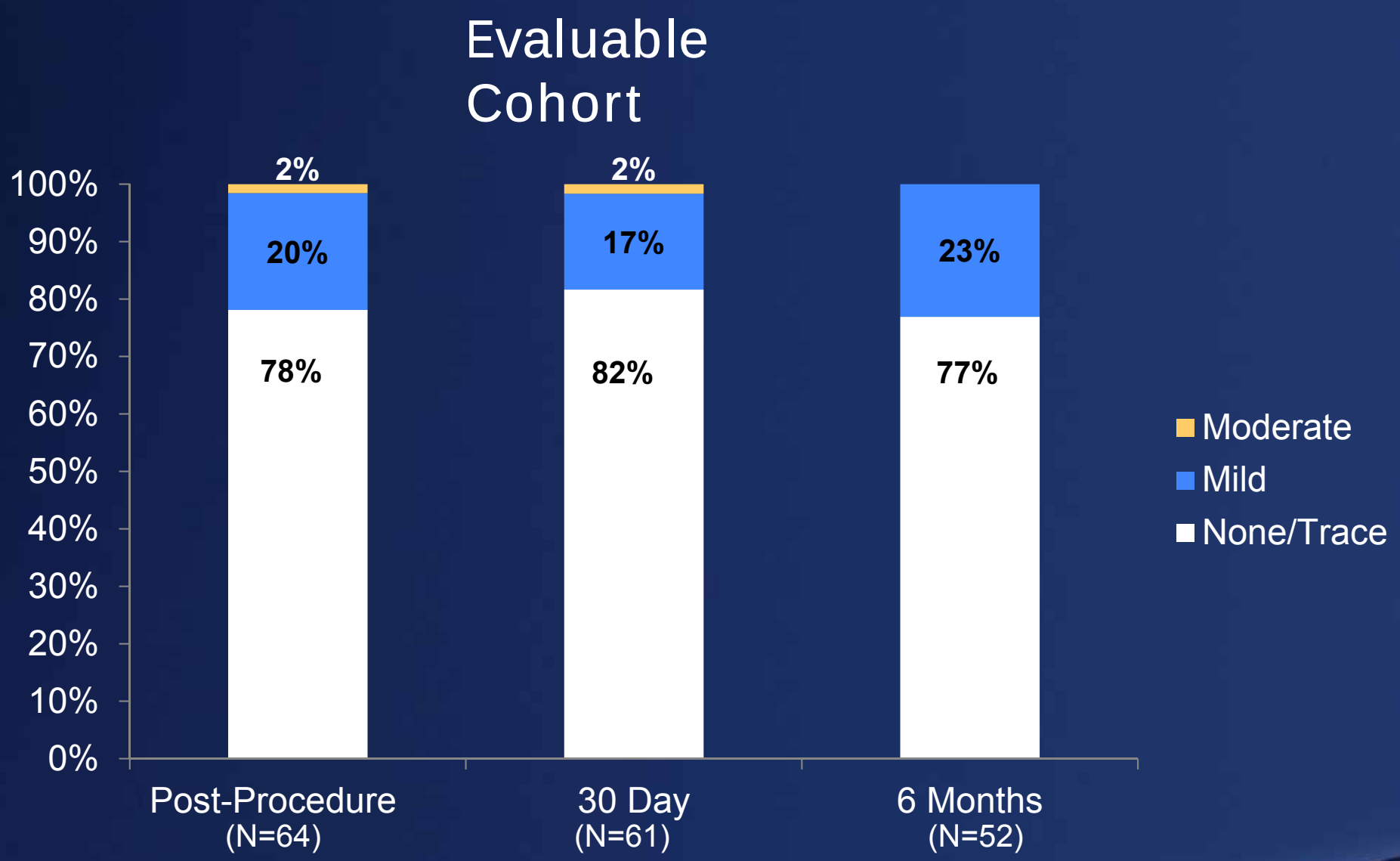
Conformable cuff design and precise positioning maximizes sealing to prevent PV leaks

Final Control before Release



DISCOVER Trial:

