Current and Future Landscape of Trans-Catheter Mitral Valve Replacement

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DISCLOSURE STATEMENT OF FINANCIAL INTEREST

In the past 12 months, I or my spouse/partner has had a financial interest/arrangement with the organization(s) listed below.

BSCI

- Scientific Advisory Board Member
- Speaker Bureau
- Equity Ownership

Mvalve™ Technologies Ltd.

- Founder/ Executive chairman
- Intellectual Property
- Equity Ownership

TRANS CATHETER MITRAL VALVE REPLACEMENT

- In recent years, with the addition of minimally invasive surgical techniques, chordal sparing procedures and more durable bio-prostheses, *Mitral Valve Replacement* has become a viable option for treatment of severe MR

- When comparing repair vs replacement in ischemic MR, Acker and colleagues, from the CTS Network observed no significant difference in left ventricular reverse remodeling or survival at 12 months between patients who underwent mitral-valve repair and those who underwent replacement. *Replacement provided a more durable correction of mitral regurgitation*.

TRANS CATHETER MITRAL VALVE REPLACEMENT

The advent of trans-catheter heart valve therapy for the Aortic valve has led to novel and lesser invasive approaches for Cardiac Valve Replacement.

TRANS CATHETER MITRAL VALVE REPLACEMENT: Challenges

- Delivery
  - Increased device size (more than aortics) with need for more folding may lead to excessive compression with serious concerns over durability
- Fixation
  - More complex structure
  - No calcium to anchor
  - Annulus is not round , particularly when diseased and less pliable
  - Orientation may be important
- Seal
  - Paravalvular leaks in mitral position are usually not well tolerated compared to aortic PVL (hemolysis)
- Function
  - LVOT obstruction may be a concern
  - Need to preserve the subvalvular apparatus remains imperative

TRANS CATHETER MITRAL VALVE REPLACEMENT: Landscape

Braile Biomedica

Braile Biomedica

CardiAQ 1st G

CardiAQ Edwards

Cephea

Direct Flow Medical

Twelve Medtronic

M-Valve

Edwards Fortis

HighLife

Navigate

Neovasc Tiara

PermaValve MID

Sinomed Abbott

Tendyne

SATURN TMVR

Mitraltech

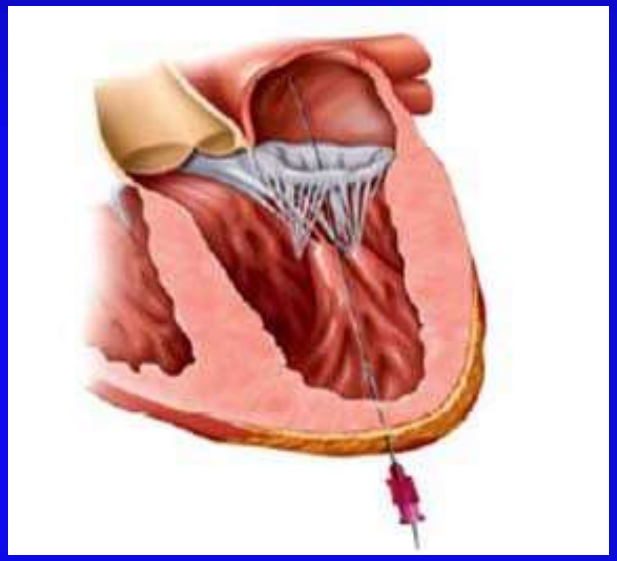
Caisson

Others: MitraHeal, Mitrassist, Mitraltech, Mehr Medical, Mitracath, Mitralix MAESTRO, Nakostech, St. George ATLAS, Transcatheter Technologies Tresillo

Transapical approach

Pros

- Straight shot
- TAVR experience



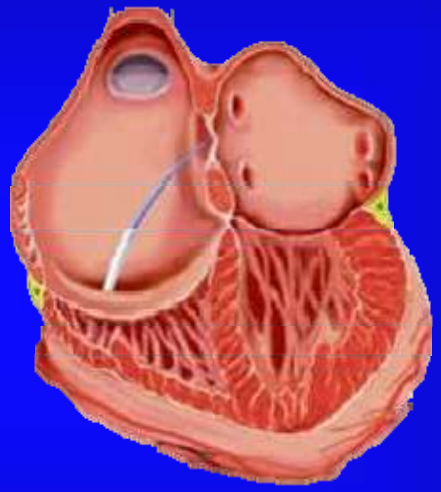
Cons

- LV dysfunction / large bore catheters (>30F)
- Retrograde approach (subvalvular apparatus entanglement)
- Thoracotomy (invasive)

Transseptal approach

Pros

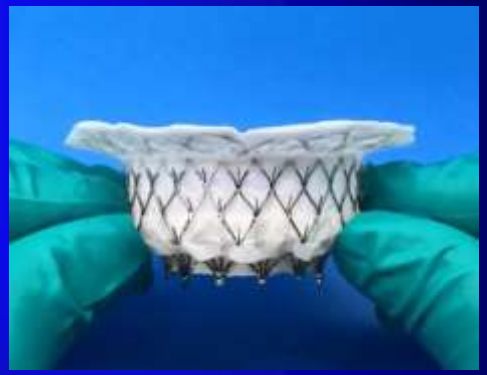
- Direct antegrade approach
- Avoids LV puncture
- Transseptal puncture

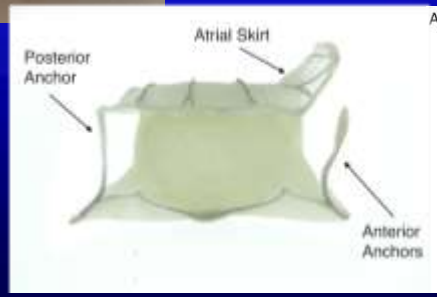


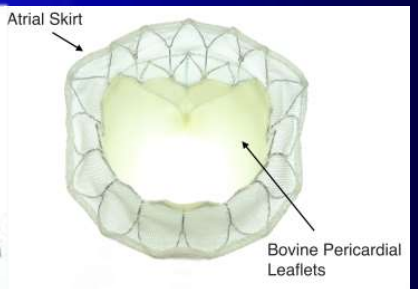
Cons

- Navigation and steering more than transatrial
- Veno-arterial access (submitral apparatus)
- Atrial septal defect / large catheter OD

TRANS CATHETER MITRAL VALVE REPLACEMENT: Where are we today !







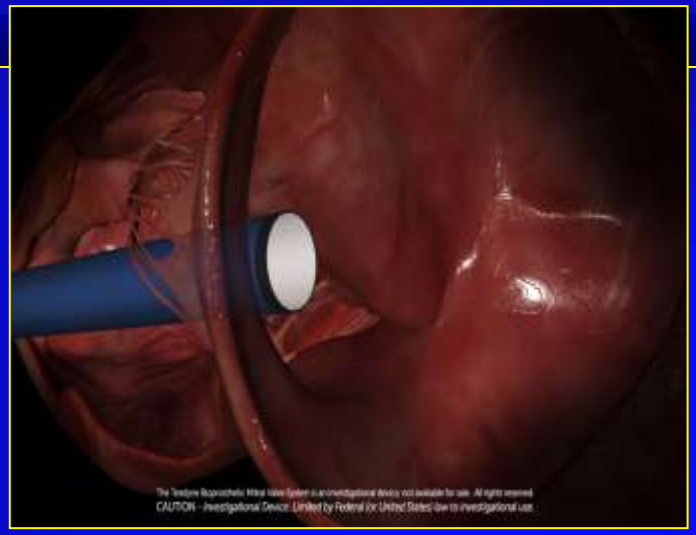
Most active clinical program to date : Abbott Tendyne™

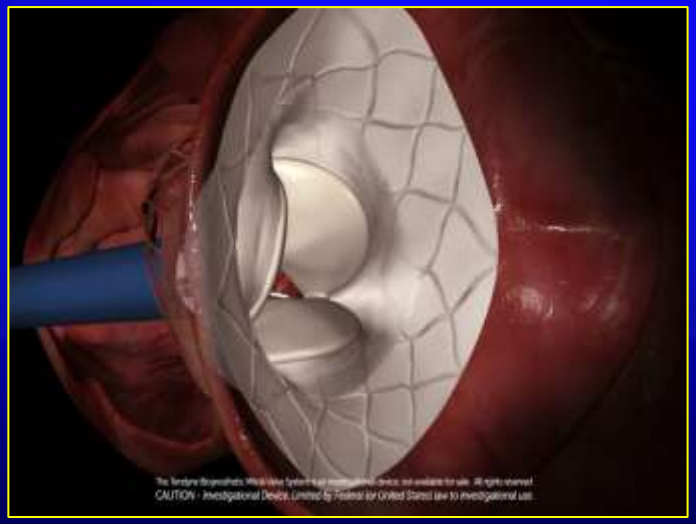
- D-shaped
- Outer and inner frame
- Anchoring tether with hemostatic pad
- Retrievable, repositionable

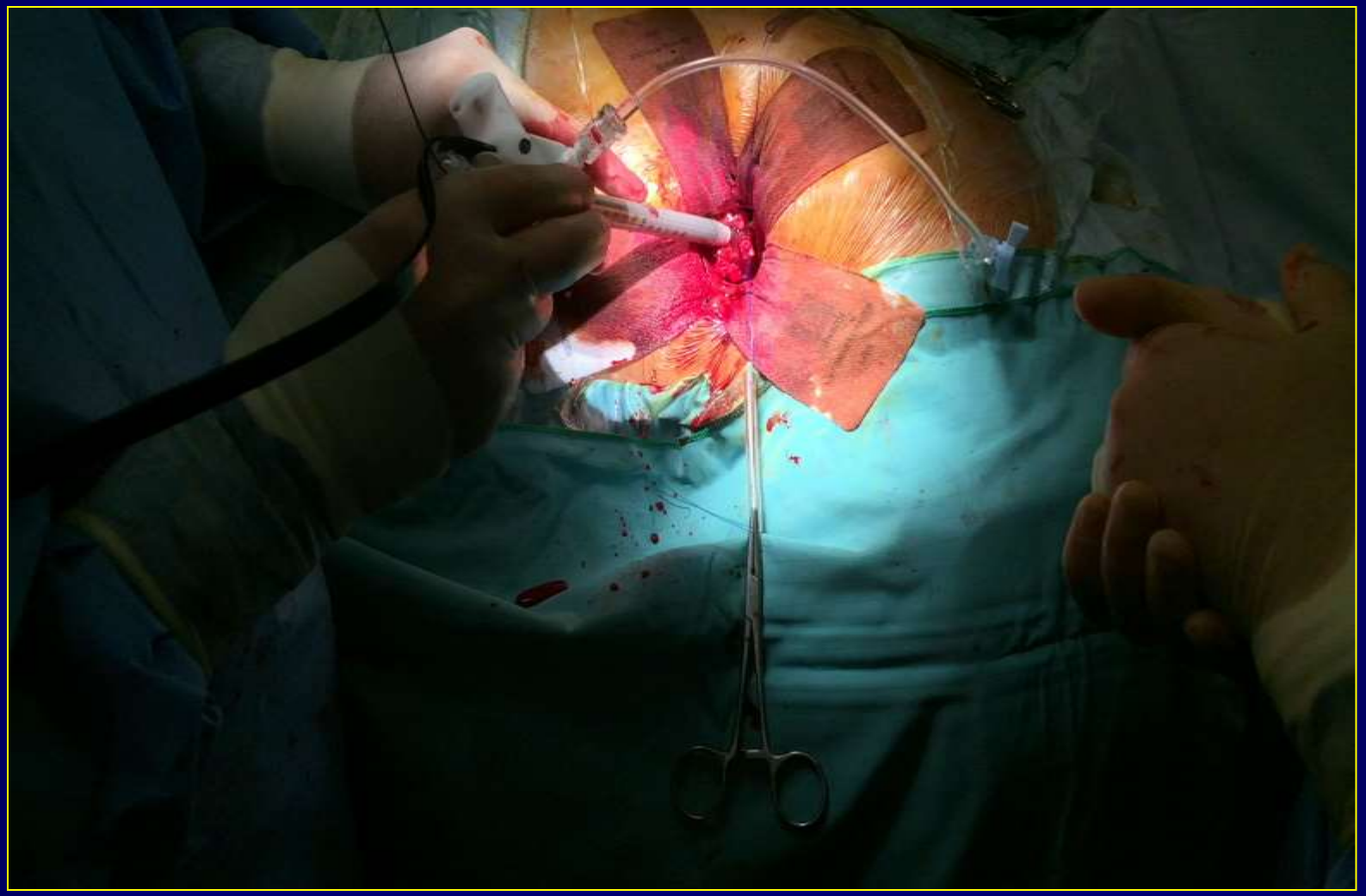
Tendyne Transcatheter Mitral Valve

Tendyne Procedure

- ✓ Insert Catheter into LA
- ✓ Align D-Shape Cuff
- ✓ Intra-Annular Deployment
- ✓ Secure Tether with Apical Pad





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TEE T: 38.6C
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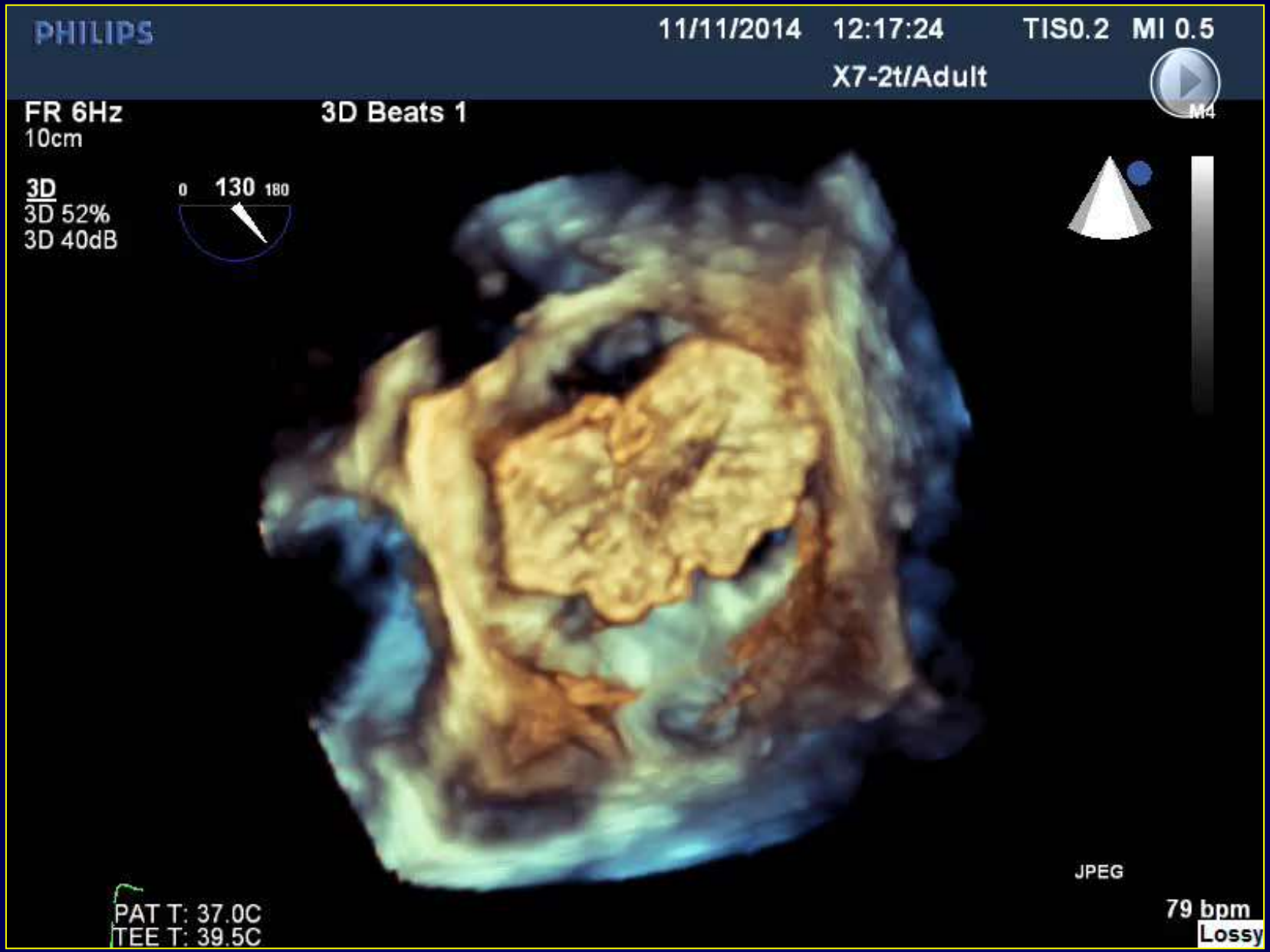
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TEE T: 39.5C
79 bpm
Lossy


