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December 9, 2021



Mitral Valve: Next Generation Devices

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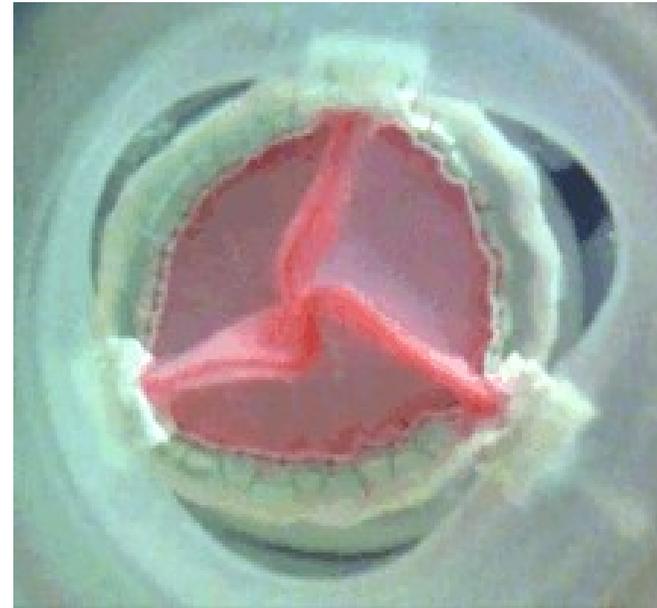
FINANCIAL DISCLOSURE

I, Eberhard Grube have the following financial interest/arrangement that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation

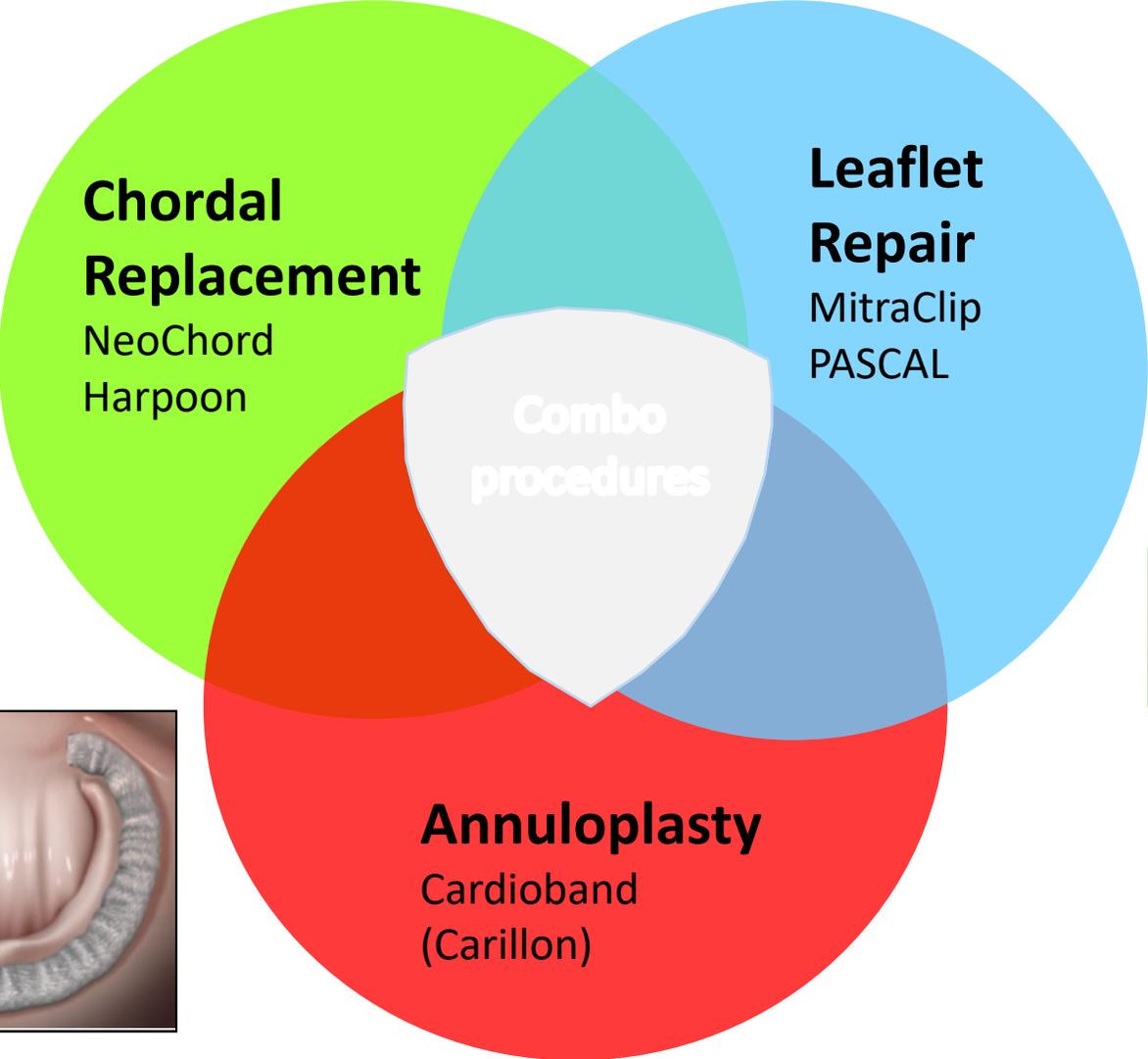
Speaker Bureau/ SAB: Medtronic, Boston Scientific, HighLife, Jena Valve, Protembis

Equity Interest: Cardiovalve, Claret, Shockwave, Valve medical, CardioMech, Millipede, Imperative Care, Pi-Cardia, Ancora, Laminar, ReNiva Medical

Painfully, we learned that the Mitral Valve is very different from the Aortic Valve



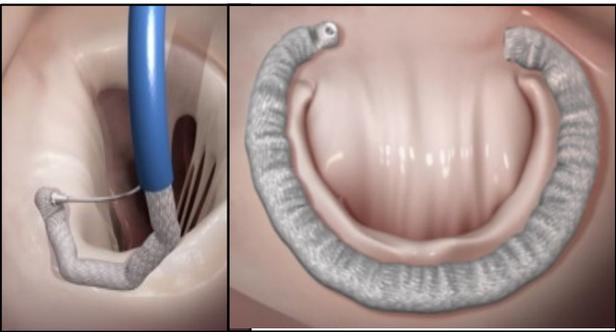
Expanding portfolio of transcatheter mitral repair and replacement



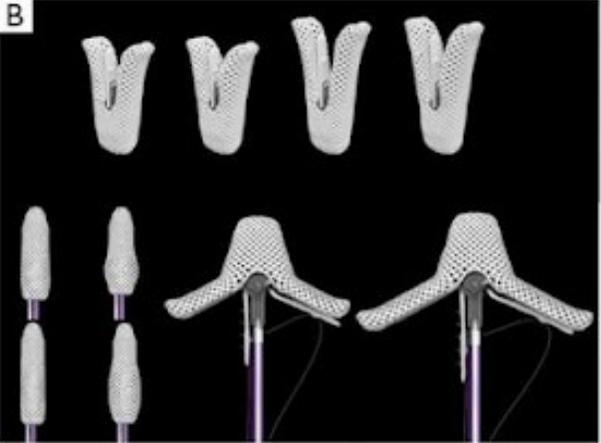
NeoChord



Harpoon



Cardioband



MitraClip XTR/W & NTR/W



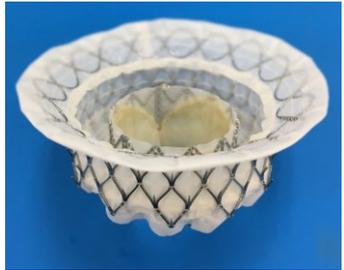
PASCAL

Replacement

Tendyne, Intrepid, Tiara, Cardiovalve, HighLife, etc.



Tendyne

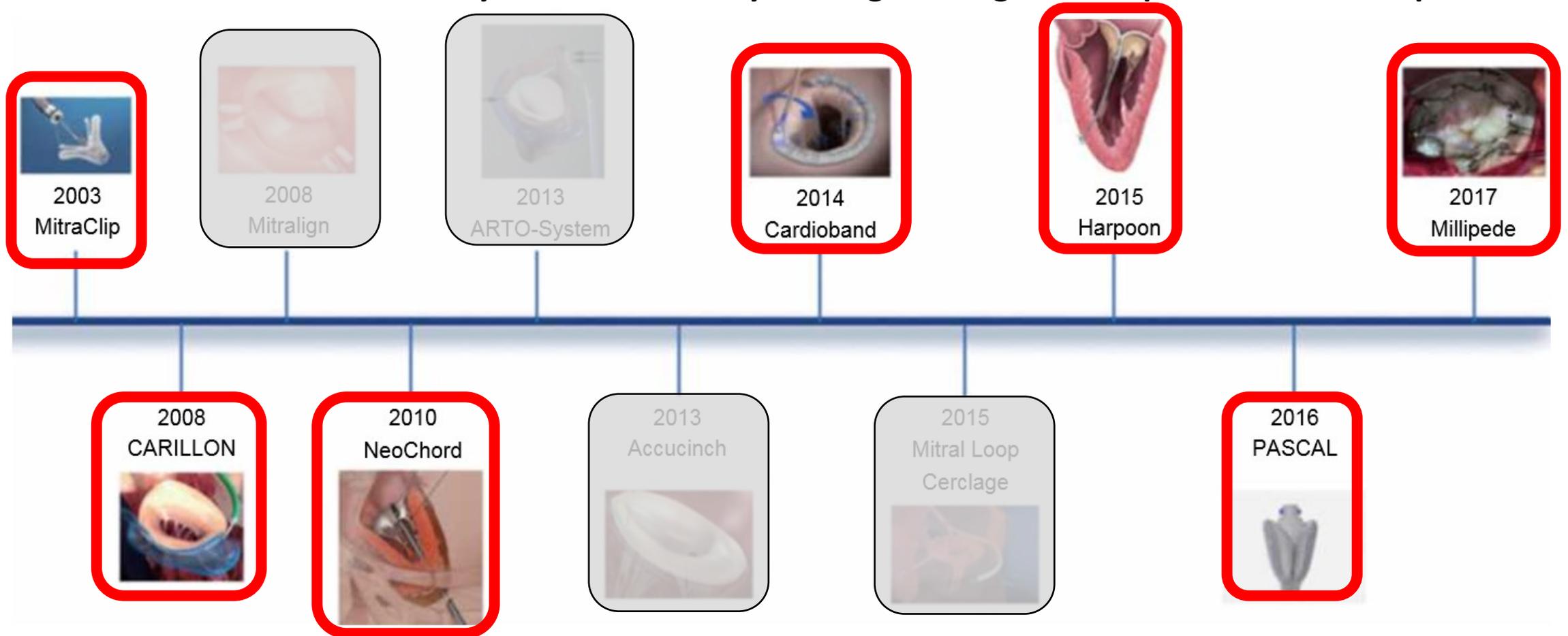


Intrepid

TRANSCATHETER MITRAL VALVE REPAIR THERAPY (TMVr)

The TMV repair landscape is rapidly changing. Data showed good safety performance but need improvement in efficacy and user friendliness

A real milestone has only been achieved by the Edge-to-Edge Technique of the MitraClip



MITRAL VALVE REPAIR – TMVr

New Devices?

