New York Transcatheter Valves 2018

PATIENT FOCUSED EVIDENCE-BASED APPROACH

Spotlight Session

Future of TMVR: The Next Generation of TMVR Beyond the MitraClip

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Eberhard Grube, MD

Physician Name	Company/Relationship
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Equity Interest:	InSeal Medical: E, AB, Cardiovalve: E, SB, Shockwave: E, AB Valve Medical: E, AB Mitra/Trialign E, AB, SB Ancora: e, AB, SB Imperative Medical: AB, E, SB

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G – Grant and or Research Support E – Equity Interests S – Salary, AB – Advisory Board
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Mitral Interventions

Mitral Regurgitation in the U.S.
Disease Prevalence

MR disease prevalence data are “deceptive”. Most patients with 1^{ry} MR are better served with definitive surgical repair and patients with 2^{ry} MR are often best treated with “optimal” or guideline-directed medical therapy!

The true MR population who would be justifiable candidates for interventional therapies is UNKNOWN!

Courtesy MB Leon

Treatment Options for MR 2017

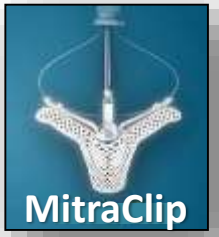
- Treatment options for high risk patients are limited and associated with poor outcomes compared to surgery
- Transcatheter therapies are needed for this large group of patients

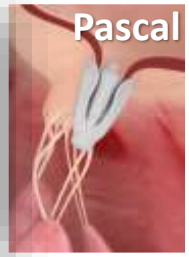
	Primary MR		Secondary MR	
	Low Surgical Risk	High Surgical Risk	Low Surgical Risk	High Surgical Risk
Surgical Repair	✓		✓	
Surgical Replacement	✓		✓	
Medical Therapy			✓	✓
MitraClip		✓		✓

A Toolbox of Treatment Options

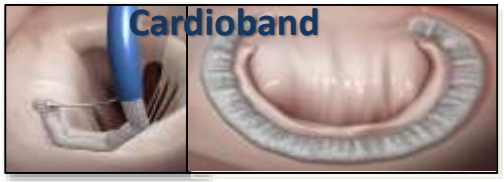
Multiple approaches are required to treat this complex and heterogeneous disease

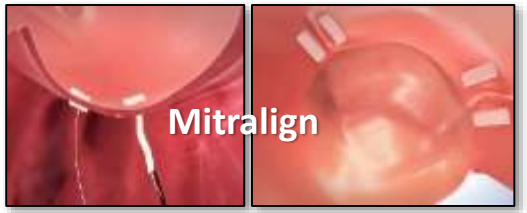
Leaflet Repair



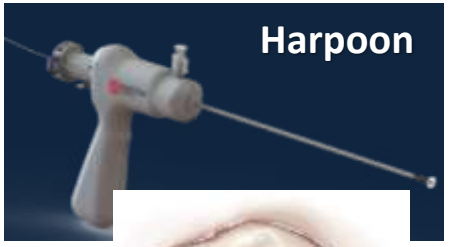


Annuloplasty

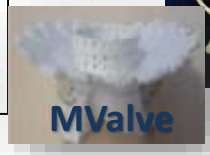




Chordal Replacement



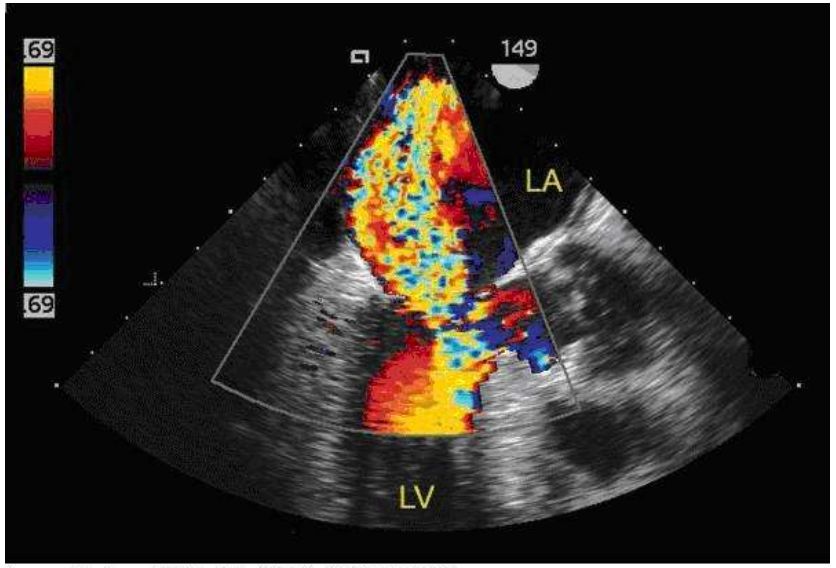
Valve Replacement



Mitral Cerclage

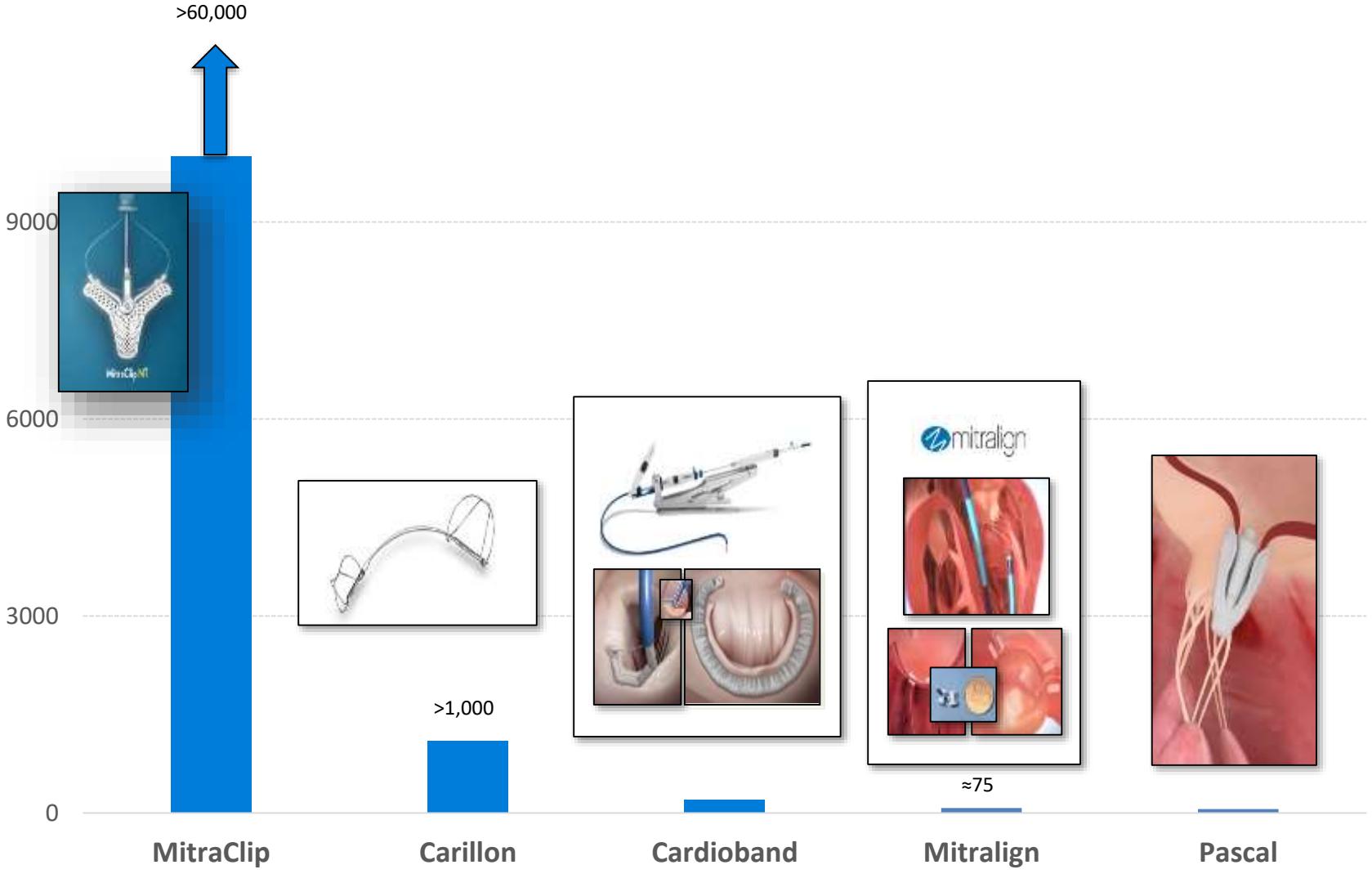
MitraClip and TMVR

Challenges and Failures



Hammerl H Journal für Kardiologie 2004; 11 (4): 176-177 ©

Mitral Repair Devices in Use



Severe FMR – Med Rx vs. MitraClip
MitraFR and COAPT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Percutaneous Repair or Medical Tr for Secondary Mitral Regurgita

J.-F. Obadia, D. Messika-Zeitoun, G. Leurent, B. Iung, G. Bonr
T. Lefèvre, C. Piot, F. Rouleau, D. Carrié, M. Nejjari, P. Ohlman
C. Saint Etienne, E. Teiger, L. Leroux, N. Karam, N. Michel, M. G
J.-N. Trochu, B. Cormier, X. Armoiry, F. Boutitie, D. Maucort-Bo
G. Samson, P. Guerin, A. Vahanian, and N. Mewton, for the MITRA-

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transcatheter Mitral-Valve Repair in Patients with Heart Failure

G.W. Stone, J.A. Lindenfeld, W.T. Abraham, S. Kar, D.S. Lim, J.M. Mishell, B. Whisenant, P.A. Grayburn, M. Rinaldi, S.R. Kapadia, V. Rajagopal, I.J. Sarembock, A. Brieke, S.O. Marx, D.J. Cohen, N.J. Weissman, and M.J. Mack, for the COAPT Investigators*

Is COAPT a Rising Tide That Floats ALL Boats?
OR…
Will It Float Only One Boat?

Courtesy M.Mack TCT 2018

Mitra-FR vs COAPT
Words of Caution

With TMVR at the horizon, in patients suitable for TMVR, only clips with perfect results should be left (applies also for the first clip of a procedure!)

Mitra-FR vs COAPT
Words of Caution

- Clip catheter too unflexible, length of catheter to0 static, therefore localization of transseptal puncture (too) is crucial
- Clip arms too small
- Clip arms do not work independently
- ***Once the clip is placed, no other options than surgery remains***

Mitra-FR vs COAPT

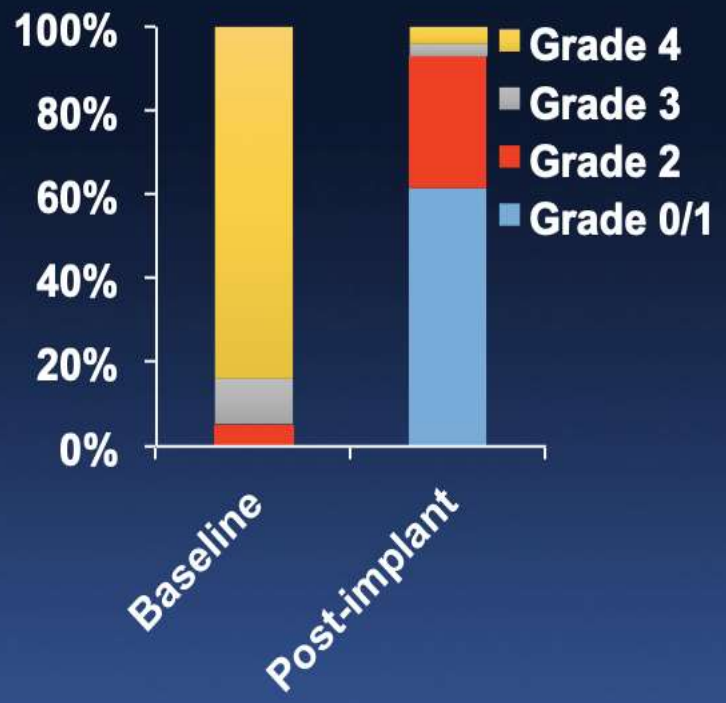
What did we learn?

1. MitraClip is safe and MitraClip reduces MR in this patient population
2. Patient selection and timing of procedure is key
3. COAPT confirms synergy of drug and device therapies in HF patients
4. Competence centers are needed to ensure proper implantation expertise and appropriate HF treatment before, during and after the procedure
5. The results of COAPT are not easily „generaliseable“ to the whole spectrum of MR therapies.

