Updates in TMVR

(Replacement)

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Disclosures

Abbott Vascular: Consultant, advisor, speaker Fees; Abiomed: Consultant, advisor, speaker fees; BioTrace Medical: Consultant, advisor, speaker Fees; Boston Scientific: Consultant; Cardiovascular System Inc.: Consultant, PI Eclipse Trial; Edwards LifeSciences: Consultant, advisor, speaker fees, proctor, research grant, PI EARLY-TAVR trial, PI PROGRESS trial; GE Healthcare: Consultant; iRythm Technologies: Consultant; Medtronic: Consultant, advisor, speaker fees; OpSens: Consultant; Pi-Cardia: Equity, consultant; Puzzle Medical: Equity, consultant; Saranas: Equity, consultant; Shockwave: Consultant, speaker fees; Siemens: Consultant; Soundbite Medical Inc.: Equity, consultant; Teleflex: Consultant; 4C Medical: Consultant, PI ALTA Valve Feasibility study

Transcatheter Mitral Valve

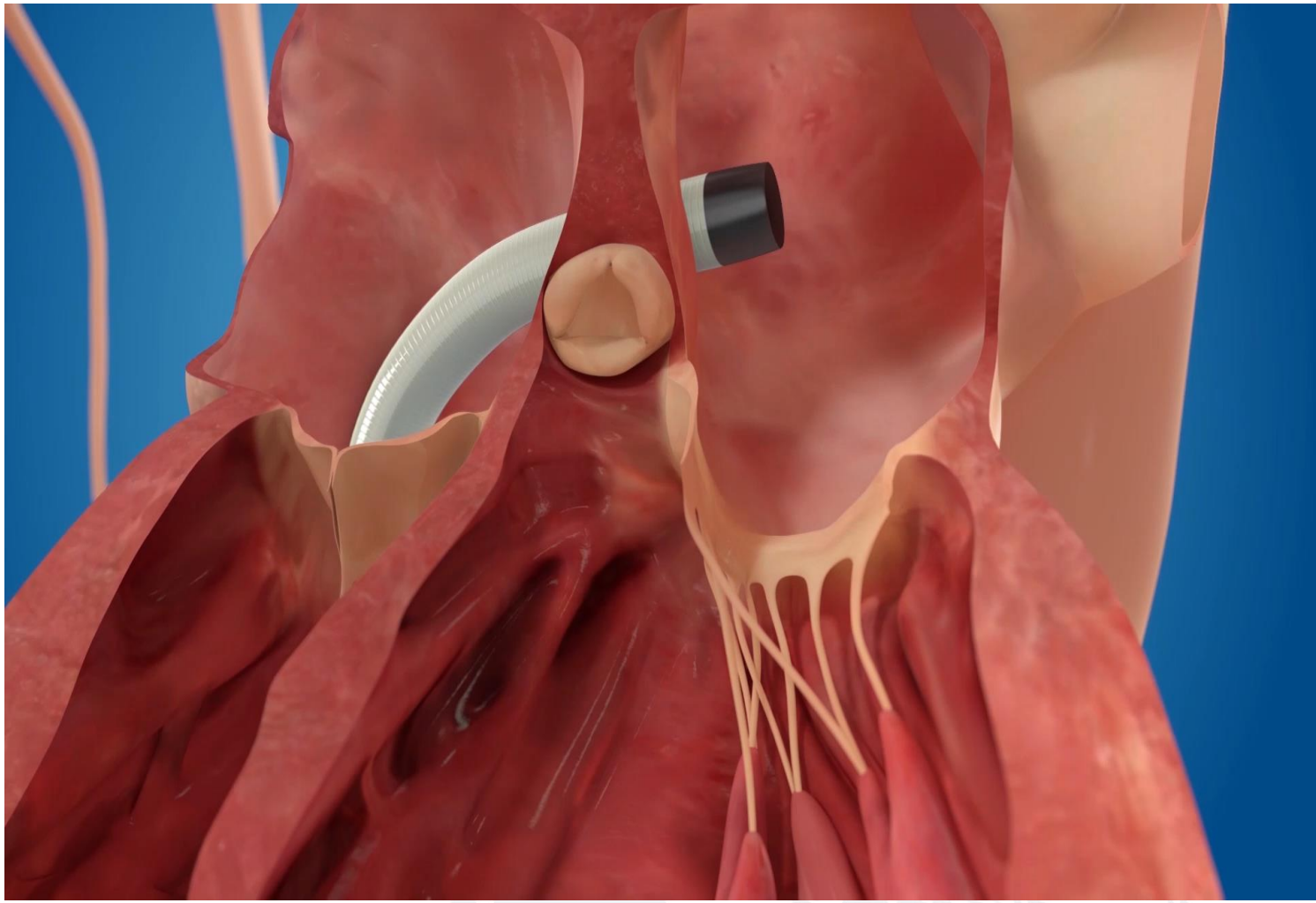
Brief Update in MV Repair

- **Functional MR: TEER**
  - MitralClip (Abbott)
- **High-risk Degenerative MR: TEER**
  - MitralClip (Abbott)
  - PASCAL (Edwards)
- **Low- and Intermediate-risk degenerative MR**
  - Studies: REPAIR MR (Abbott) and PRIMARY MR

The Dream of TMVR…

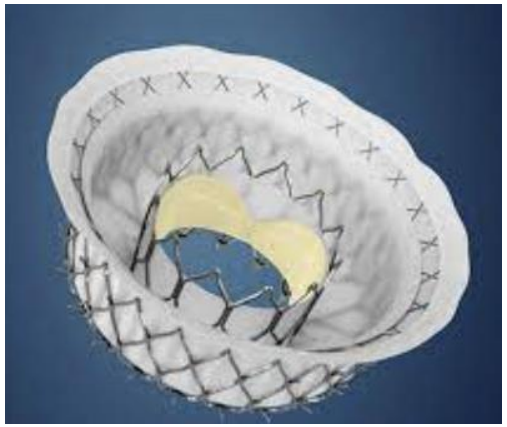
Design and Procedure Goals

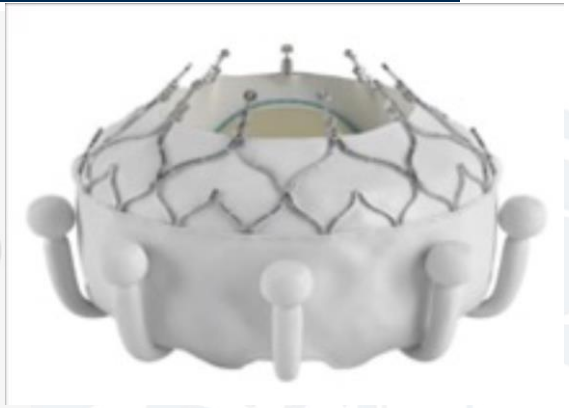
- Ease of implantation
- Agnostic to etiology of MR
- Reliable elimination of MR
- Less recurrence of MR



Agenda TMV Replacement

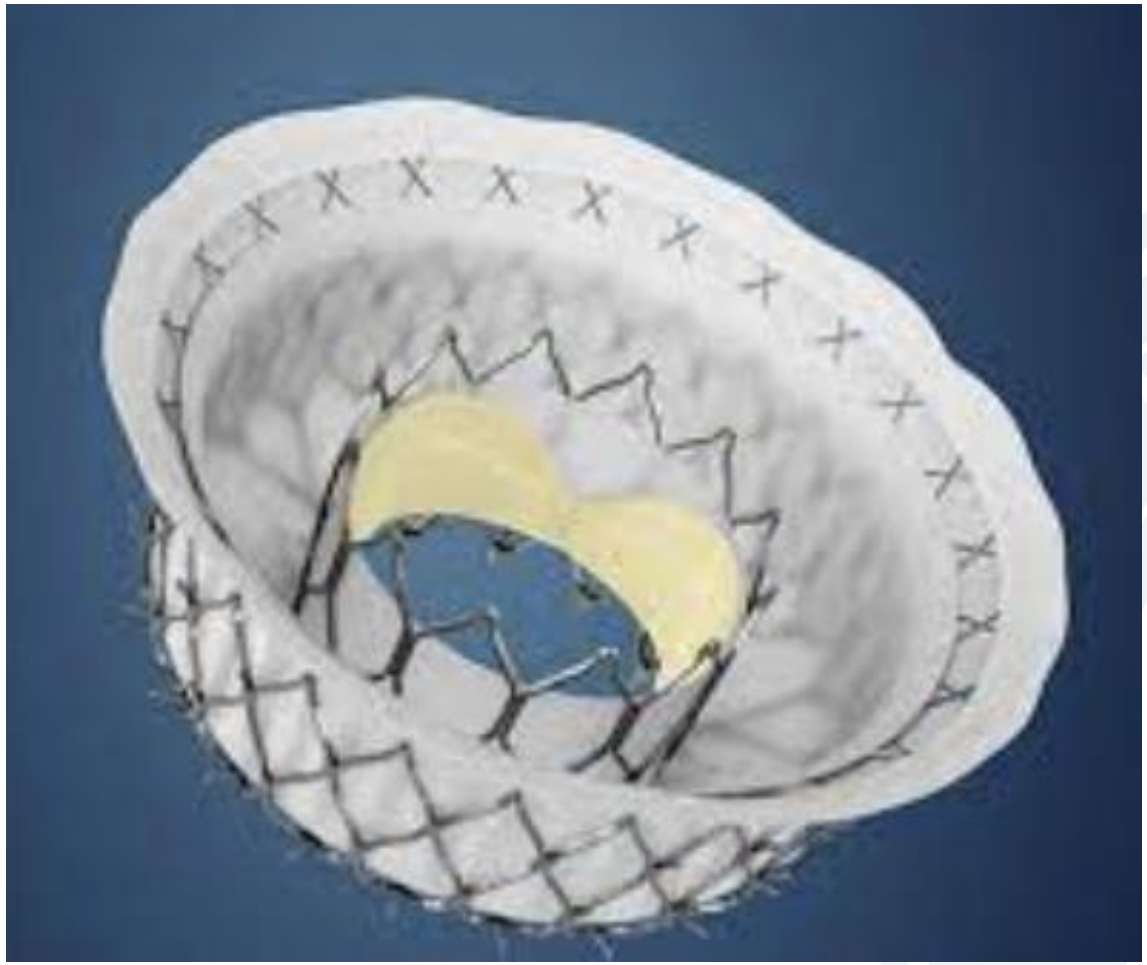
- Intrepid: Medtronic
- M3: Edwards
- Evoque/Eos: Edwards
- Tendyne: Abbott
- Cephea: Abbott
- HighLife
- CardioValve
- AltaValve: 4C Medical








Intrepid Medtronic



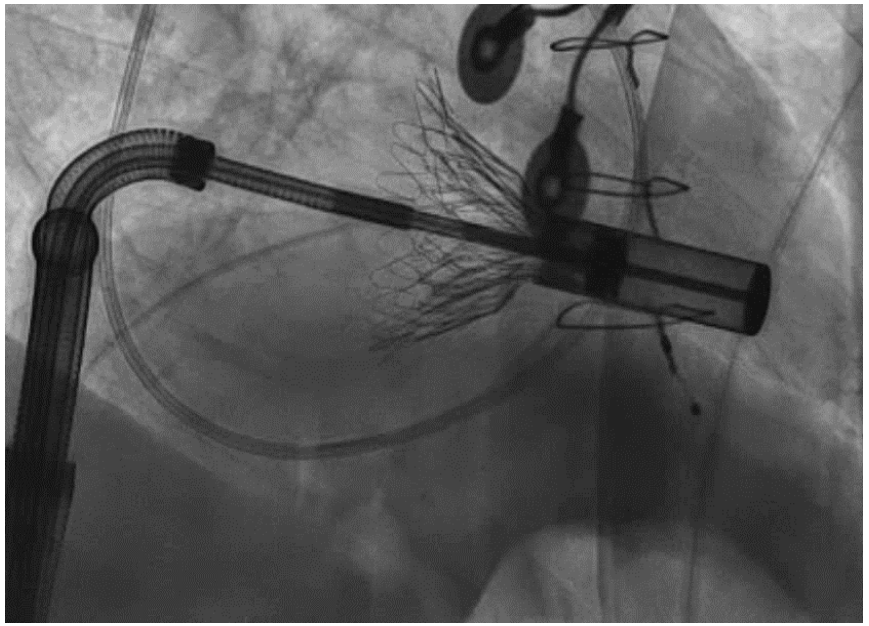
Intrepid TMVR Technology Evolution

INTREPID VALVE

- ✓ Circular inner stent with ***27 mm tri-leaflet bovine*** pericardial valve
- ✓ ***Conformable outer stent anchors*** with geometry and ***fixation barbs*** but not requiring sub-leaflet capture
- ✓ Symmetrical design without need for rotational alignment
- ✓ Predictable and controlled valve deployment with simplified echo implant criteria
- ✓ Transapical and transfemoral delivery without need for guide wire in the LV
- ✓ ***42 & 48 mm valves*** **in clinical evaluation; 54 mm valve in development**