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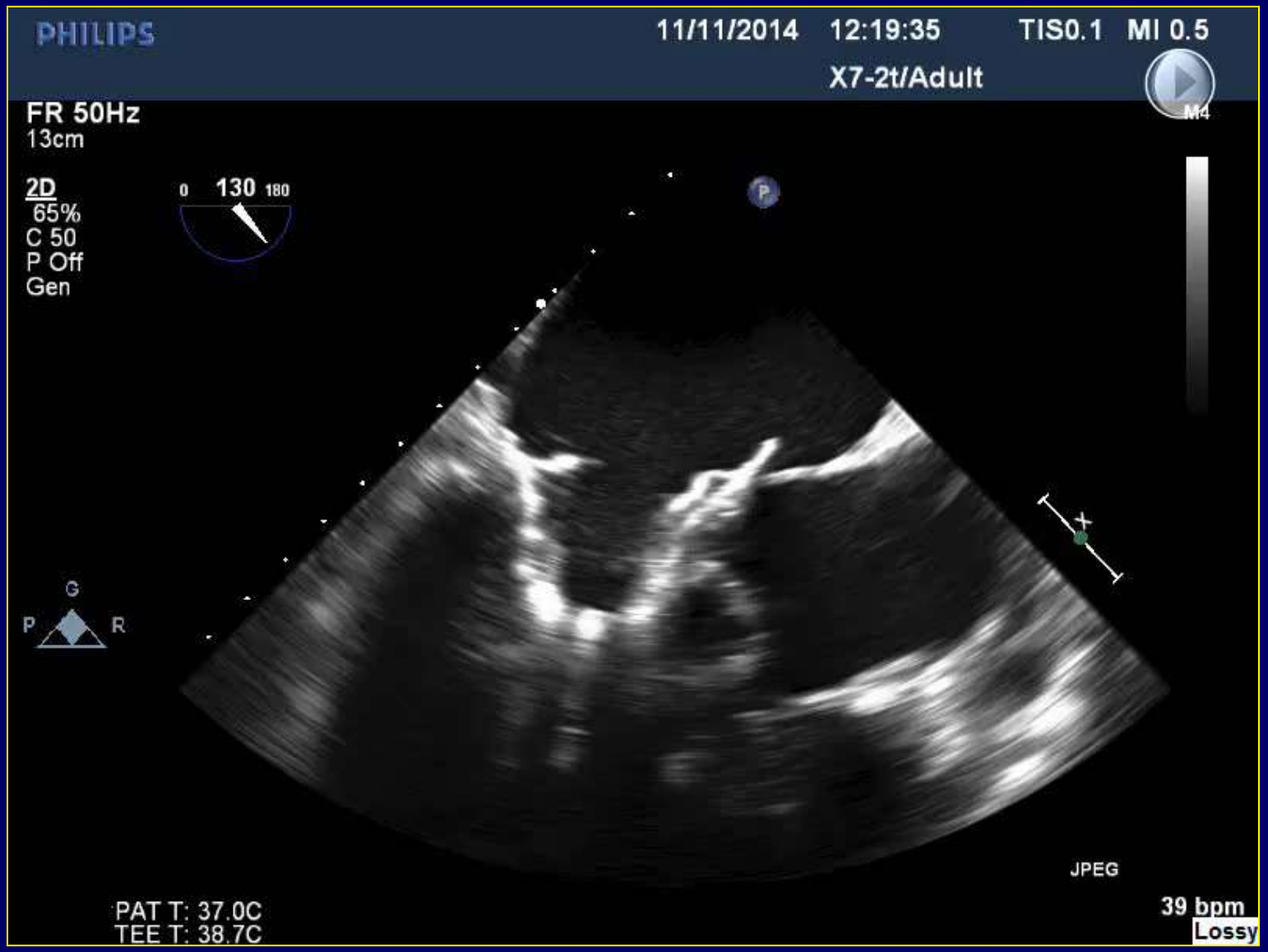
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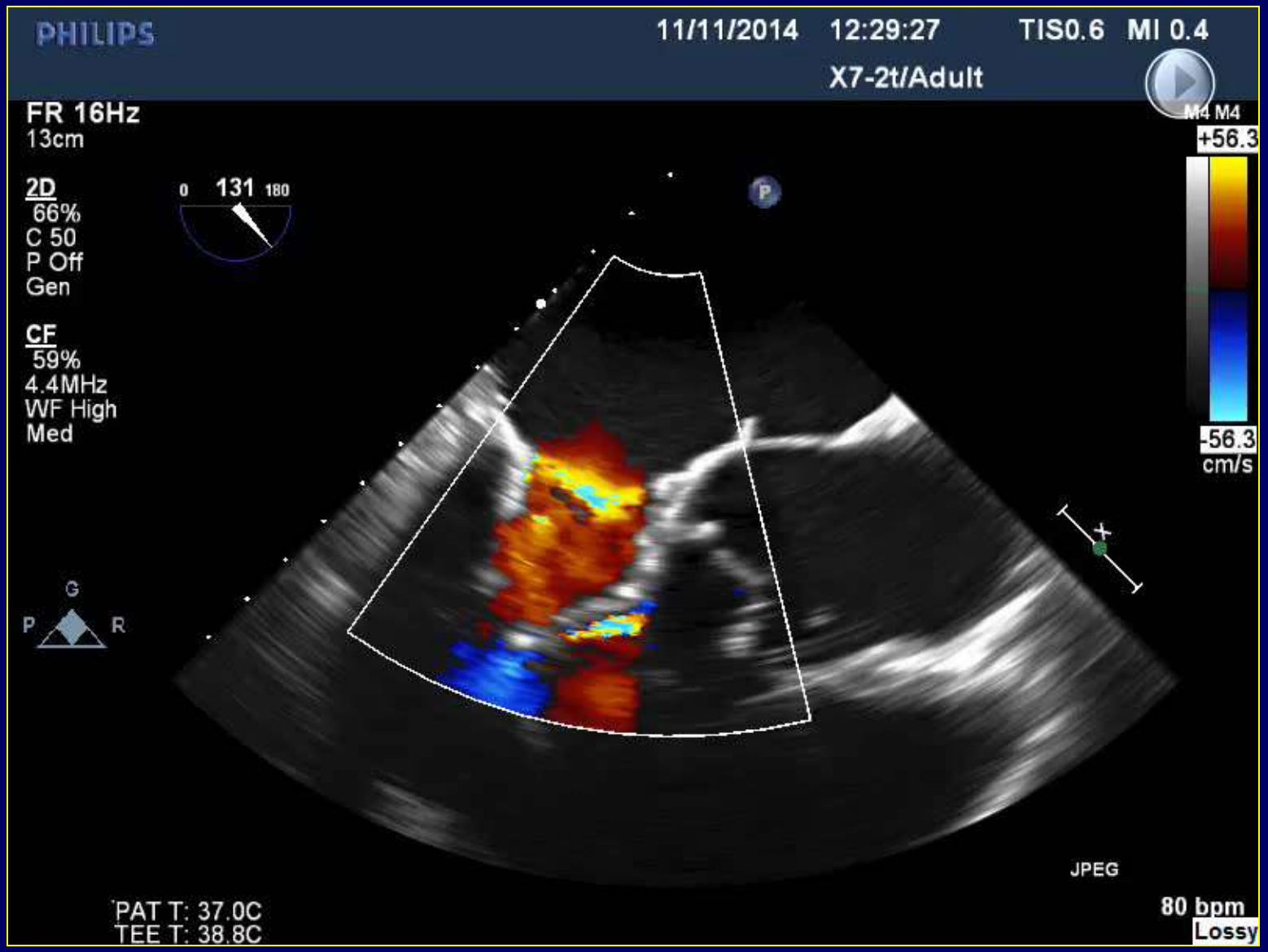
TEE T: 38.7C
39 bpm
Lossy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WF High
Med
M4 M4
+56.3
-56.3
cm/s
G
P
R
JPEG
PAT T: 37.0C
TEE T: 38.8C
80 bpm
Lossy


Lossy

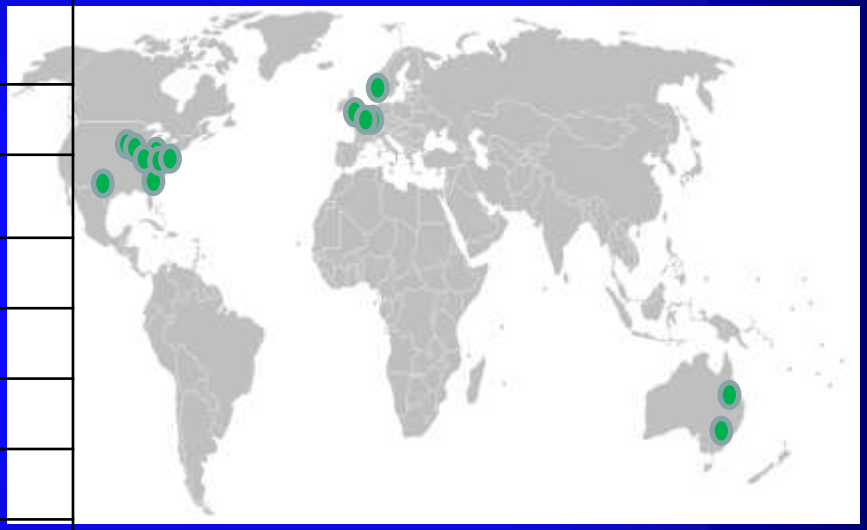

11/11/2014 12:52:43 TIS0.1 MI 0.6
X7-2t/Adult
3D Beats 1
120
LVOT
JPEG
PAT T: 37.0C
TEE T: 37.9C
80 bpm
Lossy

Apical pad placement

(Courtesy D Muller)

Tendyne Implant Experience

EFS/CE Mark Study Site Name (n=12 sites)	Patients Treated (n=54)
St. Vincent's	10
Prince Charles Hospital	6
Abbott	15
Cleveland Clinic	4
Baylor	4
Northshore	3
MedStar	3
Henry Ford Hospital	1
Pinnacle Health	1
West Virginia University	4
Oslo University Hospital	2
Emory	1



- 10 CU cases
  - 5 Royal Brompton Hospital
  - 2 University Hospital Zurich
  - 1 University of Bonn
  - 1 Abbott NW (MHI)
  - 1 Bad Nauheim

Tendyne GFS: Patient Overview (n=30)

Baseline Mitral Valve pathology	
Primary MR	3 (10%)
Secondary MR	23 (76.7%)
Mixed pathology	4 (13.3%)
Baseline LV function	**N=29**
LVEF <30%	3 (10.3%)
LVEF 30-50%	14 (48.3%)
LVEF>50%	12 (41.4%)

D. Muller, TCT 2016

GFS: Acute Outcomes

Outcome	N=30
Death (all cause)	0 (0%)
CVA	0 (0%)
Major bleeding	
Transfusion	3 (10%)
Device-related	
Device embolization	0 (0%)
Cardiac perforation	0 (0%)
Paravalvular leak	1 (3.3%)
Device Retrieval	
LVOT obstruction	1 (3.3%)
Did not properly seat - access issue	1 (3.3%)

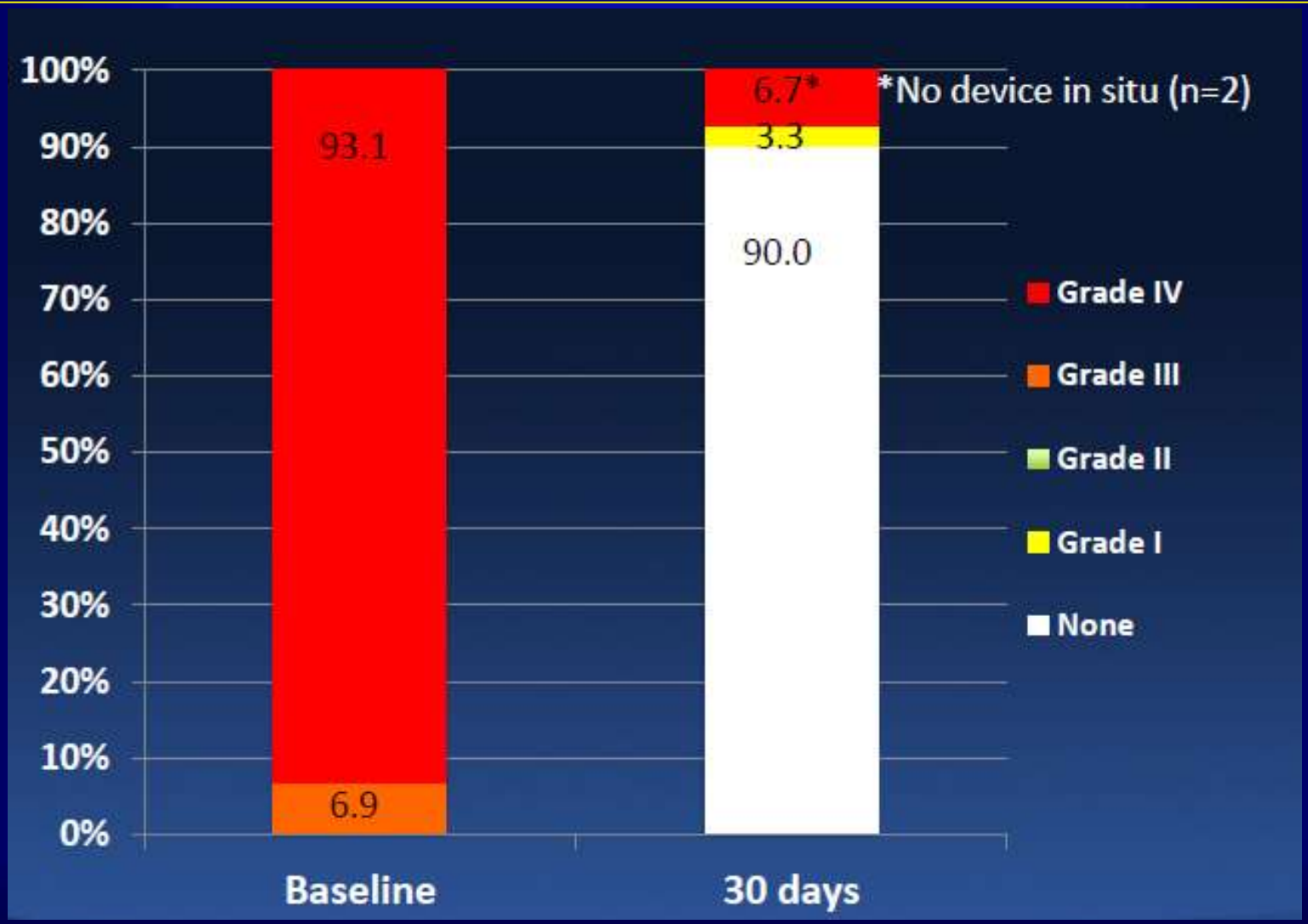
D. Muller, TCT 2016

Tendyne TMVI: D30 Outcomes

Outcome	N=30
Death (all cause)	1 (3.3%)
Cardiac	0 (0%)
Non-cardiac	1 (3.3%)
CVA	0 (0%)
MV surgery	0 (0%)
Re-hospitalisation	
Heart failure	4 (13.8%)
LVAD/transplant	0 (0%)
Other (ileus)	1 (3.3%)
Device-related	
Hemolysis, transfusion	1 (3.3%)
Leaflet thrombosis	1 (3.3%)