STS/ACC MitraClip TVT Registry

STS/ACC MitraClip TVT Registry

2,952 pts enrolled thru Sept, 2015; linked records to CMS claims data



40% with post-procedural MR ≥ 2

SLDA, 1.5%

In-hospital mortality = 2.7%

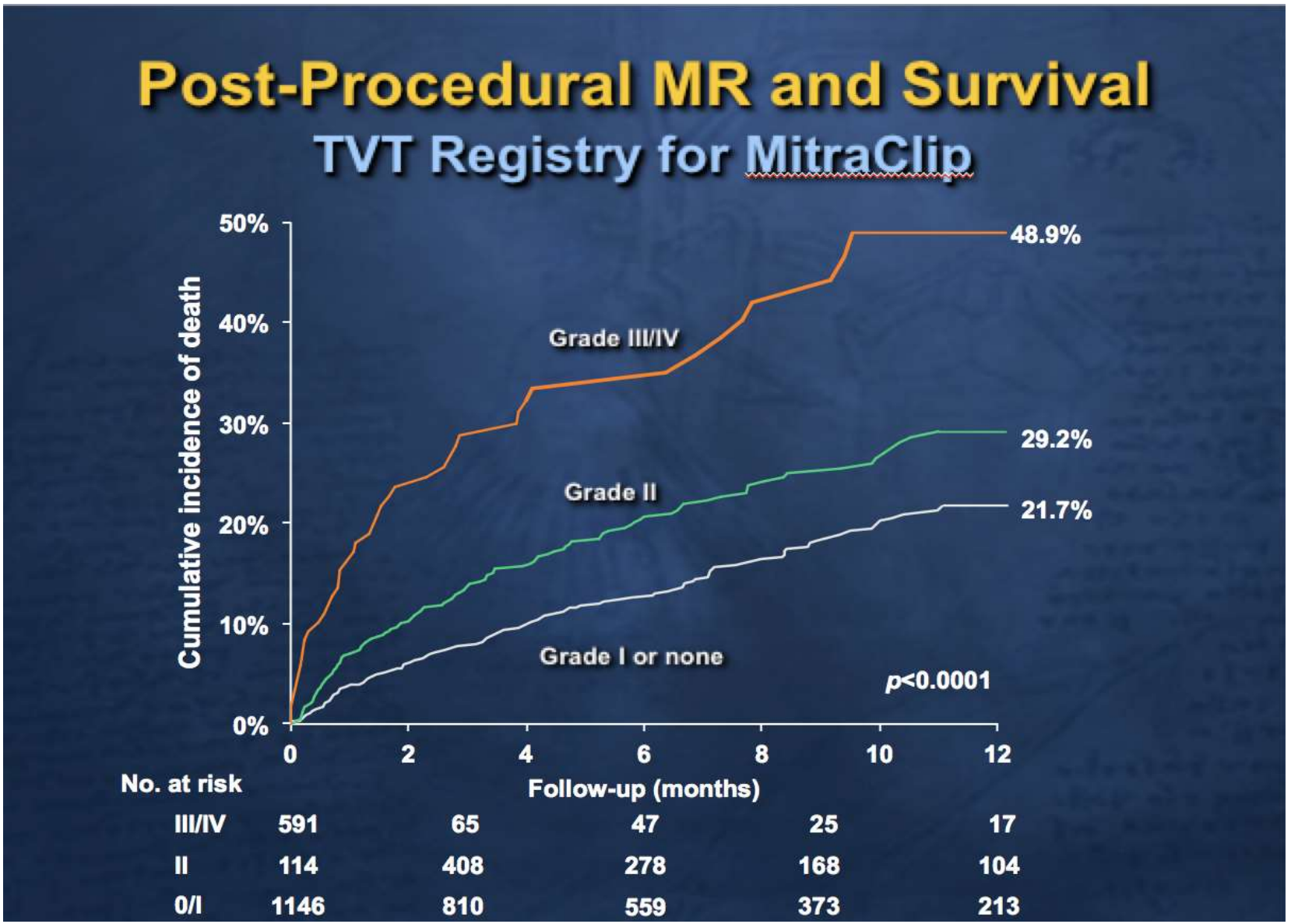
85.9% discharged home

Median LOS, 2 days (1, 5 days)

Acute procedure success = 91.8%

Post-Procedural MR and Survival

TVT Registry for MitraClip



P.Soraija

Mitra-FR vs COAPT

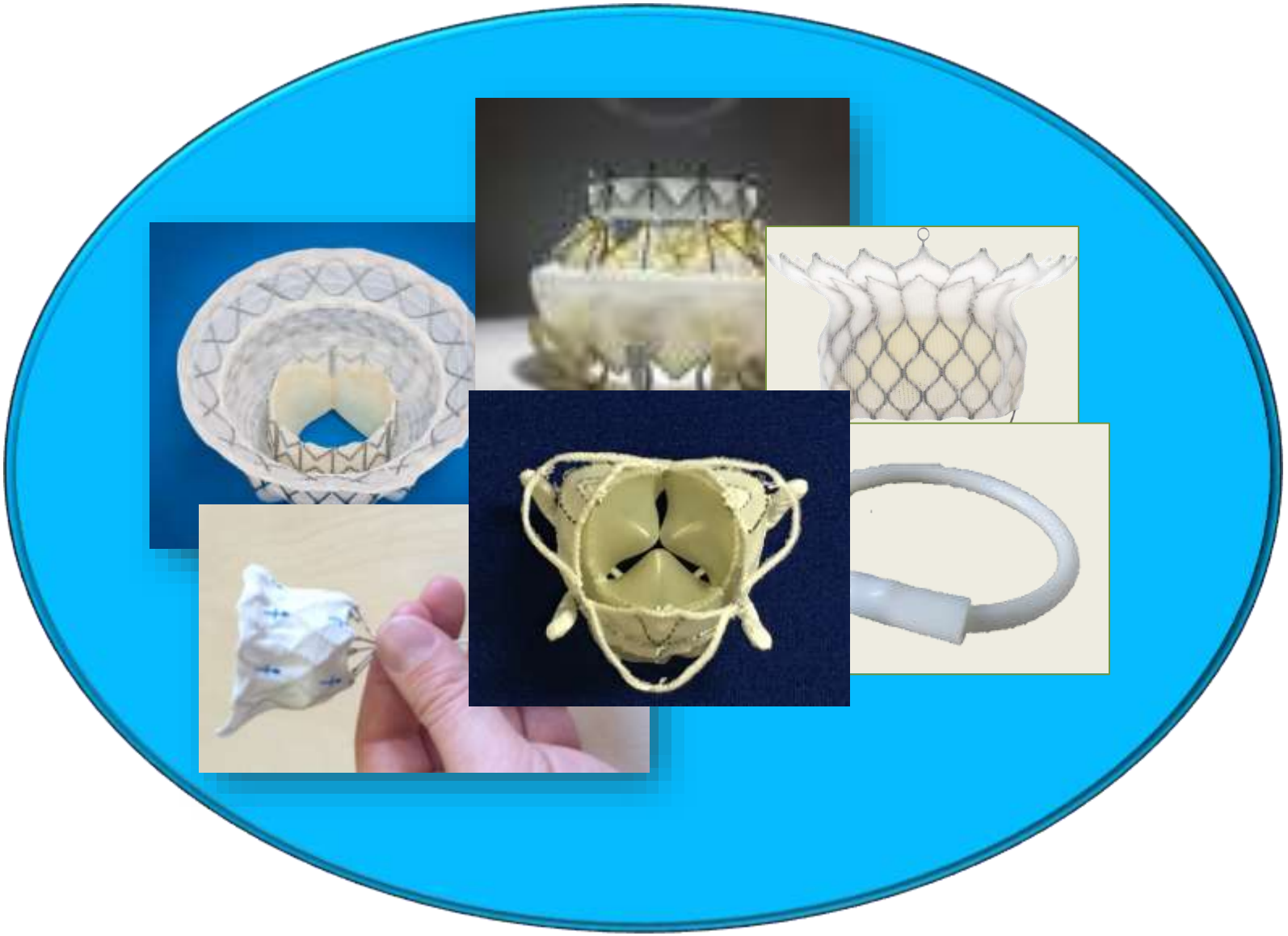
What do we still need to know?

- How do we better implement heart teams, surgeons and cardiologists together
- How do we more precisley standardize the procedure (assess EROA , 3D imaging, # of clips etc)
- What are effects based on post-clip gradient and MVA?
- What is „optimal medical management“?
- Does this work (or not work) for other MV repair therapies?

The „Mitral World“ after COAPT

- Increased optimism with MV therapies
- Trial recruitement for other devices will become problematc
- If the Clip becomes standard of care it might become comparator for other mitral innovations
- HF specialists are now more actively involved
- Safety of the Clip procedure will be difficult to match
- The results of the COAPT trial are difficult to replicate in all patients. More devices are needed.
- Surgery remains an option for DMR in younger patients and more complex anatomies....

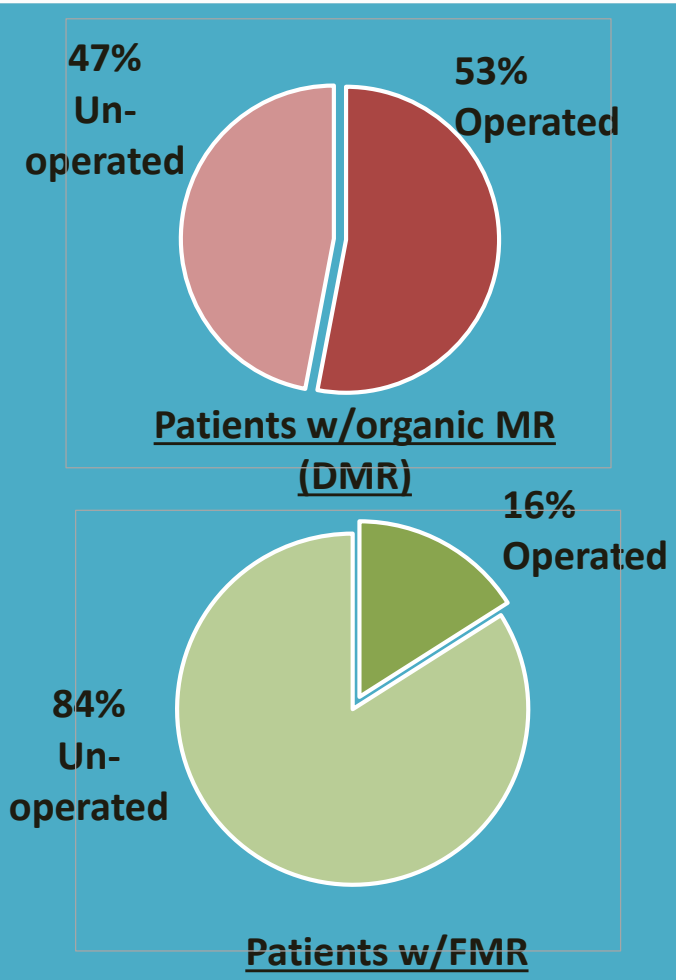
Device Parade MV Replacement (TMVR)



Transcatheter MVR
Potential advantages (replacement vs. repair)

- Applicable to primary and secondary MR, regardless of anatomy or pathology
- Ease of implantation
- Reliable elimination of MR
- Greater durability

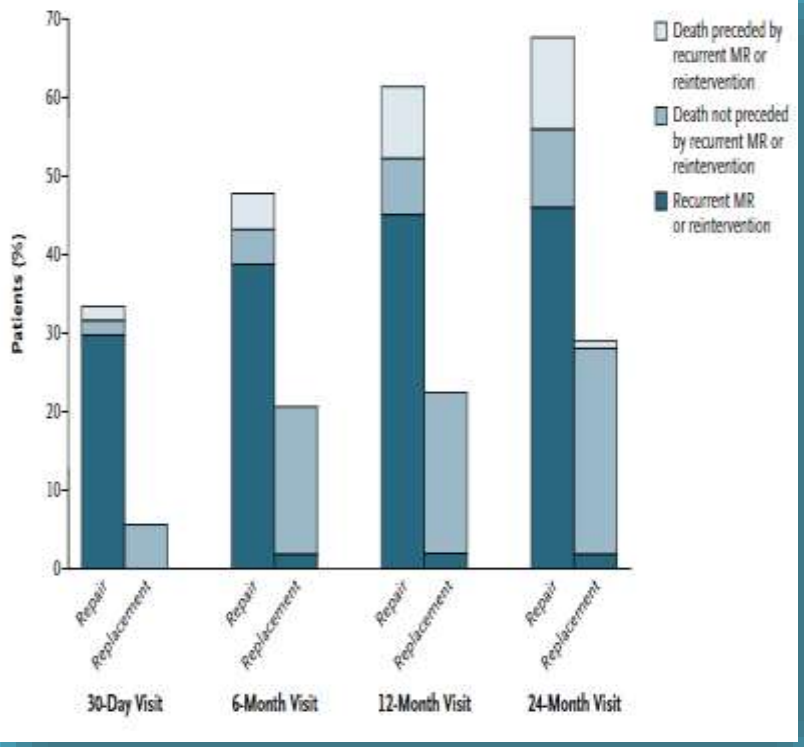
Why TMVR?

#	RATIONALE	EVIDENCE
1	**TMVR is etiology agnostic, with FMR being the larger unmet need – 80/20 split today**	
2	Evidence shows high recurrent MR with surgical repair for ischemic MR patients	
3	TMV repair that leaves residual MR has a high mortality penalty	

David S. Bach et al. JACC Vol. 54, No. 9, 2009

Why TMVR?

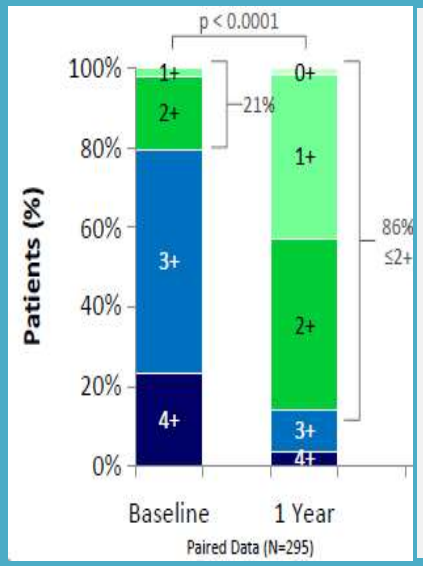
#	RATIONALE	EVIDENCE
1	TMVR is etiology agnostic, with FMR being the larger unmet need	**59%** of the patients who underwent surgical repair had recurrent MR at 2 years
2	**Evidence shows high recurrent MR with surgical repair for ischemic MR patients**	
3	TMV repair that leaves residual MR has a high mortality penalty	



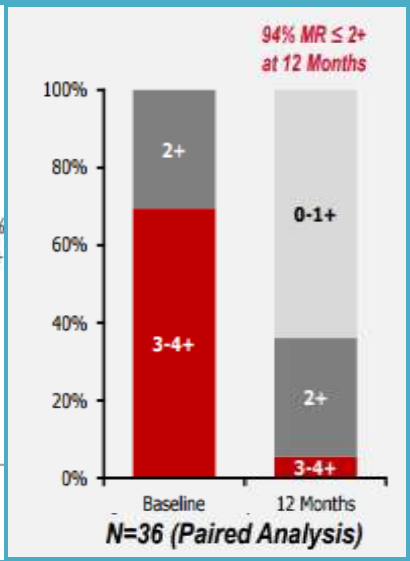
Goldstein, et al. 2015

Why TMVR?