TRANSCATHETER MV REPAIR

PERCUTANEOUS CHORDAL REPAIR

Transcatheter *transseptal* chordal replacement are the next phase for this technology but remain at an **early stage, with most devices either in preclinical development or limited human experience.**

Transseptal Systems

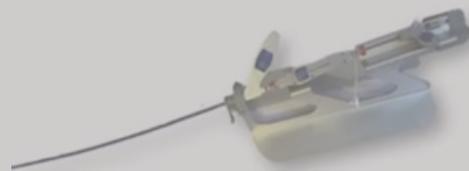


NeoChord NeXus

Leaflet capture → Anchor
→ Tensioning

Milestones:

Early experience in 3 cases

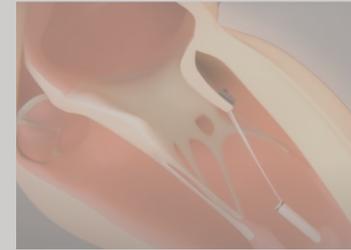


ChordArt

Leaflet → Anchor

Milestones:

Experience: 5 cases in
feasibility study



Pipeline

Anchor → Pledget →
Adjust & Lock

Milestones:

Experience: FIH completed

NeoChord NeXus

FIRST IN HUMAN EXPERIENCE

3 Patients Successfully Treated

- Discharged at day 4

Significant MR Reduction Achieved

- MR reduction from severe (4+) to maximum **trace** in both patients

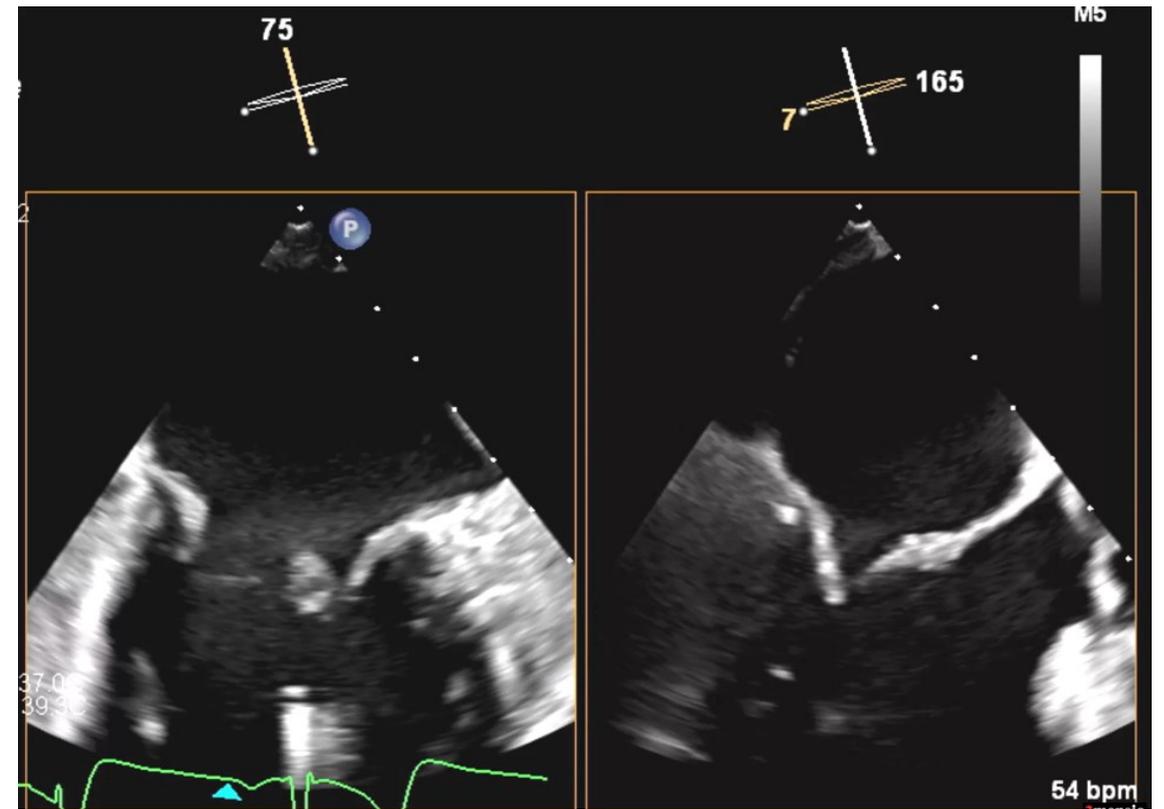
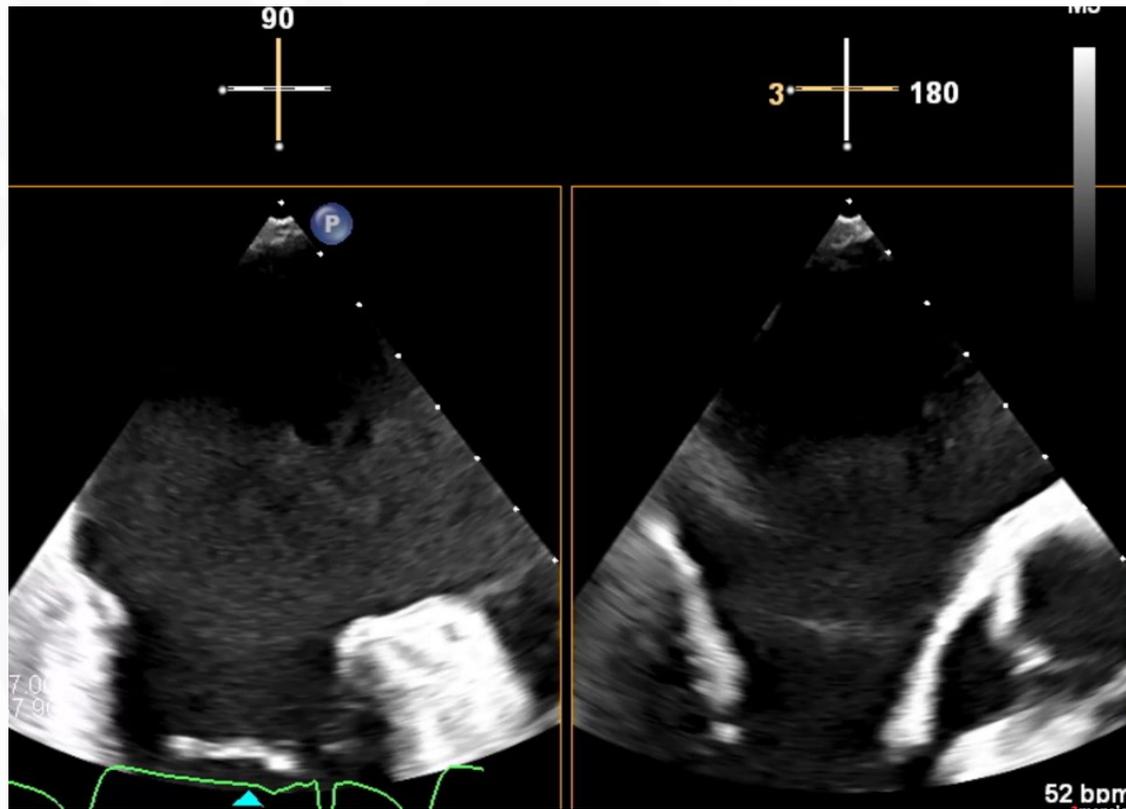
Durable & Stable Anchoring

- **Stable leaflet connection and papillary muscle anchor**, patients are doing well at 30 days (N=1) and 60 days (N=1)