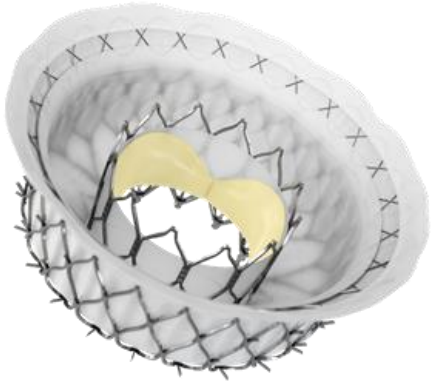
Intrepid TMVR Technology

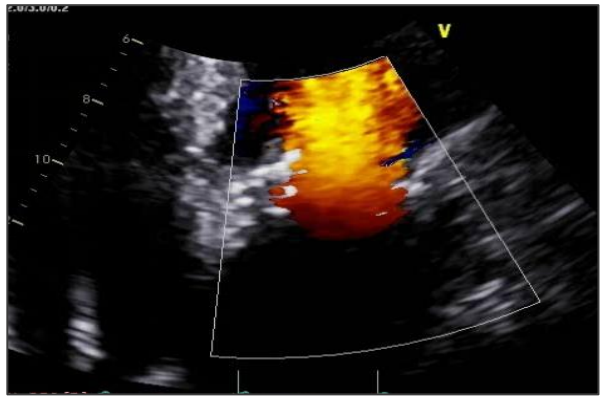
INTREPID Transfemoral Procedure



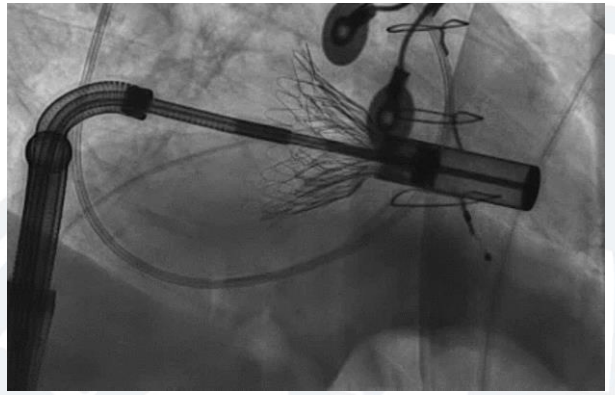
35 Fr INTREPID Transfemoral Delivery System

Intrepid TMVR Clinical Program





Intrepid TMVR at 5 Years



350+

Intrepid Valve Implants

6+ Year Follow Up

On earliest patients treated

50+

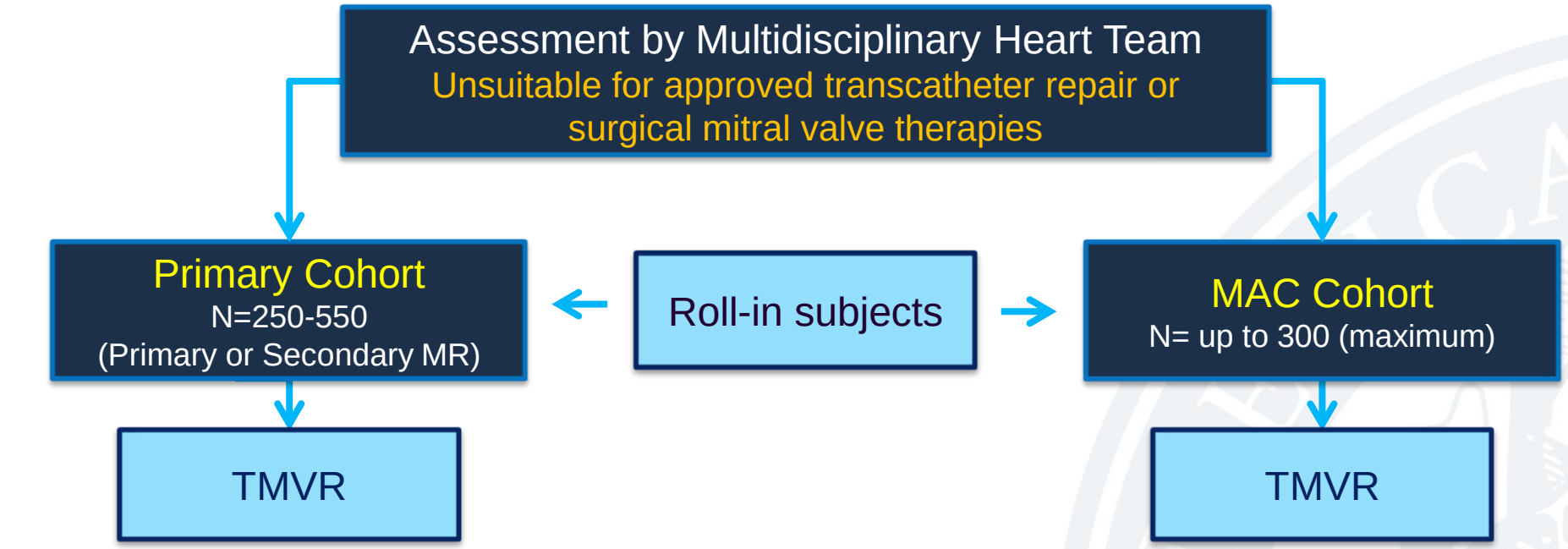
Transfemoral Cases

EFS + APOLLO

Since the original pilot in 2014

APOLLO Pivotal Trial

Targets Patients Unsuitable for Surgery or TEER



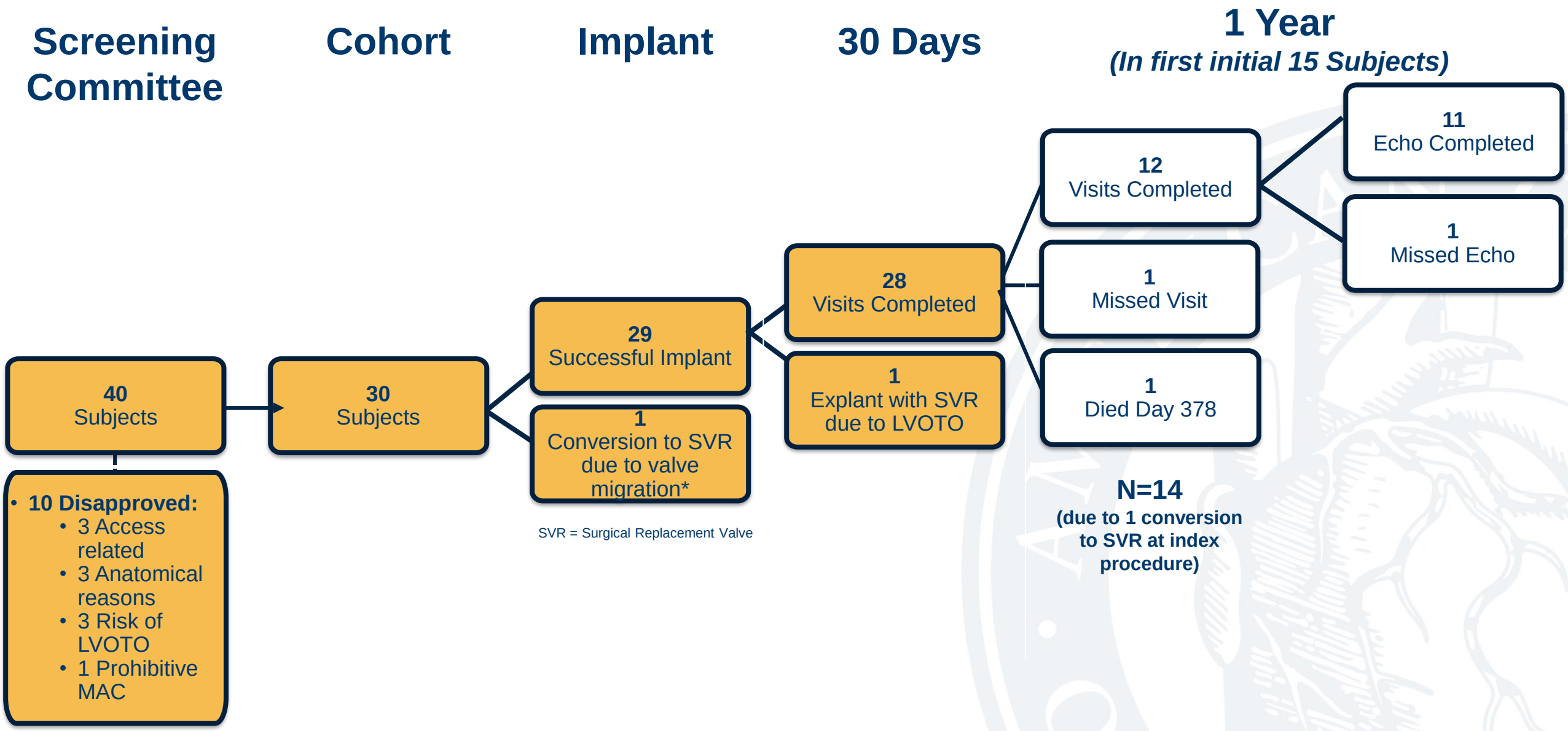
* Performance goal based on published literature

Intrepid TMVR - Transfemoral Delivery

Early EFS Clinical Outcomes (@ 1 year); first 30 patients enrolled

	N=30 Median follow-up: 7.2 (3.1, 12.0)	
	0-30 days # pts expected for visit = 30	0-365 days # pts expected for visit = 14
All-cause mortality[1]	0% (0)	0% (0)
Stroke or transient ischemic attack	0% (0)	0% (0)
Myocardial infarction	3% (1)	3% (1)
≥MVARC major vascular complications (procedural)	27% (8)	--
Reoperation (or reintervention)	3% (1)	3% (1)
Cardiovascular hospitalization	7% (2)	22% (5)
Heart failure	0% (0)	9% (2)

Patient Flow



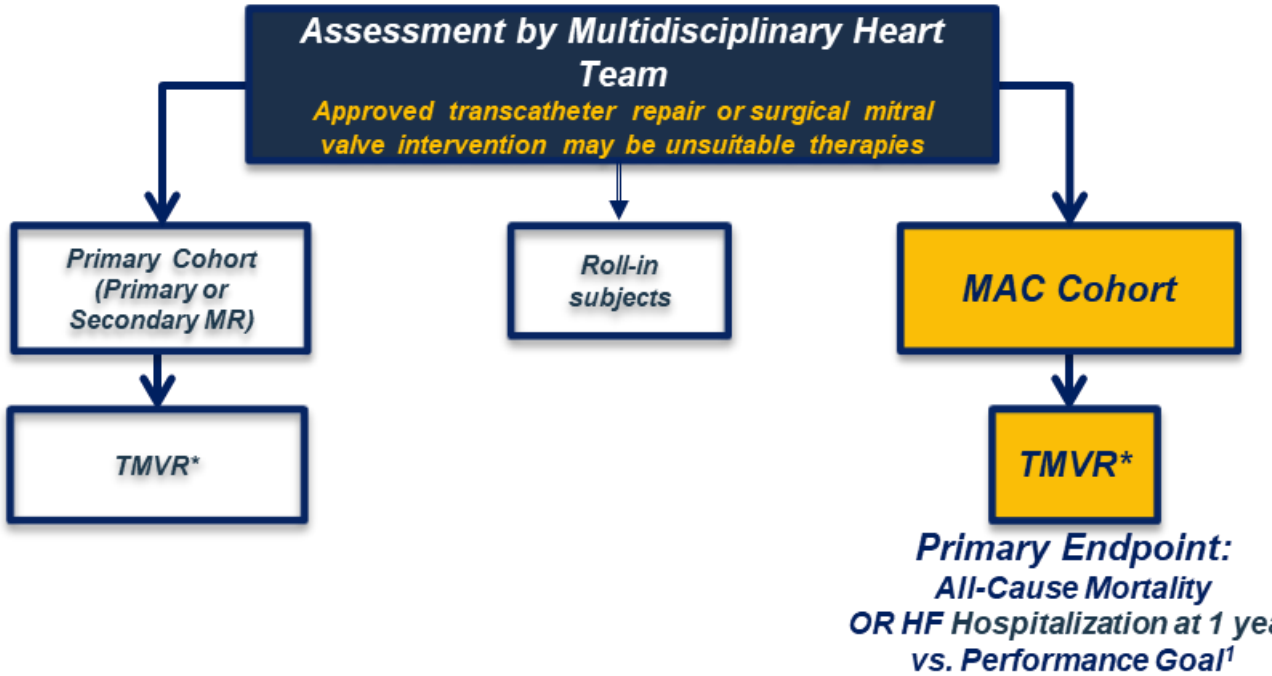
SVR = Surgical Replacement Valve

APOLLO Trial

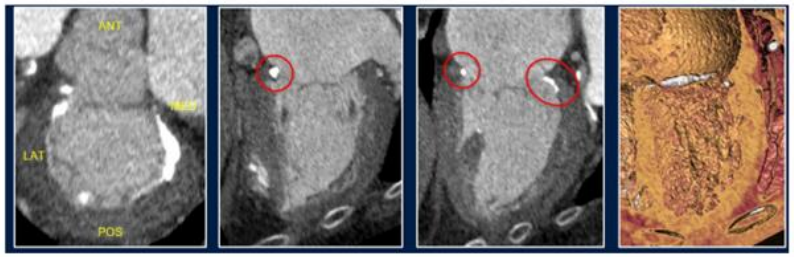
MAC Patients Suitable for TMVR

INCLUSION CRITERIA

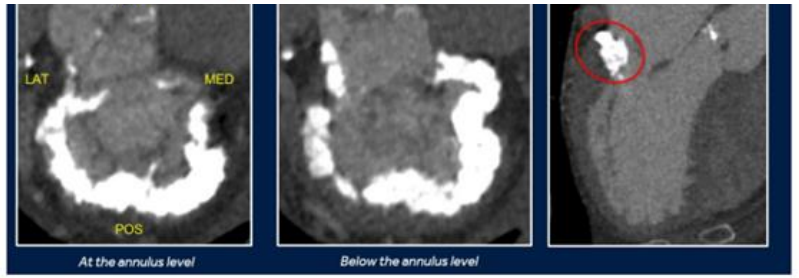
- ***Patients with MAC + Moderate-to-Severe or Severe MR, OR***
- ***Patients with MAC + Moderate MR and Mitral Stenosis***