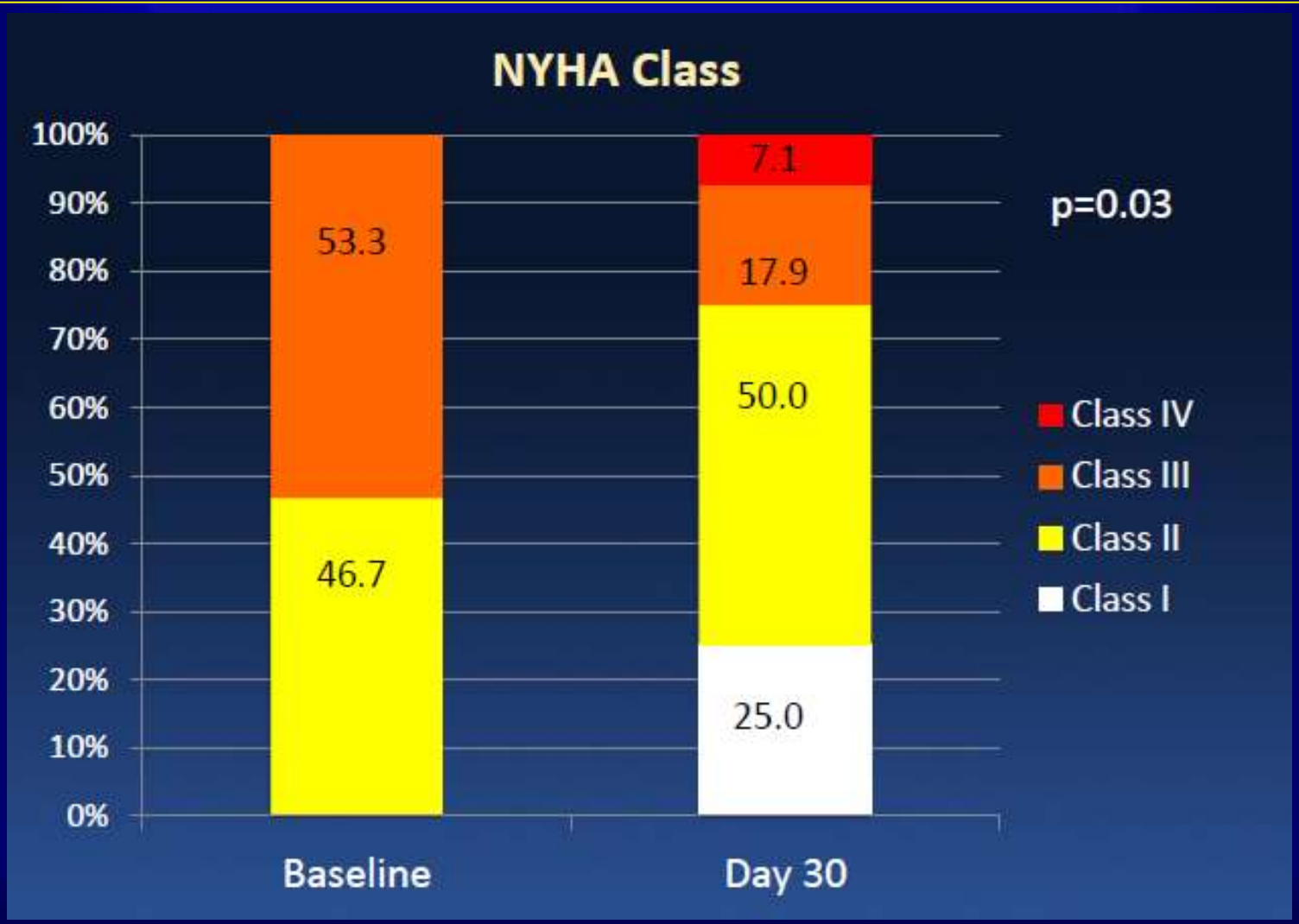
D. Muller, TCT 2016

MR severity post-TMVI (n=30)



D. Muller, TCT 2016

Functional capacity post-TMVI (n=30)

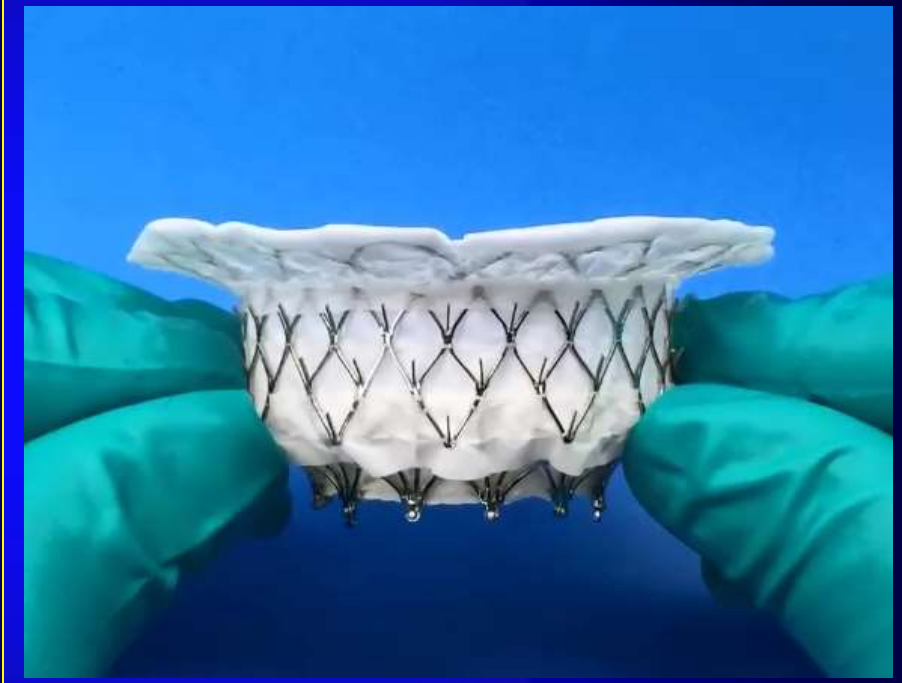


D. Muller, TCT 2016

Medtronic Twelve™ Intrepid Design Concept

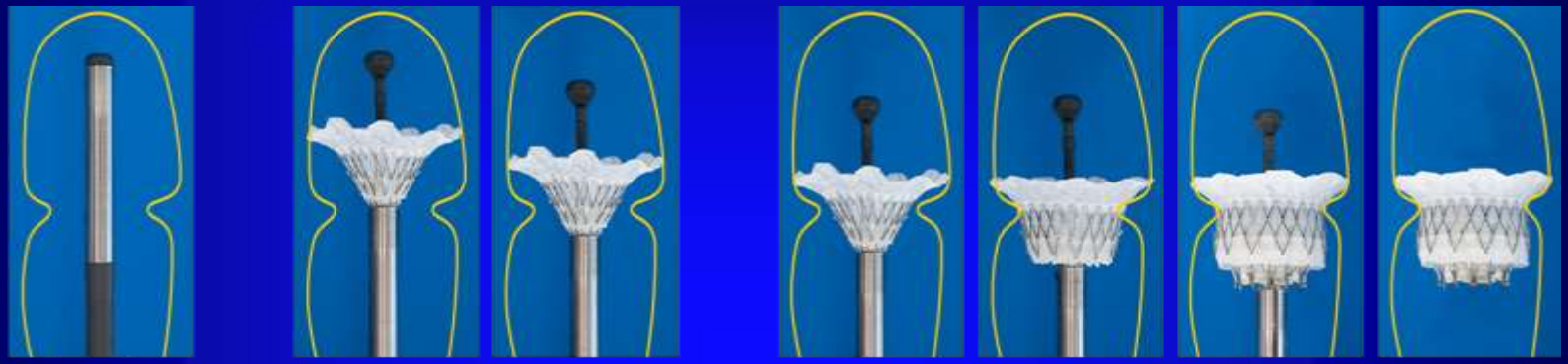
Differentiated, dual stent design

- Conforms to native anatomy
- Separates fixation & sealing from valve function
- Isolates valve from the dynamic anatomy
- Preserves native mitral apparatus
- Ensures LVOT patency
- Suits both primary & secondary mitral valve disease
- Manages all patient sizes with one valve size

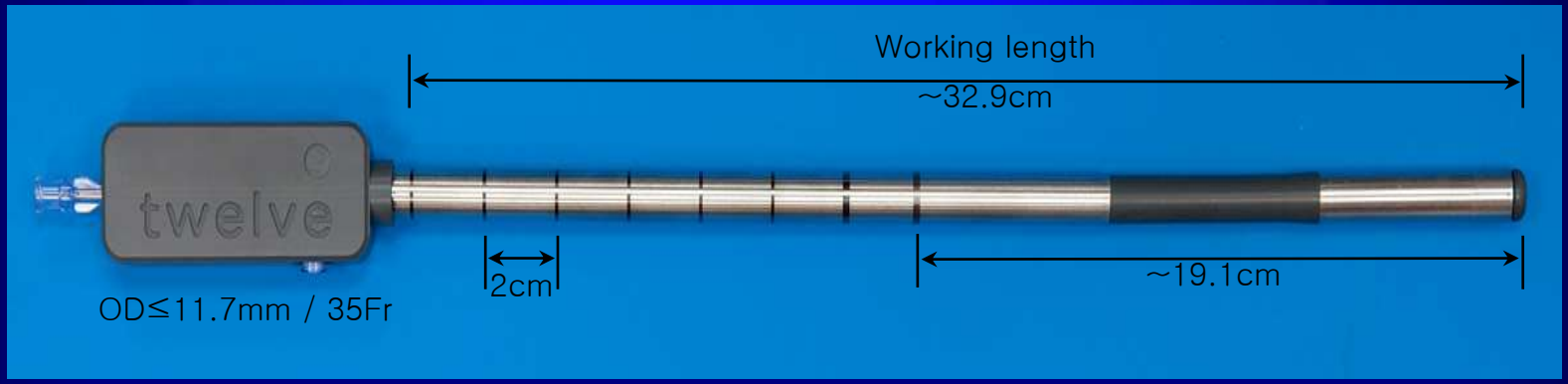


Intrepid™ TMVR

delivery system and deployment



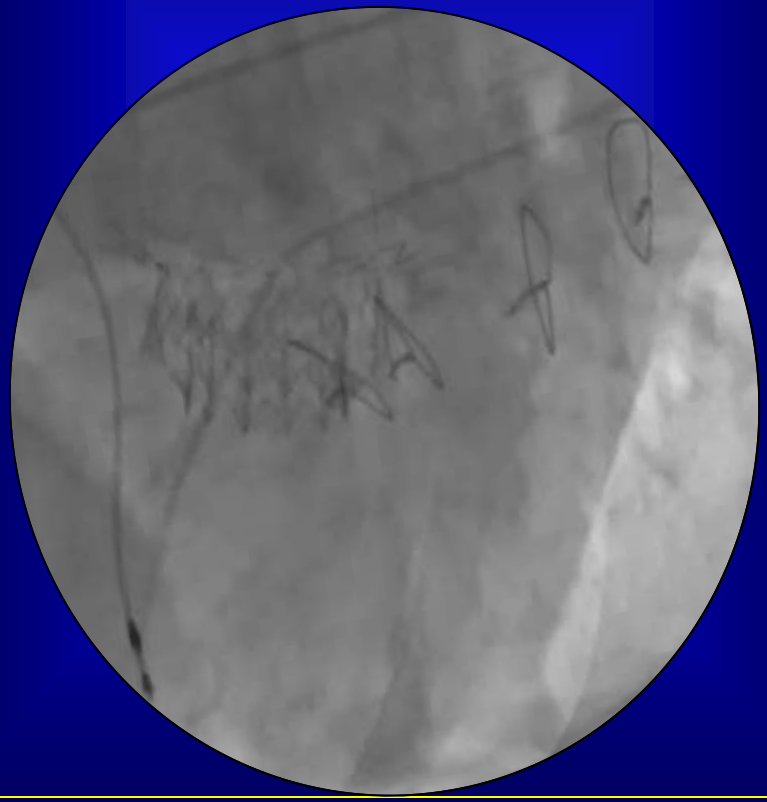
1. Advance into LA
2. Expand brim & align with annulus target
3. Retract to target & deploy