#	RATIONALE	EVIDENCE
1	TMVR is etiology agnostic, with FMR being the larger unmet need	Current transcatheter repair technologies are leaving residual MR in a large group of patients
2	Evidence shows high recurrent MR with surgical repair for ischemic MR patients	
3	**TMV repair that leaves residual MR has a high mortality penalty**	



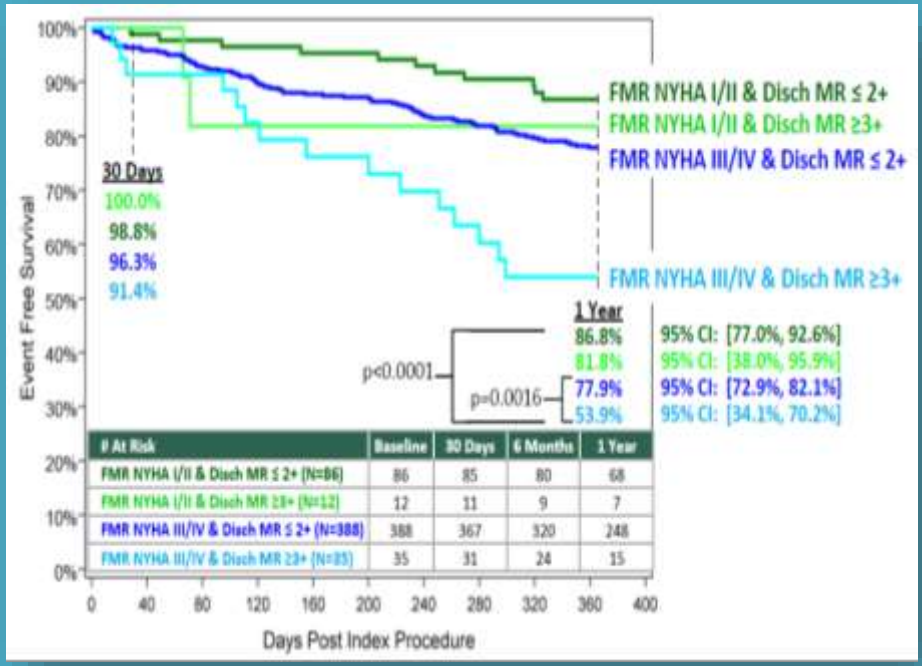
MITRACLIP[1]



CARDIOBAND[2]

1. Saibal Kar, ESC 2016
2. Thourani, TCT

Why TMVR?

#	RATIONALE	EVIDENCE
1	TMVR is etiology agnostic, with FMR being the larger unmet need	**46%** Mortality at 1 year for NYHA III/IV FMR Patients with discharge MR ≥ 3+
2	Evidence shows high recurrent MR with surgical repair for ischemic MR patients	
3	**TMV repair that leaves residual MR has a high mortality penalty**	**EVEREST II REALISM Continued Access Study**

Saibal Kar, ESC 2016

The Challenges….

Technical and Anatomical Challenges

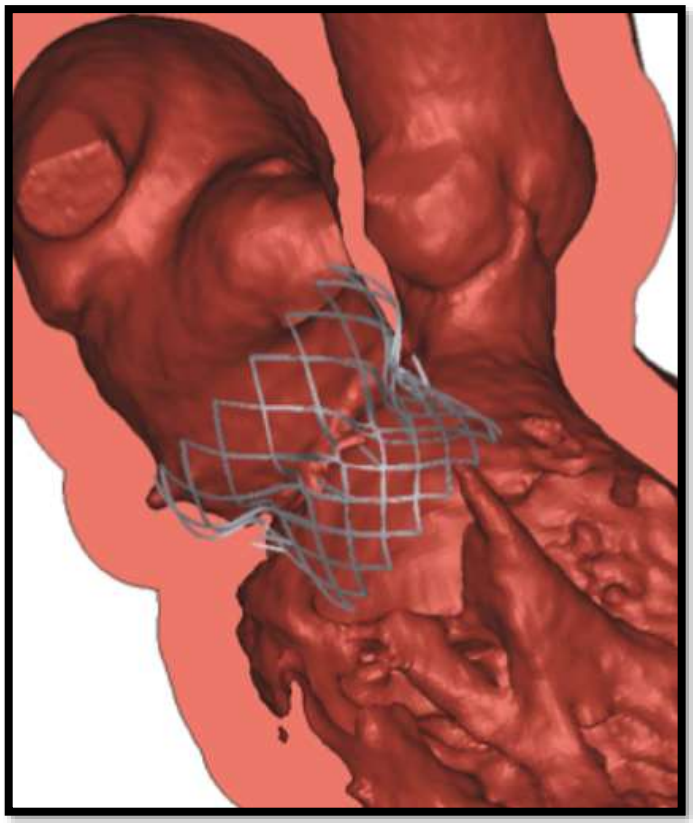
- ***High variability and instability of the anatomy***
  - No defined structure for anchoring (like calcified annulus in TAVI)
  - Dilatation of the annulus creates big range of sizes
- ***Complex apparatus with multi intra-dependencies:***
  - LVOT, SAM, Tethering, Continuous dilatation, complex flow and motion patterns through the cardiac cycle.
- ***Delivery challenges:***
  - Trans-apical - thin and dilated ventricles
  - Retrograde – size, navigation, LV interaction
  - Trans septal – size, navigation
- ***Two pathologies: DMR and FMR***

Design Targets

Anchor

Seal

Avoid interference



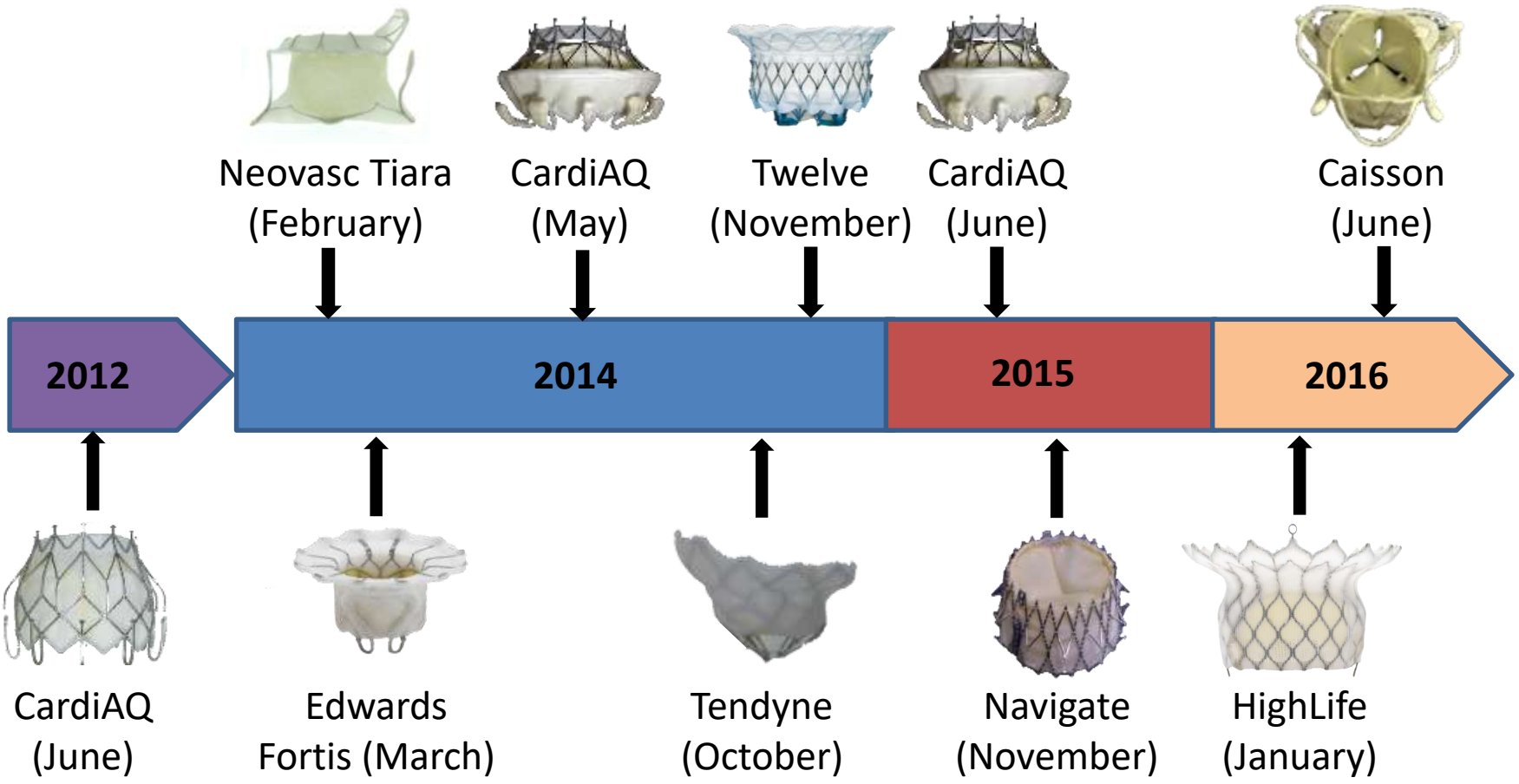
Adaptable

Recapture

Durable

User friendly

Transcatheter mitral valve replacement:
First-in-Human timeline



TMVR: Current Human Experience

Technologies	Reported Human Experience
ABT Tendyne 	100+
MDT Intrepid 	70+
EW M3 Sapien 	10+
EW CardiAQ 	23+
Neovasc Tiara 	52+
Caisson 	17+
HighLife 	15+
Cardiovalve 	5+

TCMV replacement devices

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

Tendyne Abbott

SATURN TMVR

Valtech CardioValve

Caisson

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

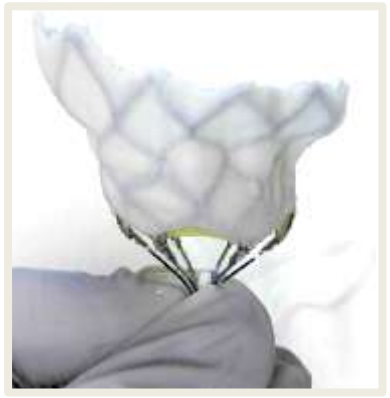
Mitral Interventions

Tendyne TMVR

Mitral Interventions

Tendyne TMVR

- Tri-leaflet porcine pericardial valve
- Self-expanding nitinol double frame
  - D-shaped outer frame, anterior cuff
- Large valve size matrix
  - Single inner valve size
  - Multiple outer frame sizes
- Large Effective Orifice Area (>3.0cm^2)
- ***Transapical access, valve tethered to apex***
  - ***Adjustable tension provides valve stability***
- Apical Pad assists in access closure
- ***Valve fully retrievable and repositionable***



Mitral Interventions

Tendyne TMVR

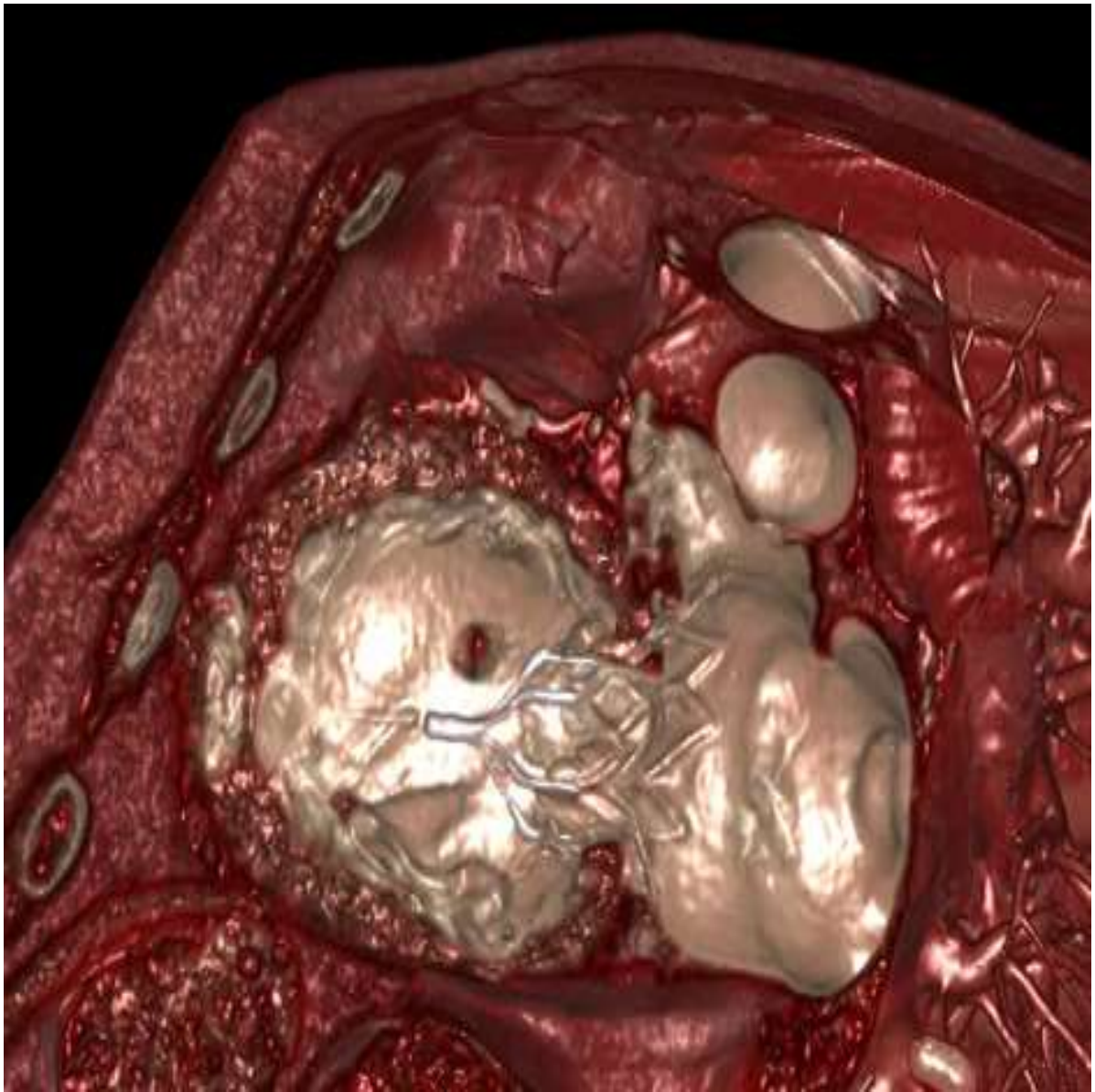


Image courtesy of D- Muller, St Vincent's Hospit

Mitral Interventions
Tendyne TMVR
Global Experience

158 patients

- **135 treated in Expanded Feasibility/CE Mark Study**
- **23 additional under Compassionate Use**