Pre and Post Implant Mitral Valve – 2D

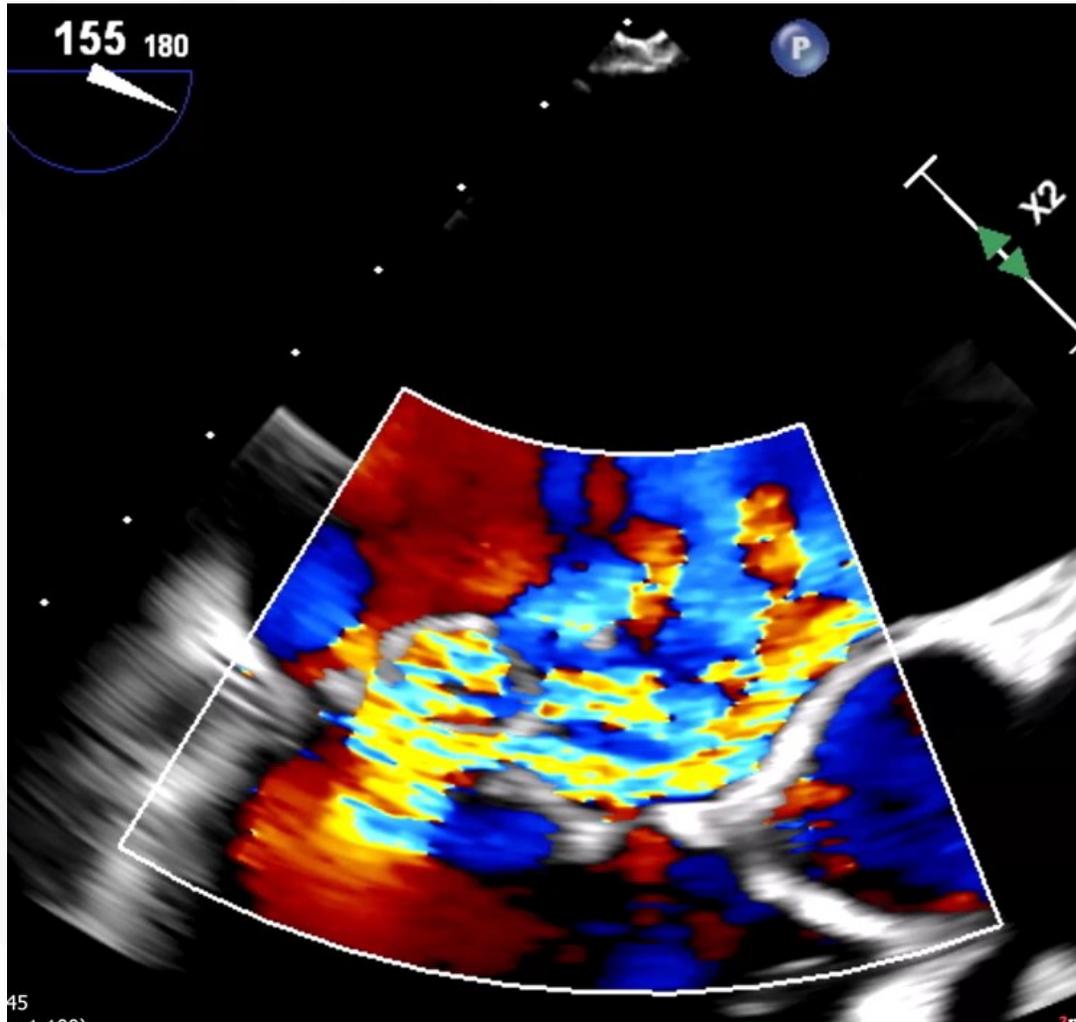
Pre-implant

Post-implant

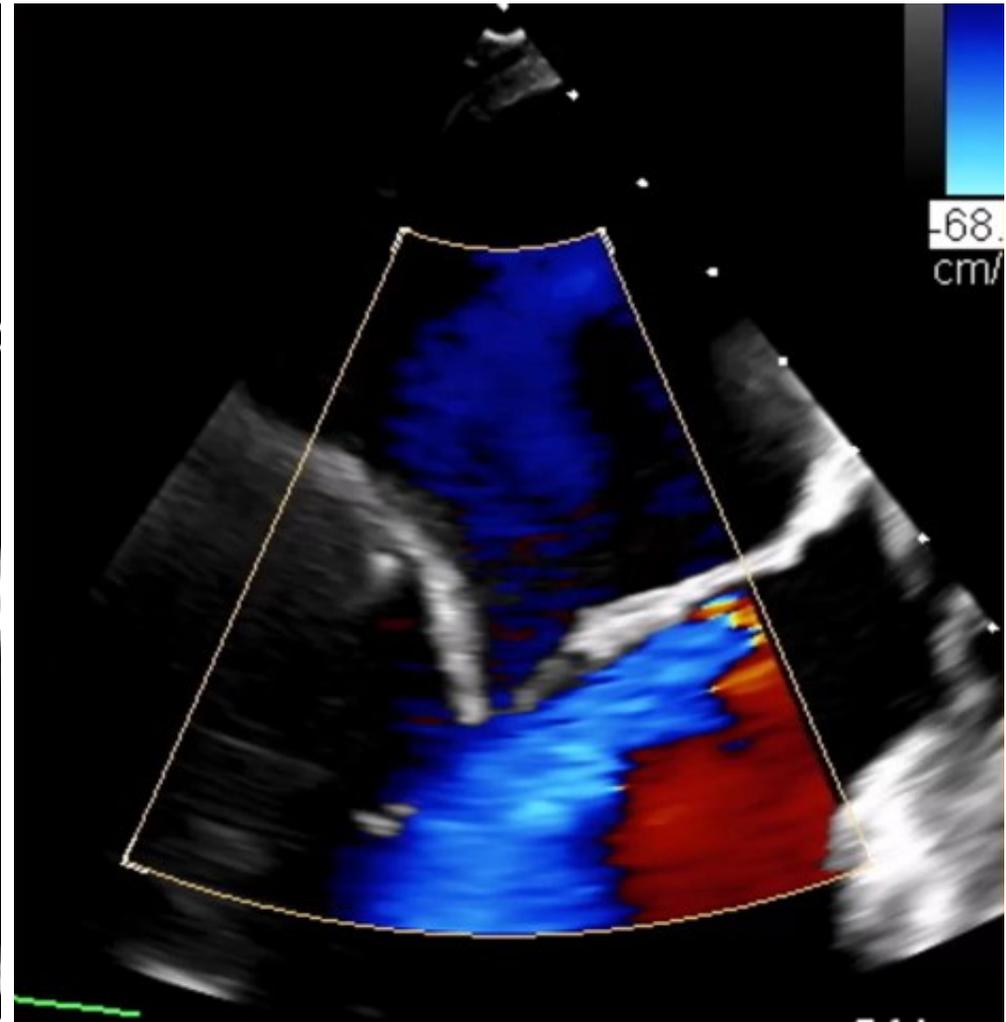


Pre and Post Implant Mitral Valve – Color

Pre-implant



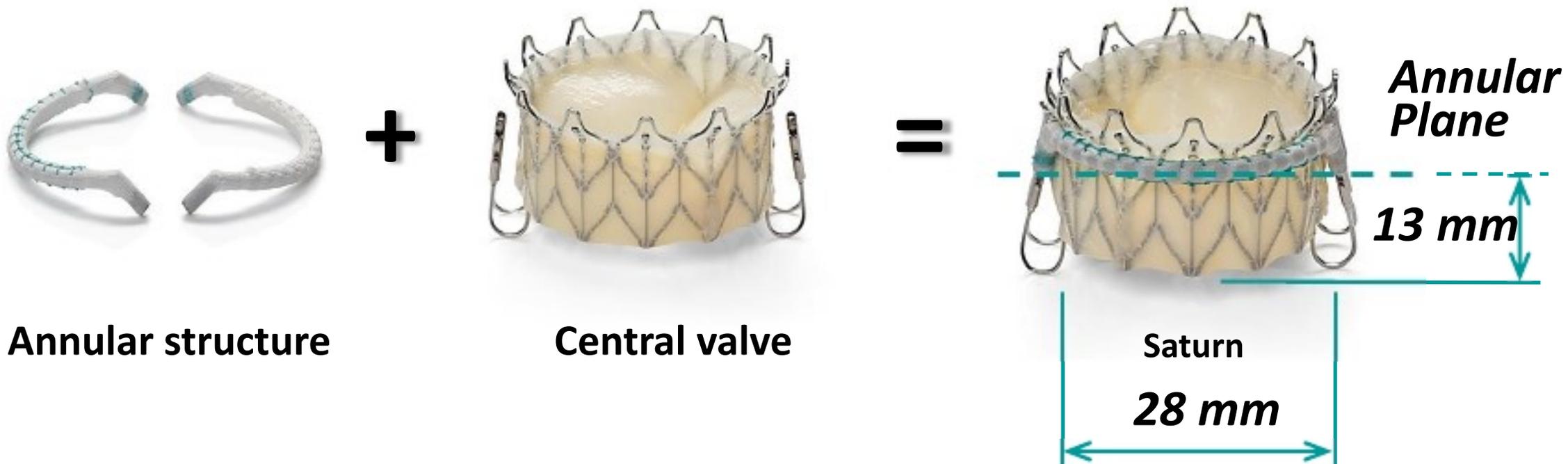
Post-implant



SATURN ADAPTIVE TECHNOLOGY (InnovHeart)

The Saturn TMVR is a single device characterized by:

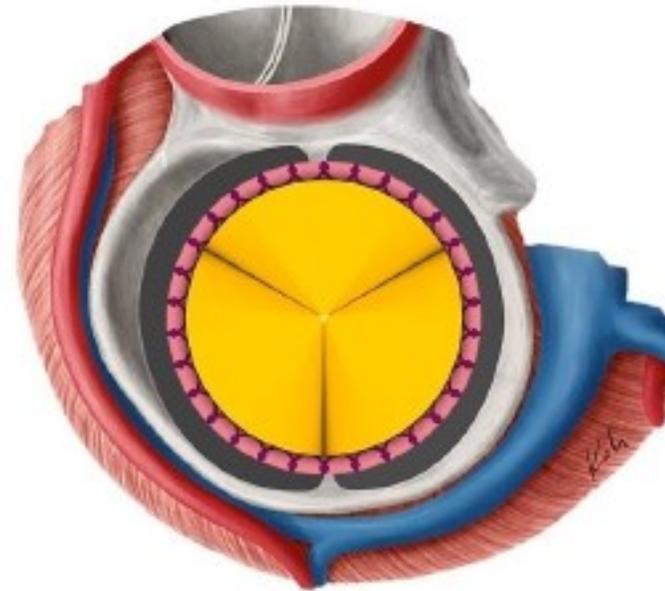
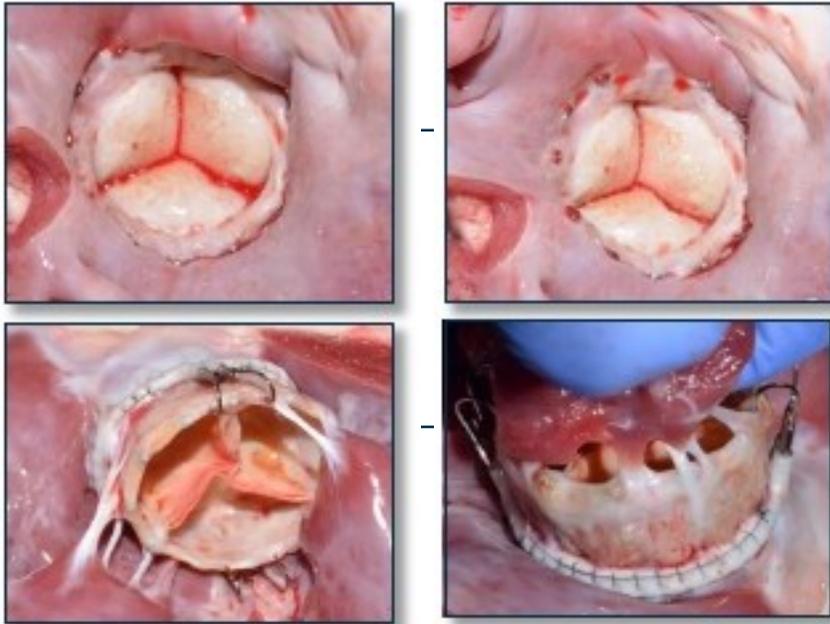
An Annular Structure mechanically connected to a Central Valve.



SATURN ADAPTIVE TECHNOLOGY (InnovHeart)

A SOLUTION TO ADDRESS THE CHALLENGES AND WIDE VARIABILITY OF NATIVE ANNULUS SIZES

- **Size reduction of the Mitral Annulus**
- **Stabilization of the Mitral Annulus**



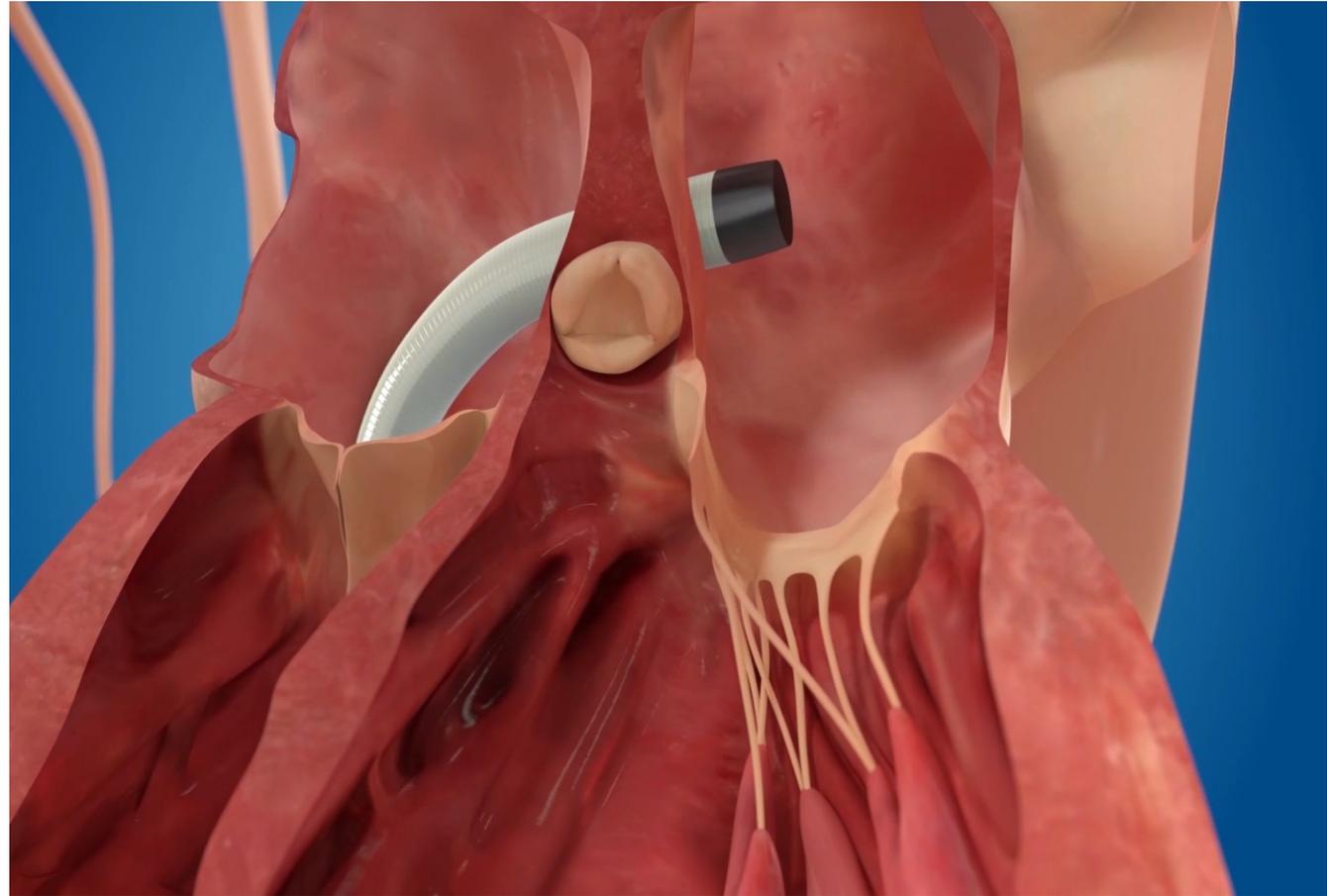
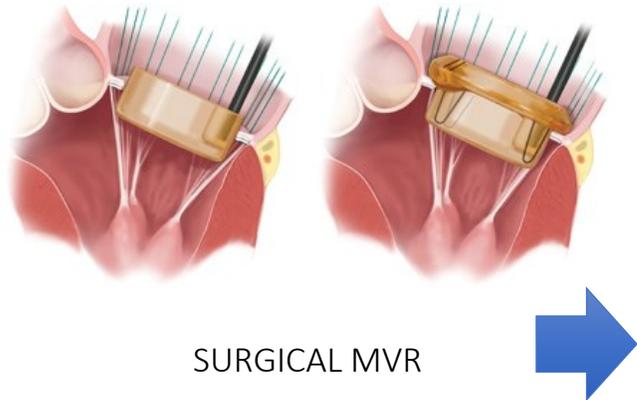
TRANSCATHETER MITRAL VALVE REPLACEMENT