Primary Endpoint:
All-Cause Mortality
OR HF Hospitalization at 1 year
vs. Performance Goal[1]

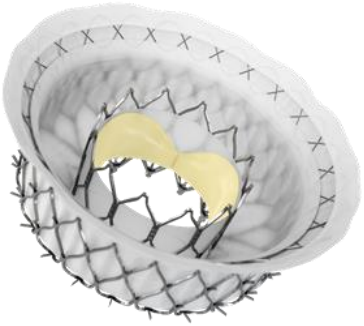


Acceptable: Interrupted, "band-like" MAC



Unacceptable: MAC with irregular shape, severe height
(Potential risk of PVL, incomplete expansion)

Next Generation Intrepid Transfemoral System



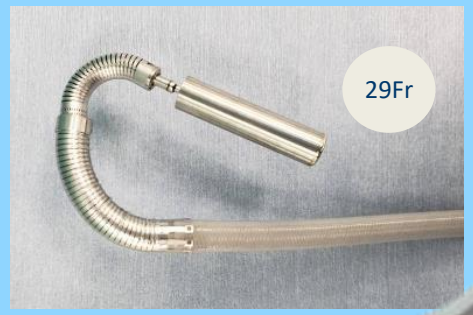
42 mm

48 mm

54 mm

Consistent Intrepid* Valve Design

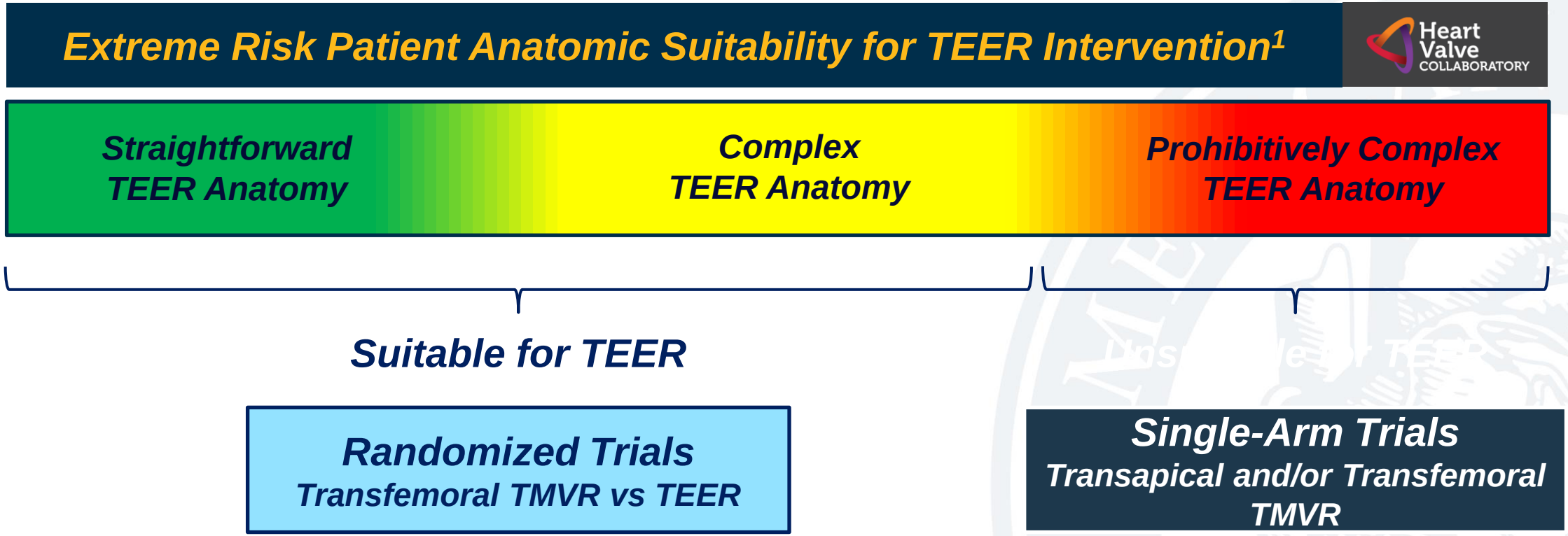
- Optimized for 29Fr Profile & LVOT
- Increased Patient Eligibility with Larger Valve Size



Updated TF System

- 29Fr Profile
- Designed for Improved Steering
- Streamlined Accessories

Future Studies
Management of Mitral Regurgitation



[1]Lim, et. al. Structural Heart. 2021;5(3):227-233

M3 Edwards LifeSciences

Edwards SAPIEN M3 System

Dock Delivery

SAPIEN M3 dock

Valve Delivery

SAPIEN M3 valve

Final Implant

SAPIEN M3 dock delivery system

Edwards Commander M delivery system

THE ENCIRCLE TRIAL

Fully transseptal TMVR system through a 28Fr steerable guide sheath

Edwards SAPIEN M3 Valve

Features the SAPIEN 3 valve tissue and frame

Specifically engineered to respect the native mitral anatomy

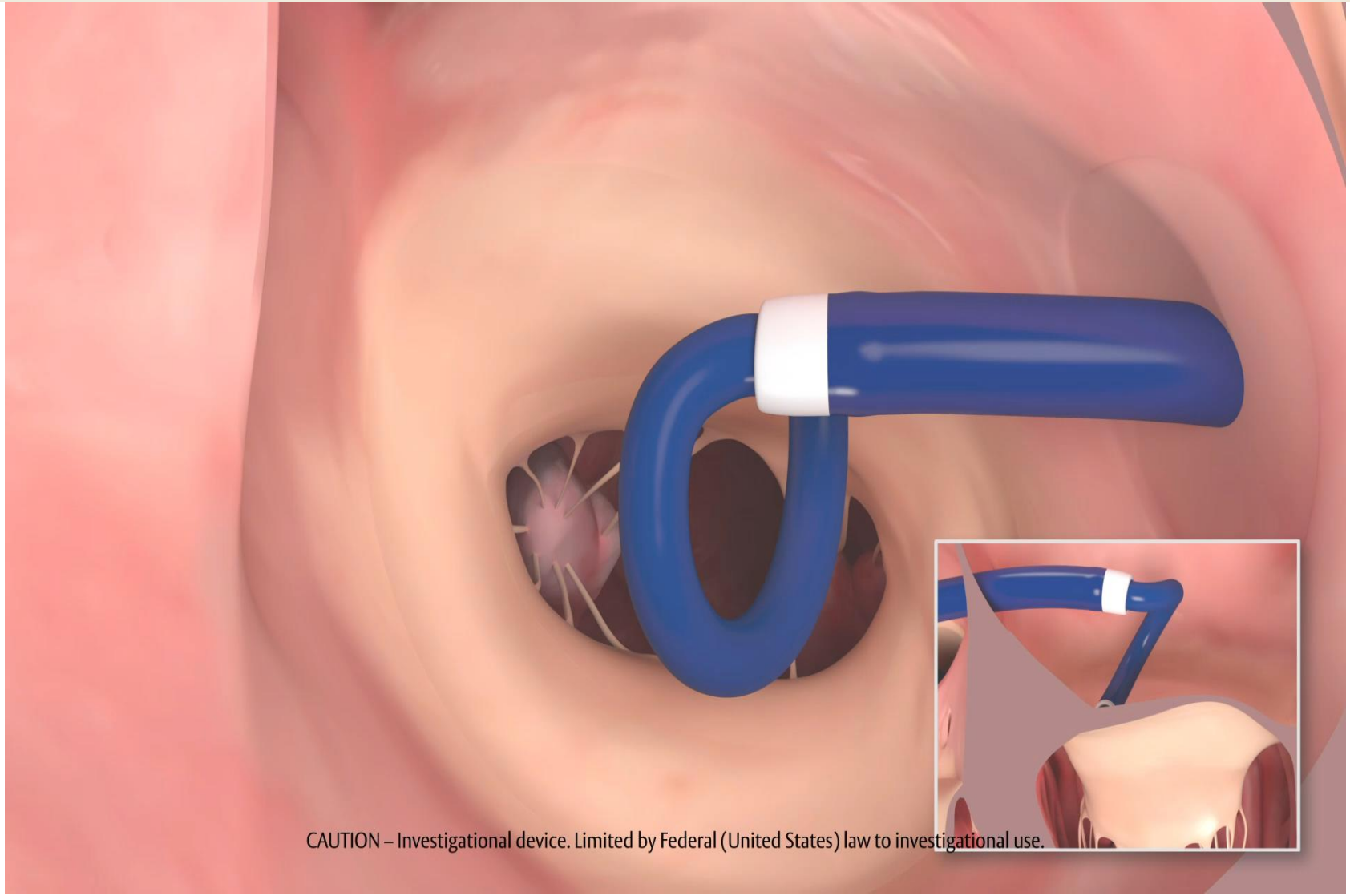
Full-frame PET skirt

29 mm valve

THE ENCIRCLE TRIAL

CAUTION – Investigational device. Limited by Federal (United States) law to investigational use.

Animation



THE ENCIRCLE TRIAL

ENCIRCLE Trial Design

Subjects Deemed Unsuitable for Commercial Treatment Options as Assessed by Heart Team

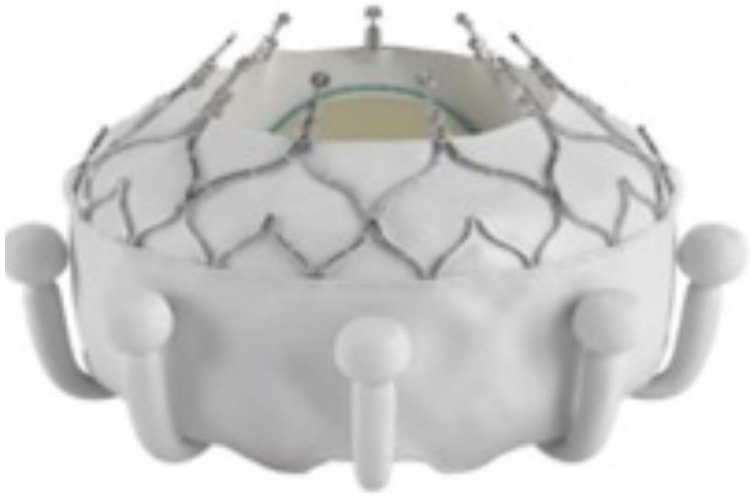
Main Study (n = Up to 300)	Failed TEER Registry (n = Up to 100)	MAC Registry (n = Up to 100)

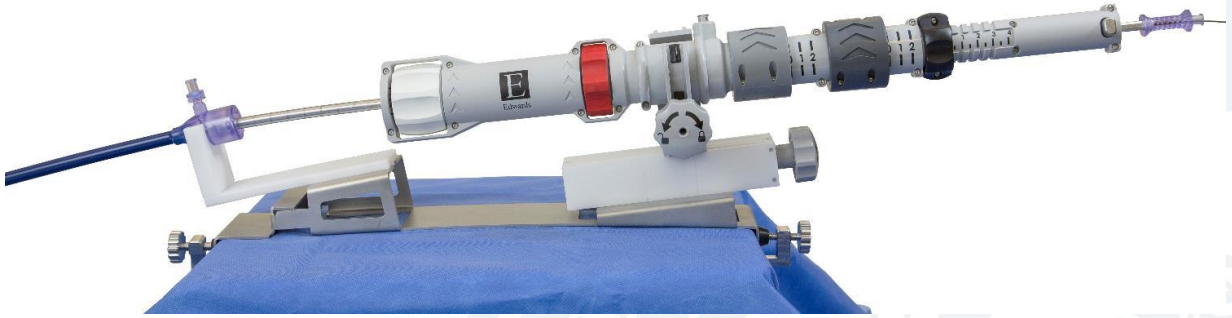
PRIMARY ENDPOINT:
Death & HF Rehospitalization at 1 Year