EFS Patient Distribution

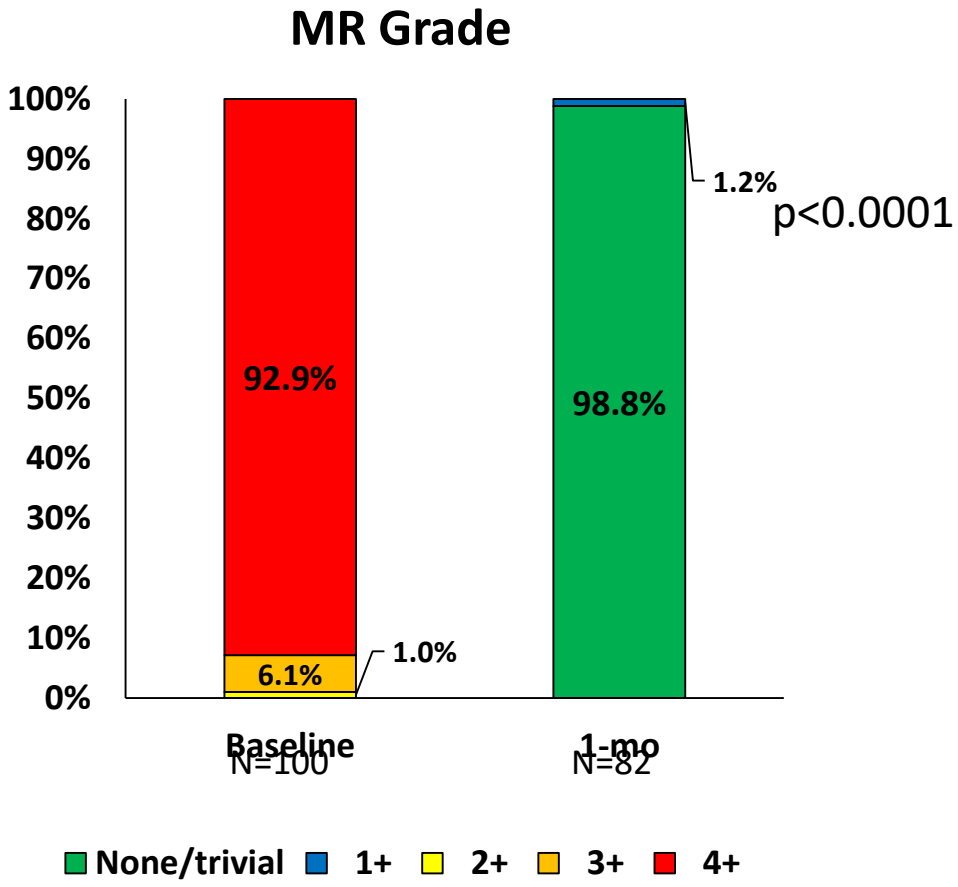
United States
N=75

Europe
N=39

Australia
N=21

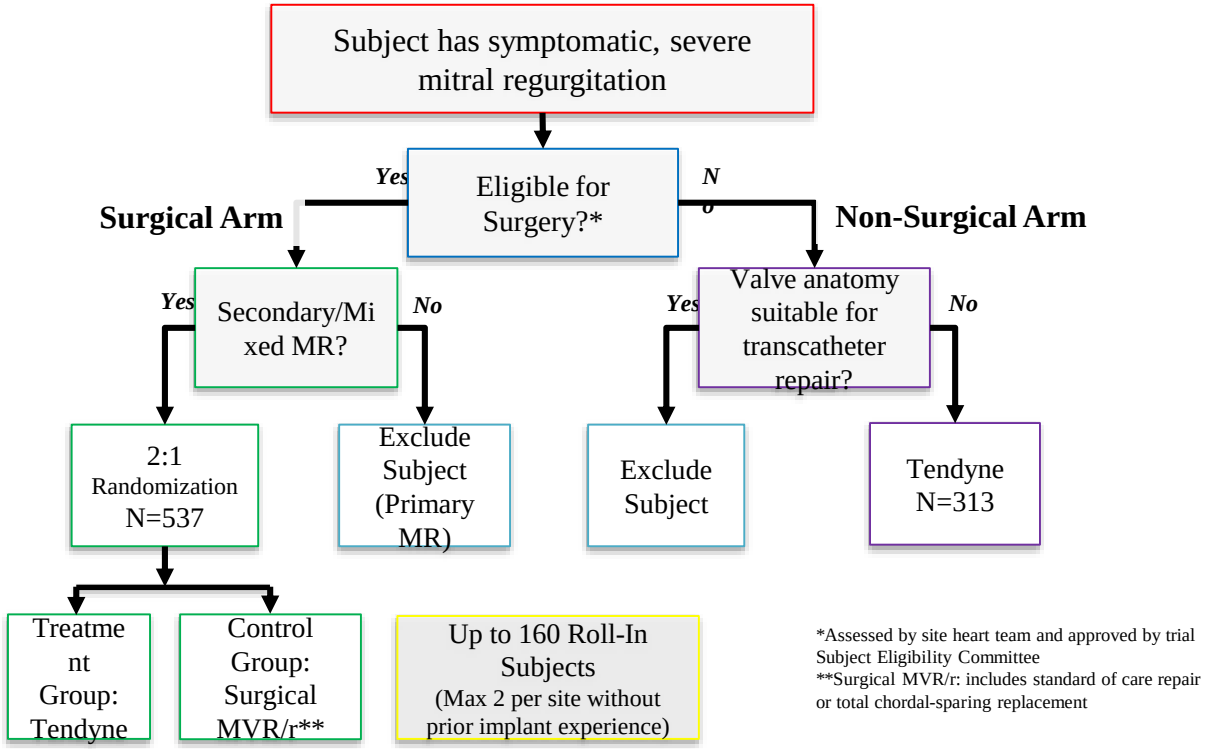
Tendyne CE Mark Study: MR Reduction

99.0% ≥ 3+ MR at baseline to 98.8% none/trace at 30 days
No patients with more than mild (1+) MR at 30 days



SUMMIT

SUMMIT Trial Design



*Assessed by site heart team and approved by trial Subject Eligibility Committee
**Surgical MVR/r: includes standard of care repair or total chordal-sparing replacement

The Tendyne MAC Study

- **Objective**
  - ***To evaluate the use of Tendyne TMVR in the treatment of mitral regurgitation in patients with severe mitral annular calcification (MAC)***
- **Type/Design**
  - Prospective, single-arm, multi-center
  - Up to 10 sites, up to 30 subjects
- **Principal Investigators**
  - Paul Sorajja, MD
  - Vinod Thourani, MD
- **Endpoints**
  - Primary Safety – Freedom from device or procedure-related SAEs at 30 days
  - Other – Technical, Patient, Device (MVARC-defined)

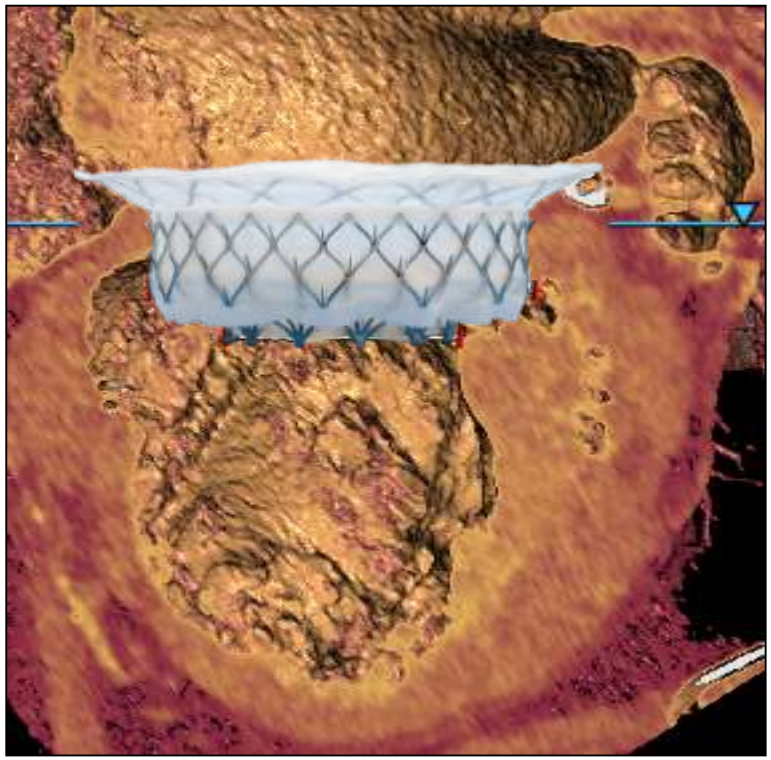
TENDYNE

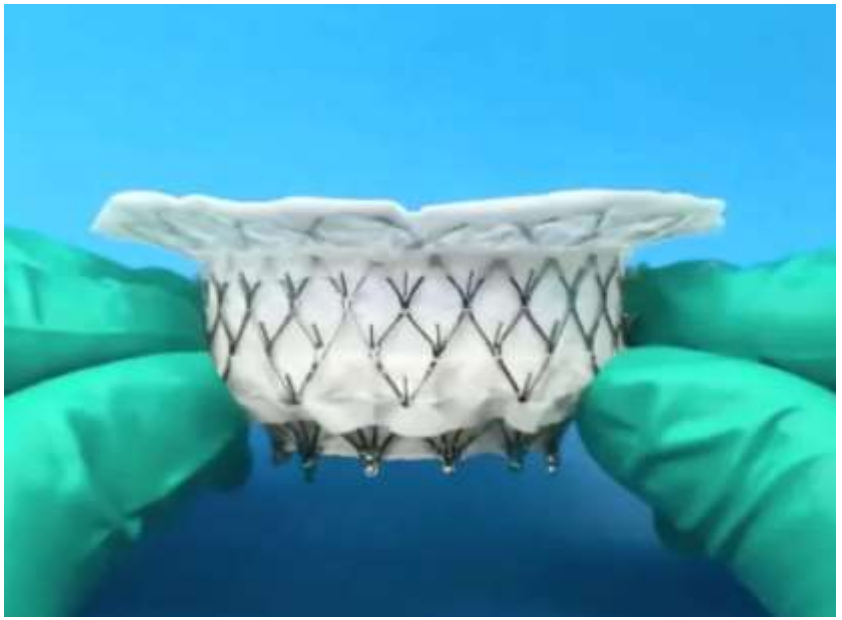
CS8005-P
MAC Feasibility Study
Feasibility study of the Tendyne Mitral Valve System in Mitral Annular Calcification

IDE Number	G140240
Version Number	Version A
Date	25APR2018
National Primary Investigator (Interventional Cardiologist)	**Paul Sorajja, M.D., FACC, FAHA, FSCAI** **Director, Center for Valve and Structural Heart Disease** Minneapolis Heart Institute - Abbott Northwestern Hospital
National Primary Investigator (Cardiothoracic Surgeon)	**Vinod Thourani, M.D., FACS, FACC** **Professor of Surgery** **Chair, Department of Cardiac Surgery** MedStar Heart and Vascular Institute Washington Hospital Center
Study Type	Prospective, single-arm, multicenter feasibility clinical study of the Tendyne Mitral Valve System
Sponsor	Tendyne Holdings, Inc. (a subsidiary of Abbott Vascular, Inc.) 177 County Road B East St. Paul, MN 55117