PROCEDURE GOALS AND CHALLENGES OF TMVR

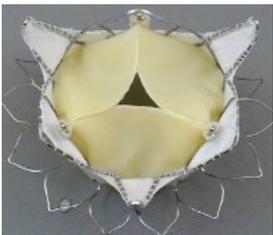
Design and Procedure Goals

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

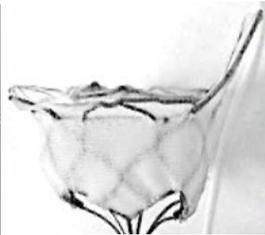


LIMITED APPLICABILITY OF CURRENT TMVR DESIGNS TO “REAL WORLD ANATOMY” (HIGH SCREENING FAILURE RATES)

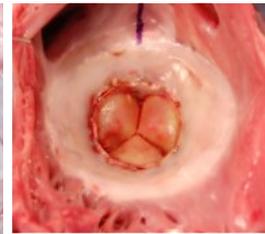
Full D-Shape
Non-Adaptable



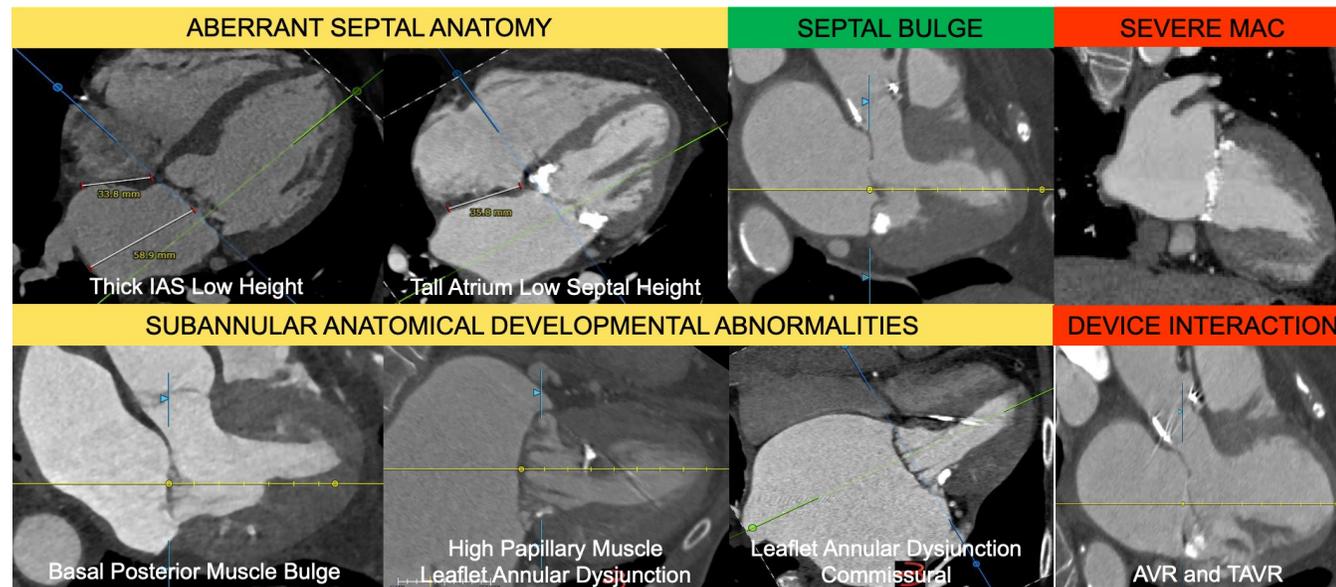
D-Shape
Adaptable



Circular
Adaptable



Circular
Non-Adaptable



TMVR designs have limited ability to cover all architectural variations seen in MR patients

Unlike TAVR, the development of a universal device tool (“one-design fits all”) may be challenging

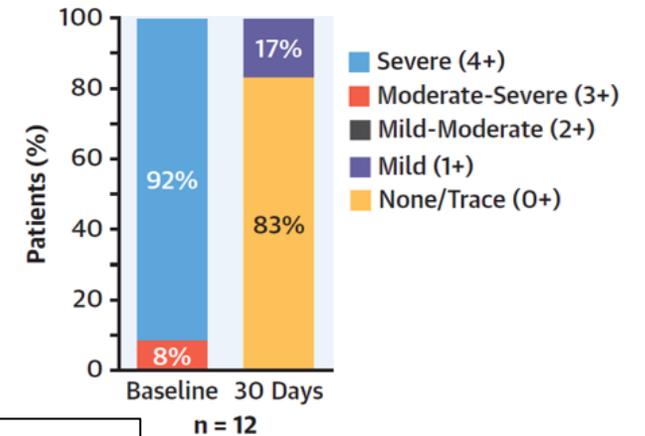
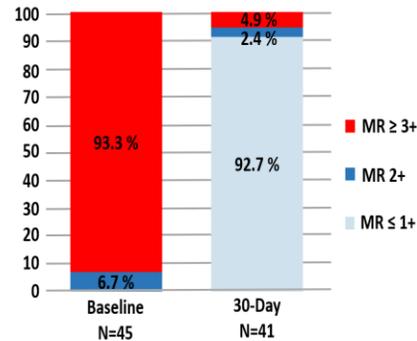
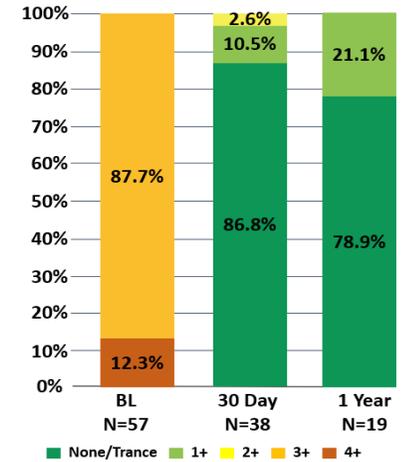
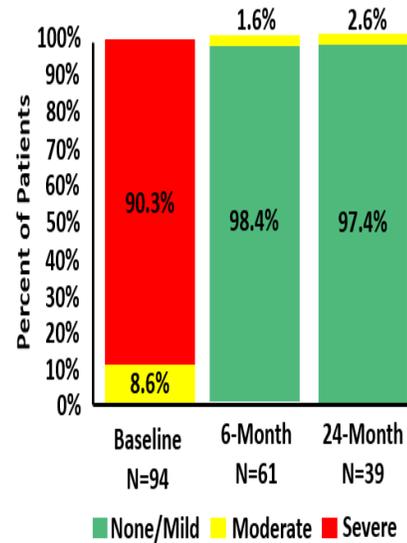
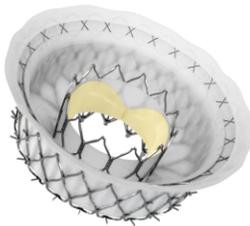
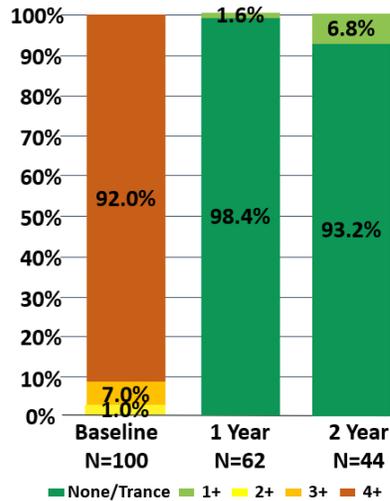
CURRENT TMVR INVESTIGATION LANDSCAPE

Access	TMVR device	Cases known	Nb of sizes	Level of maturity
TA	Tendyne	800+	13	CE-marked & US Pivotal ongoing
TA	Intrepid	300+	4	CE-mark study complete ? US Pivotal
TA	Tiara	79	2	CE-mark study complete

TS	Sapien M3	45+ TS	1	Feasibility done US Pivotal approved, not started
TS	HighLife	34 TS	1	Feasibility well underway Indication extensions coming
TS	Intrepid-TS	15+ TS	4	Feasibility
TS	Evoque/EOS	14+ TS	2	Feasibility restarted with EOS
TA-TS	4C	8+ TS		Feasibility, design changes ongoing
TS	Cephea	5+ TS	1	Feasibility to be restarted
TS	Cardiovalve	5+ TS	1	FIM complete