Paravalvular Aortic Regurgitation by Core Lab



ACURATE TF™ Aortic Bioprosthesis

SELF-EXPANDING NITINOL

Conforms to native anatomy
3 sizes: 21mm to 27mm

STABILIZATION ARCHES

PERICARDIAL LEAFLETS

Porcine pericardium
Lower profile

UPPER CROWN

Supra-annular anchoring
Stable positioning
Tactile feedback

PERICARDIAL SKIRT

Inner & outer skirt acts as seal to prevent PVL

LOWER CROWN

Minimal LV protrusion
Low risk of conduction defects

ACURATE TF™ 3-Step Implantation

Initial Alignment

1. Open upper crown & gentle pressure forward

2. Open stabilization arches

3. Open lower crown for full deployment

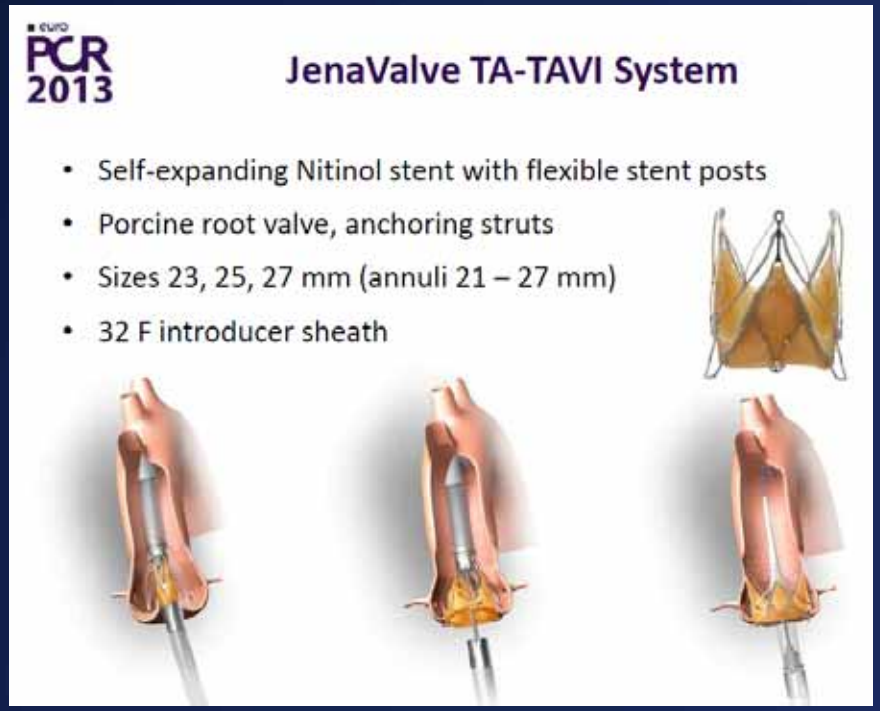
Performance

	Baseline	30D
n	89	82
Mean gradient (mmHg)	43.6 ± 17.1	8.0 ± 2.9
Mean AVA/EOA (cm^2)	0.7 ± 0.2	1.8 ± 0.3
PVL ≤ Grade 1 (none to mild) [n/%]	n/a	78 / 95.1
PVL Grade 2 (moderate) [n/%]	n/a	4 / 4.9
PVL > Grade 2 [n/%]	n/a	0 / 0.0
NYHA Class III/IV [n/%]	84 / 94.4	8 / 9.8

Pure Aortic Regurgitation | JenaValve

- JenaValve may be particularly suitable in pure AR due to fixation and has received CE Mark for this indication.
- Feasibility has been shown in published cases and in a small series from University Heart Center Hamburg, Germany[1]

JenaValve Study	N	30-day Mortality	30-day Stroke	Dislocation or Second Valve	Residual AR ≥ 2
Seiffert[1]	5	0%	0%	0%	NR



- Clip fixation of native leaflets
- No need for oversizing (less risk of annular rupture)
- No BAV or rapid ventricular pacing required

[1]Seiffert, et al., Transapical Implantation of a JenaValve Prosthesis in Patients with Non-Calcified Aortic Regurgitation. EuroPCR 2013 presentation, Paris, France;

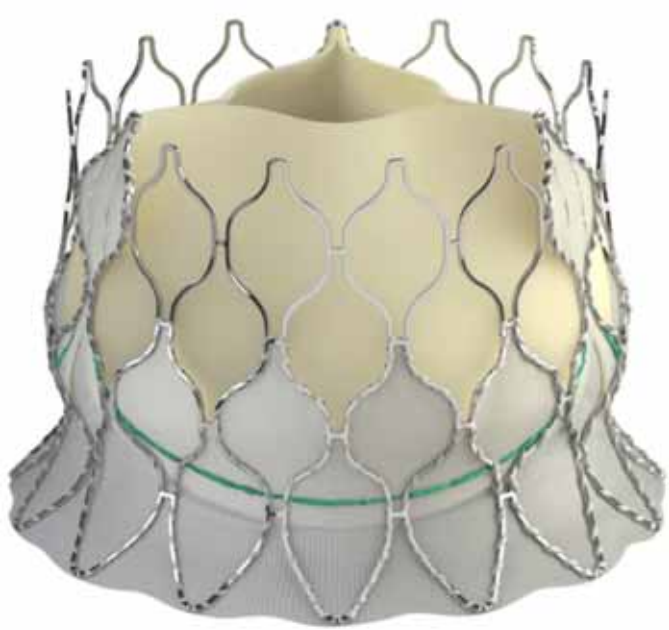
The Future

New Generation TAVI Devices Non CE Marked:

- Edwards Centera
- Medtronic CoreValve Evolut R
- Foldax Heart Valve Technology
- Valve Medical

Edwards CENTERA Transcatheter Heart Valve

- Self-expanding Nitinol frame
- Treated bovine pericardium
- Contoured frame designed for optimal seating and sealing in the annulus
- Low frame height designed to minimize conduction disturbances
- Repositionable
- 23 mm, 26 mm, 29 mm sizes