Mitral Interventions

Intrepid TMVR

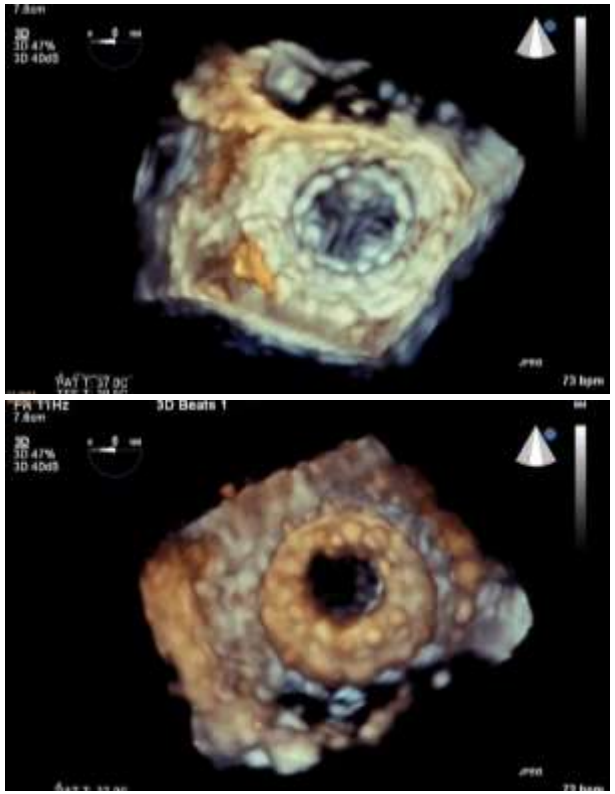


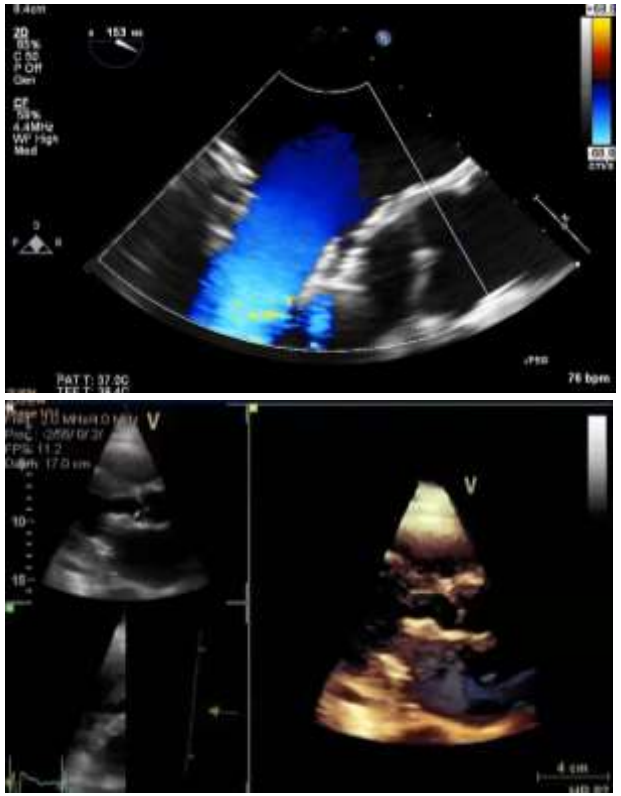


Mitral Interventions

Intrepid TMVR

Case Example





Intrepid TMVR
Global Feasibility and U.S. EFS Studies
Consecutive Cases - Mortality (n=50)

Study Aim

- To determine the feasibility of TMVR with the Intrepid valve

Analysis Cohort

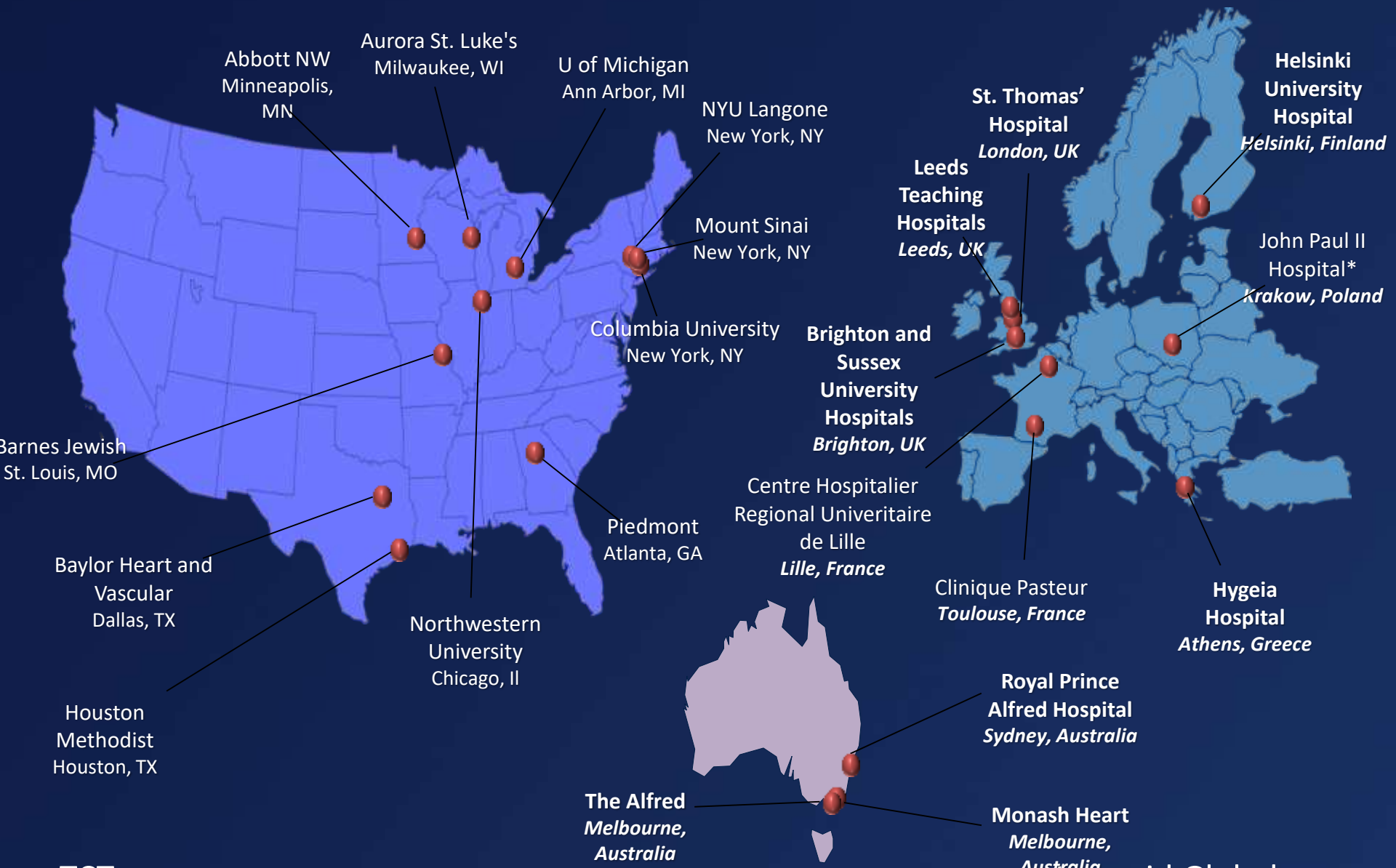
- The initial 50 consecutively enrolled patients in the pilot study

  (06 May 2015 to 21 July 2017)

Clinical Endpoints

- MVARC criteria
- An independent physician committee reviewed adverse clinical events, including mortality, stroke, myocardial infarction, bleeding, re-hospitalization, and reoperation

Participating Sites

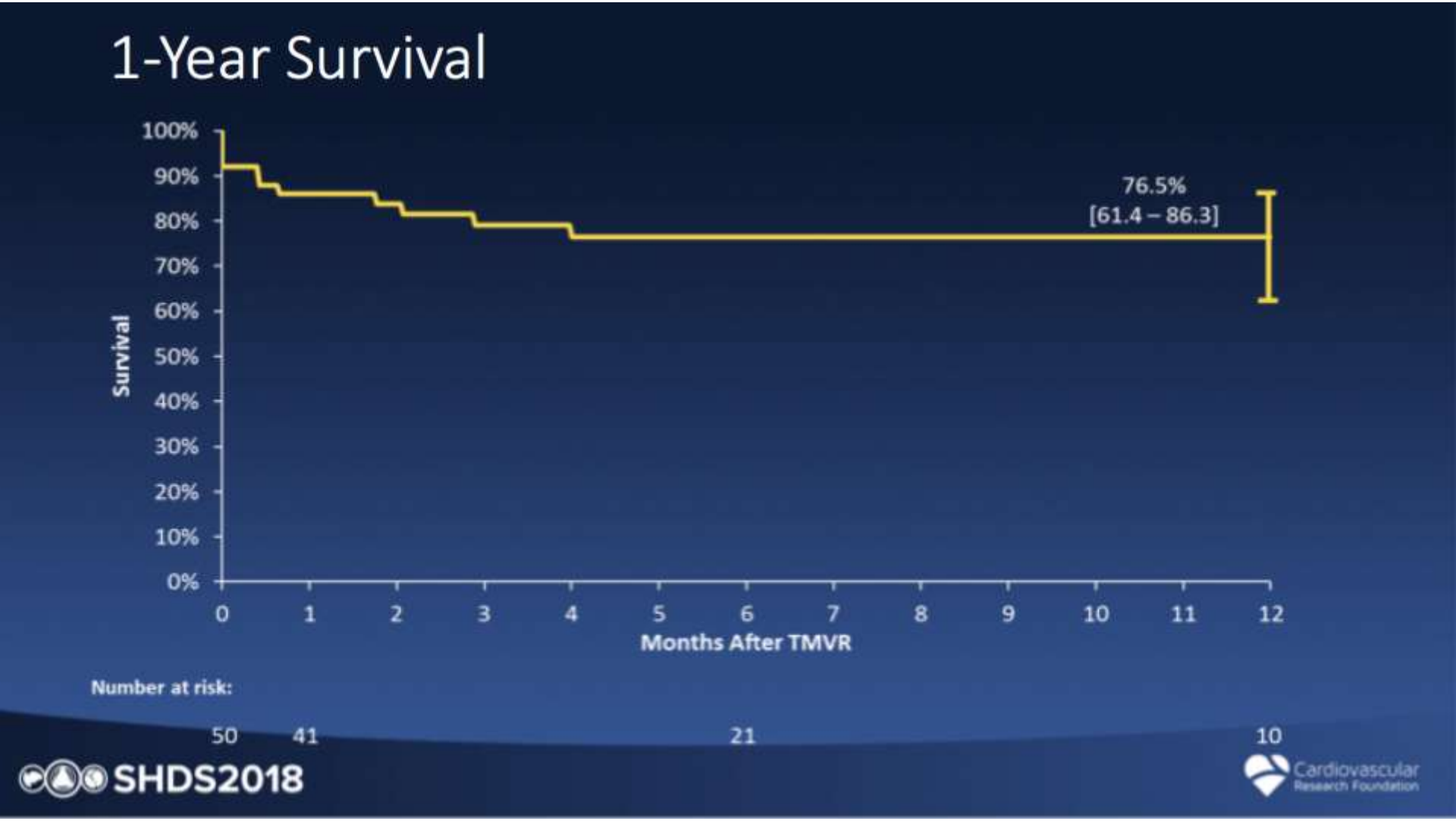


TCT.