Follow-up: 30 days, 6 mos, 1 year and annually through 5 years

THE ENCIRCLE TRIAL

EVOQUE Eos: on-hold

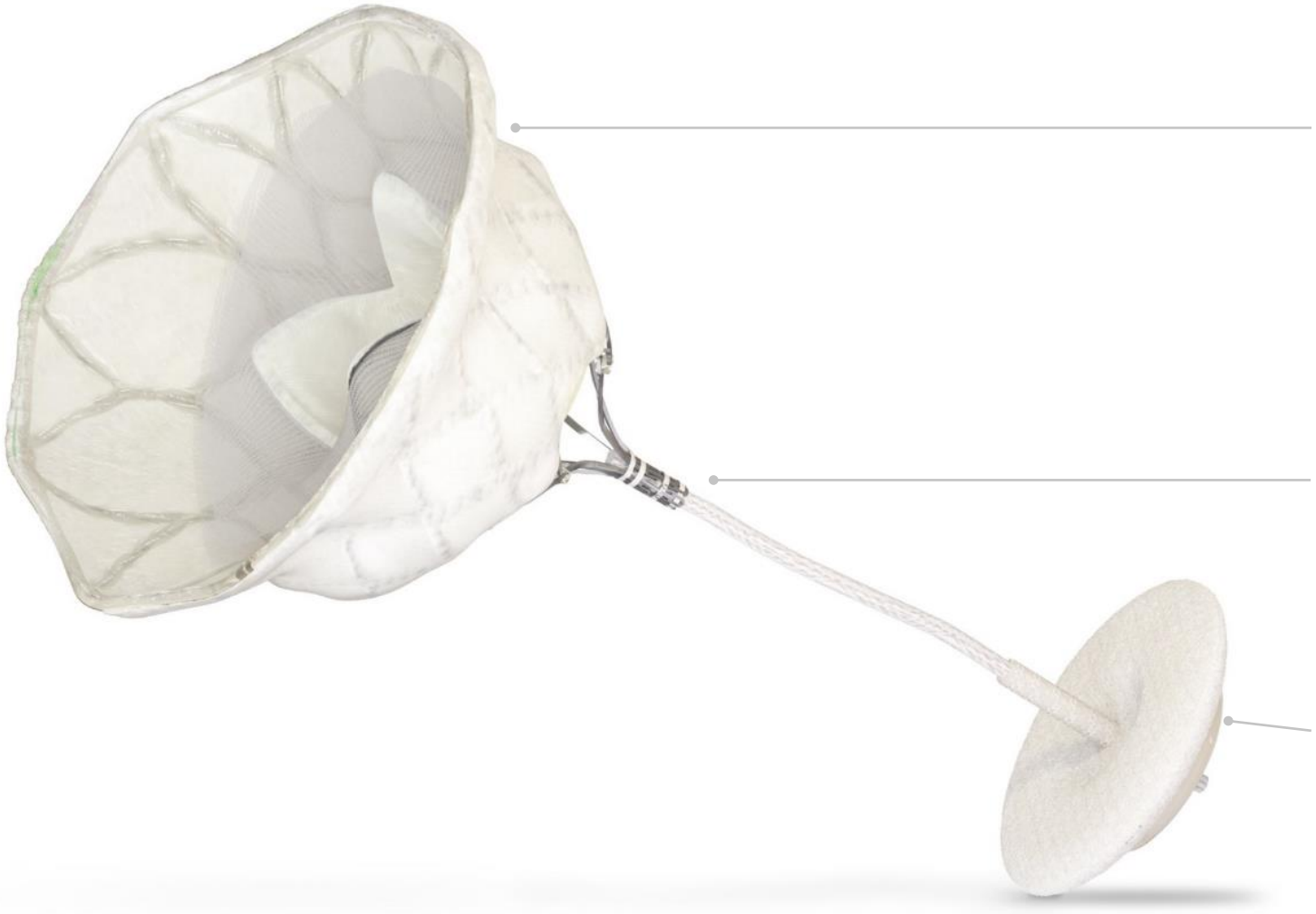




- Low profile 28Fr transseptal steerable delivery system (for both valve sizes) increases maneuverability and may reduce the need for septal closure
- Stabilizer system allows for increased ease of control during procedure
- Multiple planes of flexion enable coaxiality
- Independent depth control allows for precise positioning

TENDYNE Abbott

TENDYNE Abbott



VALVE DESIGN

- Tri-leaflet, porcine bioprosthetic valve
- Outer frame contoured to mitral annulus
- Multiple valve sizes and profiles to address broad range of patient anatomies

TETHER DESIGN

- Separates sealing from securement
- Enables full retrievability

APICAL PAD

- Placed over ventricular access site

Clinical Study Timeline and Milestones

2014 — First Tendyne Implant

2017 — EFS: first 30 pts 30-day FU

2019 — EFS: first 100 pts 1year FU

2021 — EFS: full cohort 192 pts 90-day FU

2021 — EFS: first 100 pts 2year FU

2022 — 1000 pts treated

2022 — TENDER: 108 pts 30-day FU

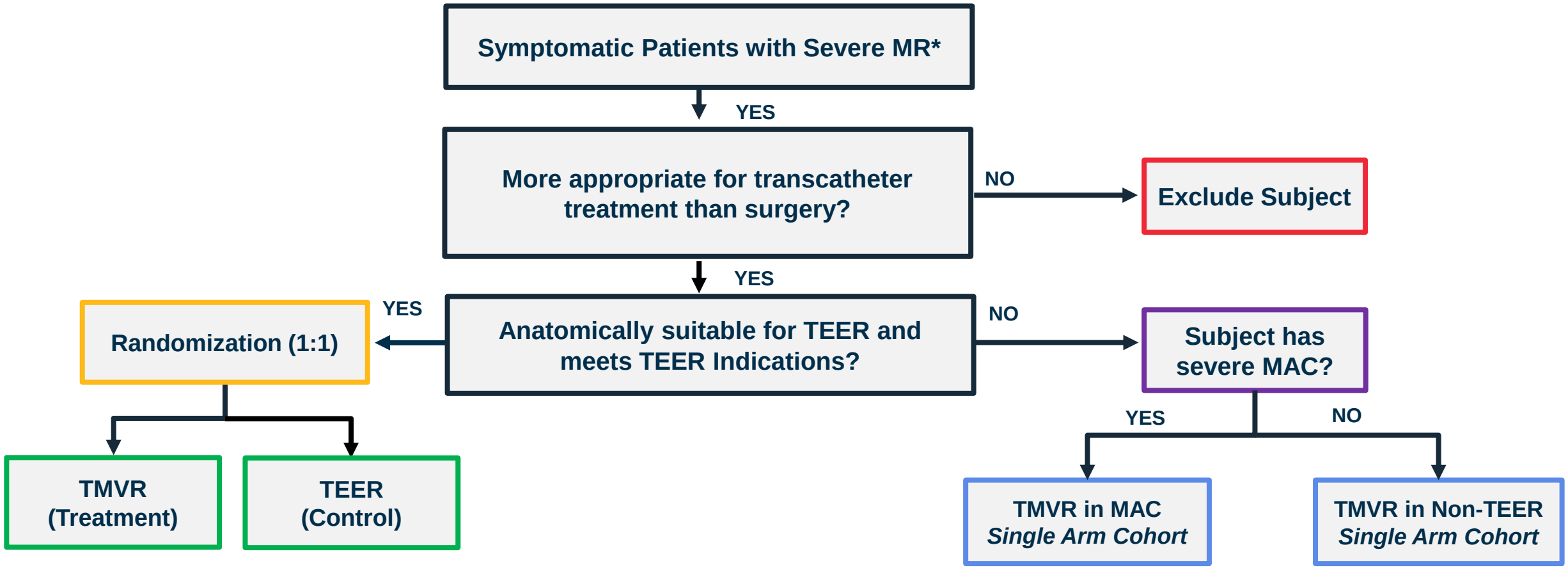
Ongoing — RESOLVE-MR
Prospective real-world study

Ongoing — SUMMIT
RCT

Ongoing — TENDER
Observational real-world study

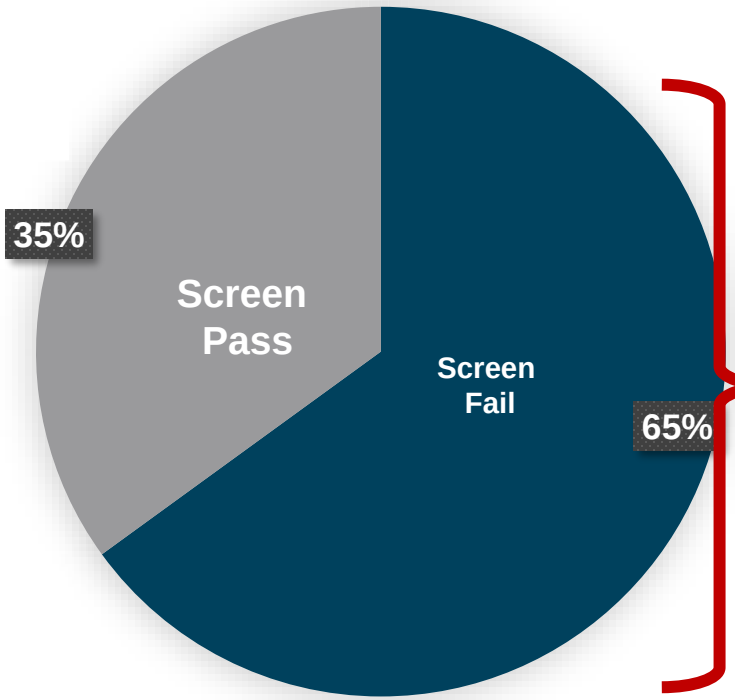
>1500 Patients Treated Worldwide

SUMMIT Trial Design

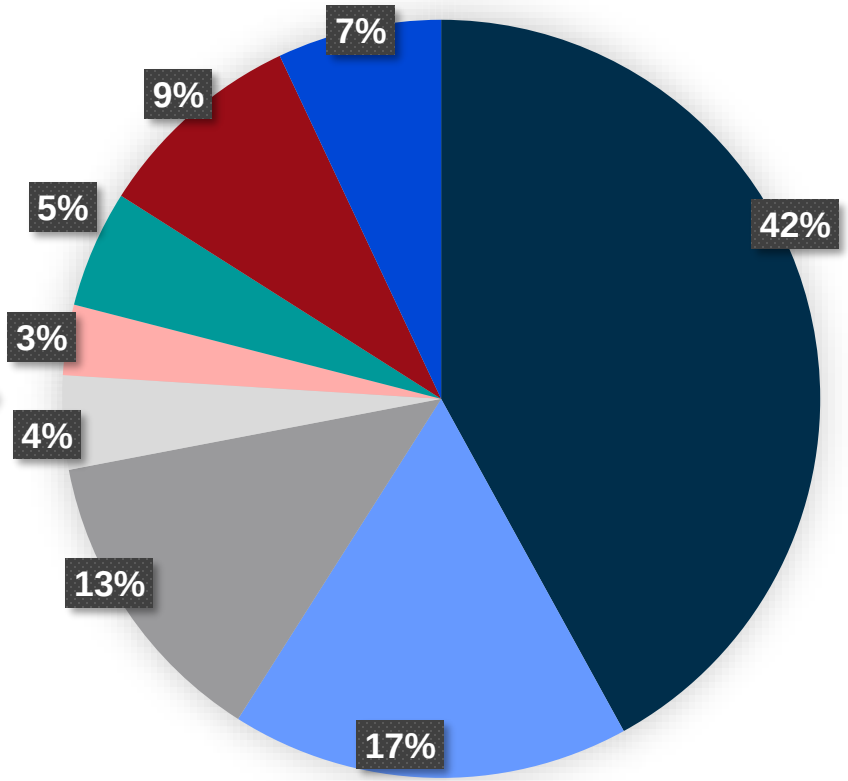


SUMMIT Screening

Screening Results



Reason for Screen Failure

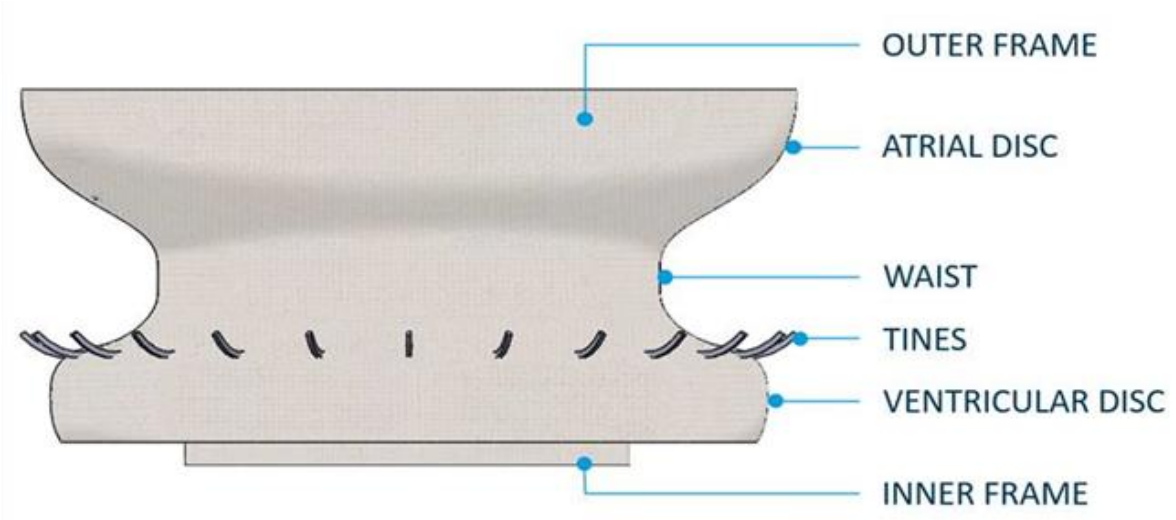


CEPHEA Abbott

CEPHEA TMVR

THREE MAIN COMPONENTS

1. *Self-expanding, radially-symmetric nitinol frames*
   - *Outer Frame – comprised of atrial and ventricular discs and waist*
   - *Inner Frame – comprised of functional valve orifice and commissure struts*
   - *Leaflets – bovine pericardial tissue (tri-leaflet)*
2. *Inner skirt – PET weave fabric*
3. *Outer skirt – PET/UHMWPE co-weave fabric*