The Edwards CENTERA System Clinical Study

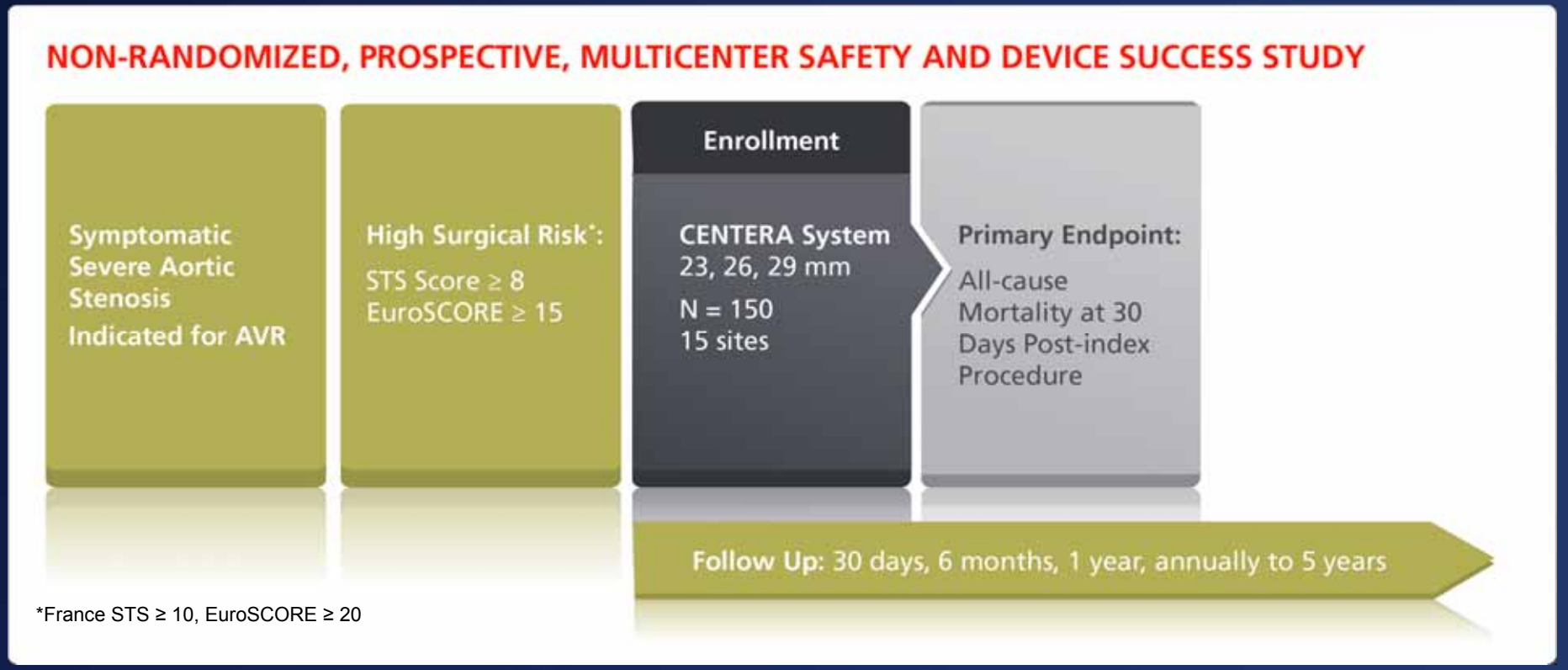
Study Devices

CENTERA Valve
23, 26, 29 mm

Controlled-release Delivery System
Transfemoral

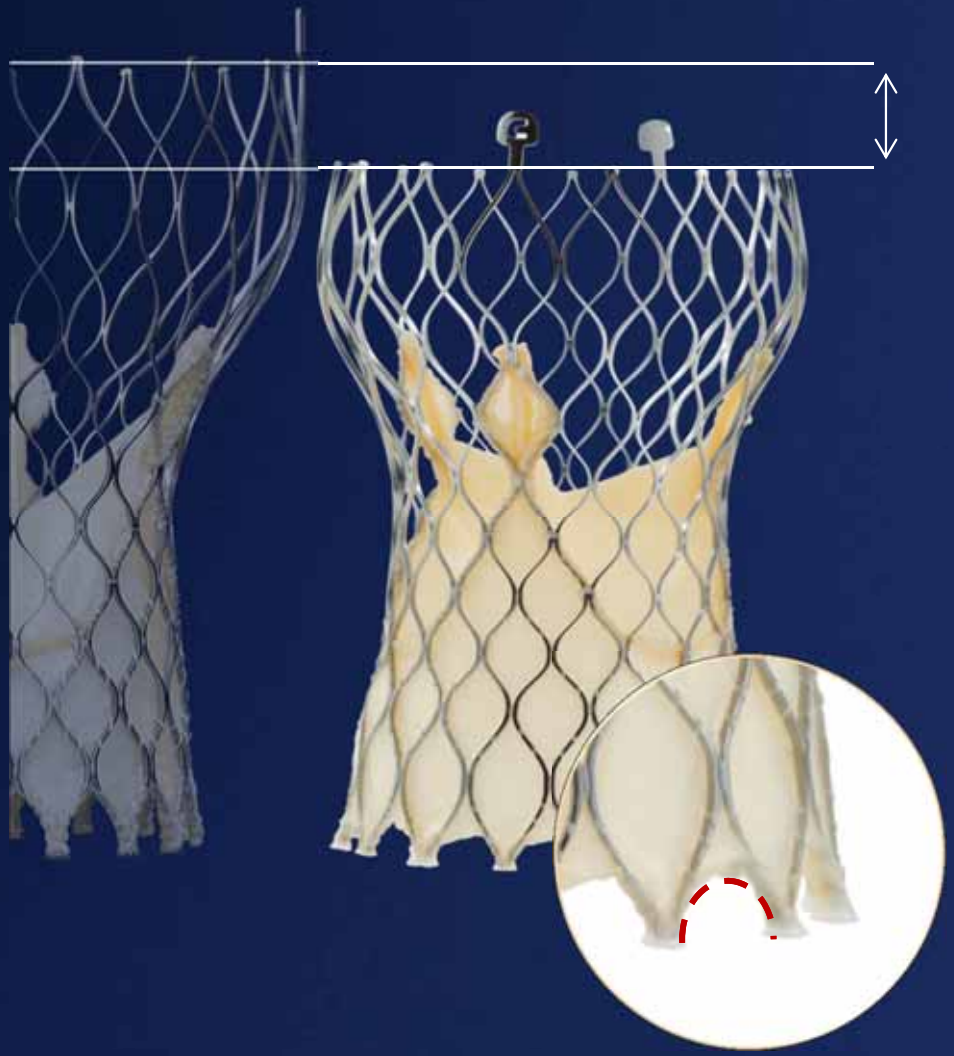
The Edwards CENTERA System Clinical Study