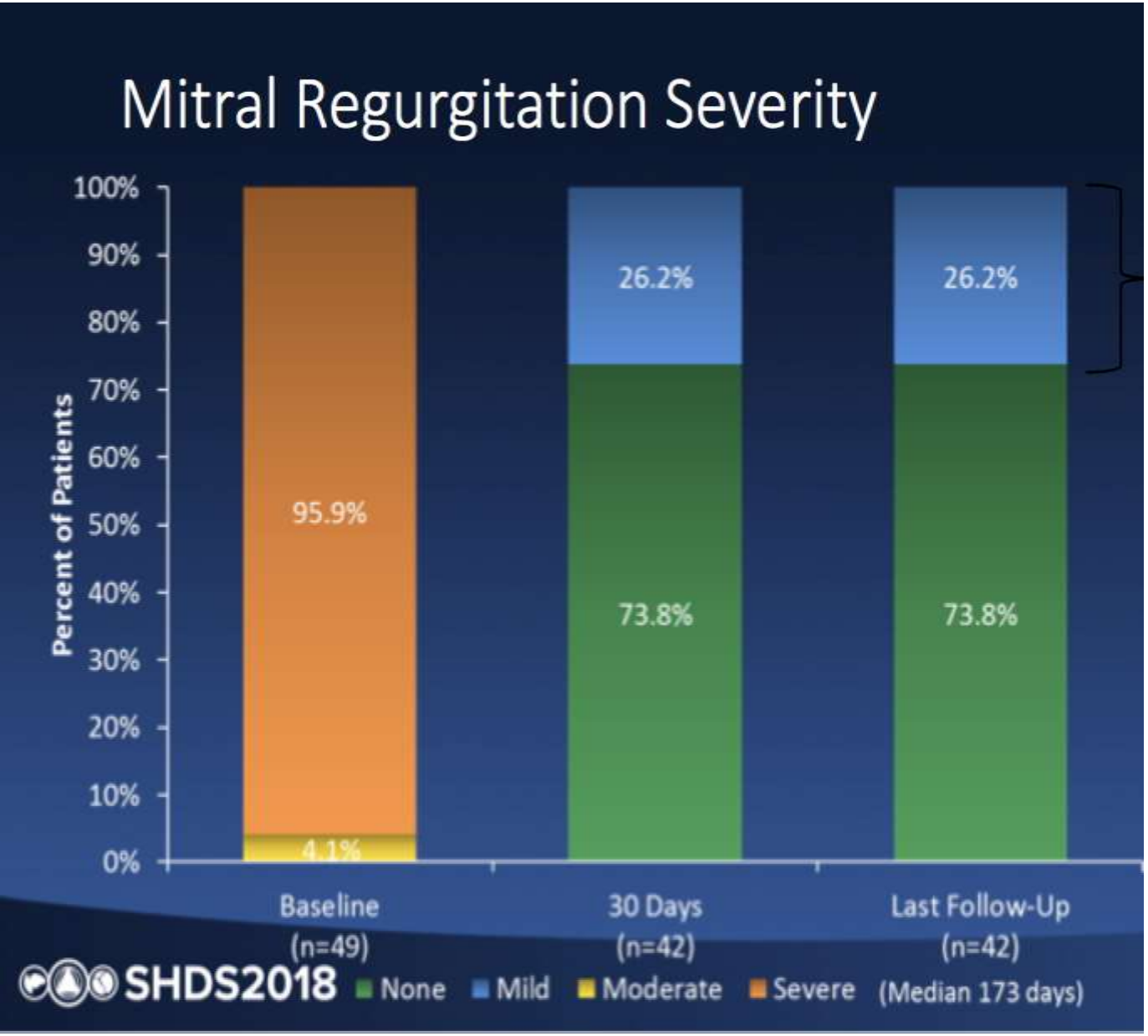
*First in human

Intrepid Global

1-Year Survival



Mitral Regurgitation Severity



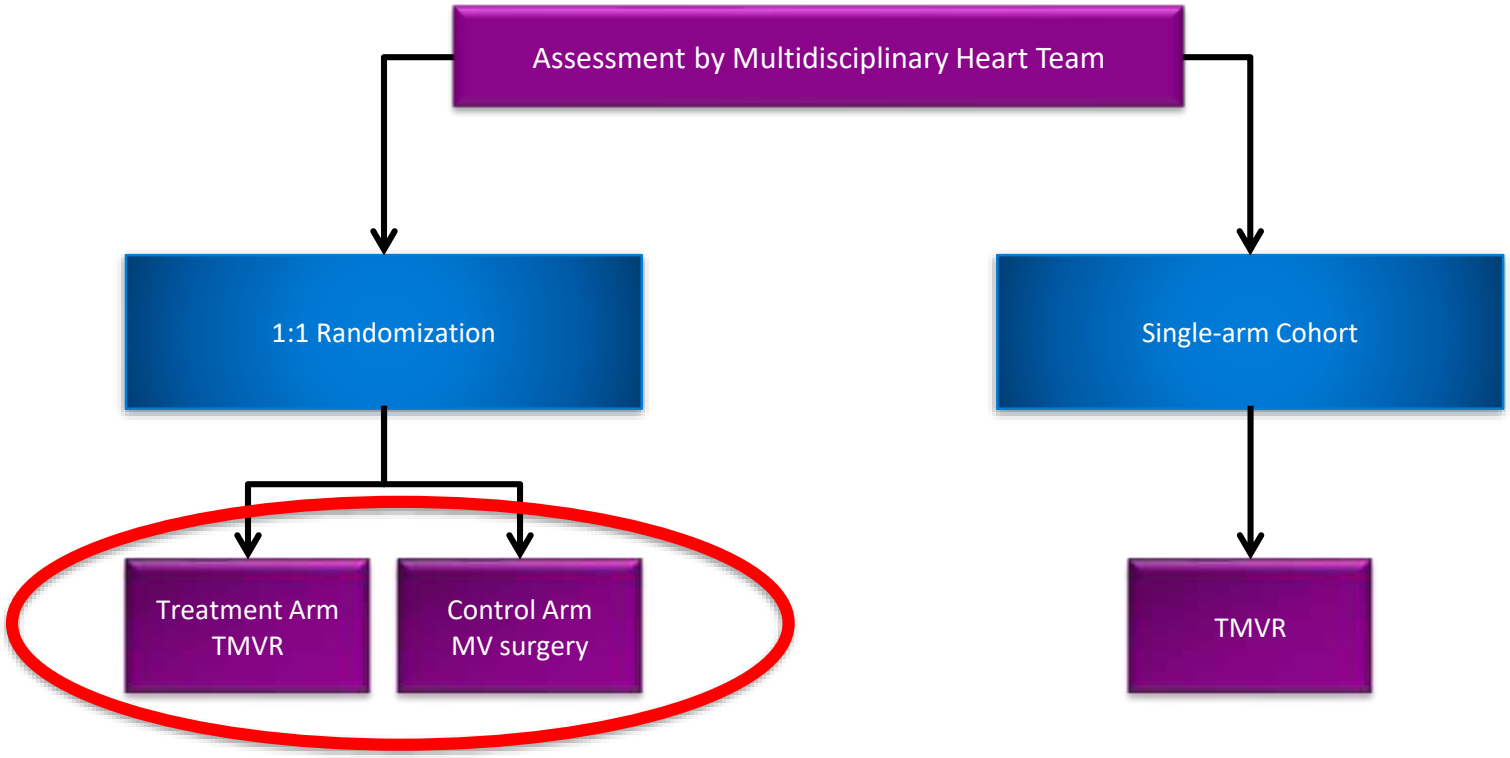
Mild MR
Paravalvular: 3 (7.1%)
Transvalvular: 8 (19.0%)

All patients with mild or no MR in follow-up

MDT APOLLO Trial Overview

Principal Investigators: David Adams and Martin B Leon
Study Chair: Michael Mack

Evaluate safety and efficacy of Medtronic Intrepid™ TMVR System in patients with symptomatic mitral regurgitation



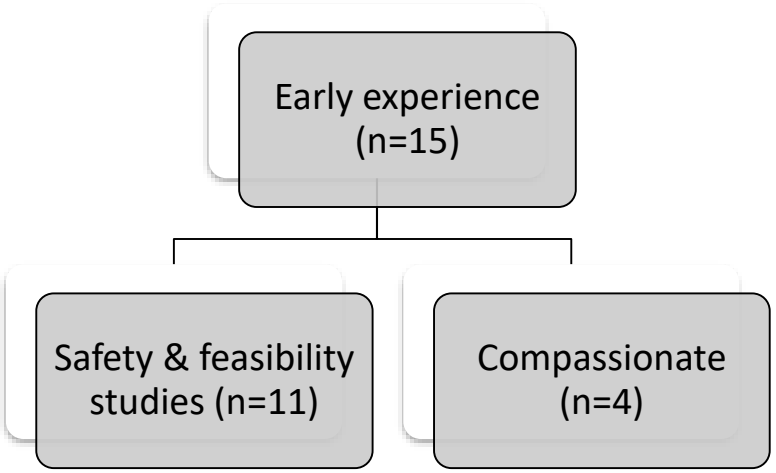
Mitral Interventions

Highlife TMVR

2-step procedure

“Valve-in-Ring”		Ring		Valve
	=		+	
		Transfemoral artery		Transseptal <u>or</u> transapical

Early feasibility experience



Demographics	
Age (years), avg. (range)	69 (50-79)
Male (%)	80
Functional MR (%)	73
Previous cardiac surgery (%)	33
LVEF (%), avg. (range)	38 (27-54)
Annular diameter (mm), range	32-52

HighLife clinical outcomes

	30 Days (n=14)	6 Months (n=7)	1 Year (n=5)
Death *	***3***	***0***	***1***
Stroke	0	0	0
Myocardial Infarction	0	0	0
LVOT obstruction	1	0	0
Paravalvular regurgitation > grade I	0	0	0
Mean Transvalvular gradient > 5 mmHg**	***1***	***0***	***0***

* Patient selection (1 severe LV dysfunction, 1 LVOT obstruction from small left ventricular cavity) and technical learning curve (1 chordal entanglement)

** Thrombosis related to subtherapeutic coumadin

First-in-Human Transseptal Highlife

- 79 year old male
- Severe functional mitral regurgitation
- Severe left ventricular dysfunction 25-30%
- Multiple recent admissions for CHF

- Moderate COPD
- Mild renal dysfunction

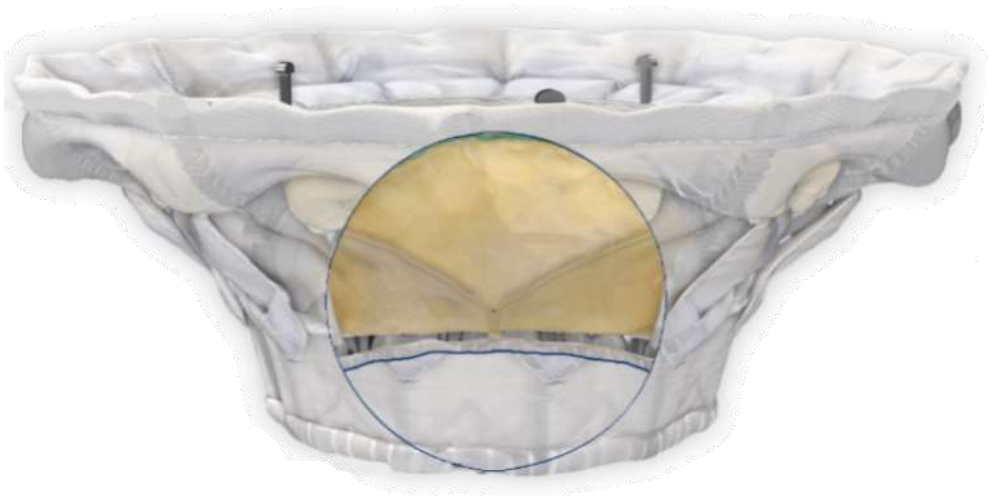

MITRALE TRANSAPICALE
Zoom: 145%
Im: 1/134 Series: 2


MITRALE TRANS-APICA
Zoom: 143%
Im: 1/130 Series: 1

Case

Mitral Interventions

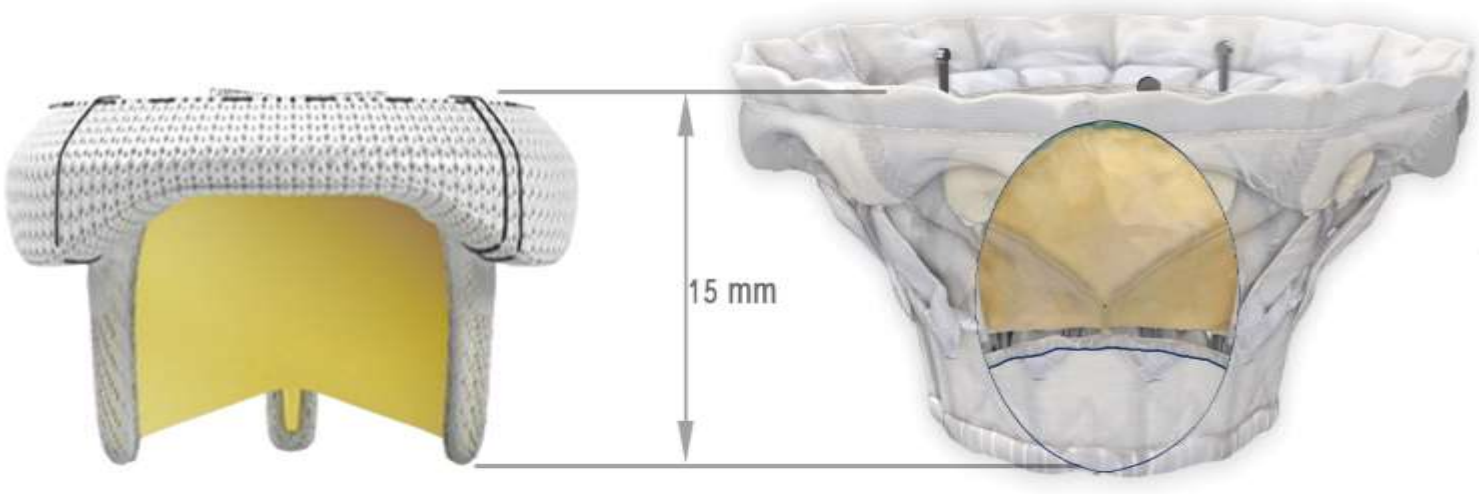
Cardiovalve TMVR



Cardiovalve TMVR: 1 valve, 2 frames, 3 steps

– ***Cardiovalve follows surgical design, adapted for transcatheter use***

- Low presence in the ventricle, no protruding atrial component
- Robust frame and classic leaflet design for durability
- 3 sizes to fit all anatomies
- Proprietary anchoring and sealing element



The **Surgical gold-standard**
Edwards Perimount Magna™

The **Transcatheter solution**
Cardiovalve™

Promising First 5 Cases

	Case 1	Case 2	Case 3	Case 4	Case 5
MR	**No**	**No**	**No**	**No**	**No**
PVL	**No**	**Trace**	**Trace**	**No**	**Trace**
LVOTo	**No**	**No**	**No**	**No**	**No**
Gradients	5 mmHg	6 mmHg	2 mmHg	6 mmHg	3 mmHg
Hemody.	Normal	Normal	Normal	Normal	Normal
DS time	30 min	23 min	40 min	30 min	21 min
Depl. time	13 min	15 min	25 min	17 min	14 min

AHEAD – Study Design

European Feasibility Study of High Surgical Risk Patients with Severe Mitral Regurgitation treated with the Cardiovalve Transfemoral Mitral Valve System (AHEAD Study)