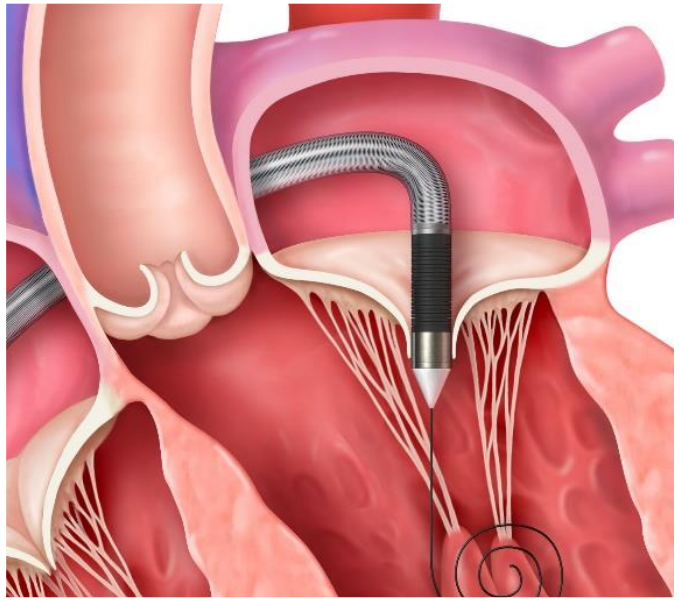


CEPHEA VALVE 36 MM

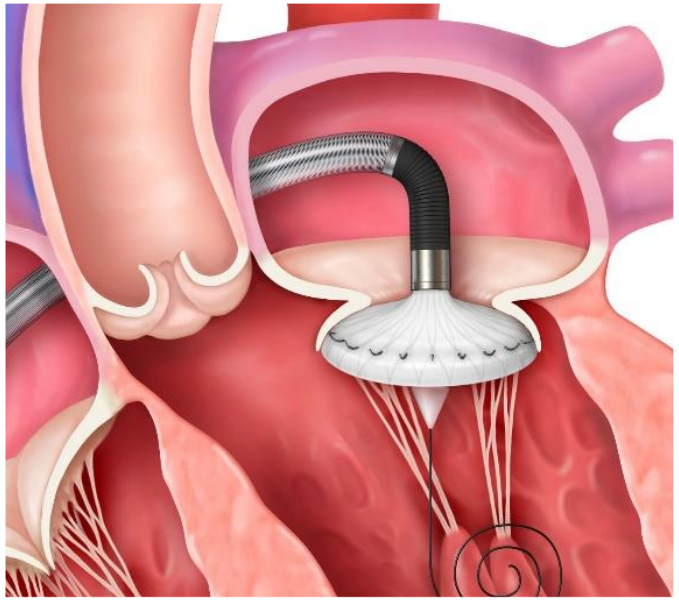
DUAL DISC DESIGN

1. *Anchoring*
2. *Self locating/self centering*
3. *Seals across a wide range of annulus sizes and shapes*

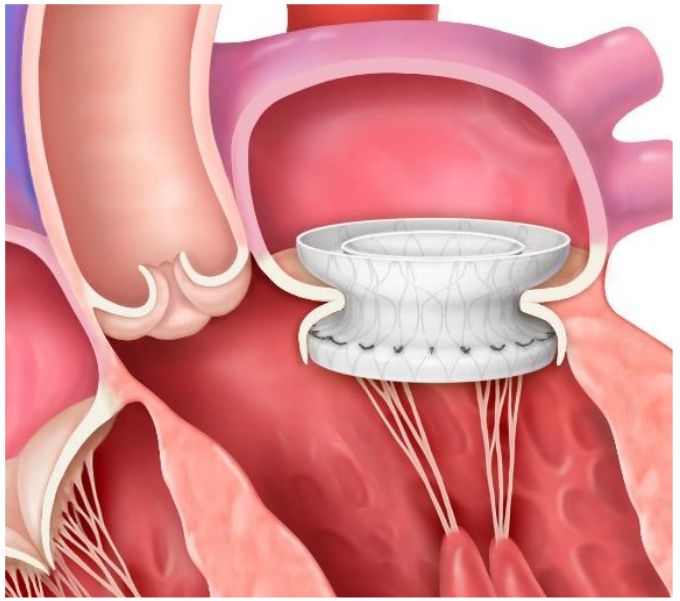
Cephea TMVR Procedure



1) After transseptal access, the delivery catheter is positioned across the mitral valve annulus using fluoro and TEE guidance.



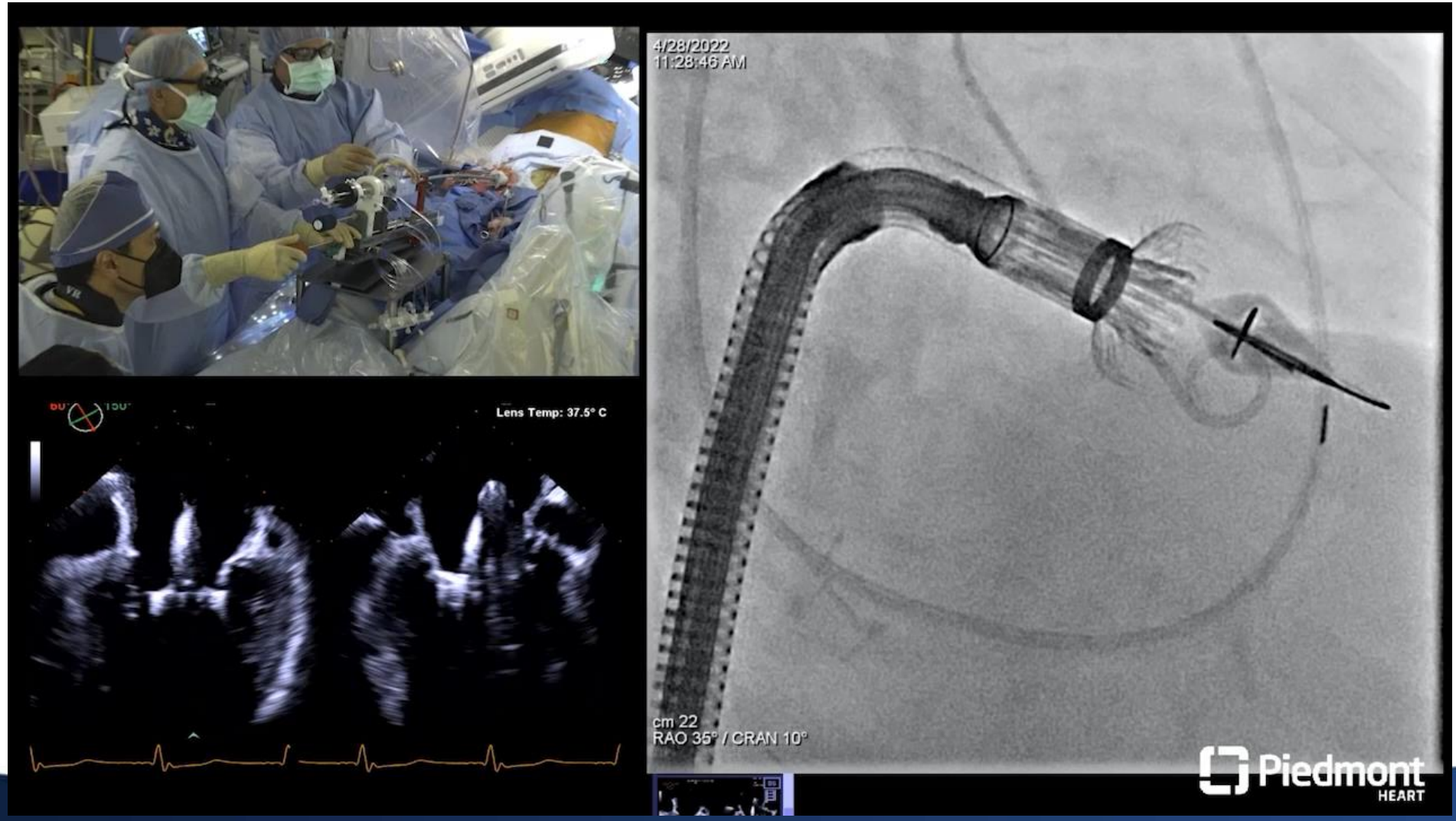
2) Valve delivery begins by drawing back valve cover to expose ventricular disc; valve seating confirmed via echo



3) Valve delivery is completed by exposing then releasing the atrial disc, at which time the valve is fully functioning

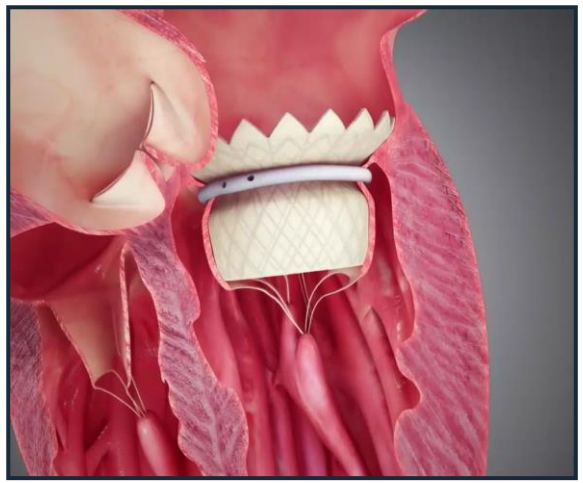
Cephea Procedure: 1st US Case

Deployment



HighLife

“Valve-in-Ring”



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Ring

Transfemoral artery

+

Valve

Transseptal delivery
(18F shaft and 29F capsule)

HIGHLIFE Clinical studies update

- **Europe/Australia study** – 6 countries, 37 activated sites, 36 patients treated, 8 pending implants
- **US EFS study** – 1 country, 8 activated sites, 2 patients treated, 2 pending implants
- **HighFLO study** – 6 countries, 11 sites activated, 2 patients treated, 2 pending implants
- **HighLife China** – 1 country, 1 site activated, 3 patients treated, 0 pending

HighLife - Clinical outcomes (n=30)

Event	n	%
Technical success	27	90
Leaving the Cathlab/OR alive	30	100
Successful access, delivery, retrieval of delivery systems	28	93
Freedom from emergent surgery or re-intervention	29	97

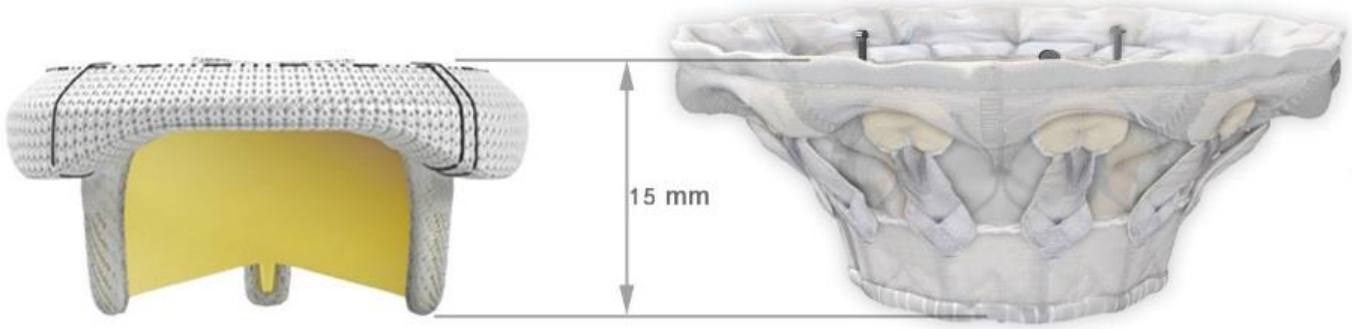
Event	30 days	30 days to 1 year
All death	3	2
Major Stroke	1	0
Conversion to surgery	1	0
Re-intervention / operation	1	0
Heart failure hospitalizations	1	6
Major Bleeding	4	0
ASD closure	0	4
Paravalvular Leak (PVL) >1+	0	1

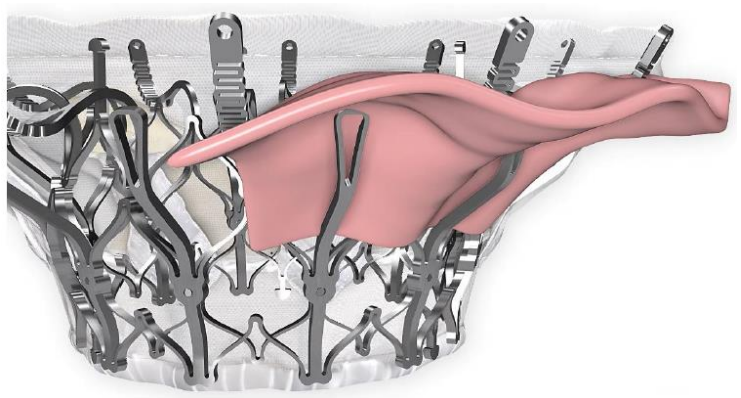
CRF TVT

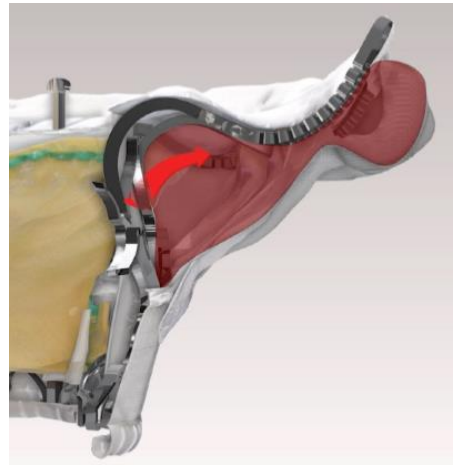
CARDIOVALVE

CARDIOVALVE

- Transfemoral trans-septal Delivery
- Low profile
- Leaflet anchoring
- Sealing cuff
- Size range 32-55 mm annular diameter





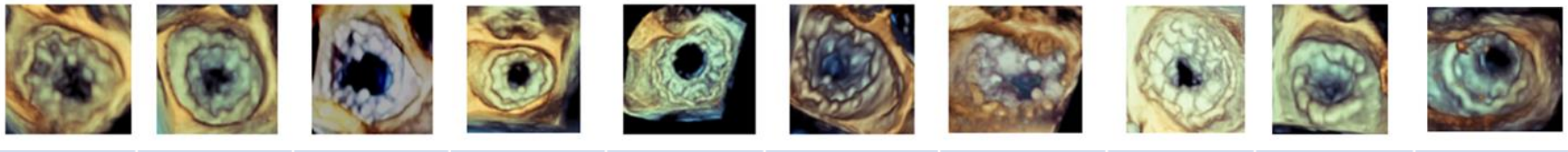


Valve Sizes

4 implant sizes in the same crimp profile

SMALL	MEDIUM	LARGE	X-LARGE
			
Fits Annular Diameter up to: **32-38mm** Prosthetic Valve Dimeter: **25mm**	Fits Annular Diameter up to: **36-43mm** Prosthetic Valve Dimeter: **27mm**	Fits Annular Diameter up to: **40-48mm** Prosthetic Valve Dimeter: **29mm**	Fits Annular Diameter up to: **44-55mm** Prosthetic Valve Dimeter: **29mm**