Study Design



CoreValve Evolut R

Goal: Enhanced Annular Seal and Reduced Conduction Disturbances

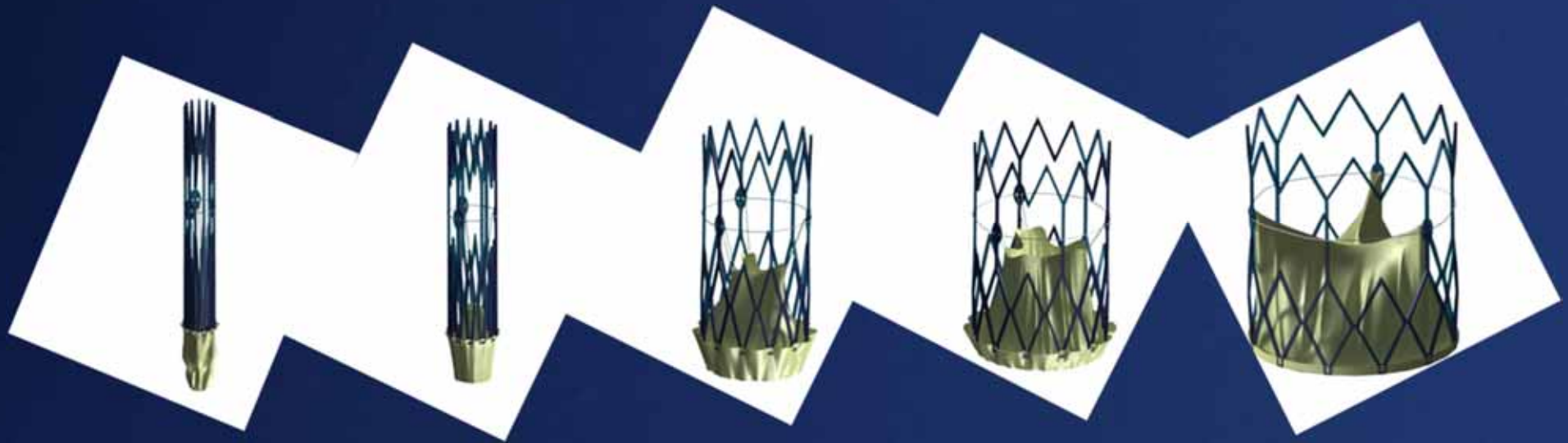


- Outflow shortened and redesigned
- Optimized cover index
- More consistent radial force across annulus range
- Extended skirt at inflow
- Less traumatic inflow edge

Future Concepts

- A fully optimized TAVR system which addresses current limitations may require a radical design change such as “Inside – Out” leaflet mounting or temporarily dissociating the support frame from the valve component