AHEAD TRIAL

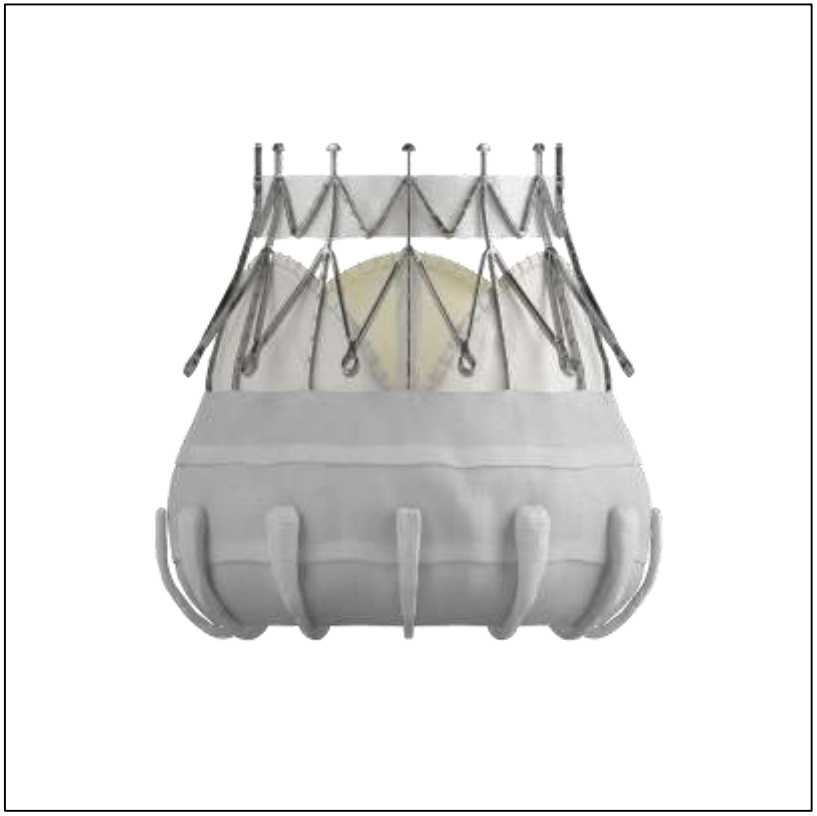
Sites	Up to 10 sites (Italy , Swiss , Germany, France)
Study Design	***Prospective, multi-center, single arm pilot clinical study***
Enrollment	***A total of 30 subjects will be enrolled in this pilot study***
Target patients	Symptomatic subjects (NYHA Class ≥ II-IV) with severe mitral regurgitation requiring mitral valve replacement who are at high risk for open chest surgery according to the Heart Team decision
Study Enrollment duration	1 year

University Hospital Zurich
First AHEAD study patient

Confidential

Mitral Interventions

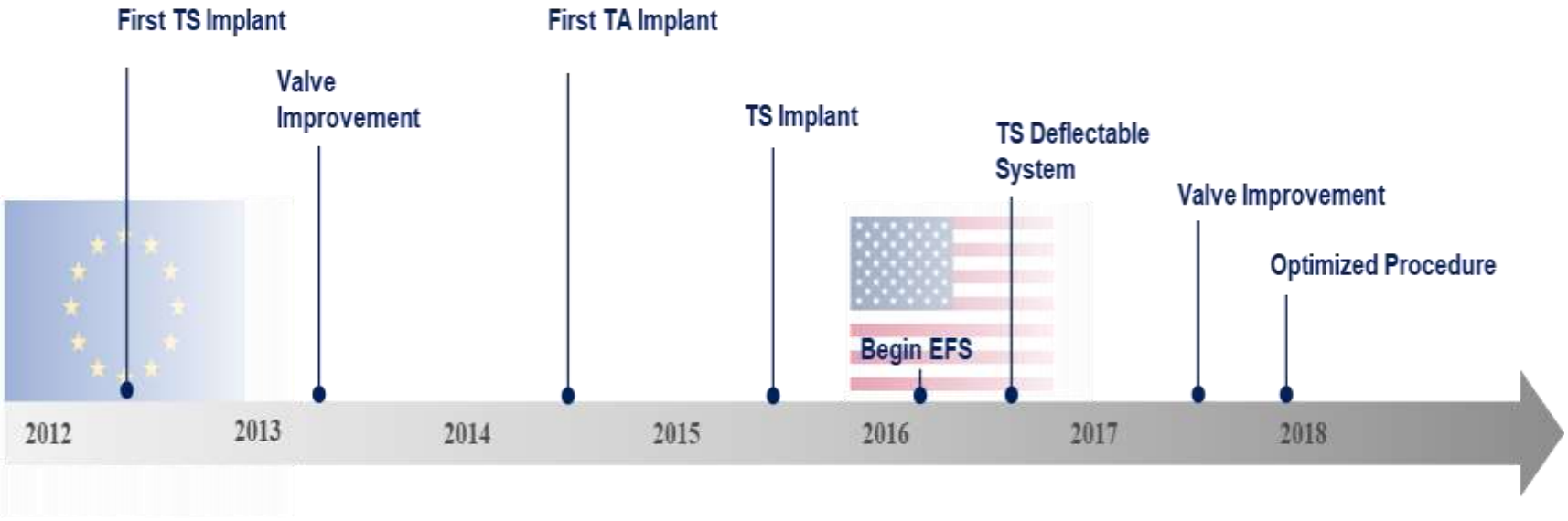
CardiAQ TMVR



CardiAQ-Edwards Transcatheter Mitral Valve Replacement System

Early learnings led to program improvements

- **Improved patient selection**
- **Device iterations: deflectable delivery system**
- **Procedure optimization: pre-2016 majority TA → now all TS with optimized procedure**



CardiAQ-Edwards Transcatheter Mitral Valve Replacement System

Program Status

- ***Recent clinical experience is encouraging***
- ***Continued focus on transseptal delivery***
- Increased enrollment cadence in US Early Feasibility Study
- Longest survivor >3 years
- Ongoing progress in product and procedural optimization
- ***Future:***

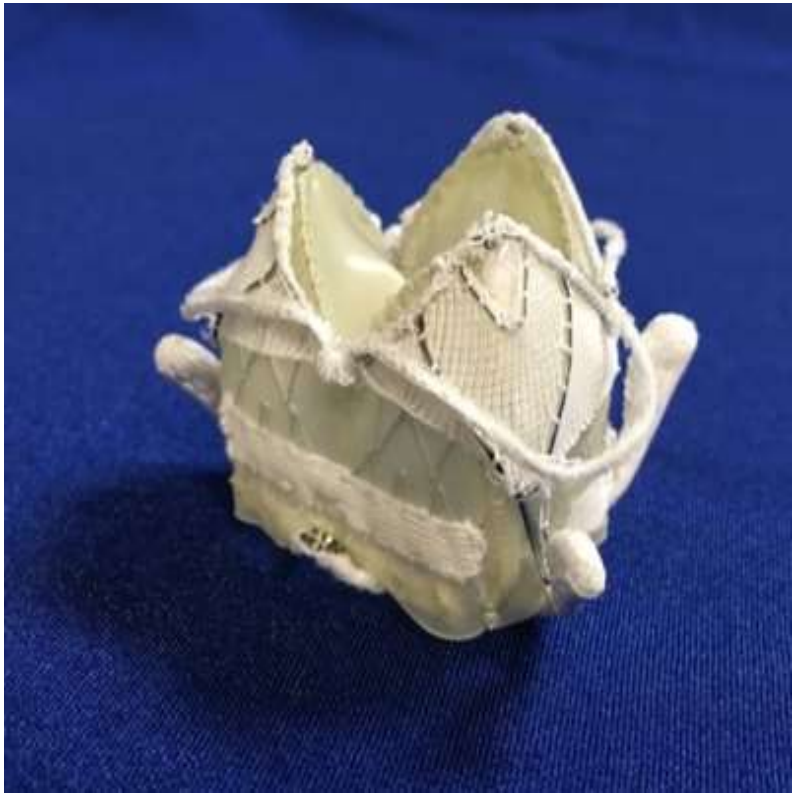
  - Valve enhancements

  - Lower profile delivery system

  - Improved steerability

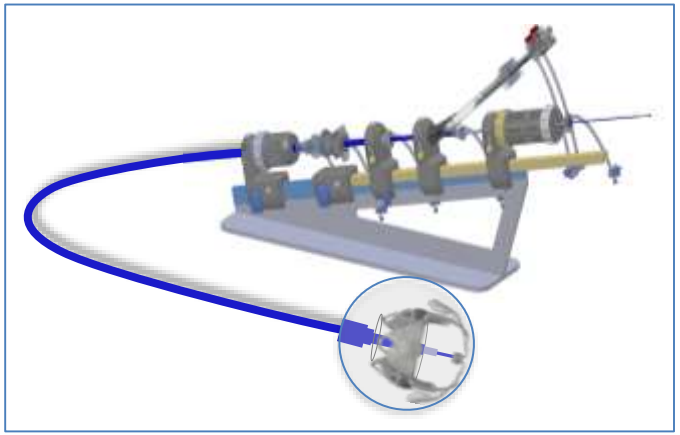
Mitral Interventions

Caisson TMVR



TMVR Clinical Design Features

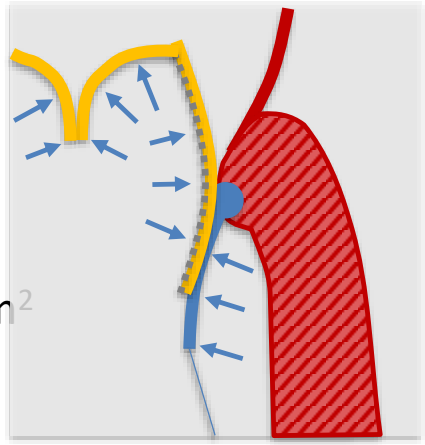
- **Endovascular Transeptal Approach**
- Venous Access
- Dual Stage Implant: Anchor and Valve
- Designed for **FMR** and **DMR**
- **Atrially-Biased valve**
- Minimizes LVOT Obstruction
- **SAM Management Feature**
- Traps A2 against valve cuff to maintain NeoLVOT area
- **Repositionable / Retrievable**
- The ability to test the performance of the implant and judge the need to adjust, deploy or remove
- Both Anchor and Valve are repositionable and fully retrievable



Implant: Anchoring and Sealing

- **Anchor**
  - Nitinol Self-Expanding Frame
  - Covered with Polyester and ePTFE
  - 4 Sub-annular Anchoring Feet
  - 3 Atrial Holding Loops

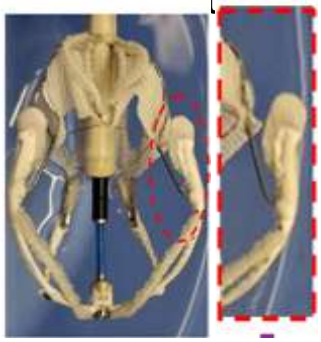
- **Valve**
  - Nitinol Self-Expanding
  - D-shaped Outer Stent
  - Porcine Pericardium
  - 3 Leaflet Circular Valve, EOA>3.0cm^2