TMVR PROCEDURE GOALS



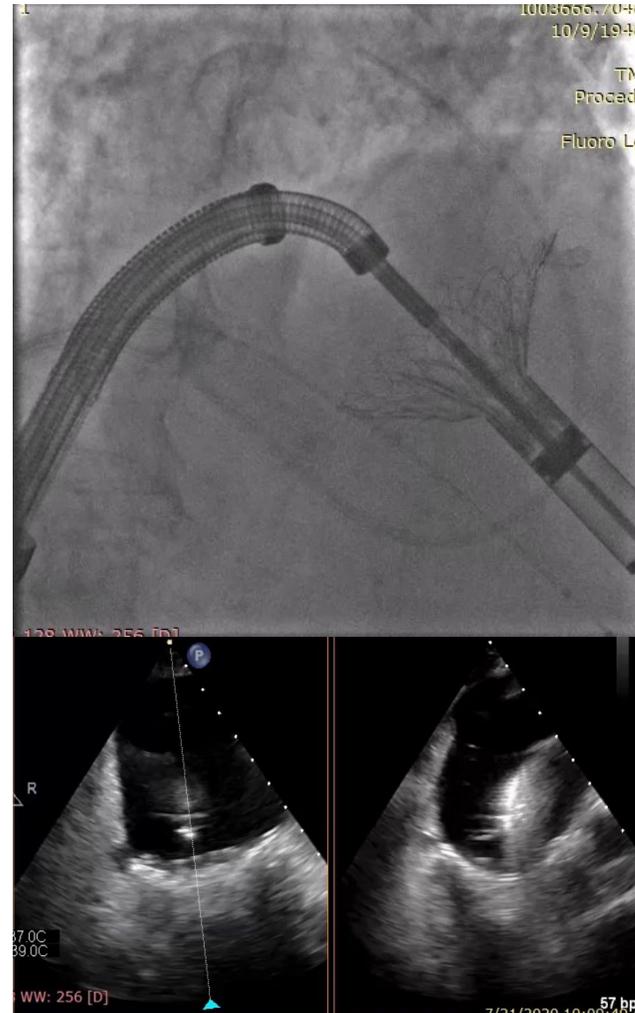
0% patients had **MR ≥ 1+ @ 1 year** with current transapical TMVR Technologies

INTREPID (MEDTRONIC) TMVR TRANS-SEPTAL SYSTEM

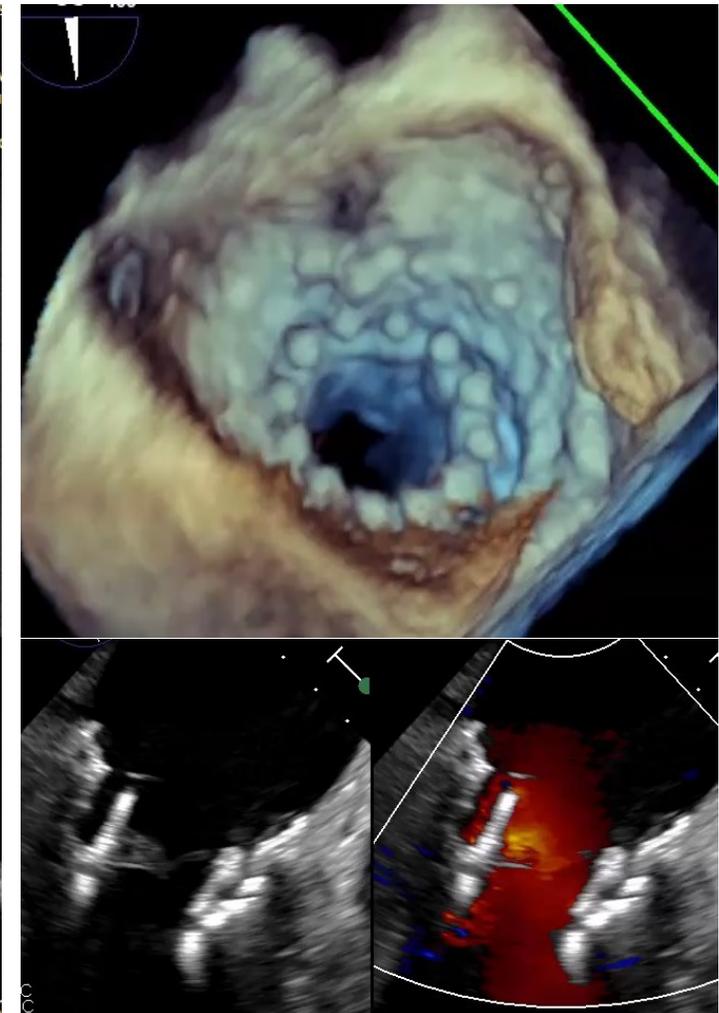
Atrial Flange Deployment



Ventricular Deployment



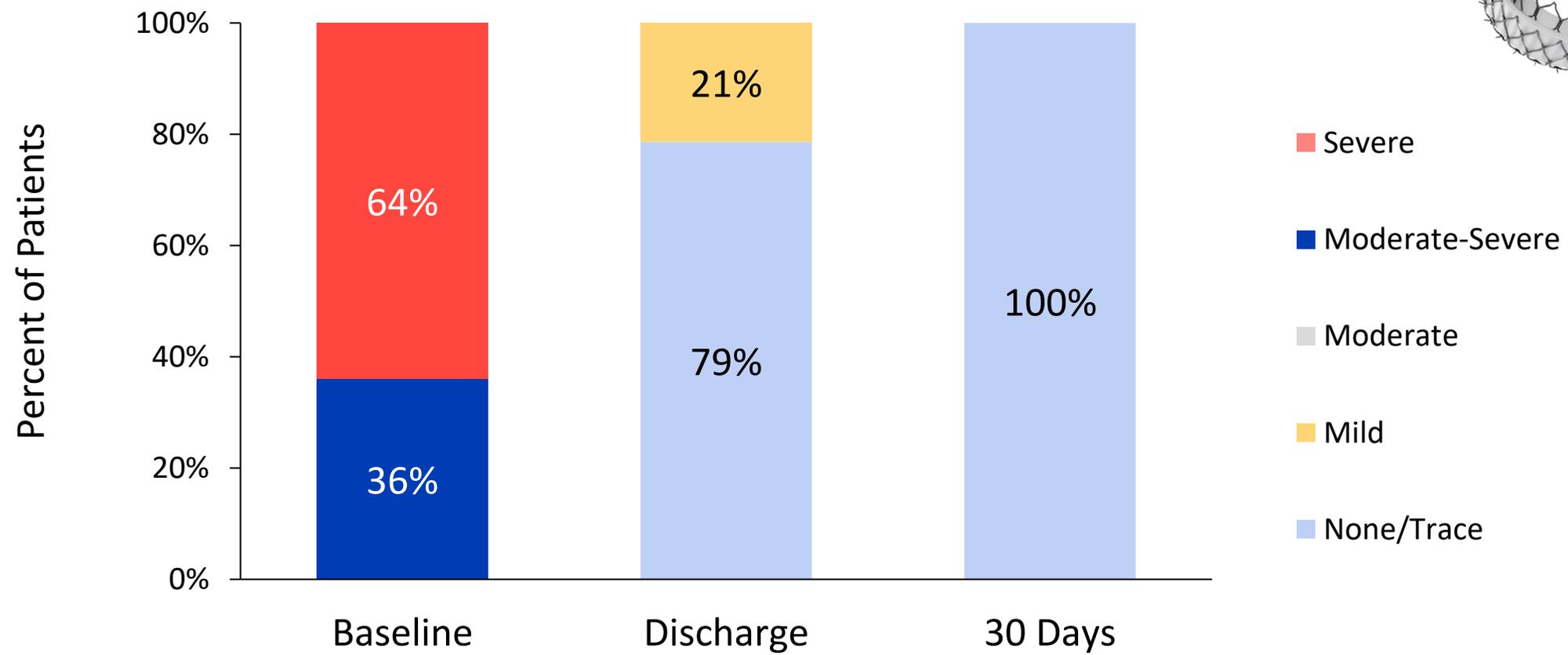
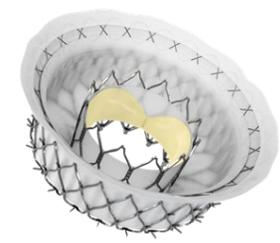
Final Result



Firas Zahr, MD, TCT2021

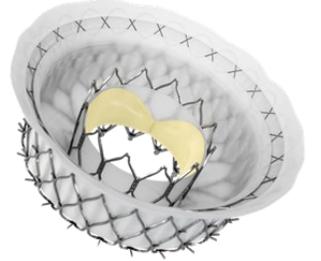
30-DAY OUTCOMES FOLLOWING TRANSSEPTAL INTREPID™ TMVR

Echocardiographic Outcomes: MR Severity (N=14)



Core lab adjudicated. Data reported on implanted cohort.

INTREPID TS – RECENT DATA RELEASED @TCT



- 15 patients reported @30days as part of an EFS
 - 2/3 DMR, 1/3 FMR
 - No mortality, stroke, reintervention or new pacemaker implantation
 - Favorable hemodynamics with almost complete elimination of MR 30d
 - Improved NYHA class
 - Technical success acute: 14/15 (93%) -> 1 conversion to surgery
 - ASD closure: 11/15 (73%)
 - 30D bleeding: 7/17 (47%)
- FDA approval to add TS delivery to the Apollo pivotal US trial

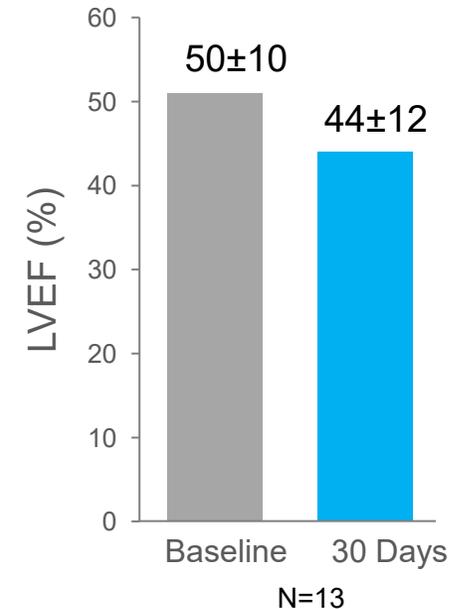
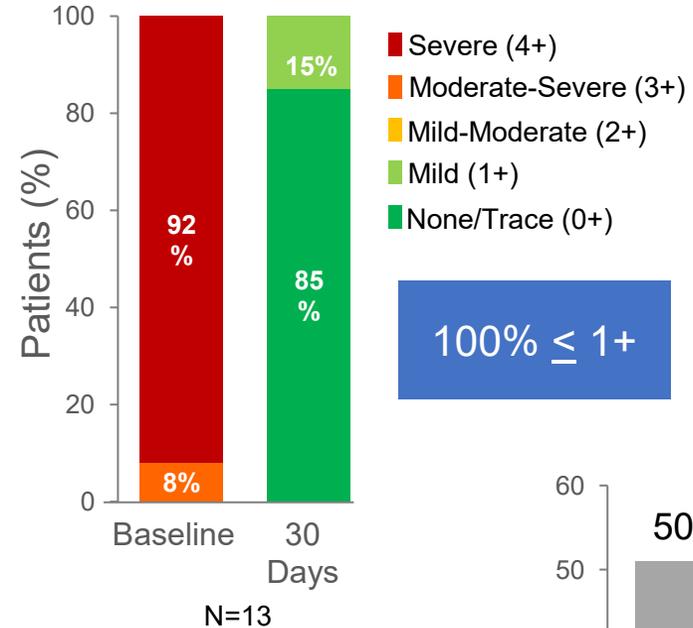
EVOQUE & EVOQUE EOS

- **Evoque**

- 15 cases in mitral reported in May 2020 (EFS +Compassionate use)
 - 93% technical success (1 conversion to surgery)
 - 186 min average procedure time
 - 14% PVL closure
 - 7% 30D mortality: 1/15
- Then, went on to tricuspid experience

- **Evoque EOS**

- **Redesign of Evoque, fully retrievable and recapturable**
- **Evaluated within EFS, just started**



MISCEND STUDY

Edwards EVOQUE Eos Mitral Valve Replacement System: Investigation of Safety and Performance After Mitral Valve Replacement With Transcatheter Device

Prospective, multicenter, single arm and non-randomized study

Purpose:

Evaluate the safety and function of the Edwards EVOQUE Eos mitral valve replacement system