FOLDAX™
HEART VALVE TECHNOLOGY



14F delivery profile available

”Stressless” tissue loading

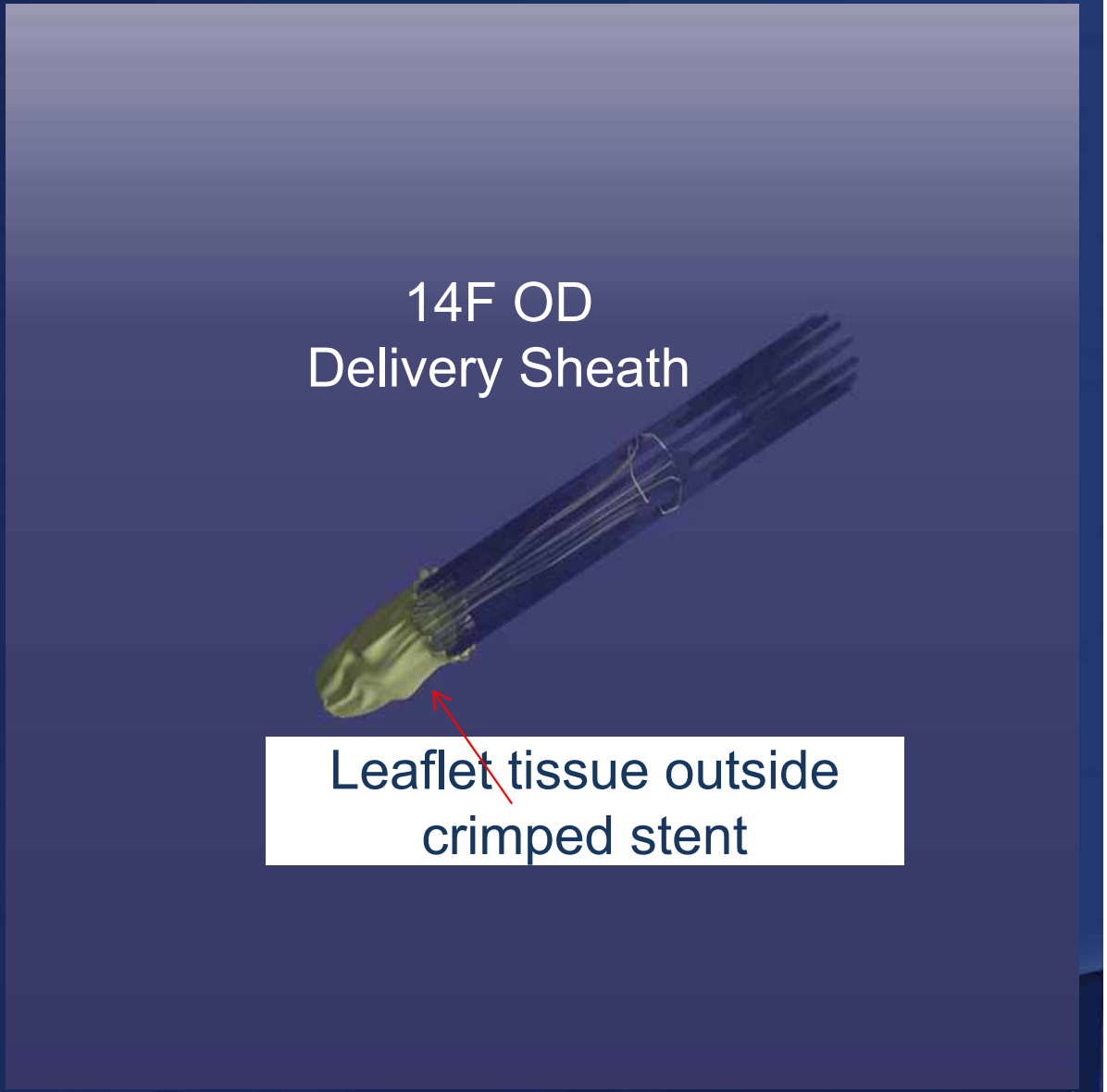
Allows use of bovine pericardium

Fully repositionable & retrievable

“Inside-Out” Leaflet Mounting

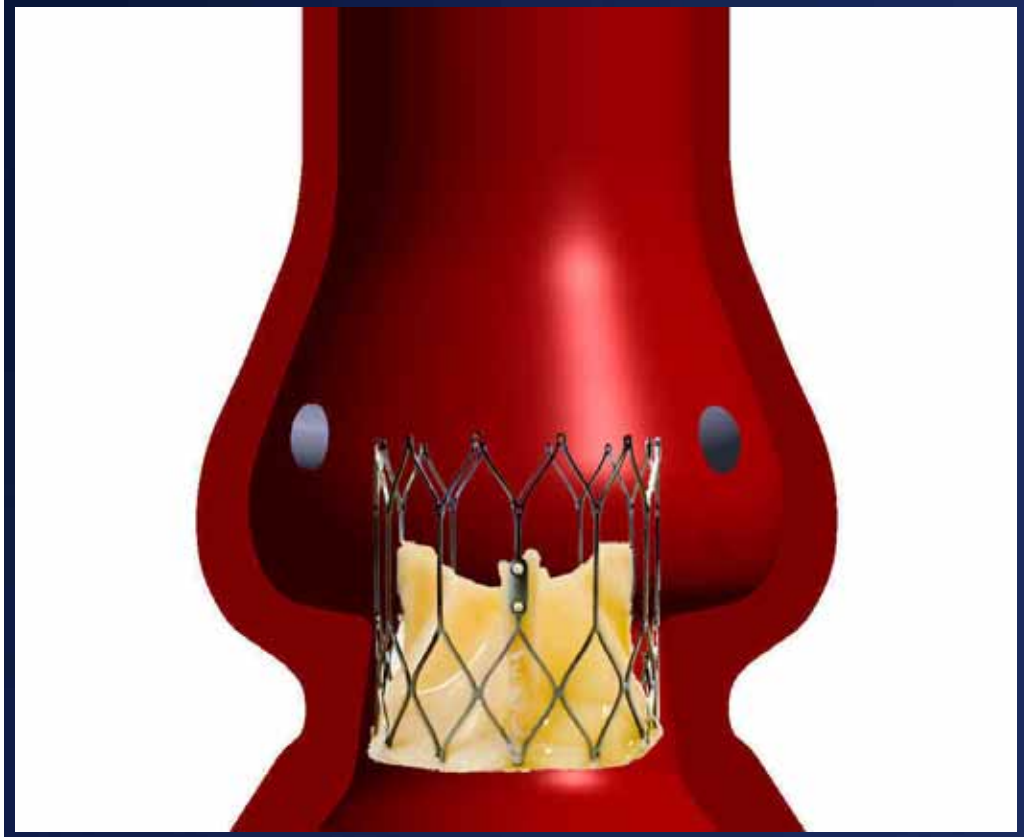
“Inside-out” Leaflet Mounting

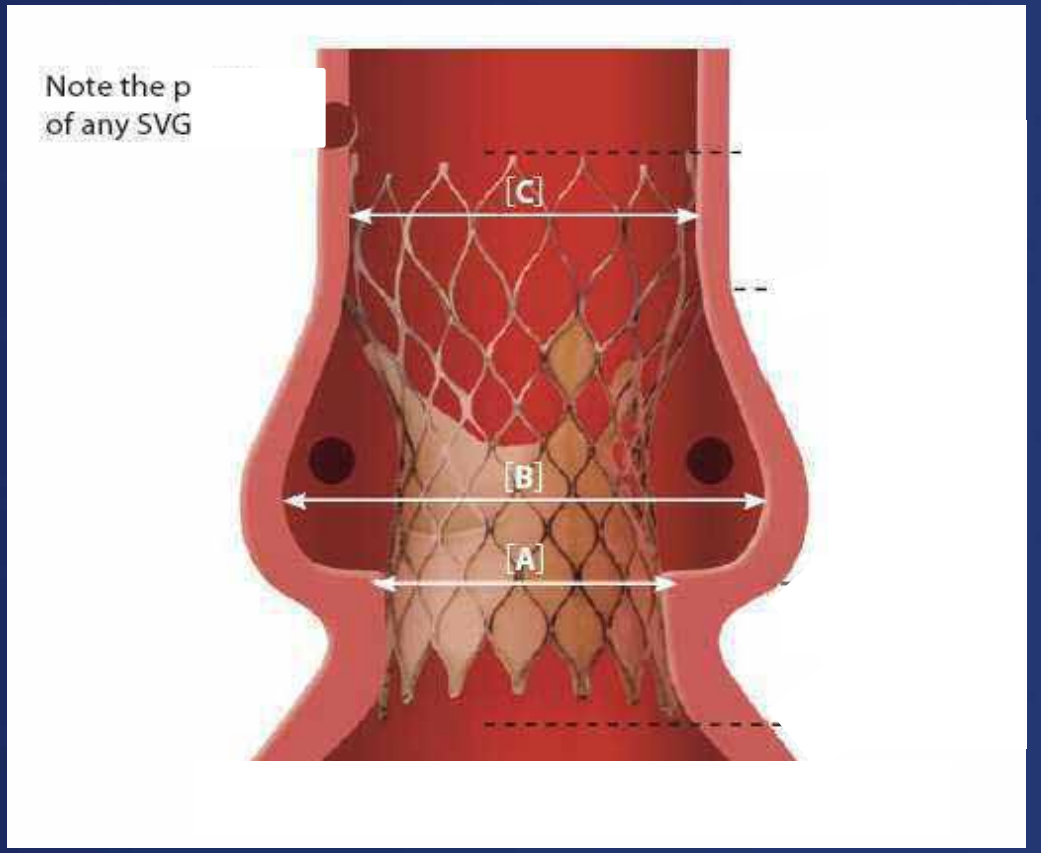
- 12Fr loaded valve profile w/ no tissue inside stent
  - Enables small/difficult vessel & acute aortic arch patients
- Eliminates compression of tissue in loaded stent