Intrepid™ TMVR

Post-deployment Images from Human implant

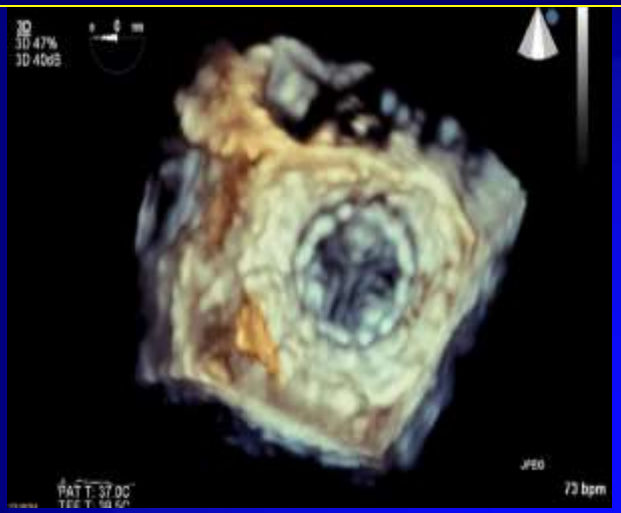
- Good sealing
- Secure fixation



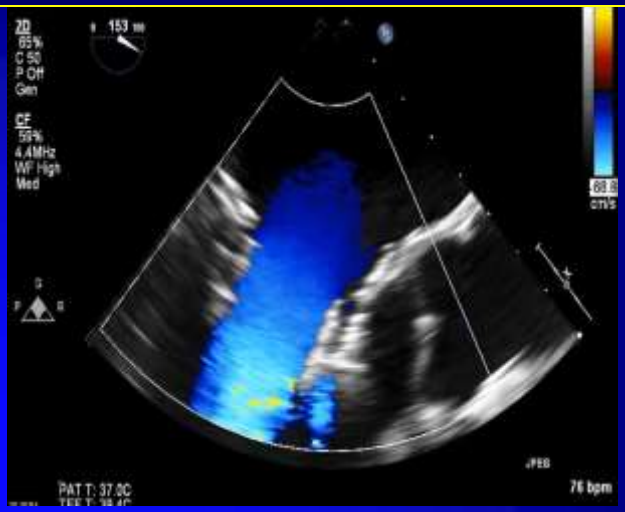
Intrepid™ TMVR

Post-deployment Images from Human implant

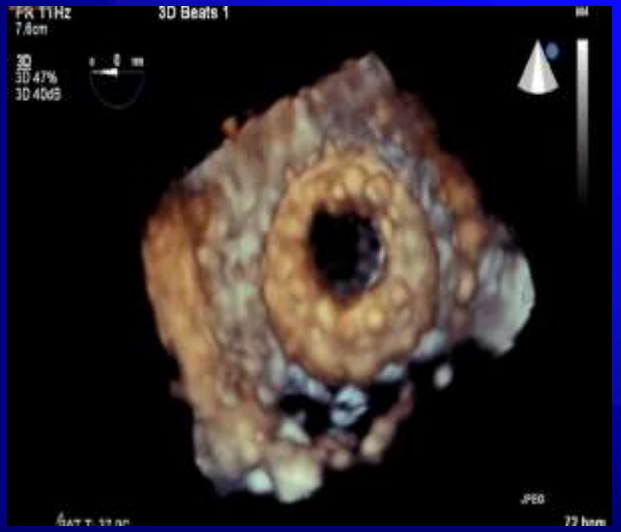
Atrial View



Intrepid Valve



Ventricular View



Patent LVOT

Patient Demographics

Pilot Study Clinical experience

Baseline Characteristics (n=38)		
Age (years)	73	(range: 48-90)
Sex (female)	12	
NYHA Functional Class		
II	4	
III	27	
IV	7	
Prior MI / Coronary Artery Disease	28	
Previous Cardiac Surgery	17	
Atrial Fibrillation	25	
Pacemaker/BiV/ICD	14	
STS Mortality score mean (%)	6.5	(range: 1-31)

Baseline Echocardiogram (n=38)	FMR	DMR
MR Etiology	30	8
LVEF mean (%)	38	53
< 30	4	0
30 – 50	22	3
> 50	4	5
MR grade ≥ 3+ (%)	100	

Results

Pilot Study Clinical experience

Procedural Outcomes (n=38)

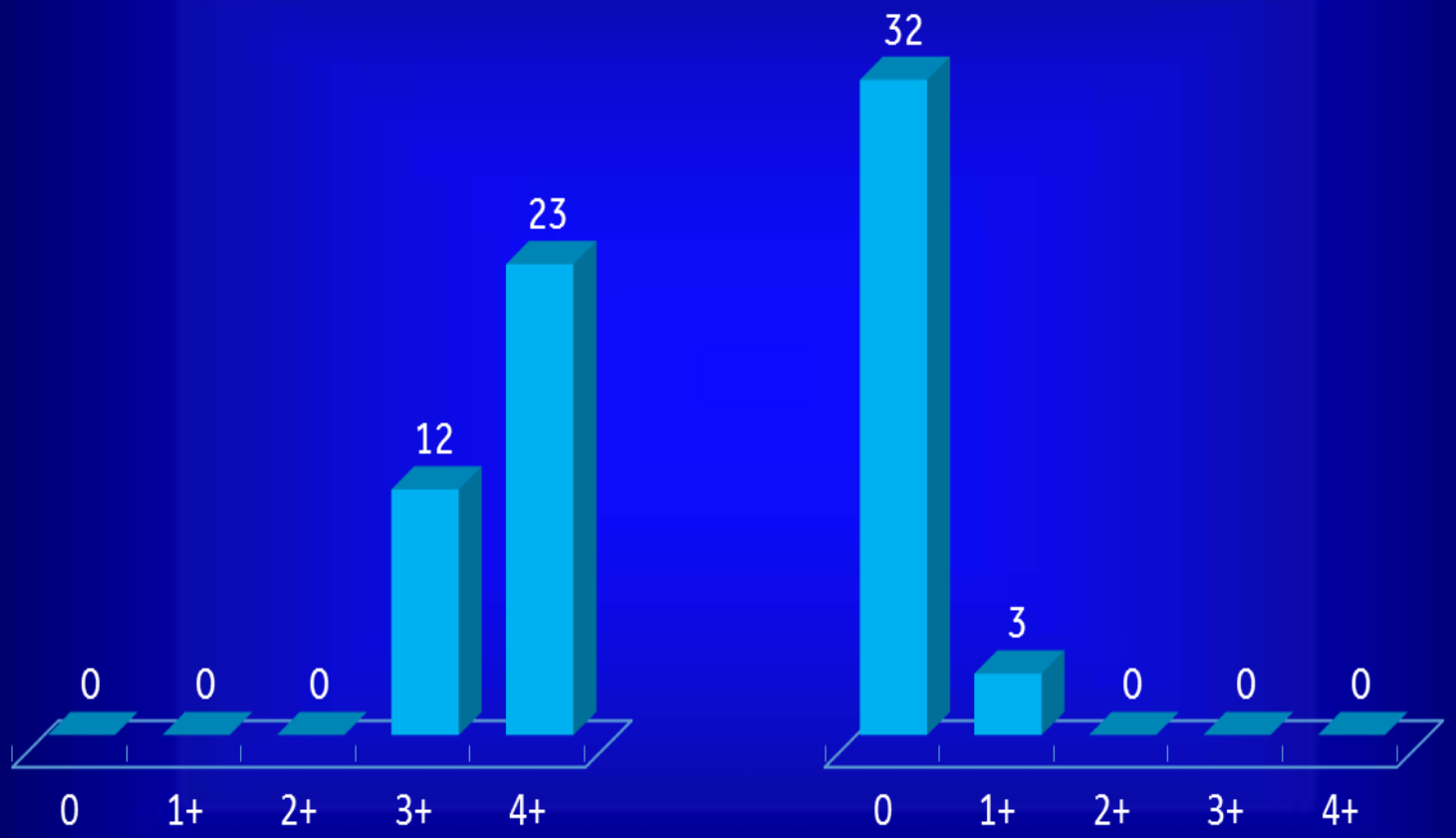
Successful Deployment	35/37[1]	
Apical Access Time (min)	30	(range: 17-53)
Deployment Time (min)	15	(range: 4-29)
Mean LVOT Gradient[2] (mmHg)	2	(range: 0-4)
Mean MV Gradient[2] (mmHg)	4	(range: 0-7)