Principal Investigators:

- Rajendra Makkar, MD

Patients with Symptomatic \geq Moderate Mitral Regurgitation

Heart Team Assessment

EVOQUE Eos mitral valve replacement system

Primary Outcome:

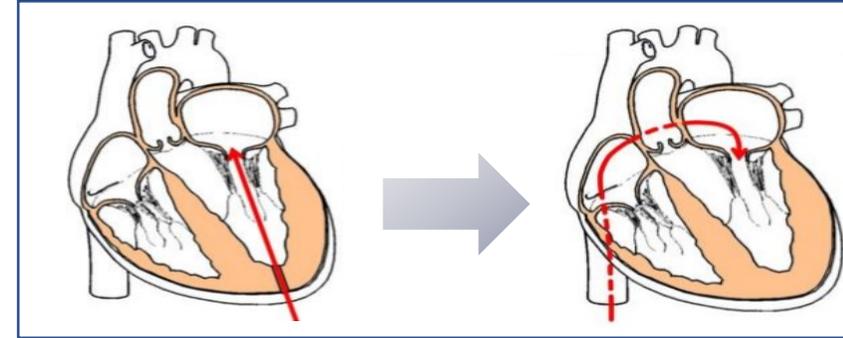
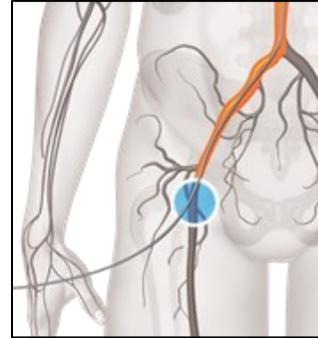
- Composite of major adverse events. Proportion of patients with major adverse events at 30 days

Follow-up: 30 days, 3 months, 6 months, 1 year and annually through 5 years

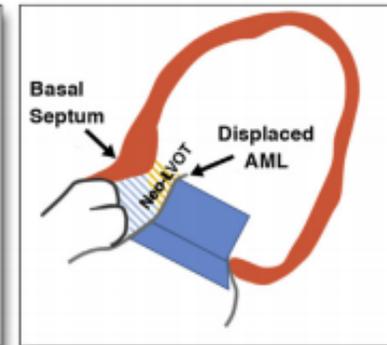
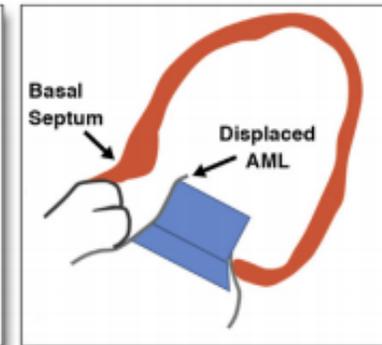
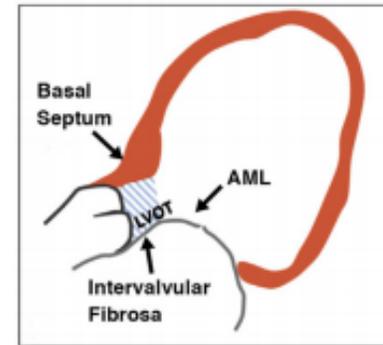
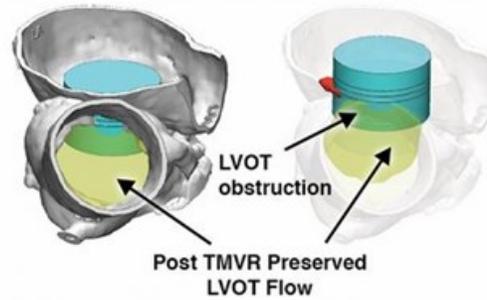
NCT02718001

TMVR THE FUTURE

Repositionability and Transseptal Delivery



Minimal Anatomic Exclusions:



Improved Imaging

CT and
3D Printing



CT	Computational Modeling 3D Printing (66)
+++	+++
++	+
+++	++
+++	+++
+++	+++
+++	+++
+++	+++



New Innovative Solutions

TRANSCATHETER MV REPAIR

Posterior leaflet enhancement/replacement

Posterior **leaflet enhancement and replacement** is a new focus area for TMV repair and these devices are early in their experience.



Polares

Posterior neoleaflet to restore leaflet coaptation

Milestones:

Experience: CU cases



SUTRA

Trileaflet valve design with annular anchoring

Milestones:

Experience: Pre-clinical



Half Moon

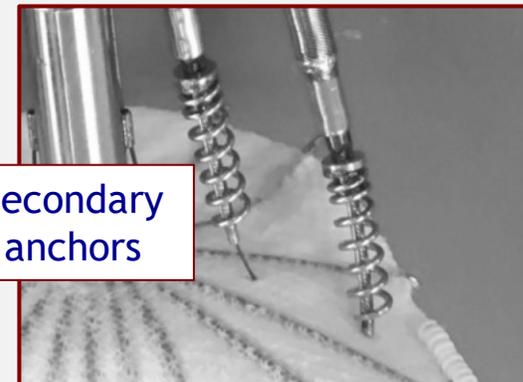
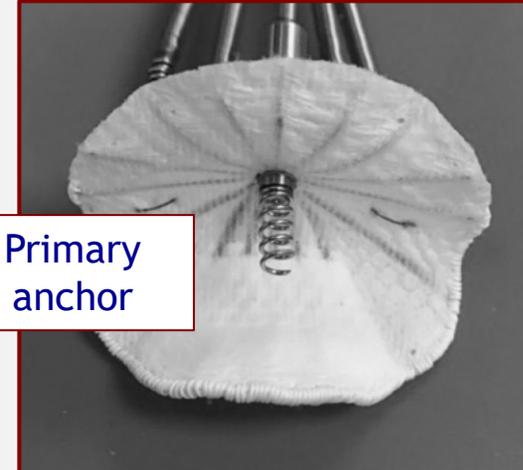
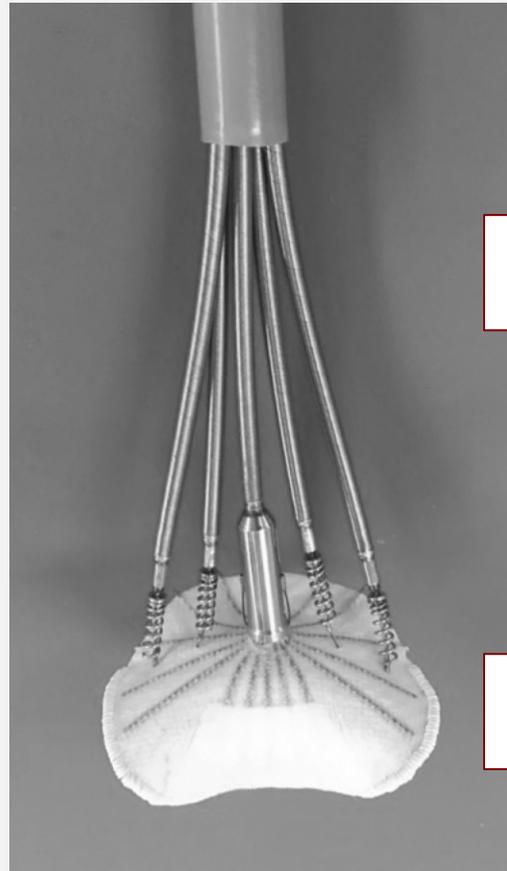
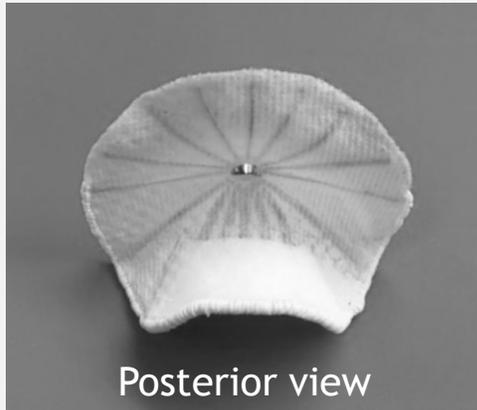
Intended to restore valve coaptation

Milestones:

Experience: FIH completed

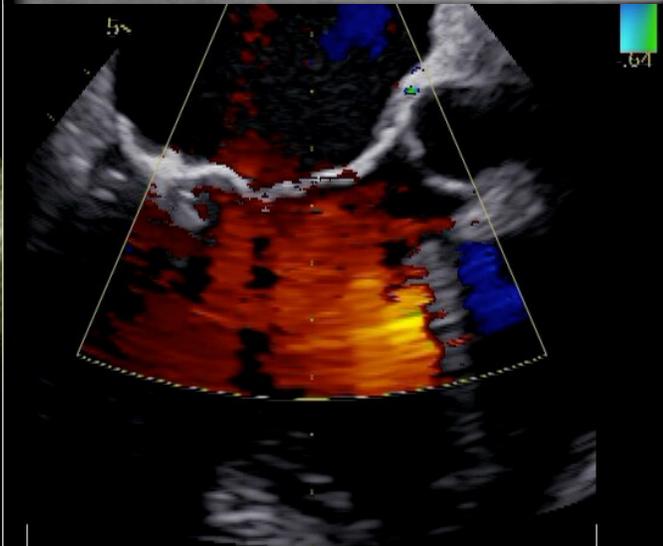
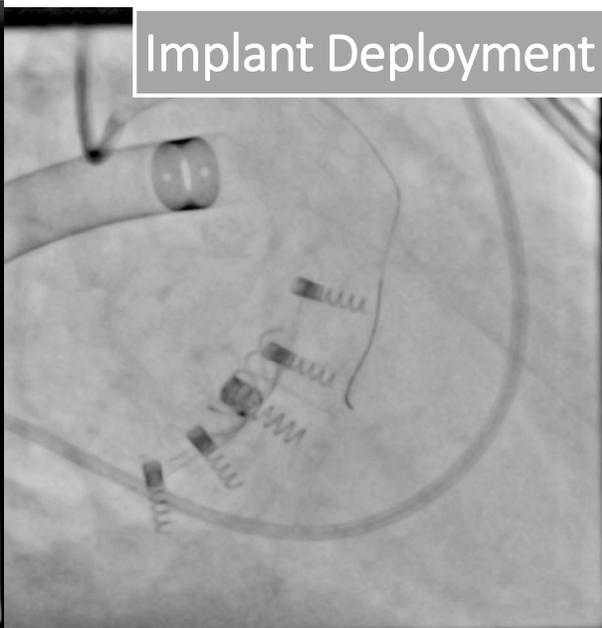
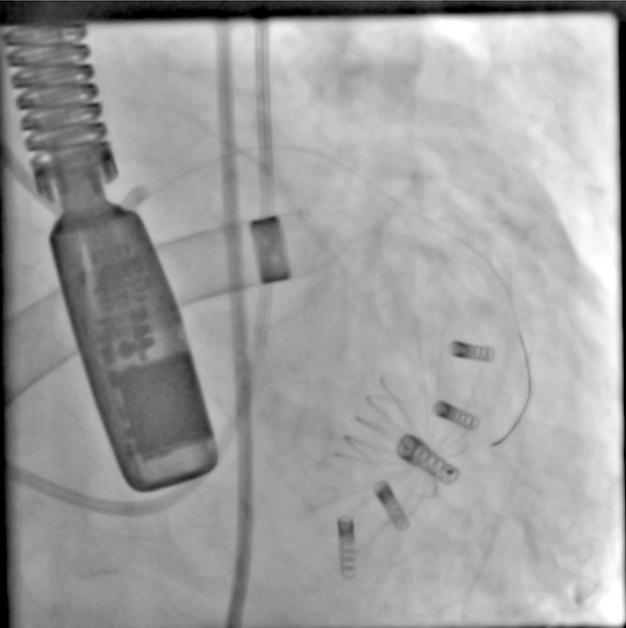
POLARES PLAR SYSTEM