  - Enhances durability
  - Uses bovine pericardium



FOLDAVALVE™ DEPLOYED

- Low profile design

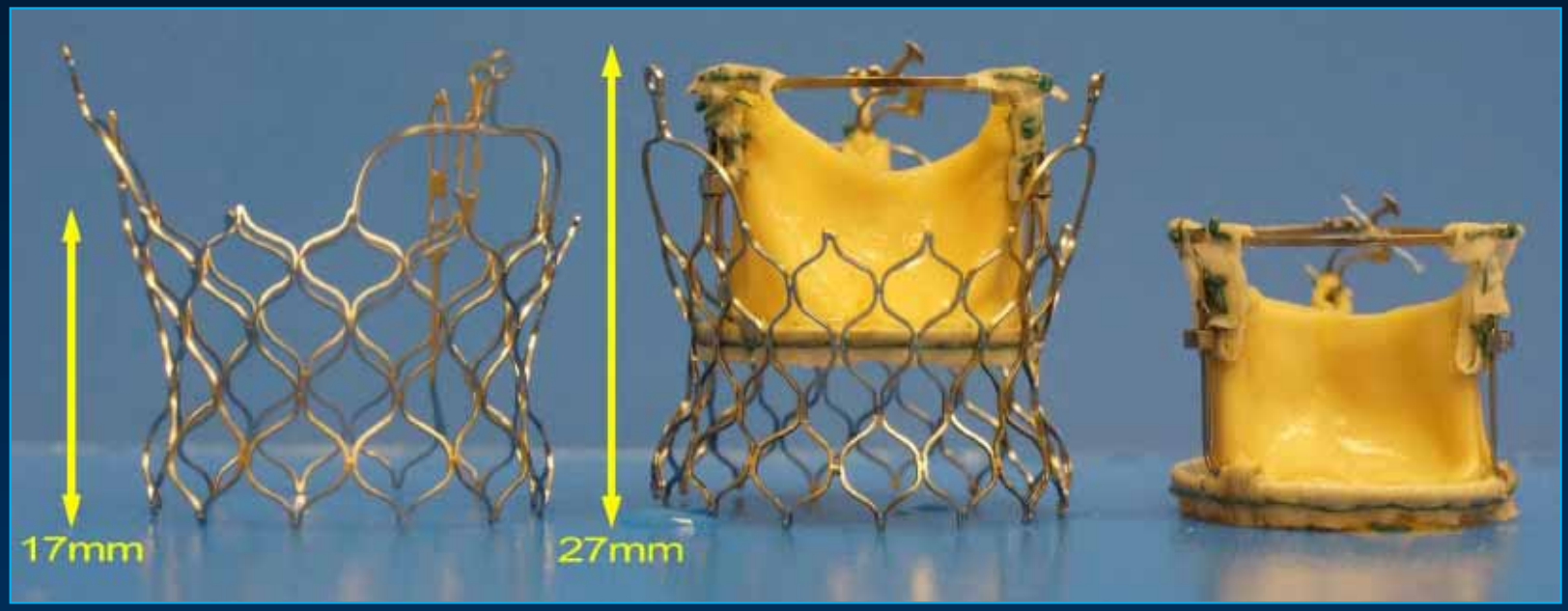




“Unique” Valve Medical Design Features

- Ultra-low profile – 12 French delivery system for all valve sizes
- Modular design (frame and valve separate)
- Folded valve design (not crimped)
- 3-D valve leaflet construction
- *In-situ* docking (valve to frame in ascending Ao)
- Coating to reduce Para-valvular regurgitation
- Temporary valve (in descending Ao) for safety