1 - in one patient deployment was not attempted
2 - latest follow-up

Results

Pilot Study Clinical experience

MR Grade



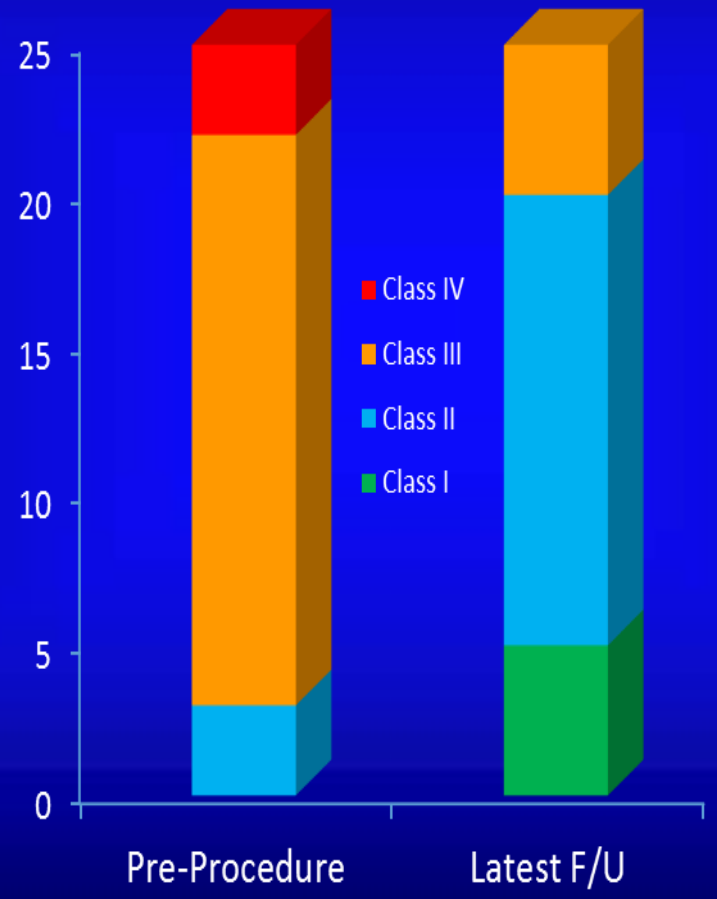
Pre-Procedure

Latest f/u

Results

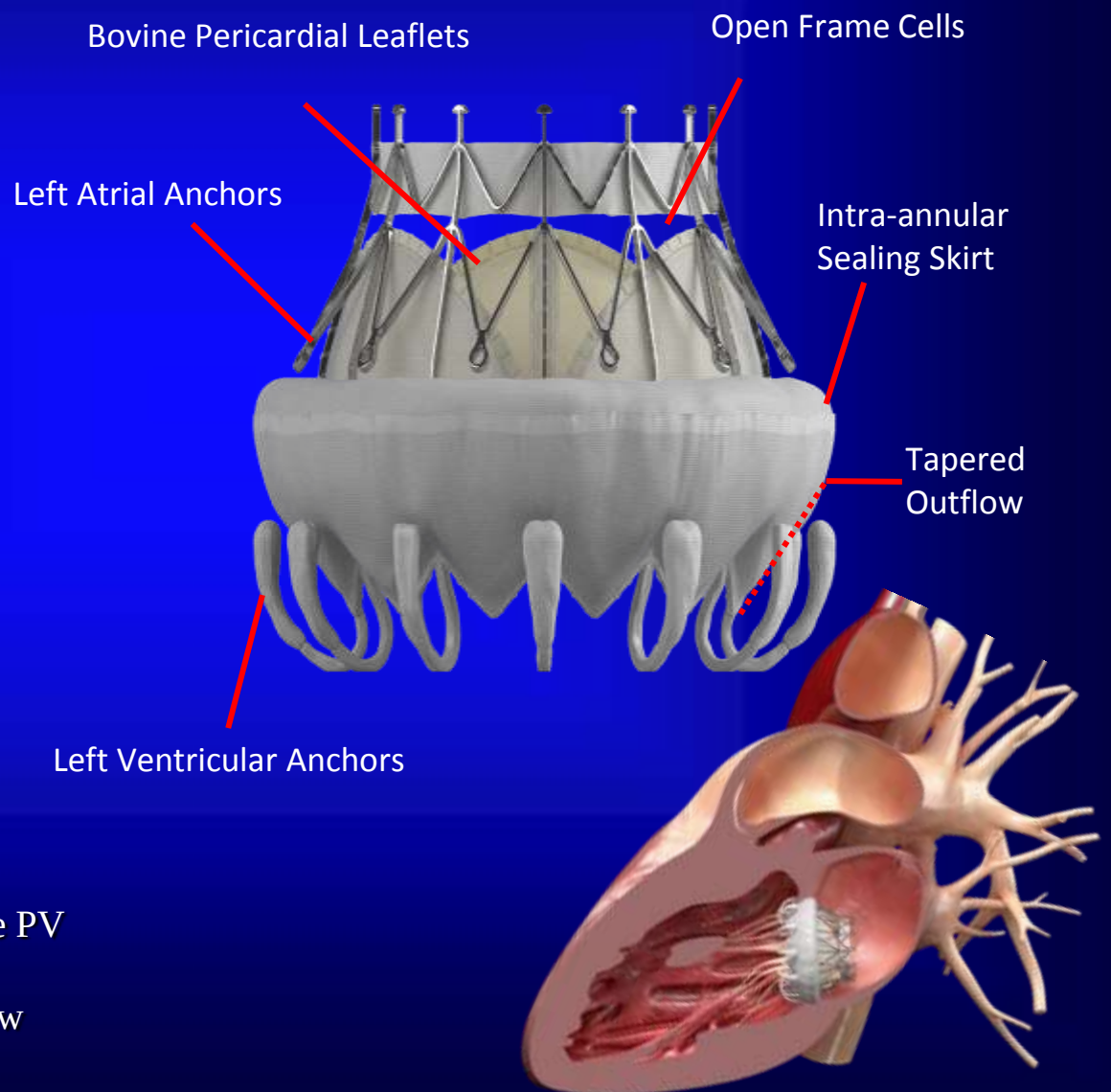
Pilot Study Clinical experience

NYHA Class

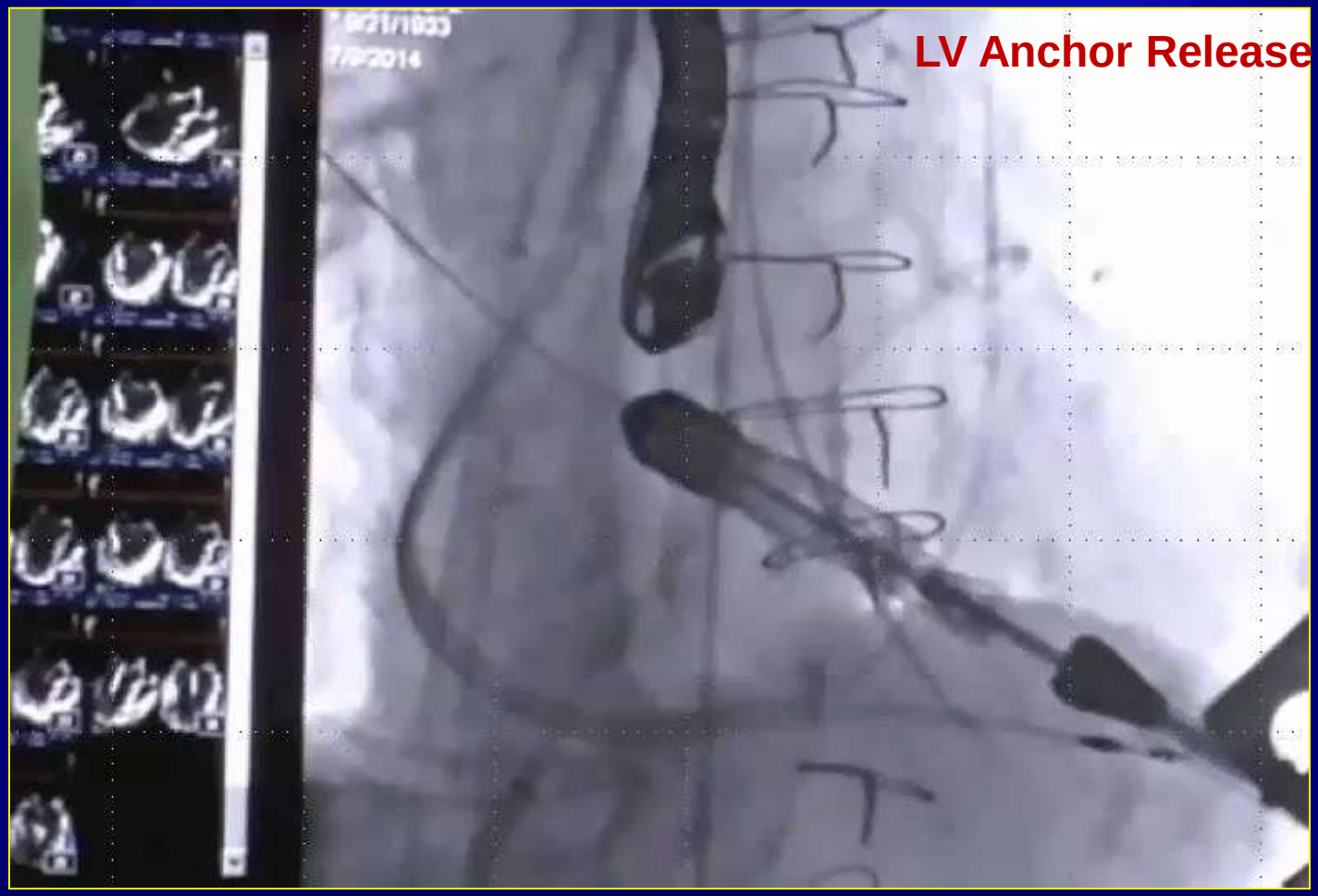


The CardiAQ™ -Edwards

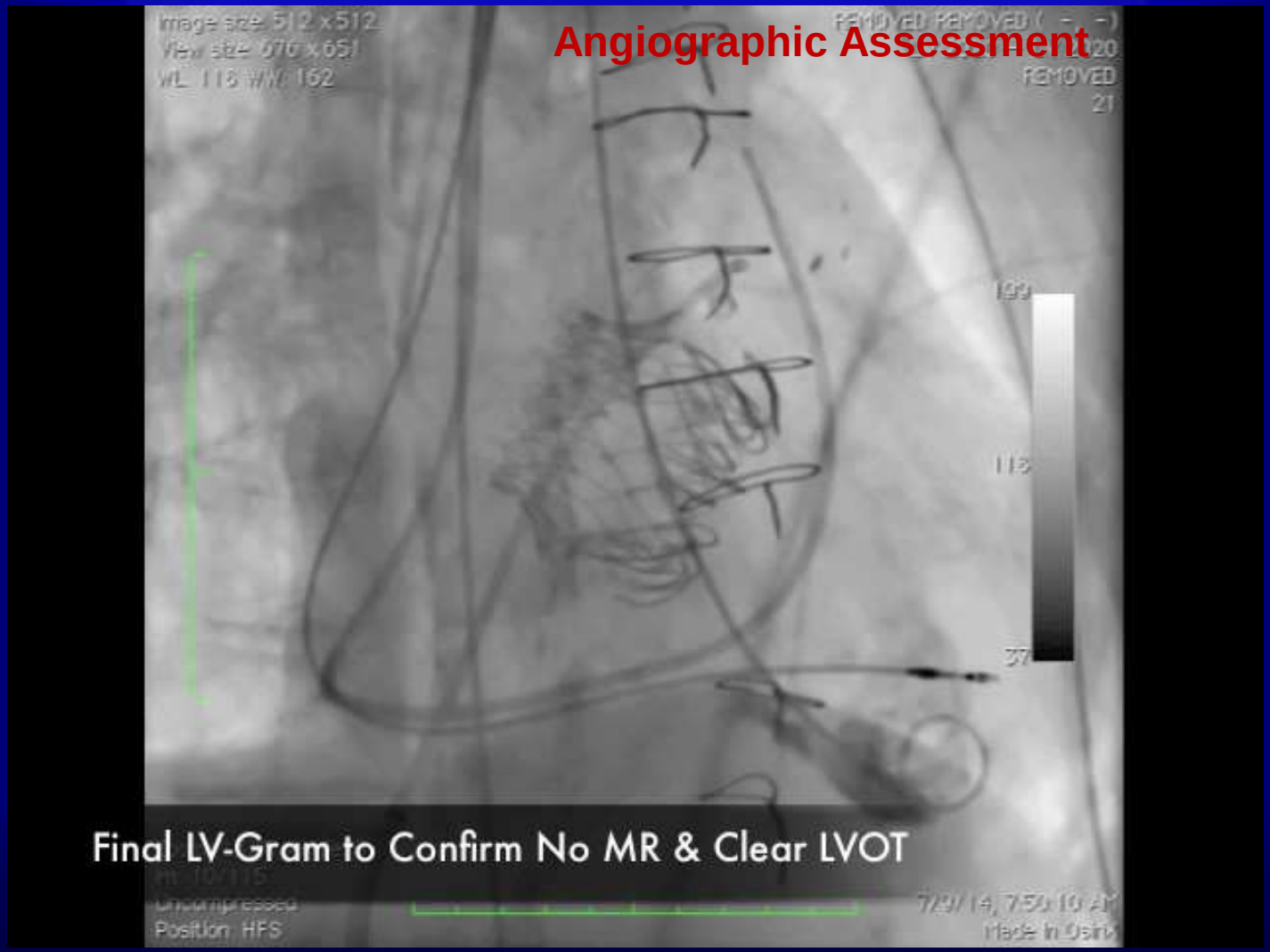
- **ONE VALVE, MULTIPLE DELIVERY SYSTEMS**
  - **TS** – Transseptal approach
  - **TA** – Transapical approach
- **ANCHORING MECHANISM**
  - Preserves chords and utilizes native leaflets
  - Promotes load distribution among annulus, leaflets and chords
- **DESIGNED TO PROMOTE PHYSIOLOGIC FLOW**
  - Eliminate mitral regurgitation
  - Supra-annular position and tapered outflow to minimize risk of LVOT obstruction
  - Intra-annular sealing skirt to minimize PV leak
  - Open frame cells to promote atrial flow



The CardiAQ™ -Edwards Transapical TMVR Procedure



The CardiAQ™ -Edwards Transapical TMVR Procedure



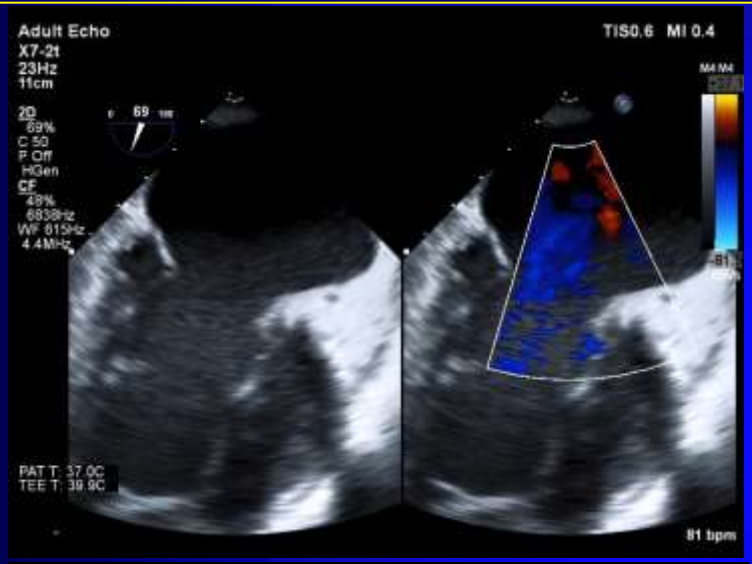
The CardiAQ™ -Edwards TMVR Early Compassionate Use Experience

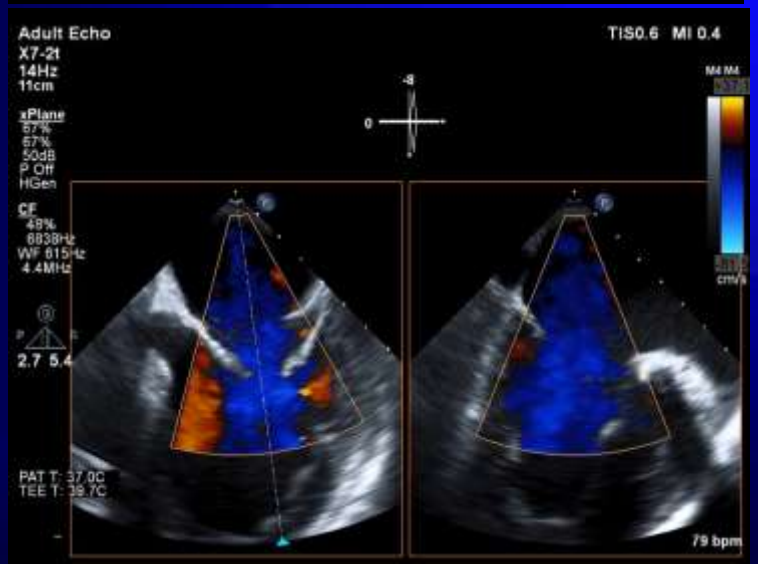
- 12 patients treated under compassionate use as of Nov 2015
  - First-ever TMVR TS patient 2012 with 1st generation device
- 11 patients with 2nd generation valve (2014-2015)
  - 82% male
  - Prior CABG: 73%
  - Etiology: 64% FMR, 36% DMR
  - LVEF range <20-72%
  - Technical success rate (successful delivery, deployment and retrieval of DS): 82%
  - Two procedure related deaths:
    - 1 interaction with mechanical AV
    - 1 malpositioning due to sub-leaflet calcification
  - Four non-valve related deaths (all had good valve function):
    - Pneumonia (PO day 9)
    - Right heart failure/cardiac decompensation (PO day 7)
    - Multi-organ failure (PO day 18)
    - Sepsis (PO day 36)

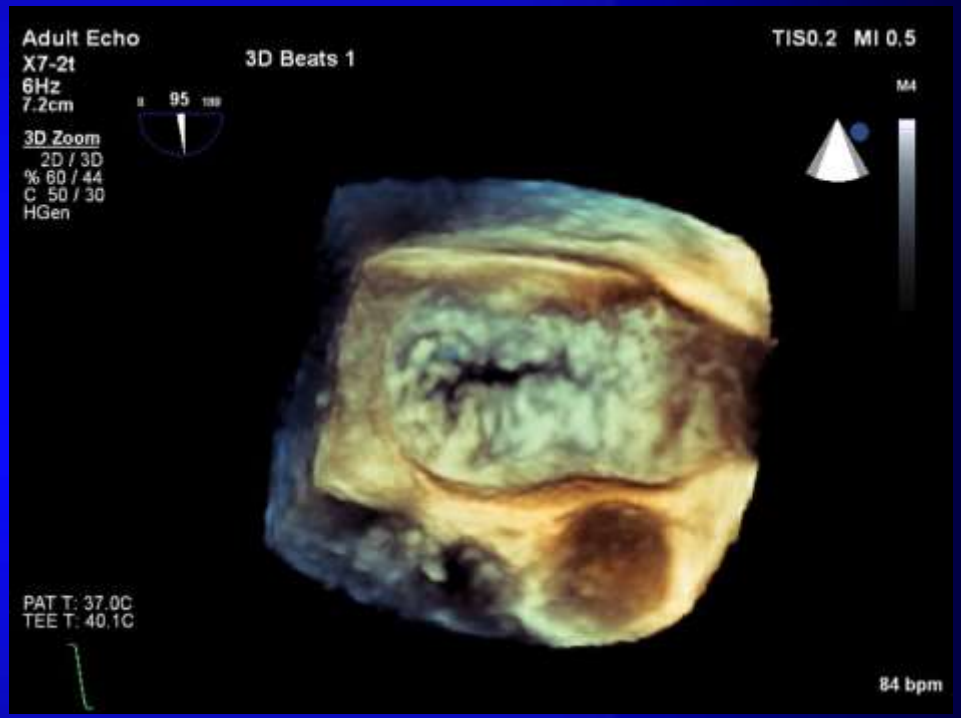
The CardiAQ™ -Edwards TMVR Clinical Program Status

- Compassionate use experience ongoing in Europe
- US EFS trial enrolling: *high risk patients*
  - *Brief pause in case scheduling while key clinical learnings were being implemented, but full patient screening is now continuing in anticipation of Q2 cases*
- Future Pipeline
  - Reduced delivery profile
  - Additional valve sizes
  - Delivery system improvements
    - Current TS approach is technically more demanding, but less invasive than transapical approach
    - *Technical improvements expected to make this procedure easier*
  - Proven valve tissue – the same bovine pericardial tissue and processes as Edwards surgical valves