The implant, its delivery and anchoring system



POLARES-IMPLANTATION

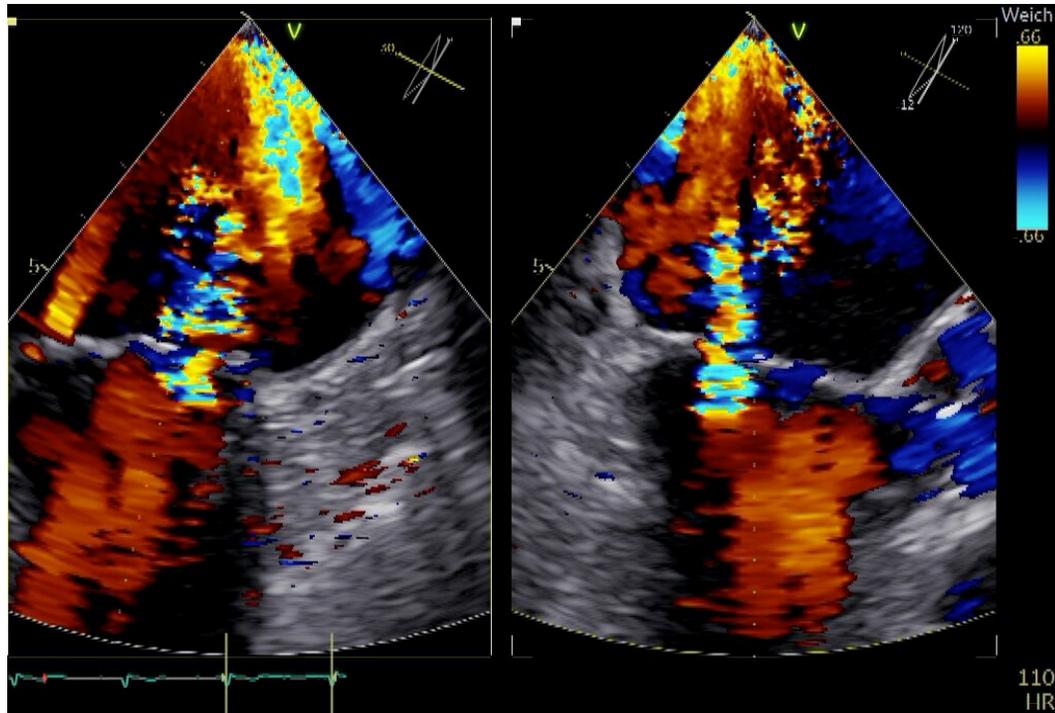
Implant Deployment and Acute Result



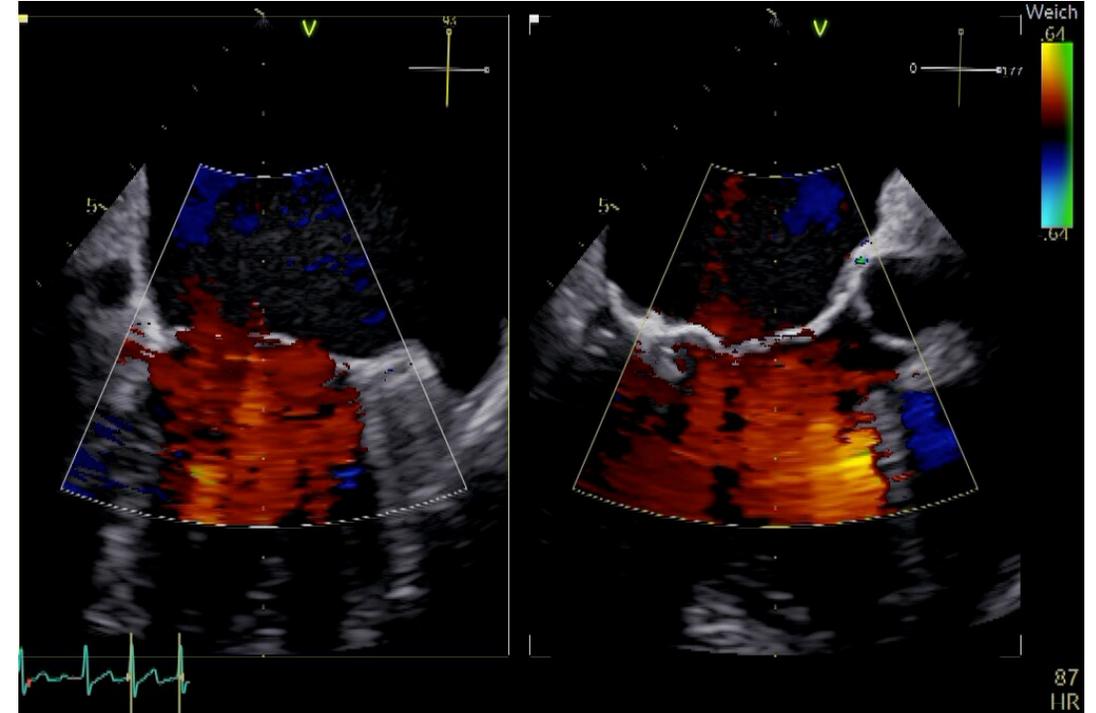
POLARES PRE AND POST RESULT

Pre-implant

Post-implant

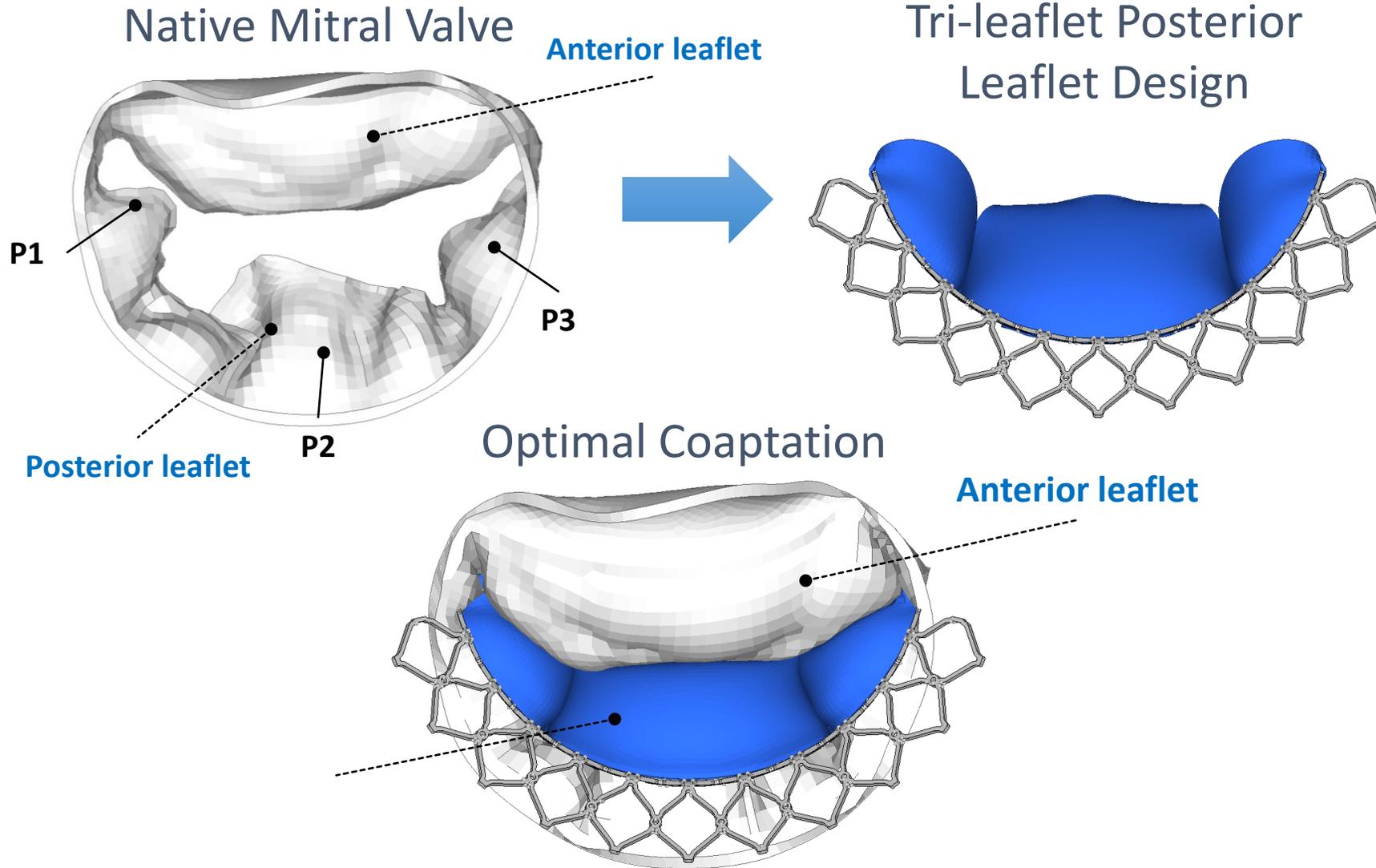


**Pre
Implant**

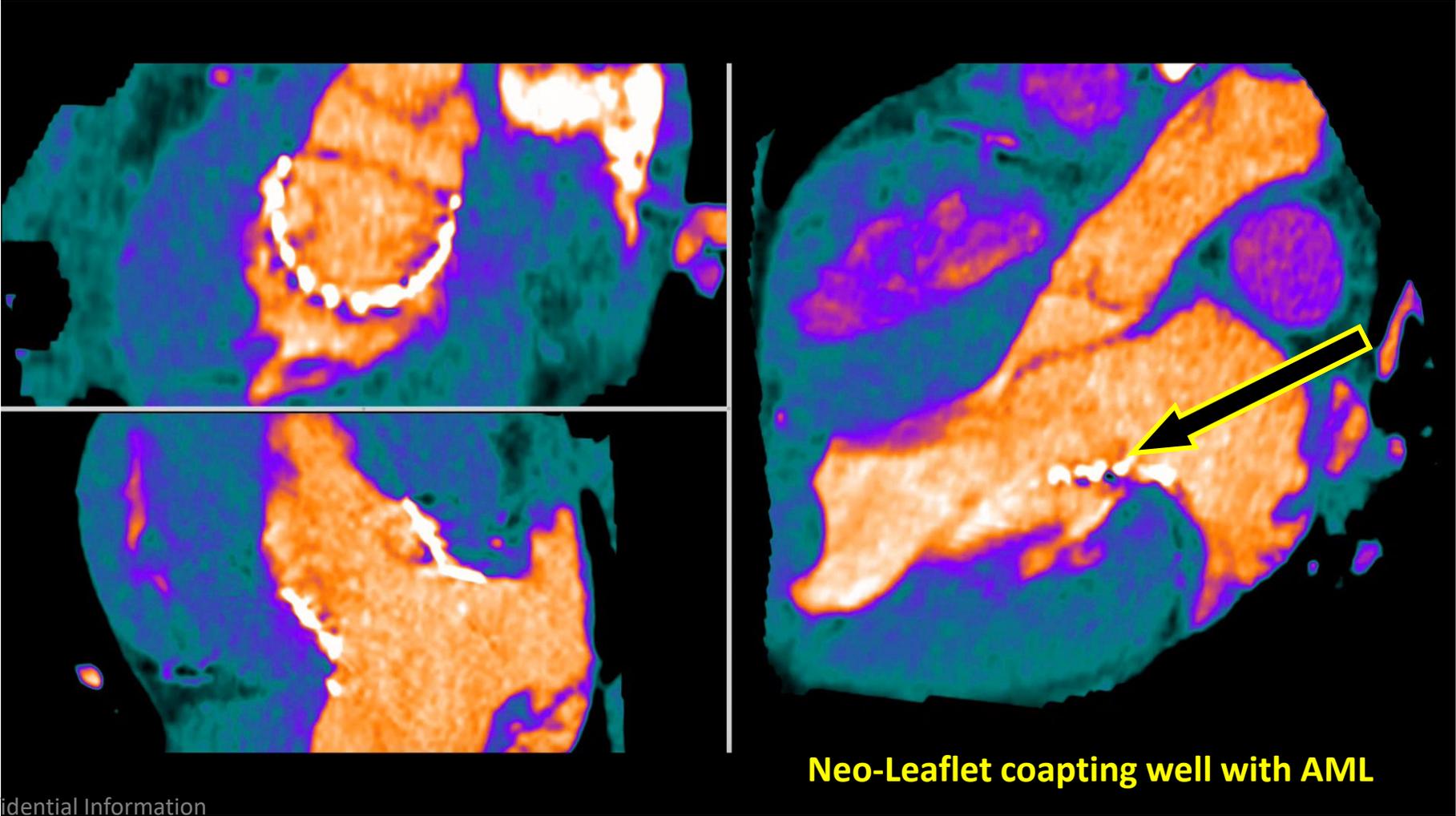


**Post
Implant**

3 LEAFLET-HALF VALVE DESIGN WITH ATRIAL ANCHORING

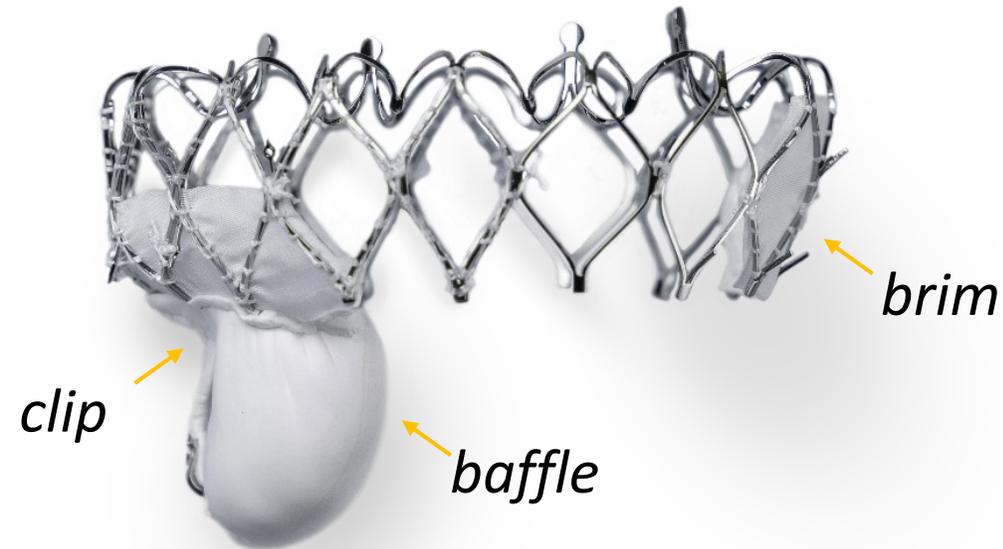


PRE-CLINICAL RESULTS 4D CT FROM ONE ANIMAL (SUTRA)



Confidential Information

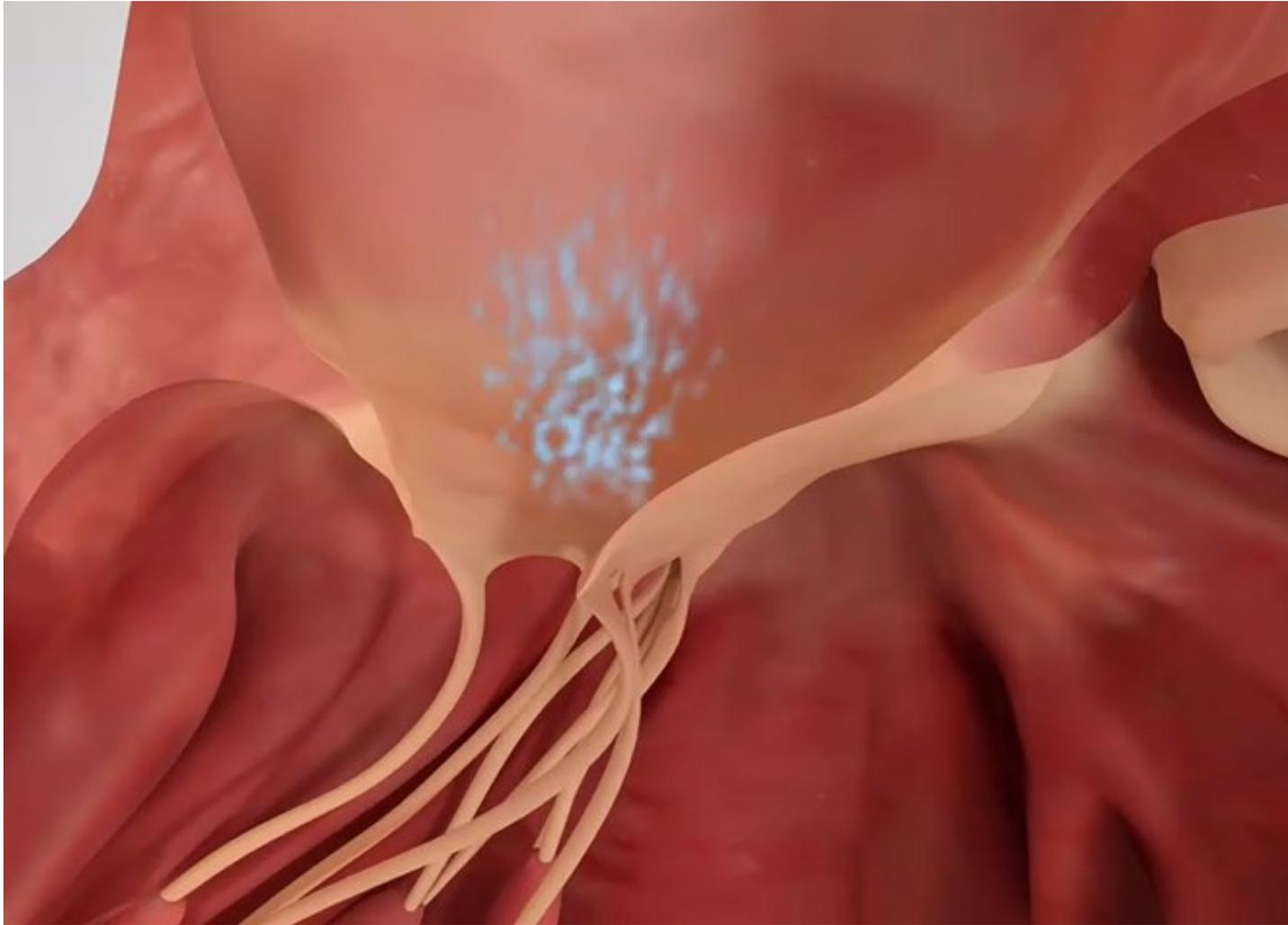
HALF MOON - COAPTATION AUGMENTATION DEVICE*



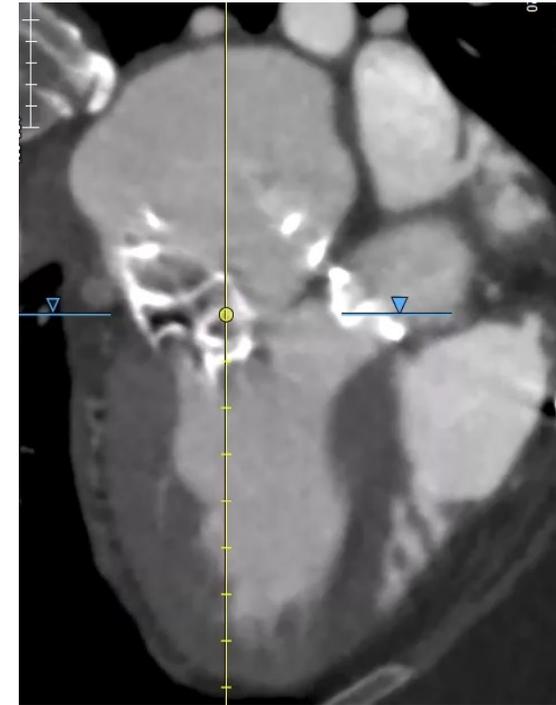