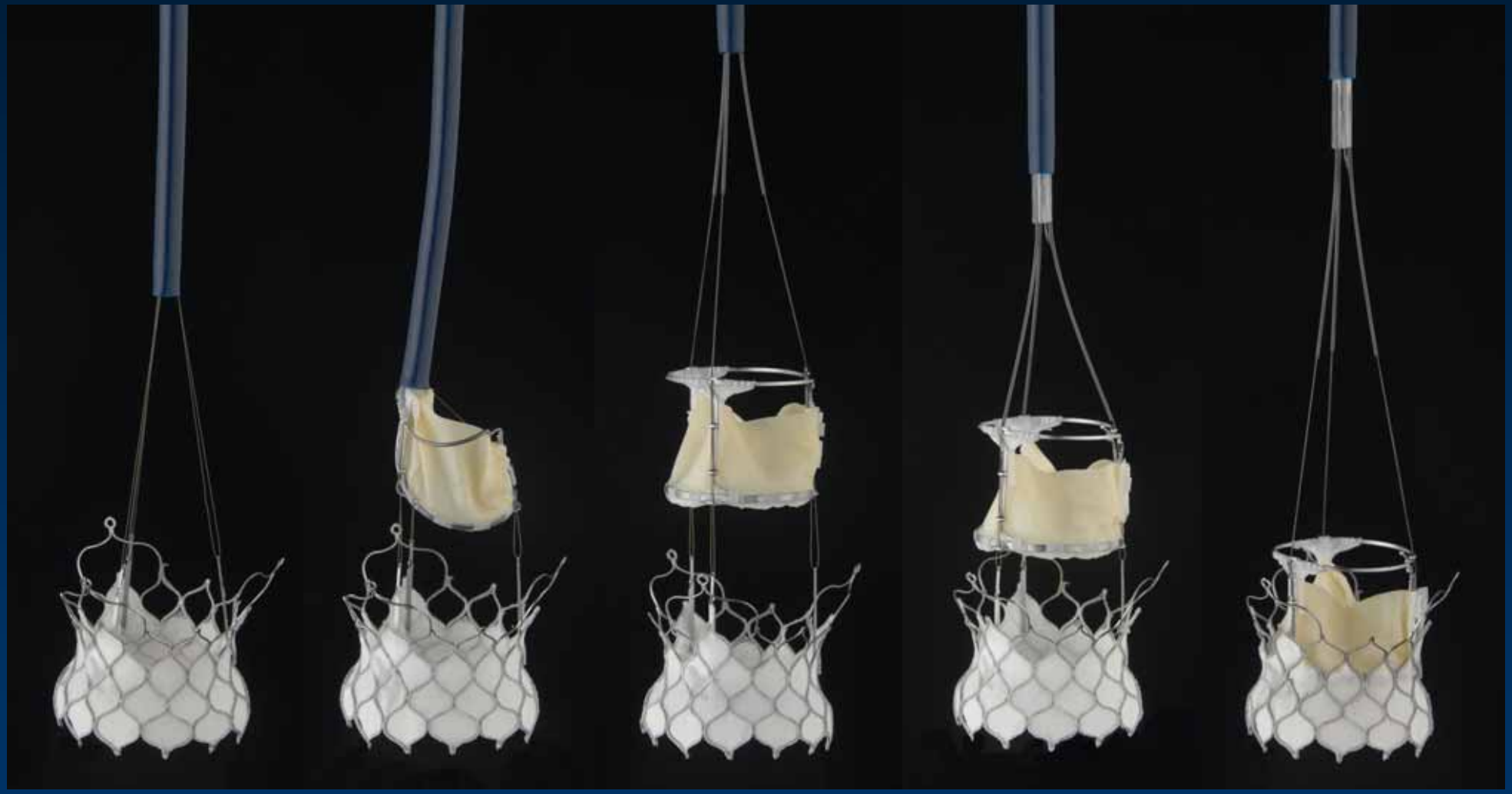
Valve Medical Device Components



Frame Module → *Assembled Device* ← Valve Module

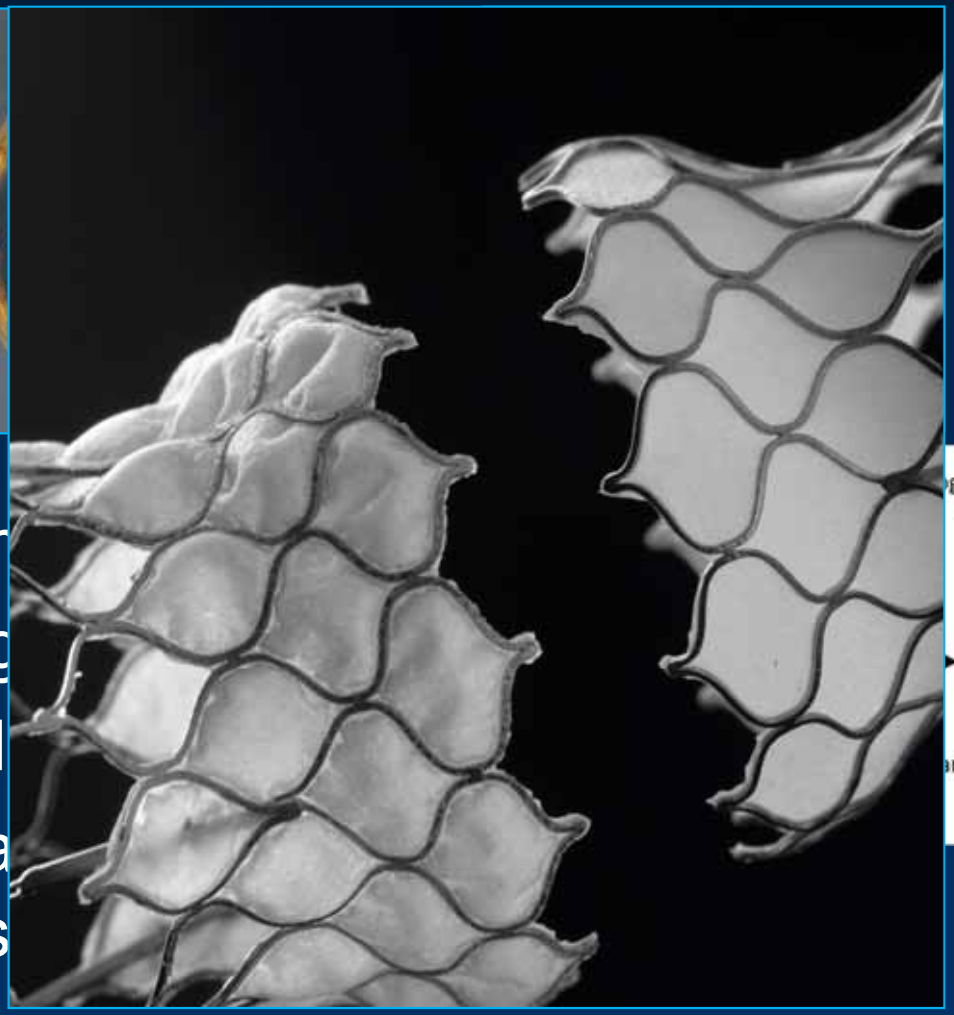
1. Nitinol self-expanding frame module inserted in optimal annular location
2. Valve module is reconstituted in ascending Ao
3. Valve module is docked to frame