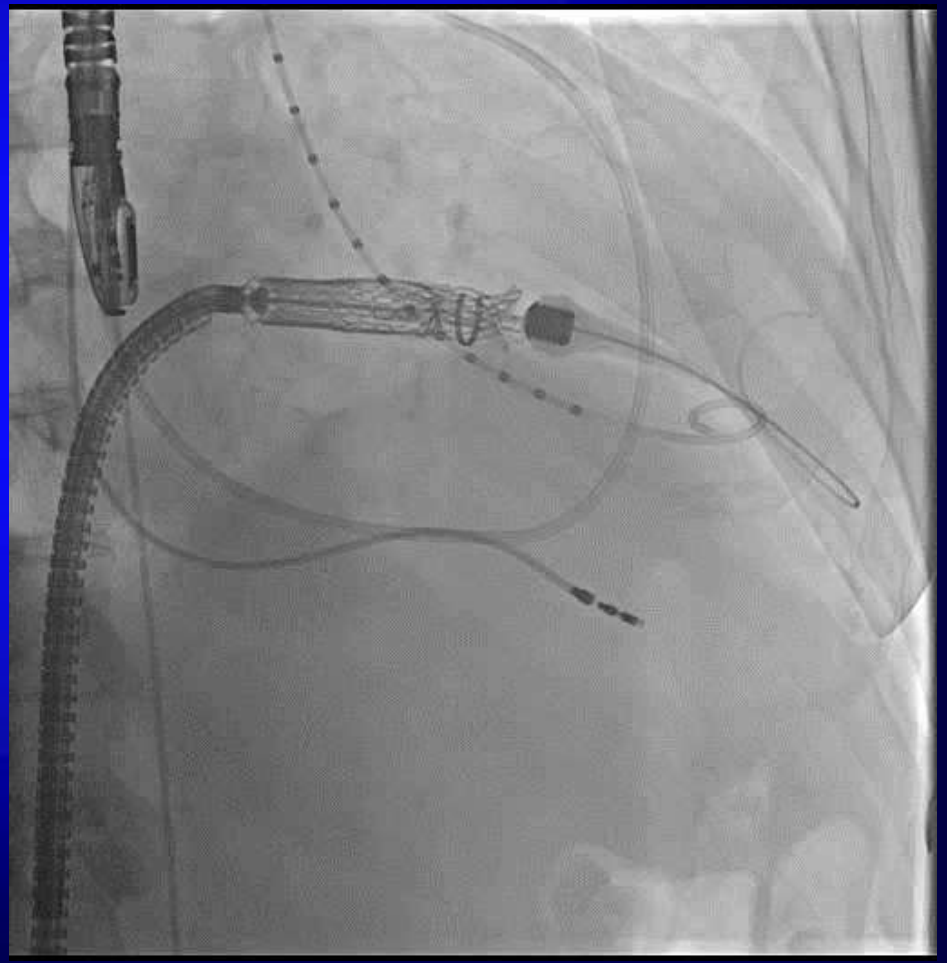
Trans-septal TMVR with CardiAQ-Edwards



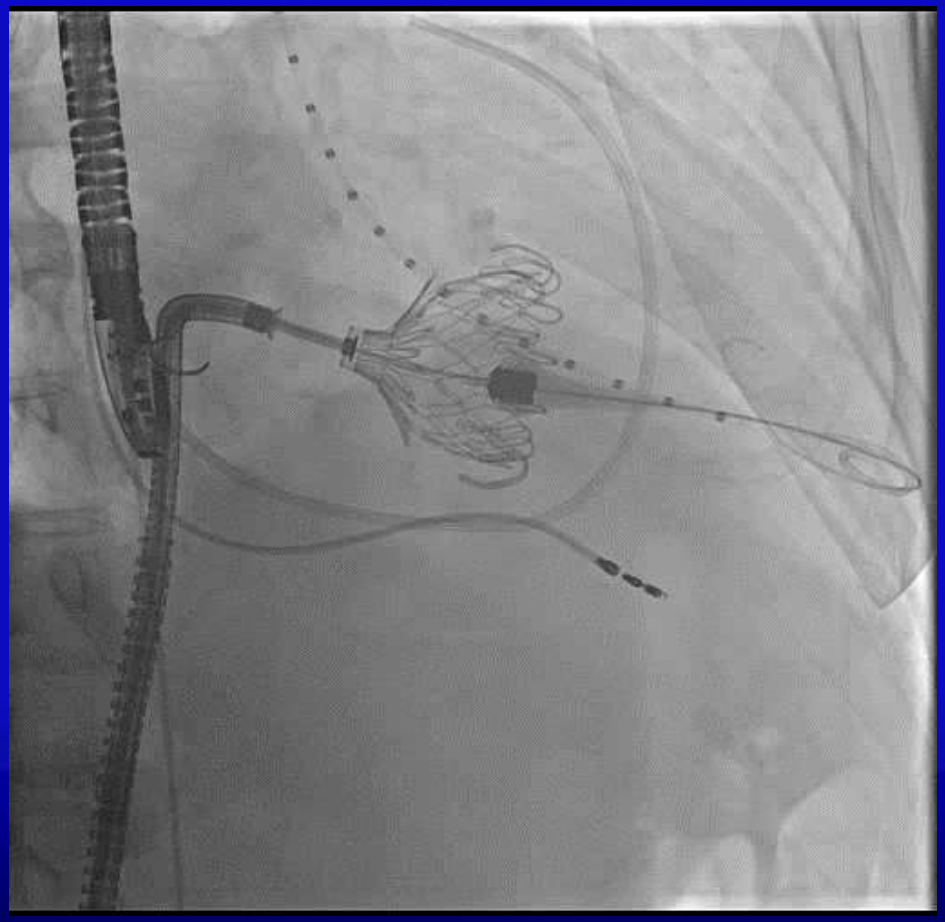




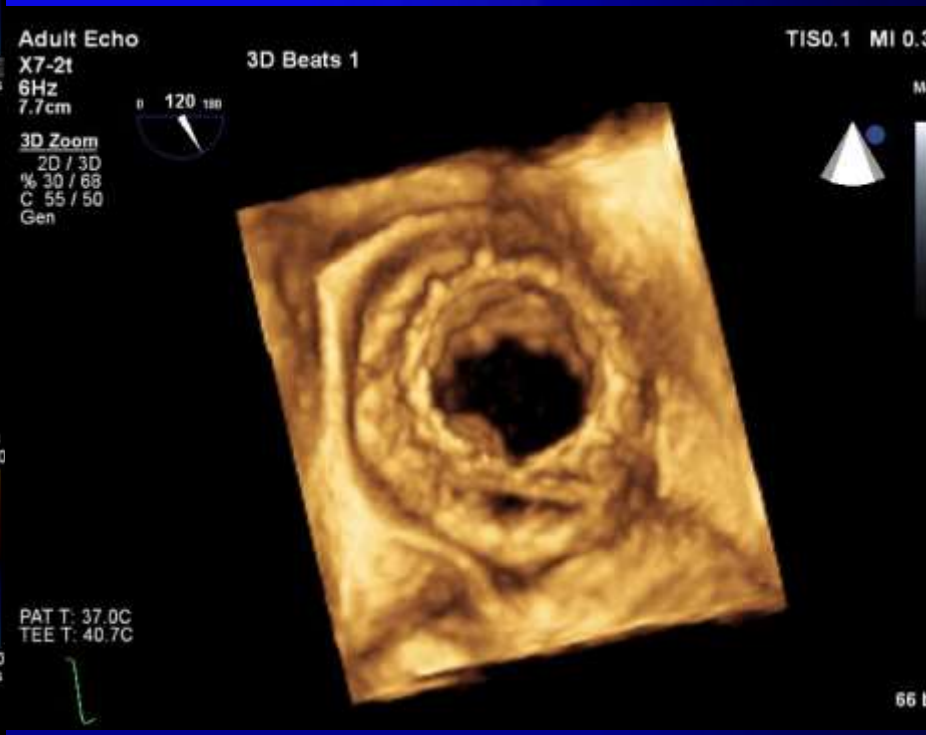
Transseptal TMVR with CardiAQ-Edwards



Transseptal TMVR with CardiAQ-Edwards

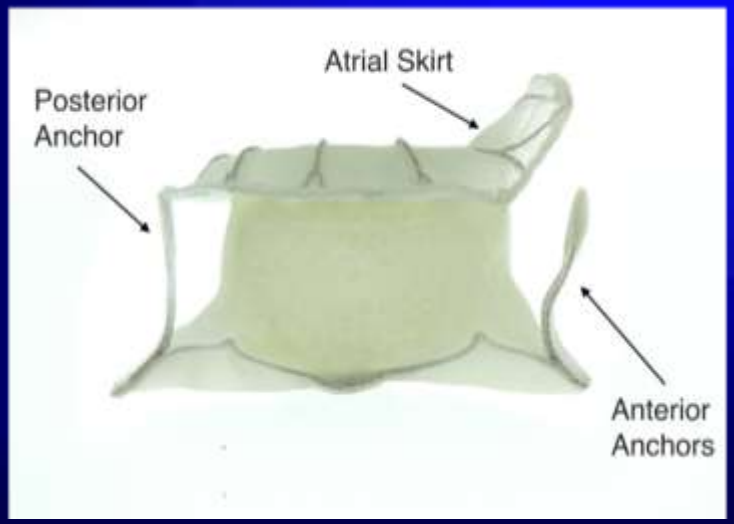


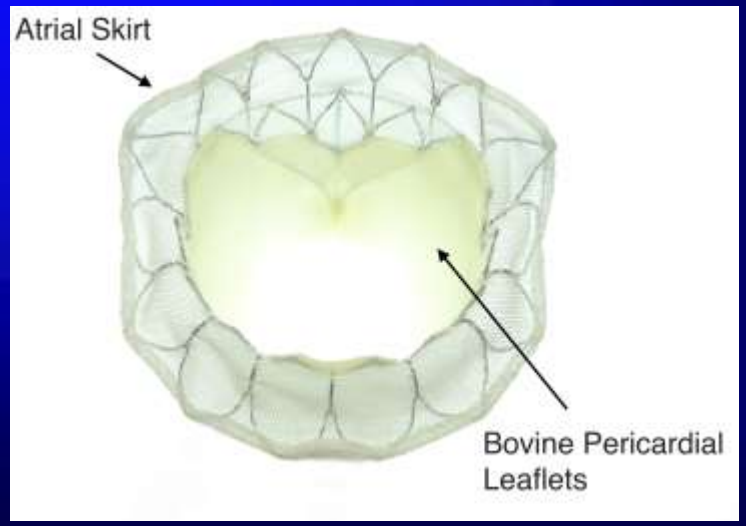
Transseptal TMVR with CardiAQ-Edwards



Neovasc TIARA™ Trans Catheter Mitral Valve

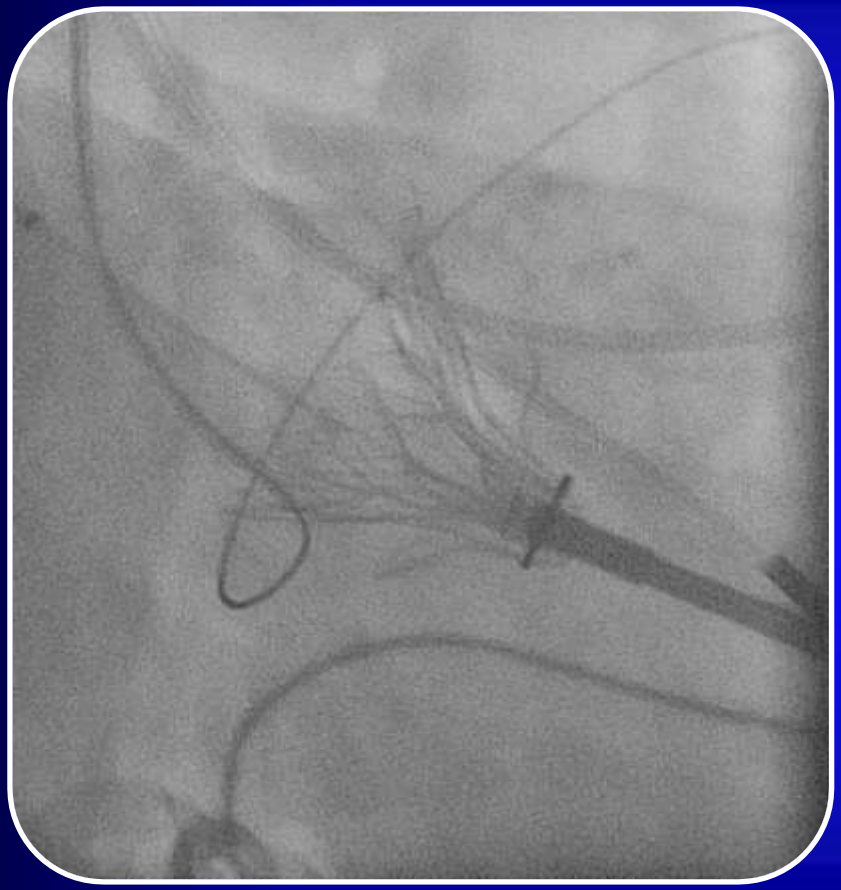
- Anatomically shaped (D-shaped)
- Nitinol based, self-expanding frame
- Bovine pericardium 3 leaflets
- Ventricular anchors to fix the valve onto fibrous trigons and posterior annulus
- 35mm and 40mm available sizes





Delivery System

- 32 F sheathless system
- Self dilating tip
- Transapical approach



Referral Sites:

TIARA-I Early Feasibility Trial Sites

- United States (Columbia University, Northwestern University, University of Washington)
- Belgium (Middelheim University)
- Canada (St. Paul's Hospital, London Health Sciences Centre, University of Alberta Hospital)

Special Access/Compassionate Use Programs

- Canada (St. Paul's Hospital, London Health Sciences Centre, University of Alberta Hospital)
- Italy (San Raffaele Hospital)
- Germany (Hamburg University Clinic Eppendorf)

Baseline Demographics (n=24)

Mitral Valve Pathology	
Degenerative MR	5 (21%)
Functional MR	15 (63%)
Mixed MR	3 (12%)
Rheumatic	1 (4%)
Baseline LVEF	
< 30%	9 (38%)
31 – 50%	14 (58%)
>50%	1 (4%)
Mean LVEDD (mm)	68 ± 11 (52 – 94)
Mean Systolic Pulmonary Artery Pressure (mmHg)	51 ± 16 (23 – 79)

Outcome	n=24
Death	0
CVA/MI	0
Permanent Pacemaker	1 (4%)
Conversion to open MVR	3 (12.5%)
Device Malpositioning/Embolization	3 (12.5%)
LVOT Obstruction	0
Major Bleed	1 (4%)

30 Day Outcomes

Day 30 Outcomes*	n=22
Death	3 (13.6%)
Cardiac	2 (Arrhythmia, VSD)
Non-Cardiac	1 (Sepsis)
CVA/MI	0
Reintervention	0

*2 patient has not reached the 30 day timepoint

Landscape of trans-catheter mitral valve replacement therapies with *early* human experience

Device	Edwards CardiAQ	Neovasc Tiara	Abbott Tendyne	Medtronic Intrepid
				
Fixation required				
Posterior leaflet	-	-	-	-
Posterior ridge	-	+	-	-
Anterior leaflet	-	-	-	-
Recapture/retrieval	-	-	Retrievable	Retrievable soon
Suitable for				
FMR / DMR	+ / +/-	+ / +	+ / +	+ / +
Sheath size	36 Fr	32 Fr	32 Fr	35 Fr
N patients treated	14	17	37	17
Procedural success	9/11 (82%)	14 (82%)	26/28 (93%)	15 (88%)
Early mortality	6/12 (50%)	3 (18%)	1/23 (4%)	4 (24%)

NEW COMERS…

HighLife
Device Characteristics and Unique Features

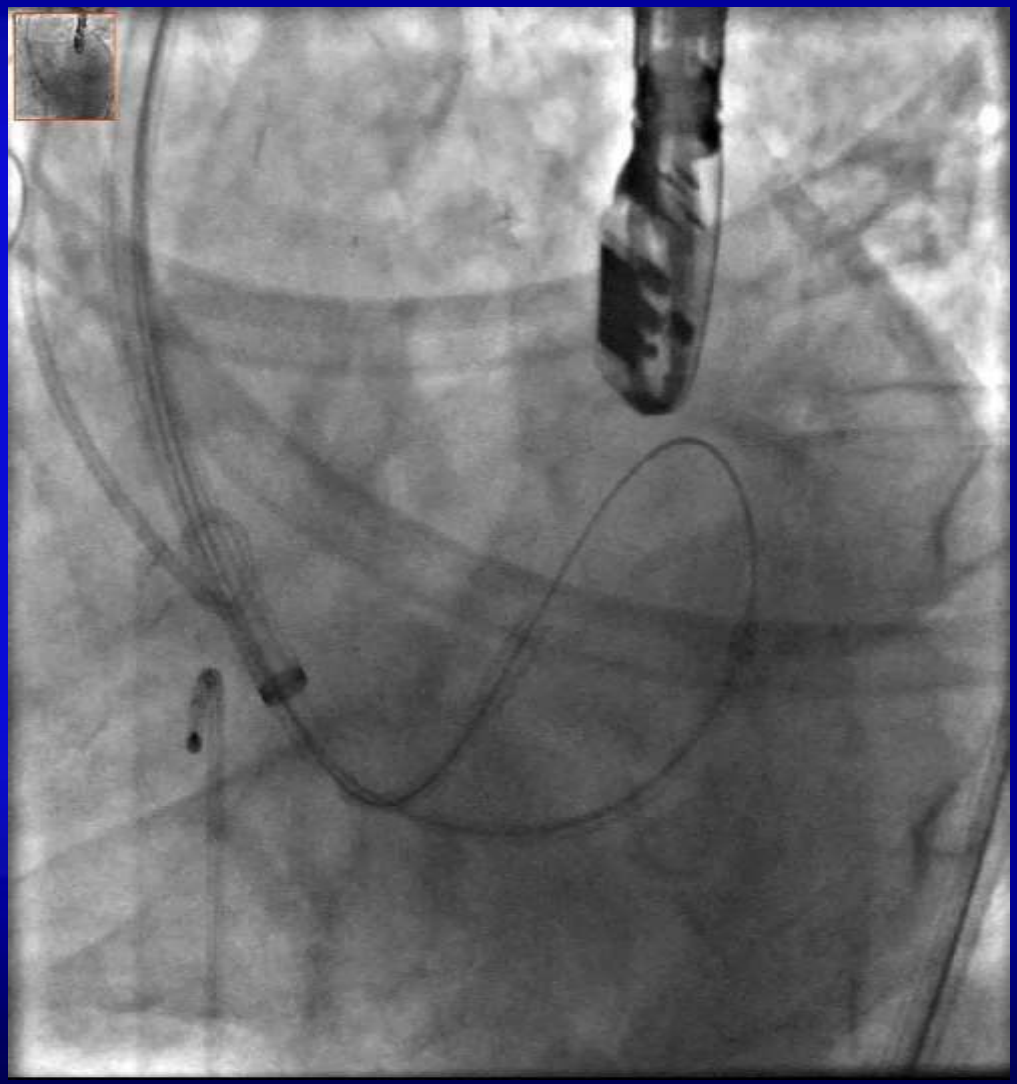
- The valve
  - 31mm **TA** valve
  - Bovine pericardium
  - Nitinol frame
  - Polyester cover