Mitral Cases – Acute results (N=13)

Patient #	L2-01 (Kaunas)	L2-02 (Kaunas)	A1-01 (Zurich)	L2-03 (Kaunas)	L2-04 (Kaunas)	CU-01-01 (Bonn)	001-02-1 (Piedmont)	001-212-1 (Mainz)	L2-05 (Kaunas)	L2-06 (Kaunas)	001-214-1 (Lubeck)	001-216-1 (Berlin)	UVA-M001 (Virginia)
PVL	No	No	No	Mild	No	Mild	Mild	Trace	Mild	Mild	Trace	No	Mild
LVOT Obstruction	No	No	No	No	No	No	No	No	No	No	No	No	No
MV Gradients [mmHg] (Core Lab)	5	3	2	5	3	3	5	2*	9	5	0*	3	3
Complete Deployment	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	yes
Technical Success	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes
DS time [min]	30	23	40	30	21	116	55	85	27	15	40	83	61
Acute Result													

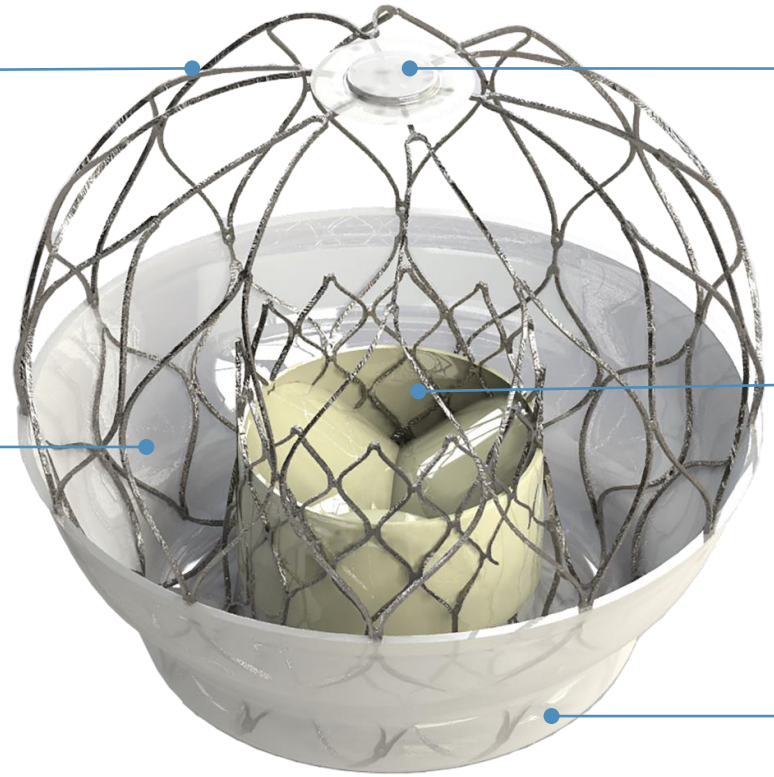
*According to site

AltaValve 4C Medical

AltaValve Implant Overview

STENT FRAME
Flexible to conform to LA anatomy and not inhibit atrial contraction

24FR STENT STRUTS
Allows future LA access for procedures



STENT CAP

TISSUE VALVE
One valve size for all implants

ANNULAR RING
Fabric covered to prevent paravalvular leakage

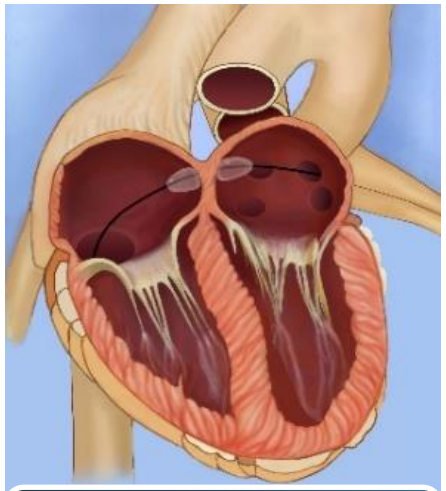
CRF TVT

**Prior to release of implant from delivery catheter (transseptal)*

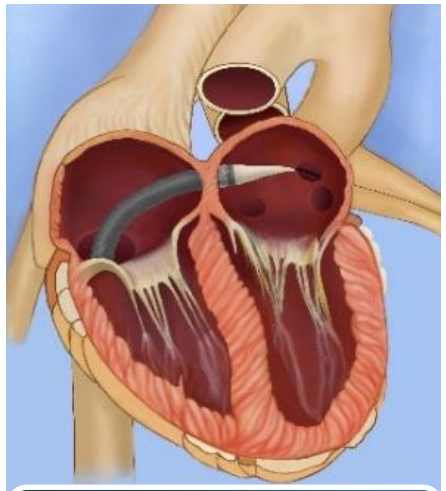
AltaValve TS Procedure

FIVE simple steps

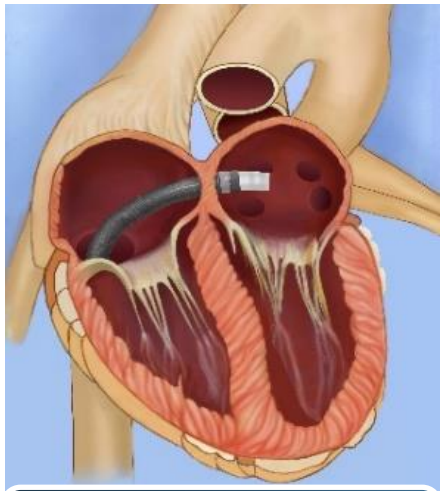
ONE-STAGE streamlined delivery



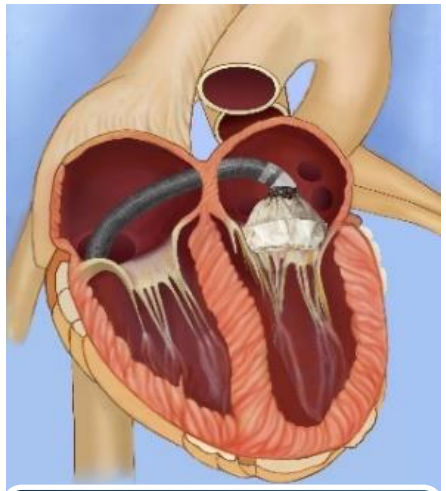
Transseptal Access



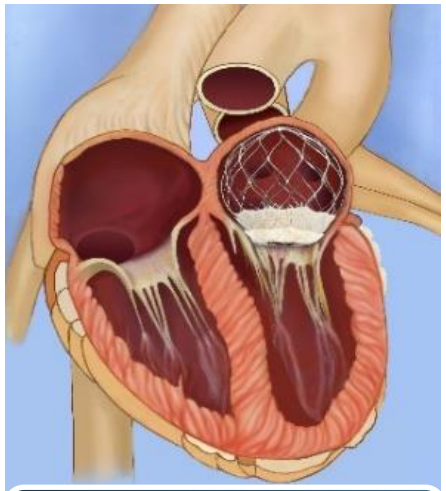
LA Access



Navigate to MVA



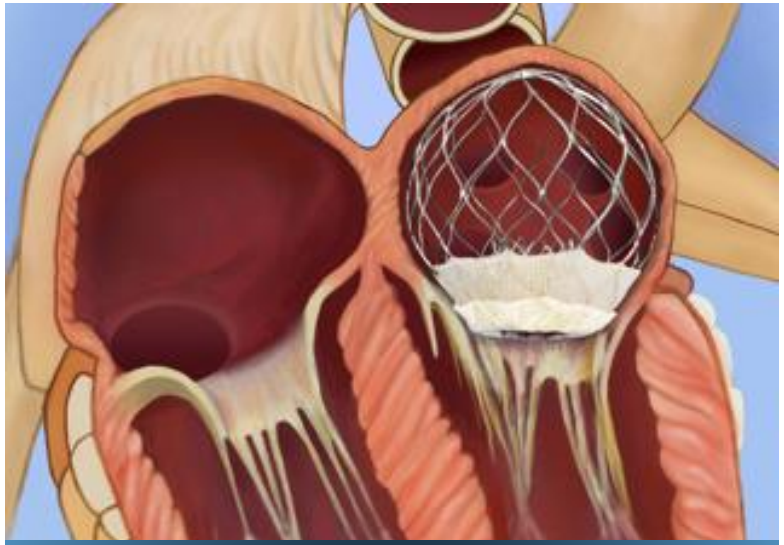
Deployment



Release

CRF TVT

AltaValve: A New Generation of TMVR



SUPRA-ANNULAR

NO HOOKS, BARBS or RIGID ANCHORING

CAUTION – AltaValve is an investigational device

High Anatomical Acceptance Rate

- Design **minimizes current anatomical TMVR limitations** including narrow LVOT, annulus size, and mitral annular calcification (MAC) while **preserving future left atrial access.**

Low Profile 29-Fr Transseptal Delivery

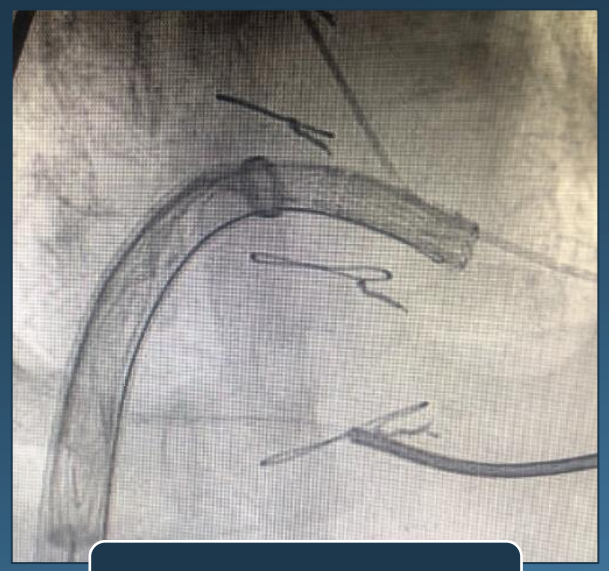
- **Single Stage deployment**
- **Ability to reposition and recapture** after full deployment*

CRF TVT

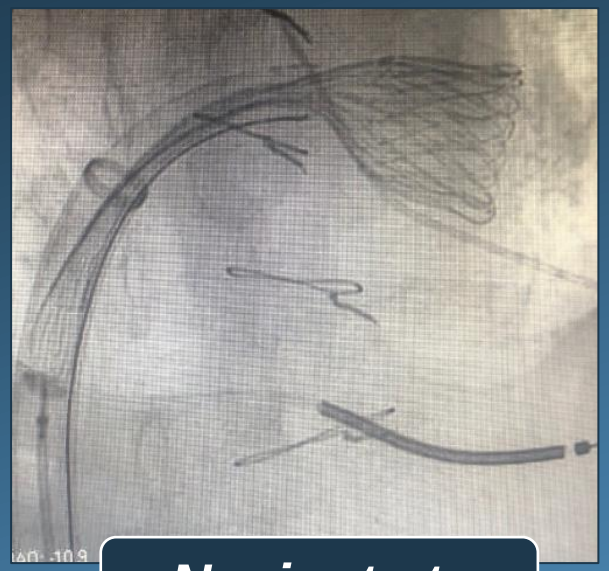
*Prior to release of implant from delivery catheter (transseptal)