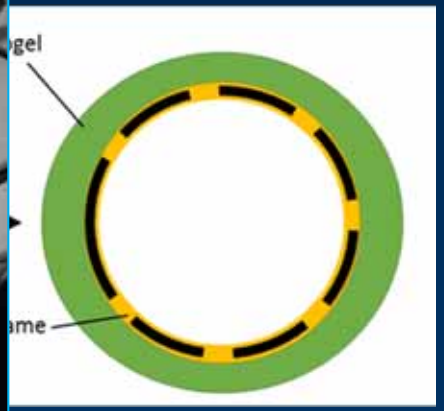
Frame and Valve Module Docking and Locking



Polymer Coating

Para-valvular leak prevention





- Two-layer polyr
- External hydrog
- Frame stored d
- Following impla
  hydrogel swells
  zone“)

Dedicated Sheath/Temporary Valve

- Placed in descending Ao (‘Hufnagel’ position)
- Incorporated into dedicated 12Fr sheath
- Mono-leaflet, polymeric ‘parachute’ type valve
- Optimizes patient safety; provides hemodynamic stability during AR with valve docking maneuver

Improving Clinical Outcomes: Competitive Landscape.

	 CoreValve	 Sapien XT	 Direct Flow	 Lotus	 Portico	 Symetis	 Sapien 3	 Centera	 Evolut R	 Valve Med
Frame Material	Nitinol	Cobalt chromium	Polyester fabric	Braided Nitinol	Nitinol	Nitinol	Cobalt chromium	Nitinol	Nitinol	Nitinol
Tissue	Porcine pericardial inner skirt	Bovine Pericardial inner skirt	Bovine Pericardial	Bovine Pericardial with PET outer skirt	Bovine Pericard-ial inner skirt	Porcine Pericard-ial inner and outer skirt	Bovine Pericard-ial Polyester outer skirt	Bovine Pericard-ial inner skirt	Porcine pericardial inner skirt (outer skirt in development)	Bovine Leaflet
Valve Design	Supra-annular	Intra-annular	Intra-annular	Intra-annular	Intra-annular	Intra-annular	Intra-annular	Intra-annular	Supra-annular	Intra-annular
Vascular Access	ID: 18Fr OD: 21.7Fr	ID: 18-22Fr OD: 21-30Fr (16Fr eSheath)	ID: 18FR OD: 21.7FR	ID: ? OD: 21.7Fr	ID: 18Fr OD: 21.7Fr	ID: 18Fr OD: 21.7mm	ID: 14FR eSheath OD: 26FR *	ID: 14FR eSheath OD: 22FR *	ID: 18Fr OD: 18Fr (14Fr Inline Sheath)	ID: 12FR OD: 14FR
Other	AOA®	ThermaFix®	Anti-Ca++ Recapture	Recapture	Linx™ Recapture	None	Therma-Fix Future GLX	Therma-Fix Future GLX Recaptur e	AOA® Recapture	Modular approach

Improving Clinical Outcomes: Competitive Landscape










	CoreValve	Sapien XT	Direct Flow	Lotus	Portico	Symetis	Sapien 3	Centera	Evolut R	Valve Med
Survival									TBD	TBD
Major Vasc									TBD	TBD
PPM Rate									TBD	TBD
PVL									TBD	TBD
Durability	200M Valve 600M Frame								TBD	TBD
Stroke									TBD	TBD
Coronary Occlusions				NR	NR	NR	NR	NR	TBD	TBD
Annulus Rupture				NR	NR	NR	NR	NR	TBD	TBD
MI						NR	NR	NR	TBD	TBD

- Near optimal performance
- Performance acceptable but not optimal yet
- Performance acceptable but not optimal, competitive disadvantage
- Performance not acceptable nor technically feasible

Final thoughts…

- TAVR in 2014 has been integrated as an important component of the optimal management of complex AS patients.
- Although clinical outcomes appear favorable, there are still areas to refine, including appropriate case selection, procedural complications (esp. strokes, vascular events, and PVL), and selection of specific THVs
- Future device development and clinical research are needed to resolve these issues!