- The ring **TF** implant
  - Polymer tube
  - Nitinol hook
  - Polyester cover

HighLife
Device Characteristics and Unique Features

- 3 step approach
  - Guide wire looped around mitral leaflets
  - Ring implanted over guide wire loop
  - Valve-in-Ring implantation

Ring insertion and closure



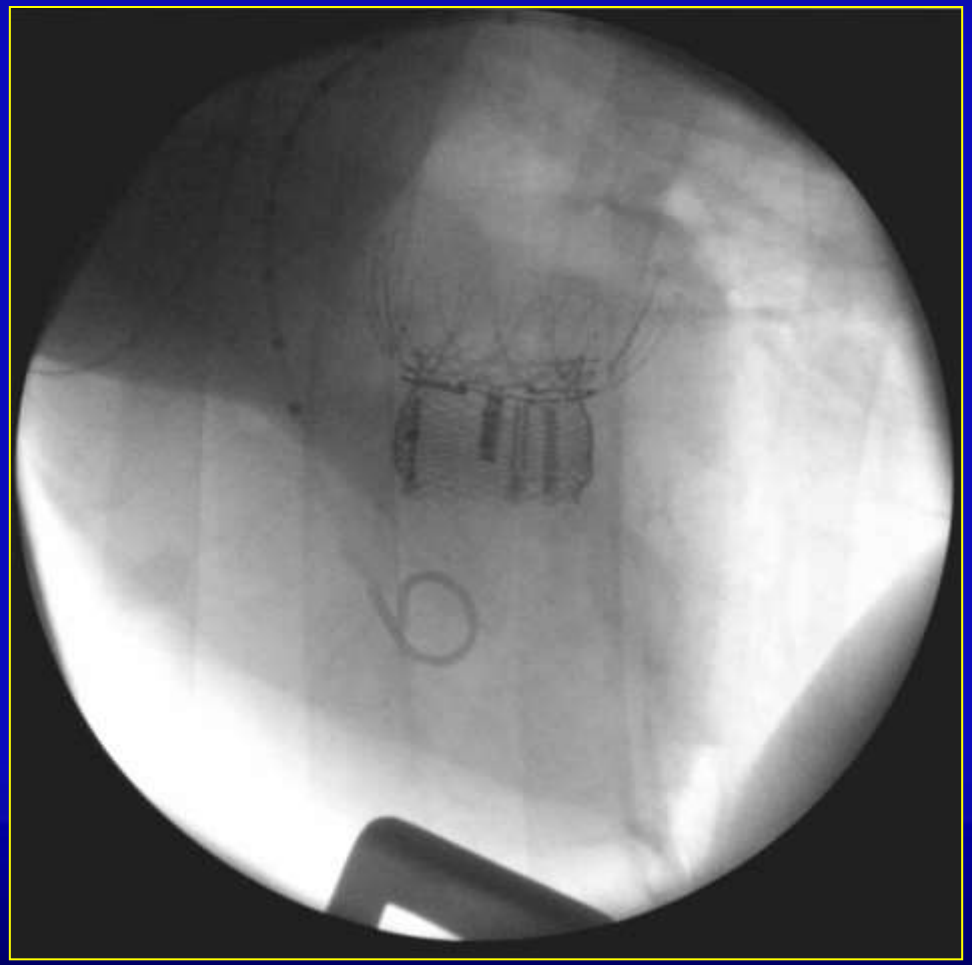
MValve™

- MValve is developing a similar approach to valve in valve, this time enabling *Trans- catheter* valve replacement, without a prior surgical prosthesis in the mitral position:
  - Step 1 – deployment of a proprietary valve support/dock device around the native mitral annulus
  - Step 2 – deployment of a transcatheter valve prosthesis within the Docking support system.

Advantages of the MValve™ System approach

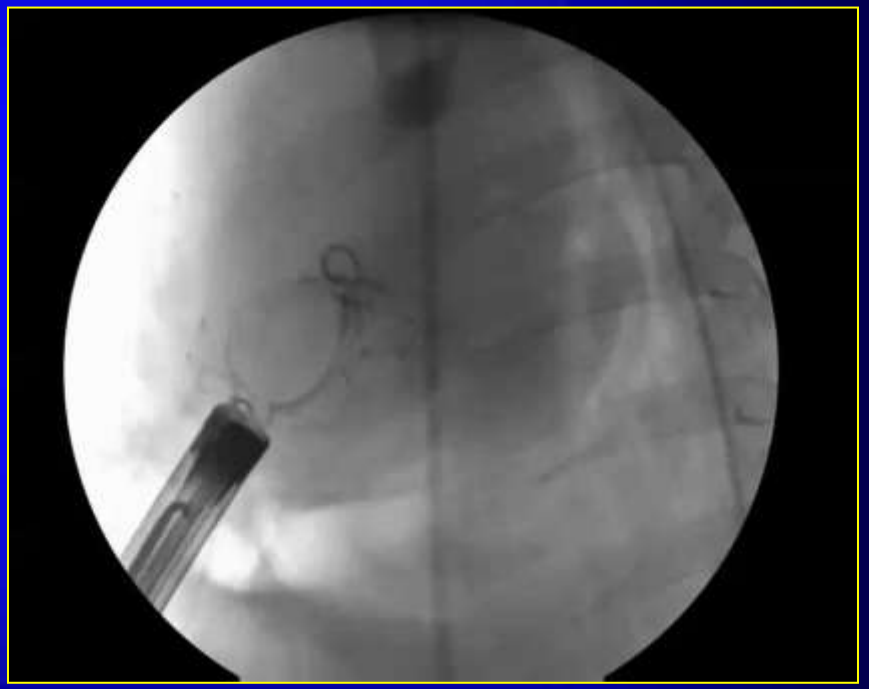
- The MValve™ dock is designed as a UNIVERSAL device fully compatible with a variety of commercially available as well as proprietary trans-catheter valves.
- The docking system enables accurate and optimal positioning of the valve prosthesis given it's:
  - Excellent fluoroscopic visibility
  - Sealing with minimal/no paravalvular leaks

Lotus™ in MValve™ (in vivo swine model)

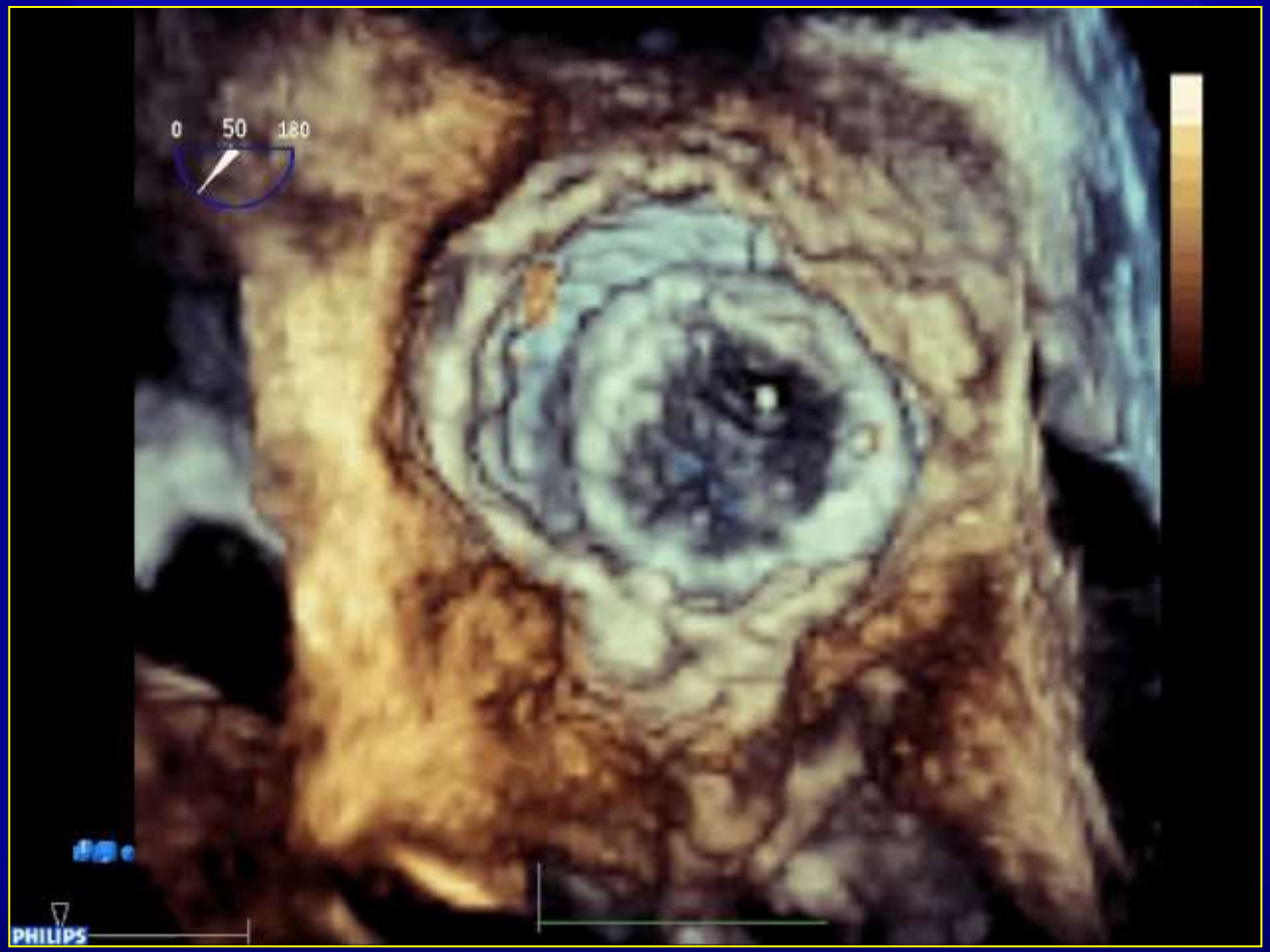


MValve™ System is fully retrievable

Using a custom retrieval system, the MValve™ dock can be re-captured, collapsed and fully withdrawn



First Human Experience



Caisson TMVR System

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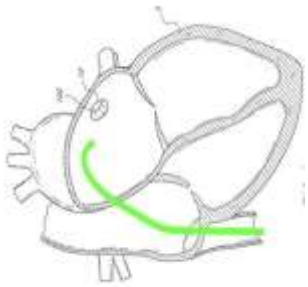
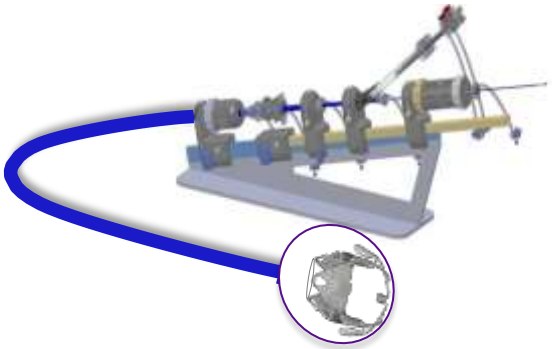
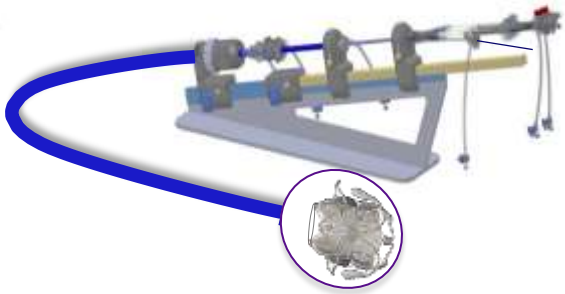




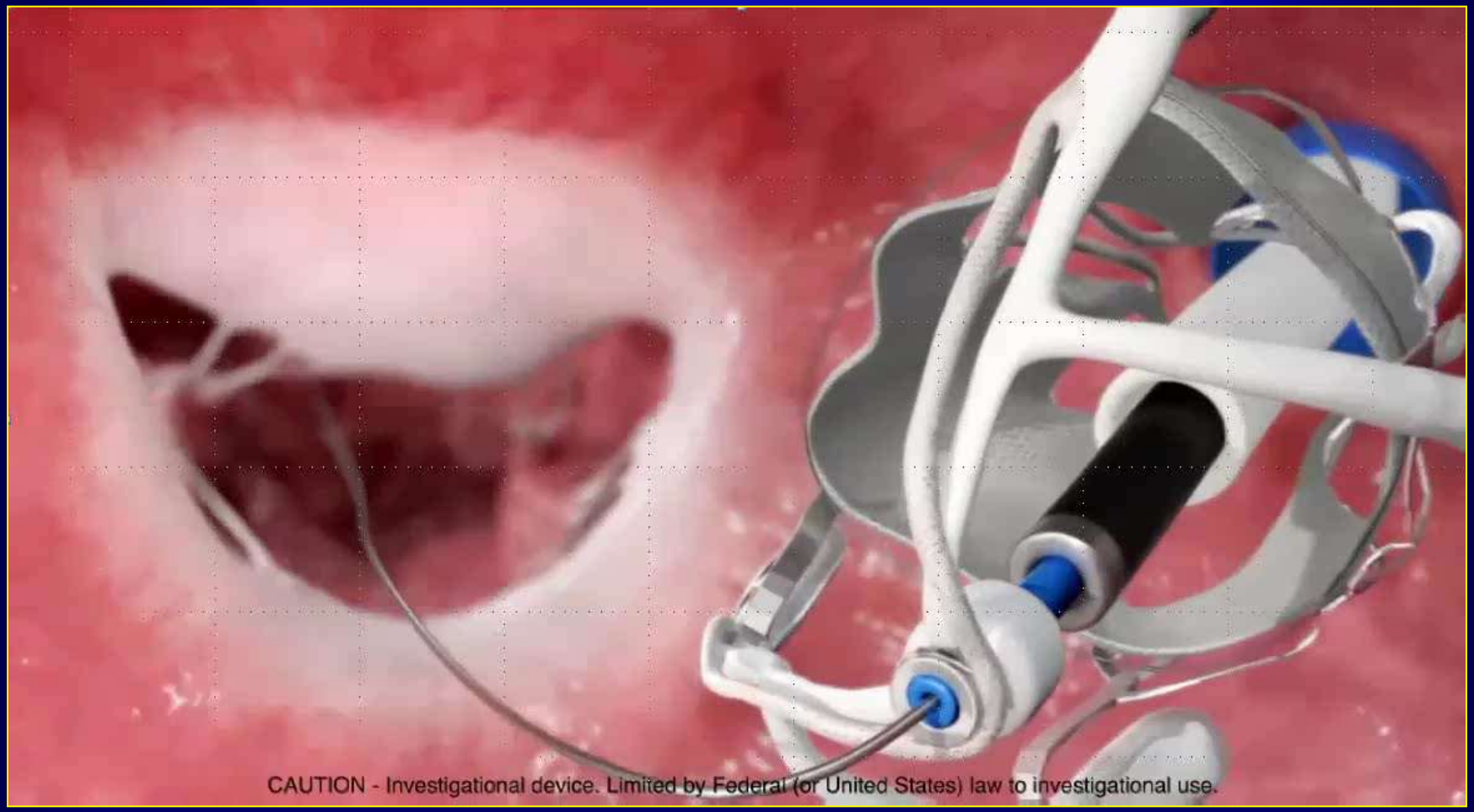


Transeptal System

Controlled Delivery

Repositionable/ Retrievable

Caisson TMVR System



FIH Outcomes (n=5)