First in Human Transseptal (TS) AltaValve Procedure

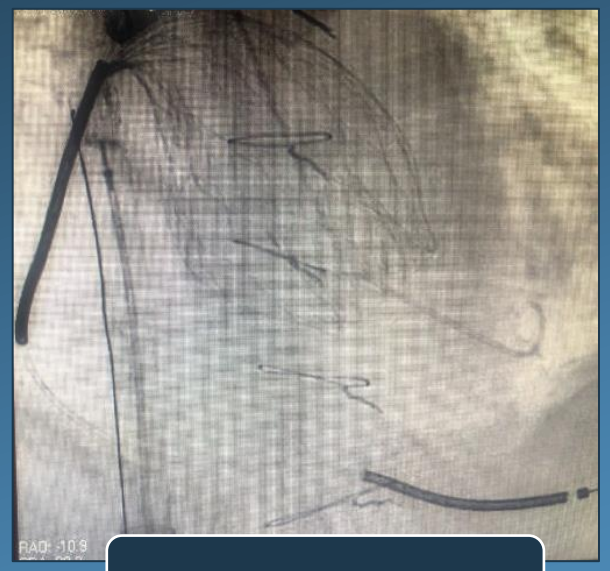
1st Gen System



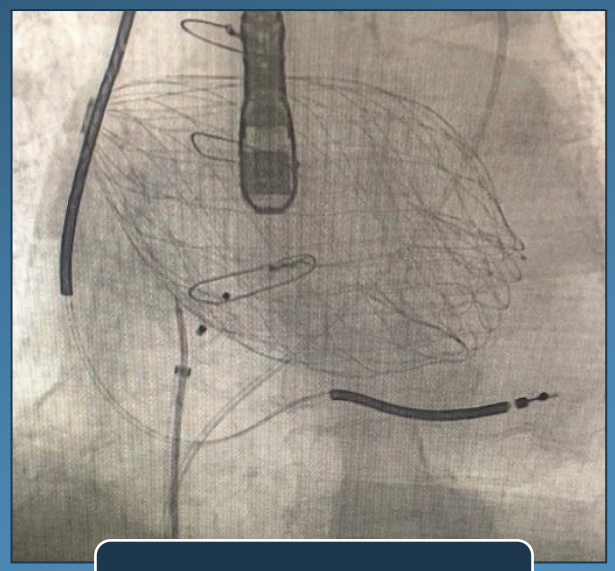
LA Access



Navigate to MV annulus

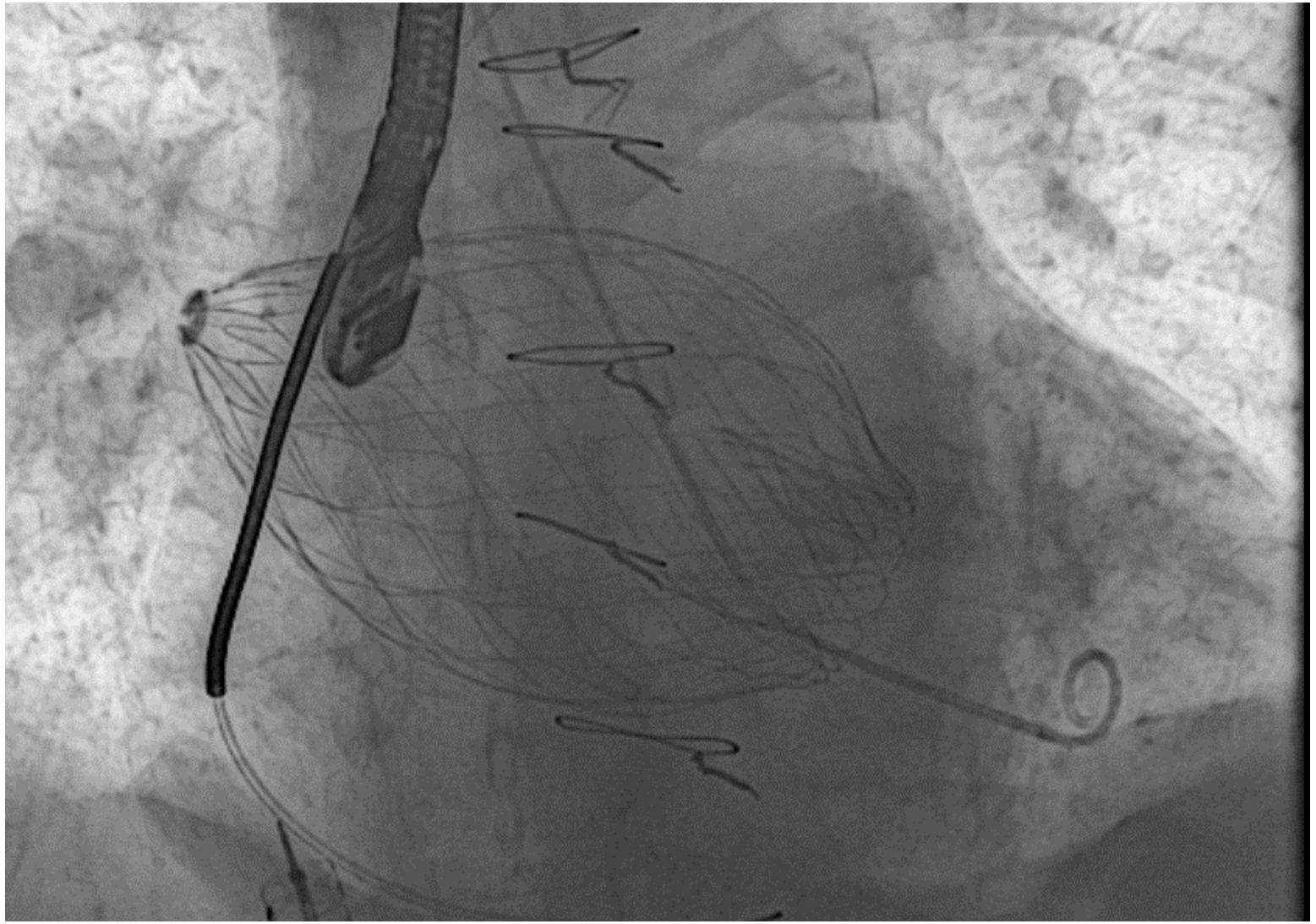


Deployment



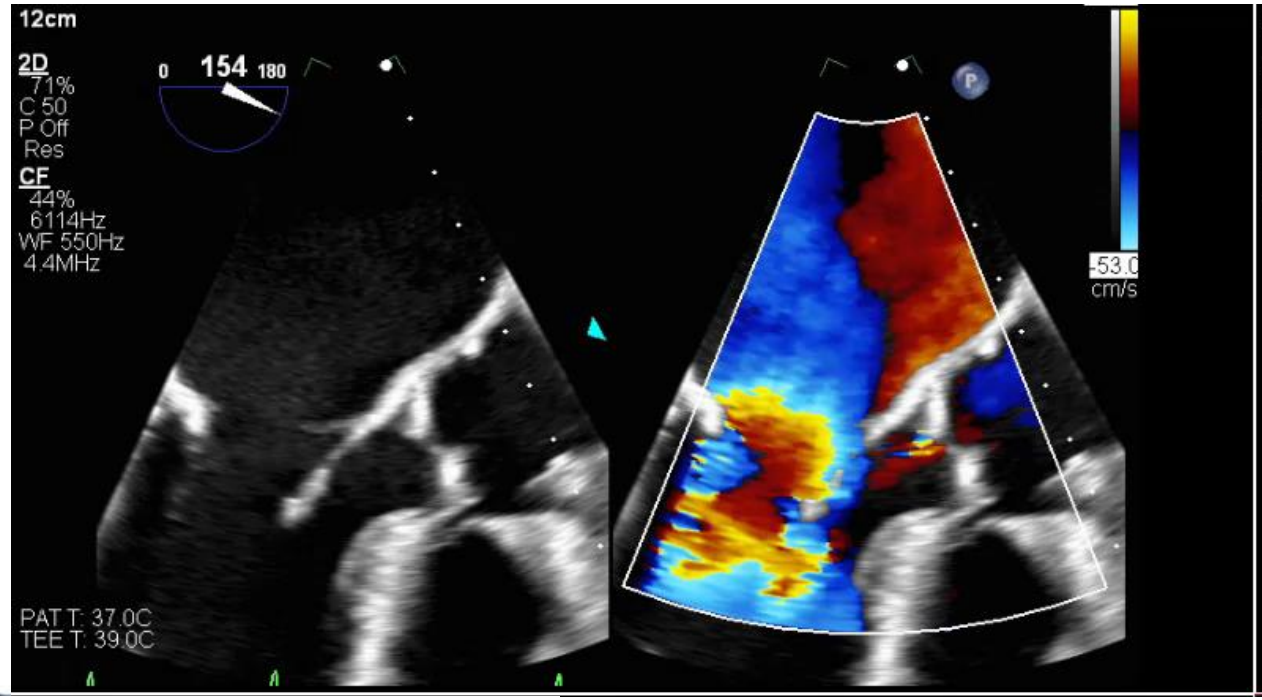
Release

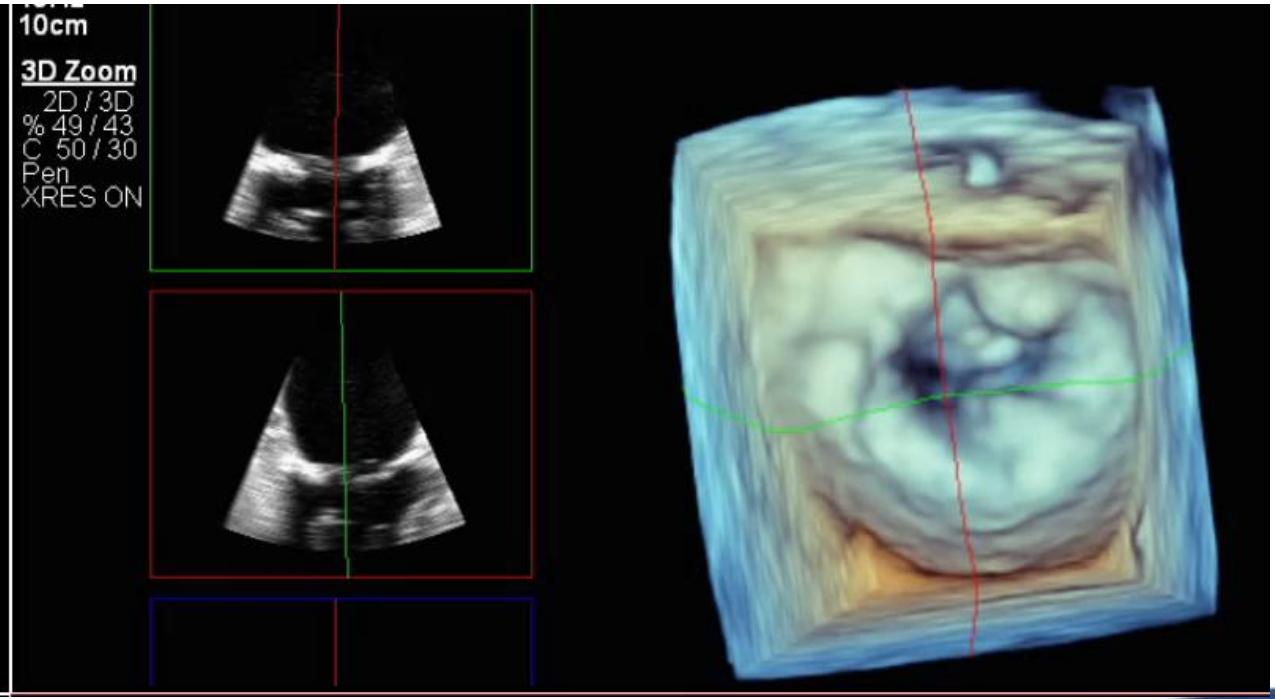
First-in Human TransSeptal 4C AltaValve



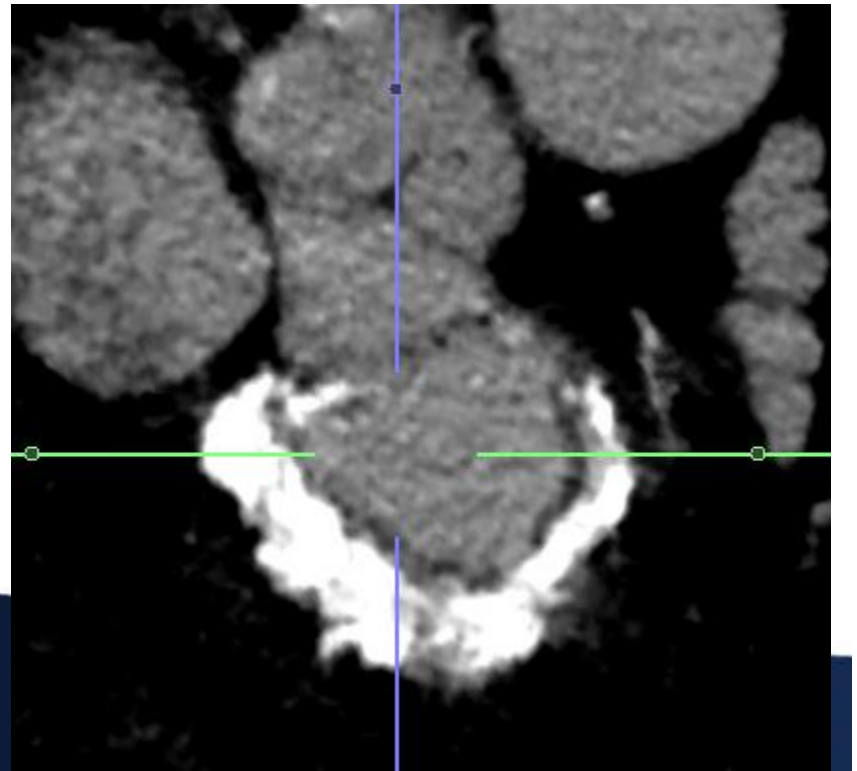
Morristown Medical Center (Morristown, NJ, USA)
Philippe Généreux, Robert Kipperman, Kosta Koulogiannis, Jim Slater, Leo Marcoff, Sept 23 2019

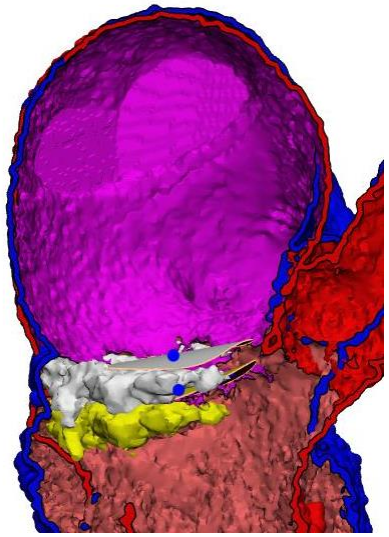
Severe MR, Severe MAC
Not TEER candidate
Turned down by other TMVR platforms