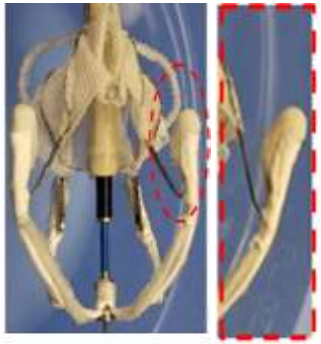
Device Design Improvements

Optimized Anchor Foot geometry

Original

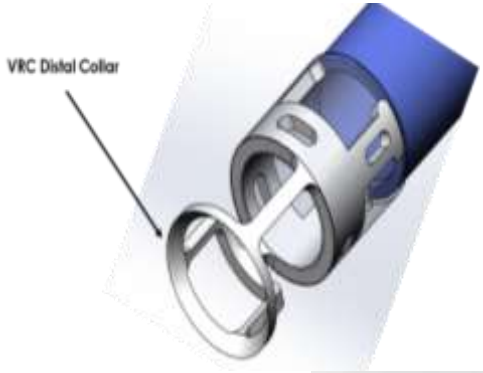


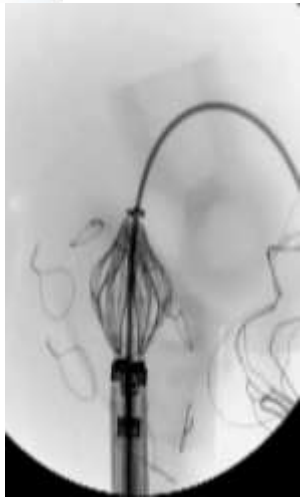
Modified



Easier leaflet insertion

Addition of Valve retrieval catheter

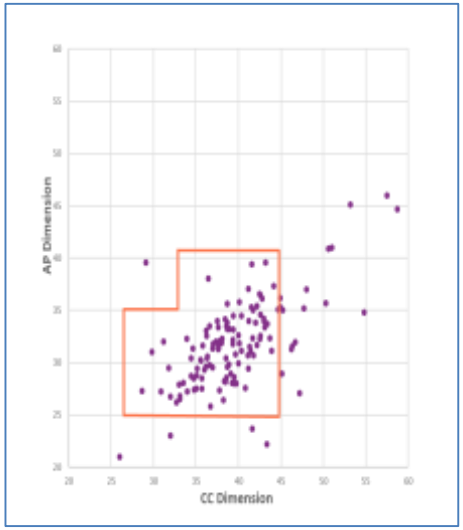




Robust Valve retrieval

3 sizes available

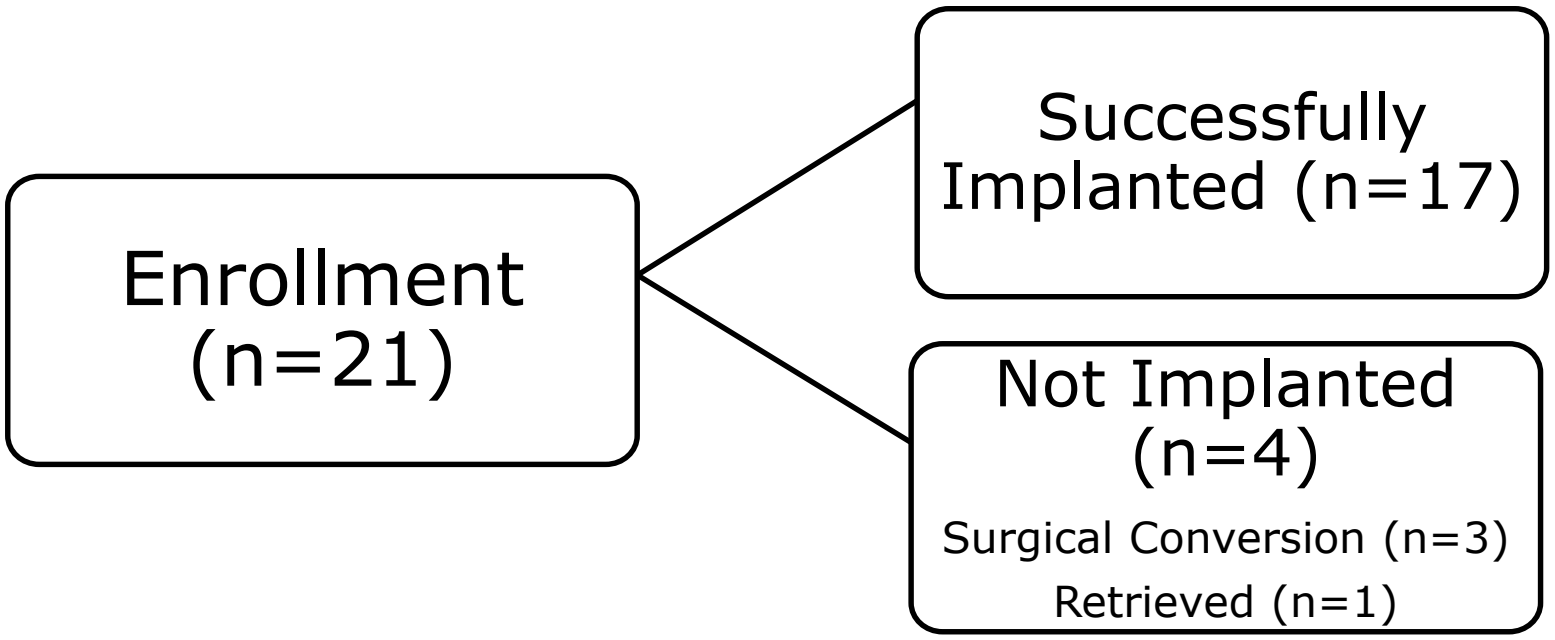
Implant Size	CC Range (mm)	AP Range (mm)	Perimeter Range (mm)	Shape
36A	30mm - 36mm	26mm - 32mm	91mm - 118mm	
42A	36mm - 42mm	28mm - 34mm	106mm - 127mm	
42B	36mm - 42mm	32mm - 38mm	113mm - 138mm	



Larger treatable population

Patient Disposition

Enrollment → Implantation



Caisson Transcatheter Mitral Valve Replacement

Study Status

- ***Enrollment has successfully concluded for PRELUDE and initiated for the INTERLUDE US study***
- ***Multiple implant sizes available***

Implant Performance

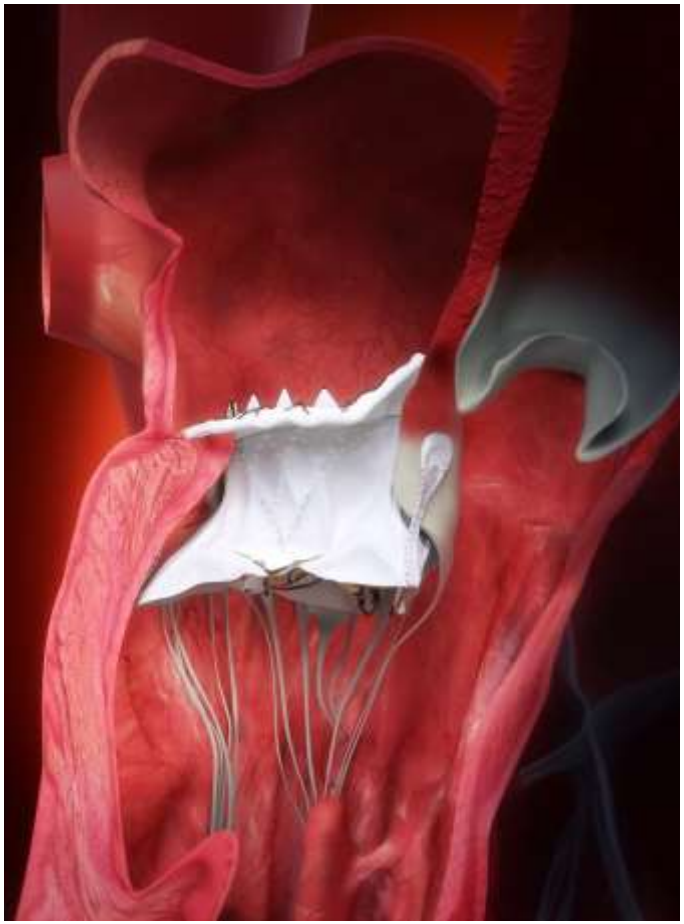
- Follow-up results show positive acute valve performance which is maintained over time
- Patient outcomes are encouraging

Procedural Performance

- New procedural methods and device improvements have enhanced operator experience and confidence
- Success at multiple centers demonstrates procedural repeatability

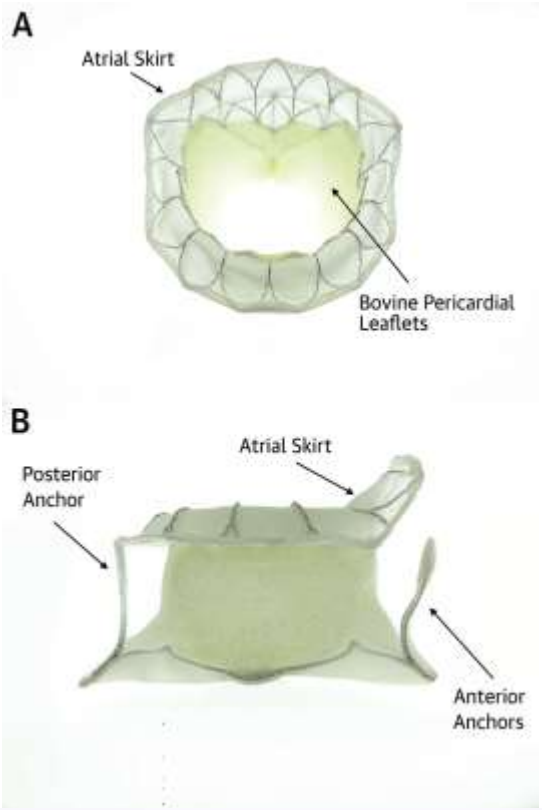
Mitral Interventions

Tiara TMVR



Mitral Interventions

Tiara TMVR



- Fits anatomical shape of native valve
- ***Quick and repeatable transapical implantation procedure and well-established, efficient preparation procedure***
- 35 mm and 40 mm size in clinical use and CE mark study
- ***Trans-septal delivery system under development***
- Device and delivery systems covered by multiple patent applications and issued patents

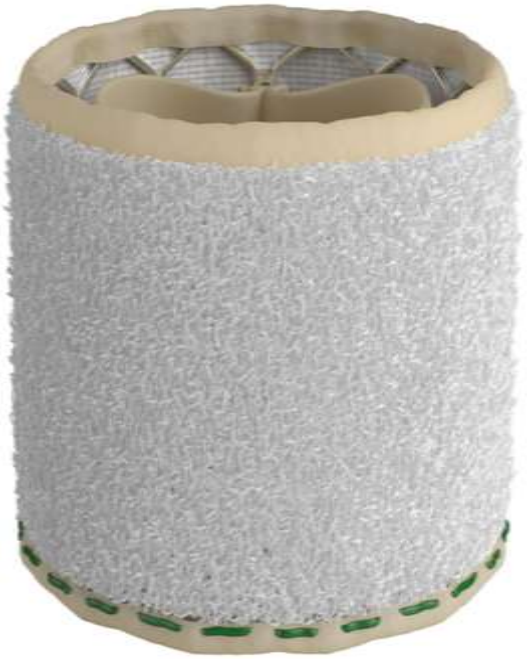
Mitral Interventions
Tiara TMVR

- ***58 patients treated to date: (Belgium, Canada, Germany, Israel, Italy, Switzerland, UK and US)***
  - ***20 in TIARA-I***
  - ***16 in TIARA-II***
  - ***22 under Compassionate Use (longest follow-up 4 years)***
- Procedure outcomes very encouraging with average implantation procedure time of approximately 20 minutes (Shortest implantation procedure time to-date: 8 minutes)
- Successfully treated patients with all types of Mitral Valve pathologies, and pre-existing prosthetic aortic valves (both mechanical and bioprosthetic) and prior surgical mitral valve repair

	Since 2014	2017	TIARA-II
TREATED	58	21	16
30 Day SURVIVAL RATE	**90%** (52/58)	**95%** (20/21)	**94%** (15/16)

Mitral Interventions

Edwards Sapien M3 Valve and M3 Dock

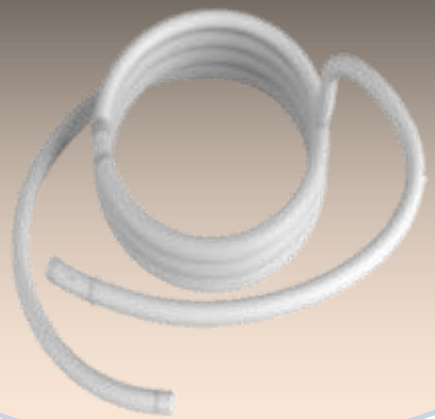


Mitral Interventions

Edwards Sapien M3 Valve and M3 Dock

Dock Delivery

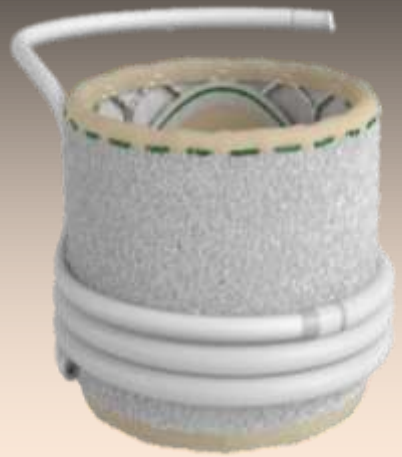
SAPIEN M3 Dock



Valve Delivery

SAPIEN M3 Valve

Final Implant



SAPIEN M3 System

All Participating Centers

Center	Investigator (MD)
St. Paul's Hospital Vancouver, BC	John Webb
Cedars-Sinai Medical Center Los Angeles, CA	Raj Makkar
Intermountain Medical Center Salt Lake City, UT	Brian Whisenant
Northshore University Health System Evanston, IL	Mayra Guerrero
Mayo Clinic Rochester, MN	Charanjit Rihal

SAPIEN M3 System
Procedural Outcomes

Case #	Baseline LVEF (%)	Procedure Length (hrs)	Procedural MR Grade		Procedural Adverse Clinical Event	30 day MR Grade	30 day Clinical Status
			Pre	Post			
1	60	4	Severe	Trace	None	Severe[1]	Alive
2	33	7.3[2]	Moderate-Severe	Mild	Chordal Rupture	Trace	Alive
3	35	2.5	Severe	Mild	None	None	Alive
4	30	2	Moderate-Severe	None	None	None	Alive
5	32	2.1	Severe	None	None	None	Alive
6	42	1.8	Severe	Trace	None	Trace	Alive
7	32	3.7	Severe	Mild	None	Trace	Alive
8	30	3.8	Severe	Mild	None	Trace	Alive
9	41	2.5	Moderate-Severe	None	None	None	Alive
10	40	1.3	Moderate-Severe	None	None	Mild	Alive

[1]PVL was closed with a plug which reduced post-30 day MR to 2+

[2]Chordal rupture during dock deployment resulted in severe PVL; closed intra-procedurally with plugx2; stroke (POD 02)

SAPIEN M3 System
First 10 Cases - Data Summary

	N=10
Technical Success*	9
Alive	10
Successful access/Delivery	10
Deployment	10
Freedom from Reintervention	9[(1)]

Clinical Outcomes at 30 days*	N=10
All-cause Mortality	0
All Stroke	1[(1)]
Rehospitalization (Device/Procedure related)	0
Hemolysis	0
LVOT Obstruction	0

There was no Conversion to Surgery, Device Embolization, Device Migration or Implantation of more than one valve observed.

*Site reported

[1]Case #2: Chordal rupture during dock deployment resulted in severe PVL; closed intra-procedurally with plugx2; stroke (POD 02)

What's the clinical reality?

- Many screening failures (clinical and anatomic factors)
- Imaging knowledge and skills are critical

What's the clinical reality?

- Many screen failures (clinical and anatomic factors)
- Imaging knowledge and skills are critical
- Poor left ventricular function = poor outcomes
- Assessment of LVOT obstruction

What's the clinical reality?

- Large delivery profiles (>30F)

What's the clinical reality?

- Large delivery profiles (>30F)
- Mitral regurgitation is usually eliminated
- Heterogeneous clinical outcomes across device platforms
- Optimal antiplatelet/antithrombotic therapy uncertain

Lingering questions . . .

- What is the addressable patient population for TCMV replacement? Primary vs. secondary MR? Risk profile?

- How can we overcome the challenges in patient and device selection – futile versus high risk? Appropriate imaging for anatomical screening and procedural guidance?

- What skill sets are required to perform transcatheter mitral valve interventions? Training requirements? Role of the Heart Team?

Lingering questions . . .

- What type of clinical trial designs for regulatory approval? What will be the impact of the COAPT or RESHAPE-HF-2 trials on the approval process of other TCMV therapies? What can we learn from these ongoing trials?

- What should be the primary safety and efficacy endpoints?

- How do we evaluate treatment success (survival, symptoms, MR reduction, LV remodeling, hospitalization, progression to heart failure/transplant) ?

Lingering questions . . .

- Should referral patterns and patient selection criteria be different for centers of excellence? By what standards do we define centers of excellence (volume, benchmark measures)?

- Will the future market be dominated by repair or replacement? Combination repair techniques?

- Predictions about adoption rates? Reimbursement strategies?

Thank you very much for your attention!

Thank you for your kind attention!