Pt.	Days Since Implant	Status	Intra-Op PVL	30 day PVL	Device Embolization	Device Retrieval
02-001	(28)[1]	Deceased	Mild	None [2]	No	No
02-002	116	Alive	None	None	No	No
SAP	96	Alive	None	None	No	No
02-003	89	Alive	None	Mild	No	No
02-004	N/A[3]	Alive	N/A	N/A	No	Yes

1: Death day 28 following Colectomy
2: None on Day 25 TEE
3: Patient received MitraClip following Device Retrieval

FIH 30-Day Quantified Outcomes (n=5)

Pt.	Days Since Implant	NYHA: BL -> 30d	MR: BL -> 30d	EF: BL -> 30d
02-001	(28) [1]	III -> N/A	4 -> Trace [2]	30% -> N/A
02-002	116	III -> I	3+ -> 0	57% -> 68%
SAP	96	III -> II	4+ -> 0	28% -> 35%
02-003	89	III -> II	4+ -> 1+	58% -> 70%
02-004	N/A[3]	III -> N/A	4+ -> N/A	40% -> N/A

1: Day of death
2: Day 25 TEE
3: Patient received MitraClip following Device Retrieval

Cephea's TMVR System

(1) Antegrade Delivery Approach
- Trans-atrial and trans-septal

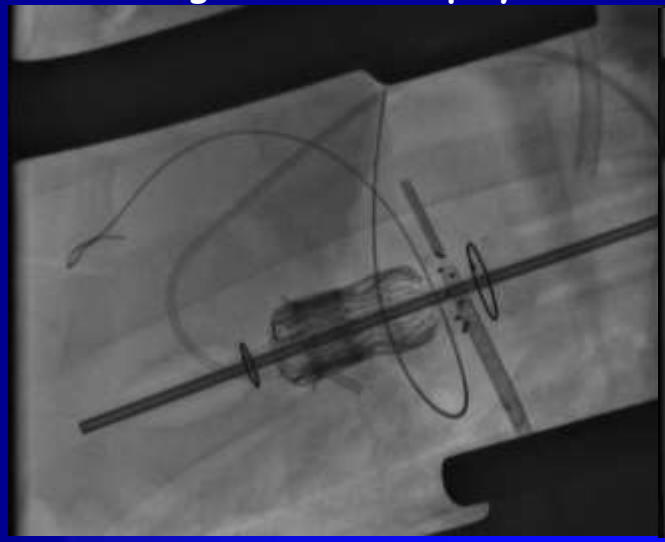
(2) Low Profile Frame Structure
- Sub-annular anchoring
- Minimal LVOT interference and sub-valvular injury
- Enables trans-septal delivery

(3) Suspension Leaflet Central Core
- Isolates leaflets function from dynamic annular compression
- Flexibility in design of anchoring elements

(4) Optimized AV Hemodynamics
- Smooth transition from LA to LV

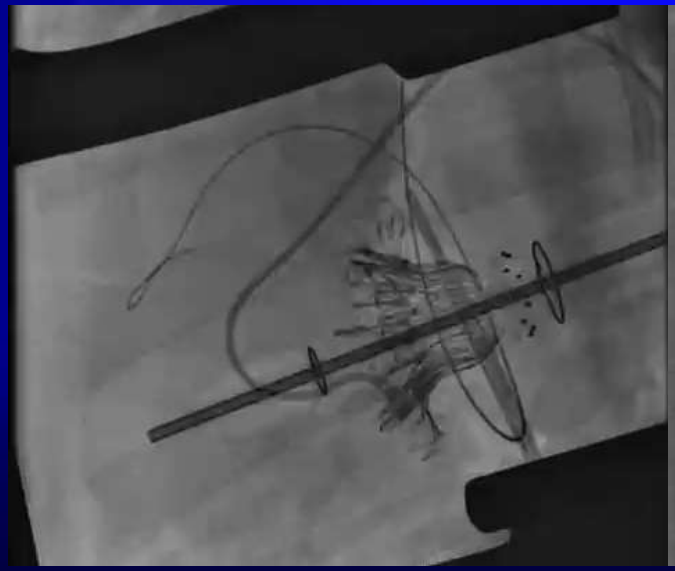
Cephea's TMVR System

Positioning + Partial Deployment

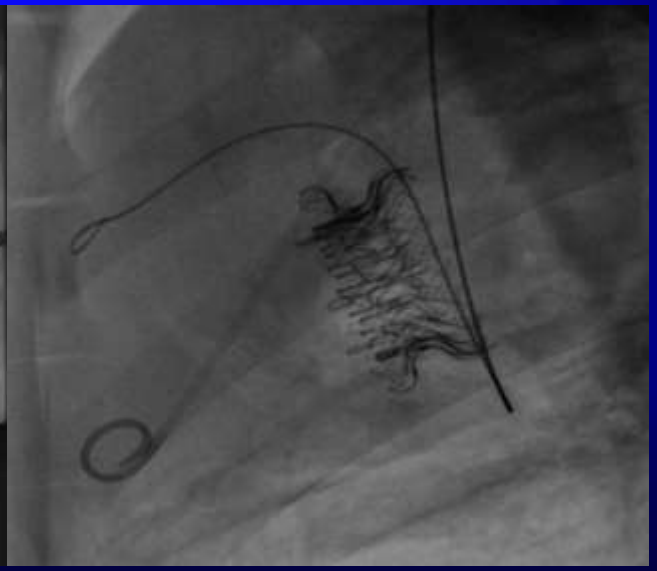


Ventricular Disk Deployment

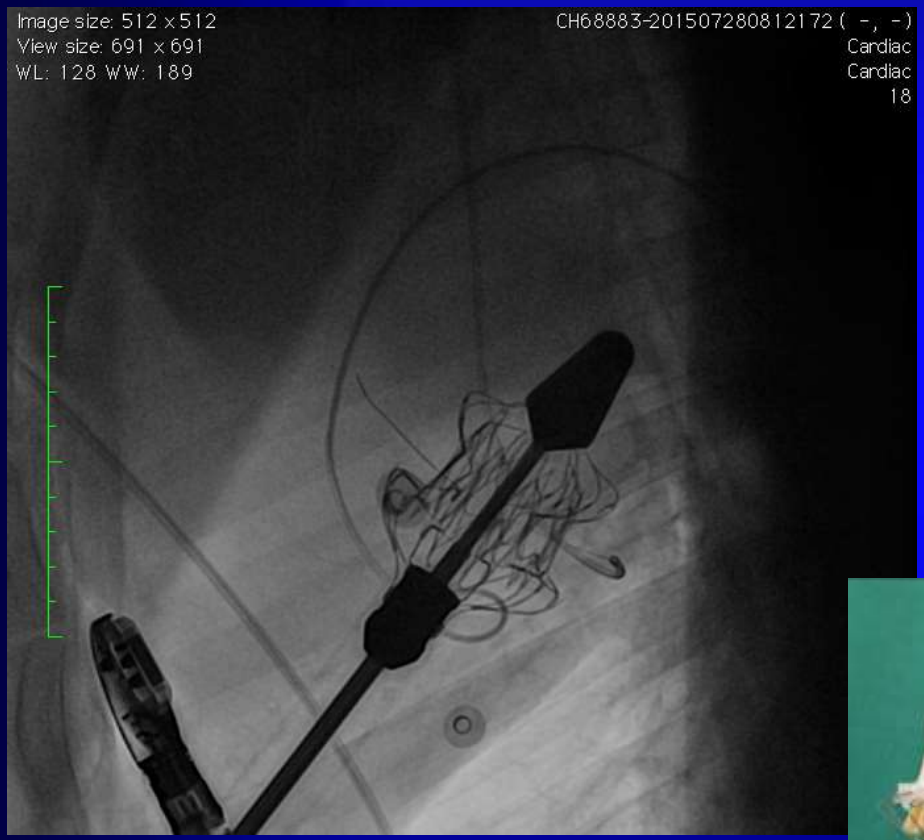
Full Device Deployment

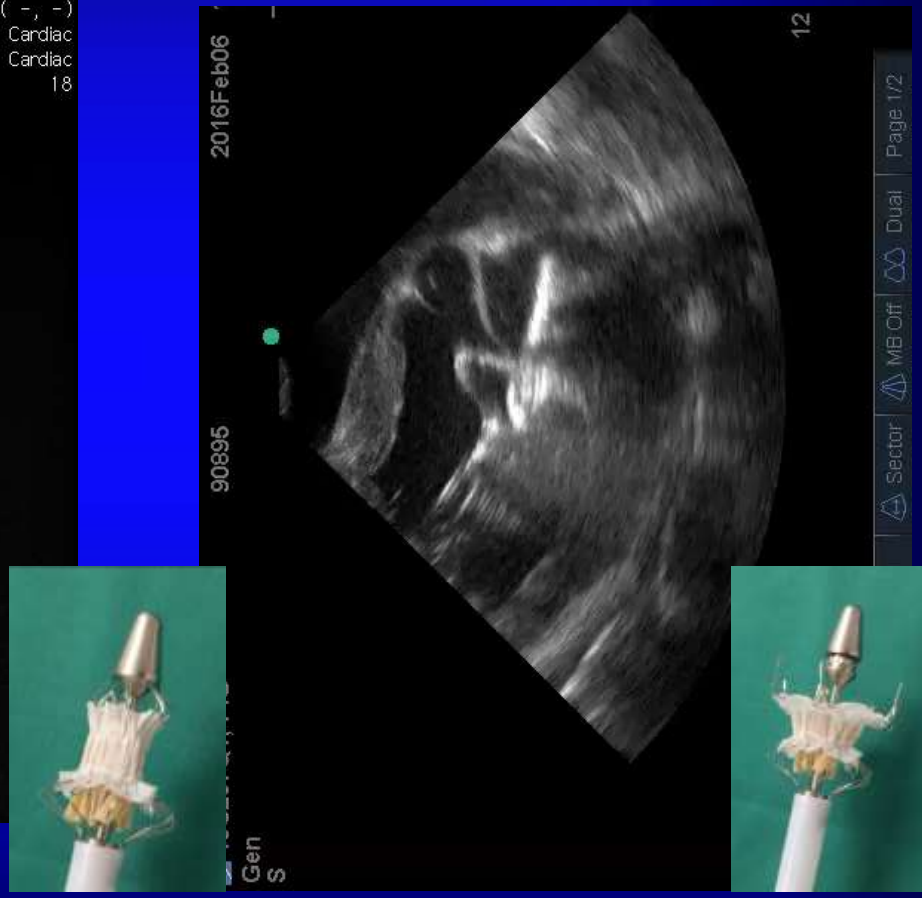


Post-Deployment



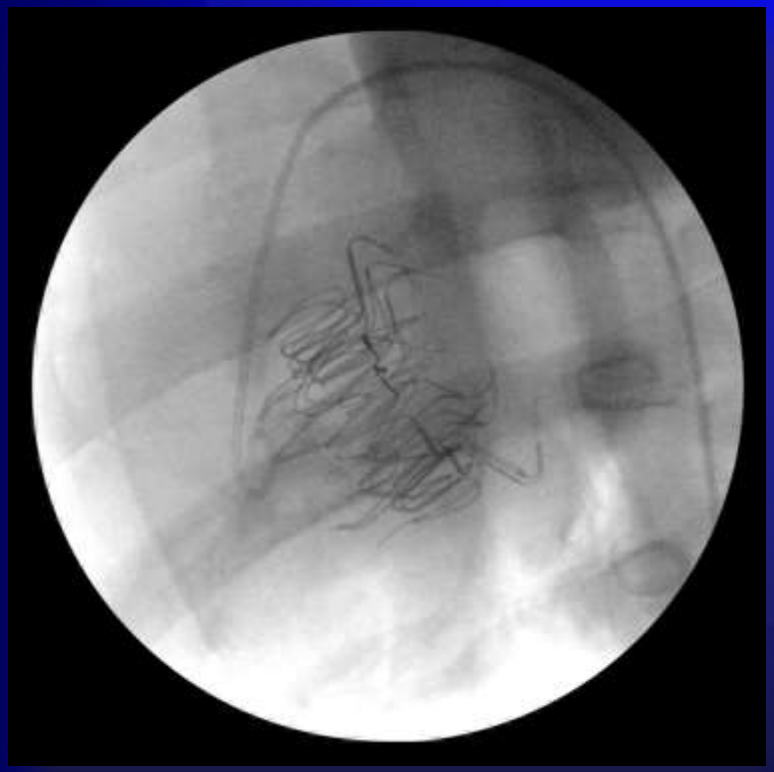
Accufit™ Sinomed TMVR System

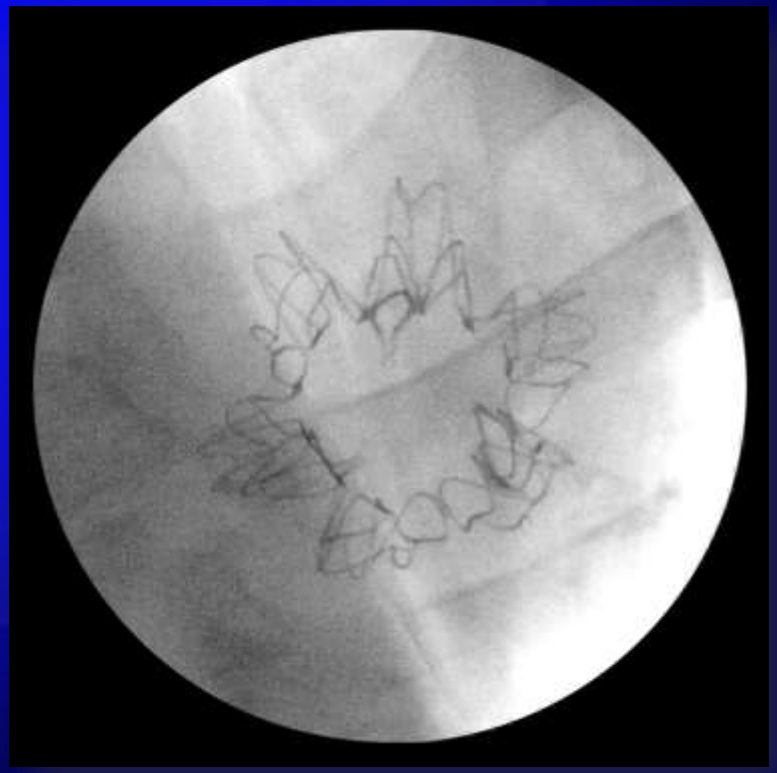




Accufit™ Sinomed TMVR System

Chronic animal experiments





THANK YOU