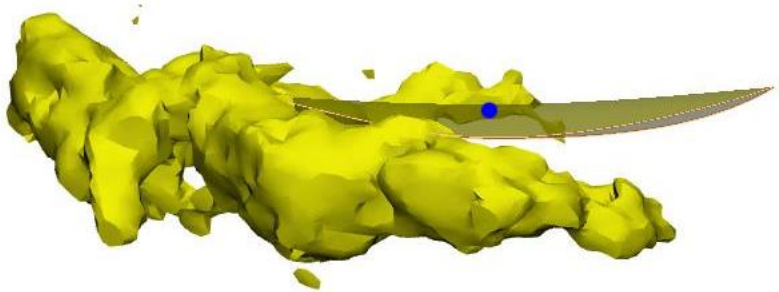


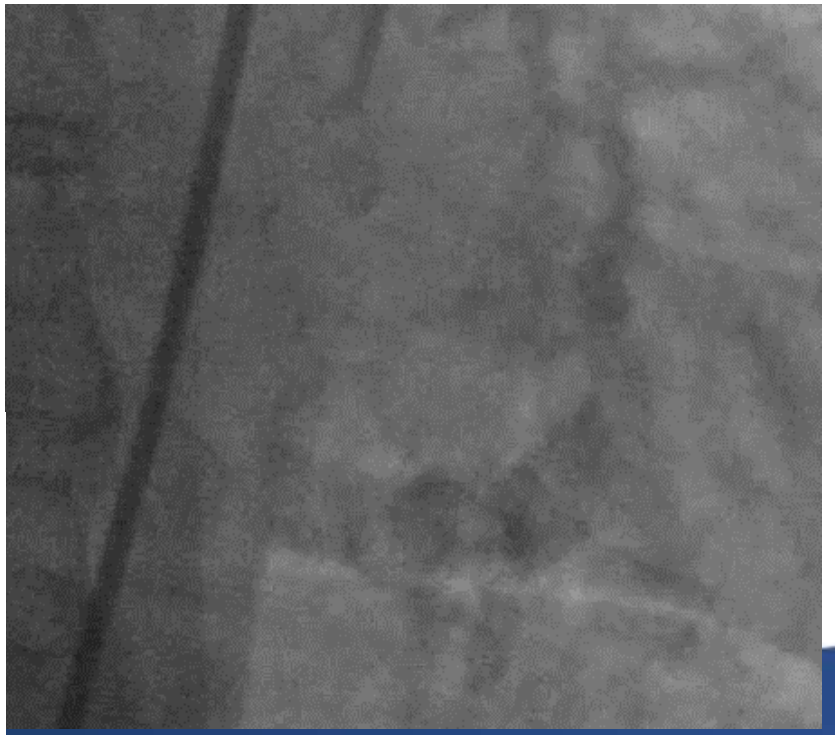


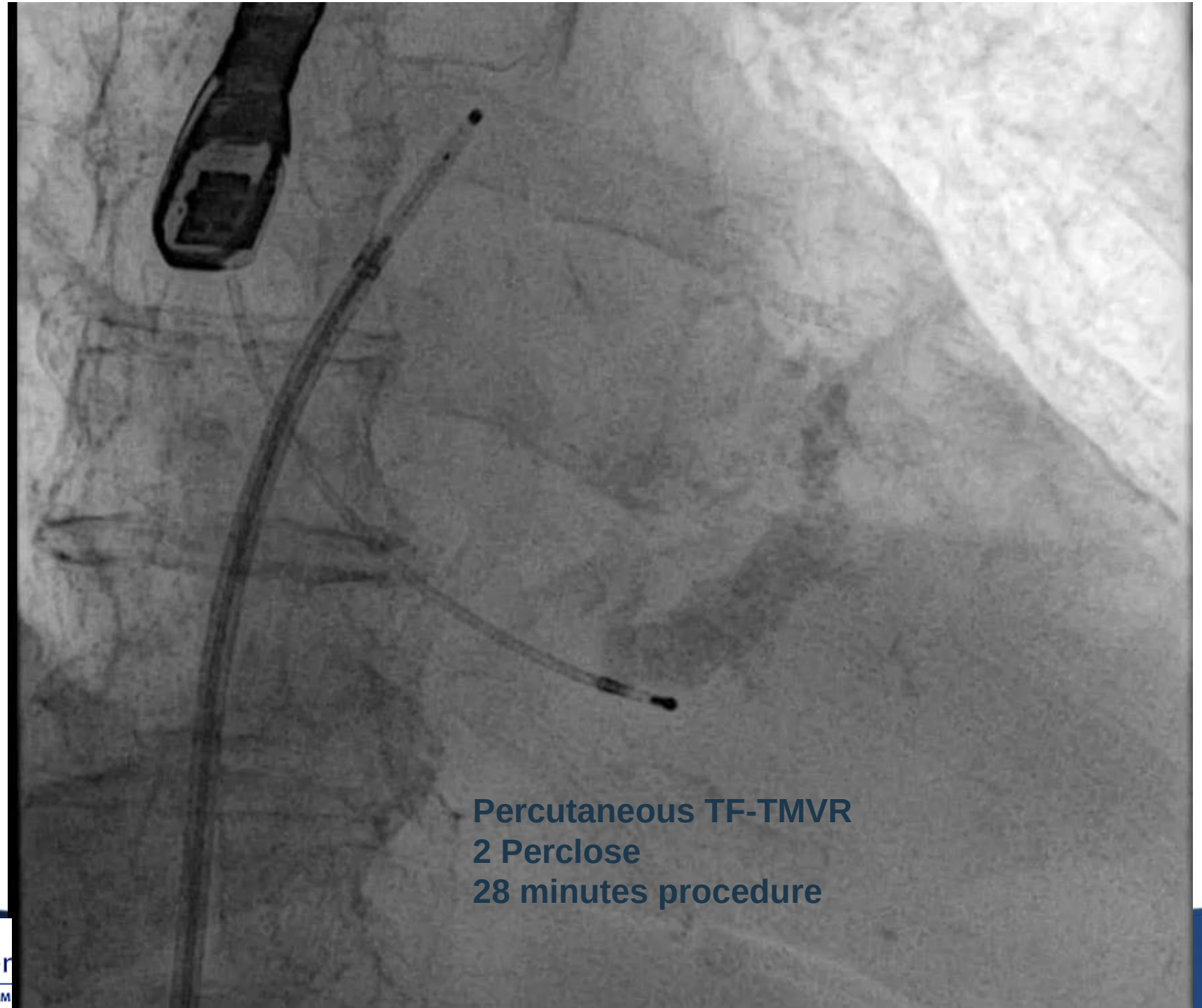
Severe MR, Severe MAC
Not TEER candidate
Turned down by other TMVR platforms



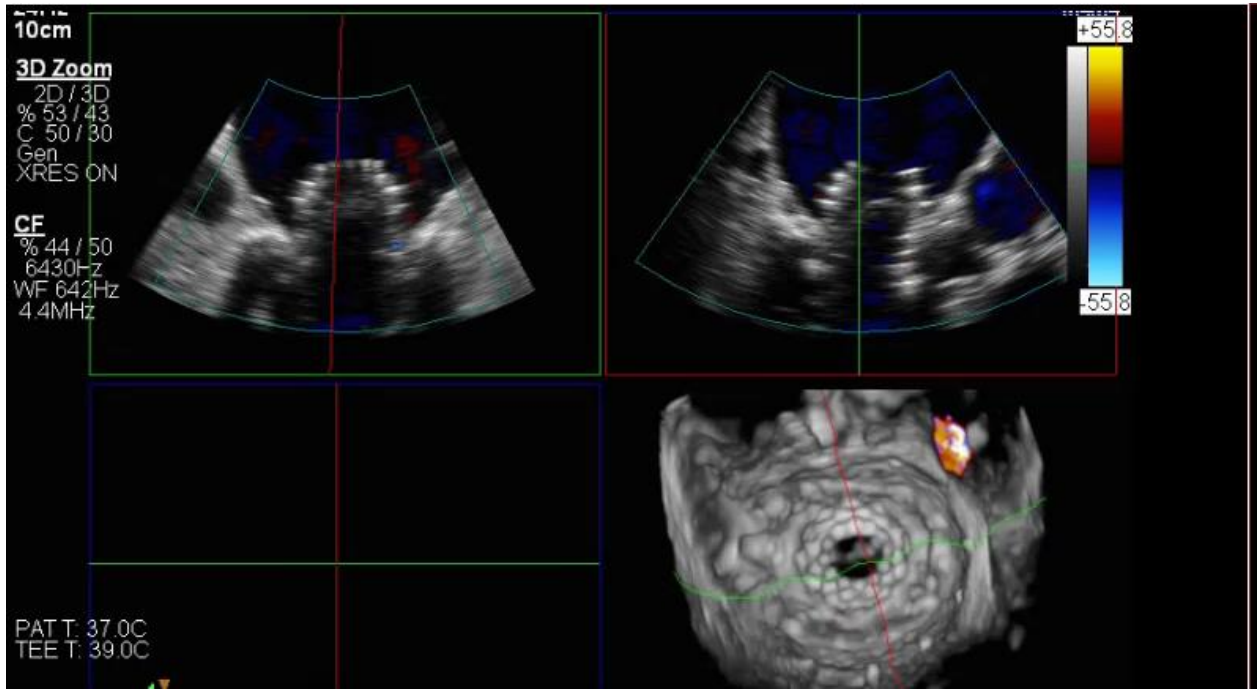


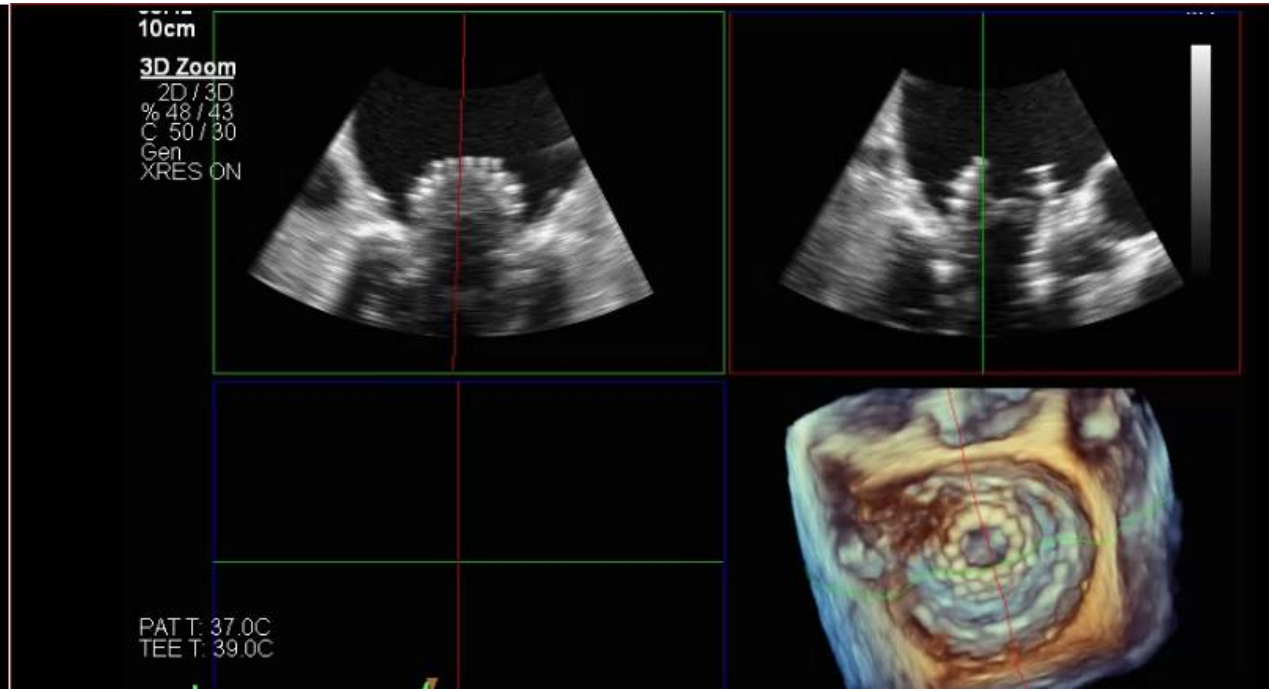




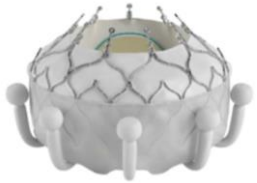

Percutaneous TF-TMVR
2 Perclose
28 minutes procedure

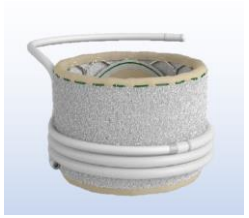
Post TMVR AltaValve 4C Medical
Mean gradient 1mmhg, Trace PVL





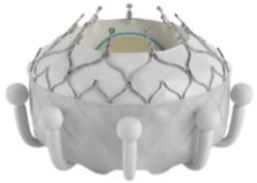
Current TMVR Investigation Landscape

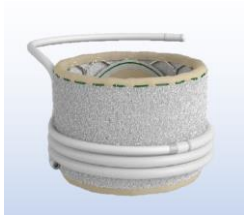




TMVR device	Access	~Cases	Status
Tendyne	TA	>1500	CE-marked & US Pivotal ongoing
Intrepid	TA	>300	CE-mark study complete ? US Pivotal
Tiara	TA	>80	CE-mark study complete
Sapien M3	TS	>200 TS	Feasibility done US Pivotal
HighLife	TS	>50 TS	Feasibility well underway Indication extensions coming
Intrepid-TS	TS	>30 TS	Feasibility
Evoque/EOS	TS	>30TS	Feasibility restarted with EOS; on hold
4C	TA-TS	>30	Feasibility on going
Cephea	TS	>10	Feasibility on going
Cardiovalve	TS	>15	Feasibility ongoing

Current TMVR Investigation Landscape





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Evoque/EOS	TS	>30TS	Feasibility on hold
4C	TA-TS	>50	Feasibility on going
Cephea	TS	>10	Feasibility on going
Cardiovalve	TS	>15	Feasibility ongoing

Conclusion TMVR

- **TEER will probably still dominate for ~5-10y**
  - Ease of use/Safety/scalable
  - Strategy of TEER first than TMVR on failed TEER possible
- **Remaining TMVR challenges:**
  - Planning/Sizing/Screen failure still ~30 to 50%
  - Sheath-device profile/ASD
  - Navigation/Positioning/Anchoring/Stability
  - LVOT obstruction
  - PVL
  - Valve thrombosis
  - Re-capturability (“1 shot deal”)
  - Need for systemic anticoagulation
  - Re-treatability