Designed to eliminate regurgitation by restoring physiologic coaptation in a diseased mitral valve

- *Design details*
 - Contoured ePTFE **baffle** fills regurgitant orifice from the posterior side and provides a new coaptation surface for the native leaflets
 - Posterior **clip** orients device and provides sub-annular fixation
 - Flexible atrial **brim** provides additional fixation and supra-annular stabilization
 - Transfemoral delivery via **29 Fr** system enables repositionability and recovery

HALF MOON - COAPTATION AUGMENTATION DEVICE*



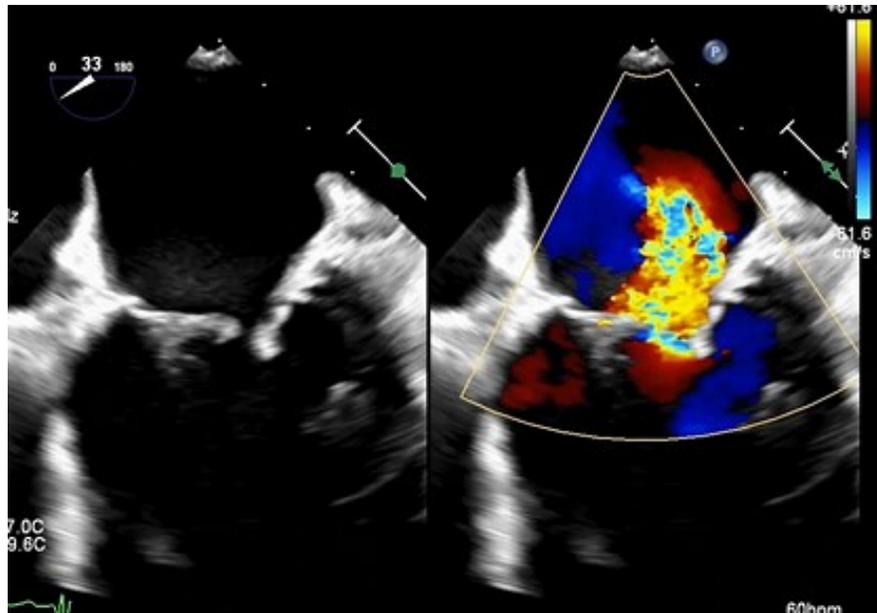
- Baffle designed to swing anteriorly during systole
- Clip and Brim work in tandem to provide fixation



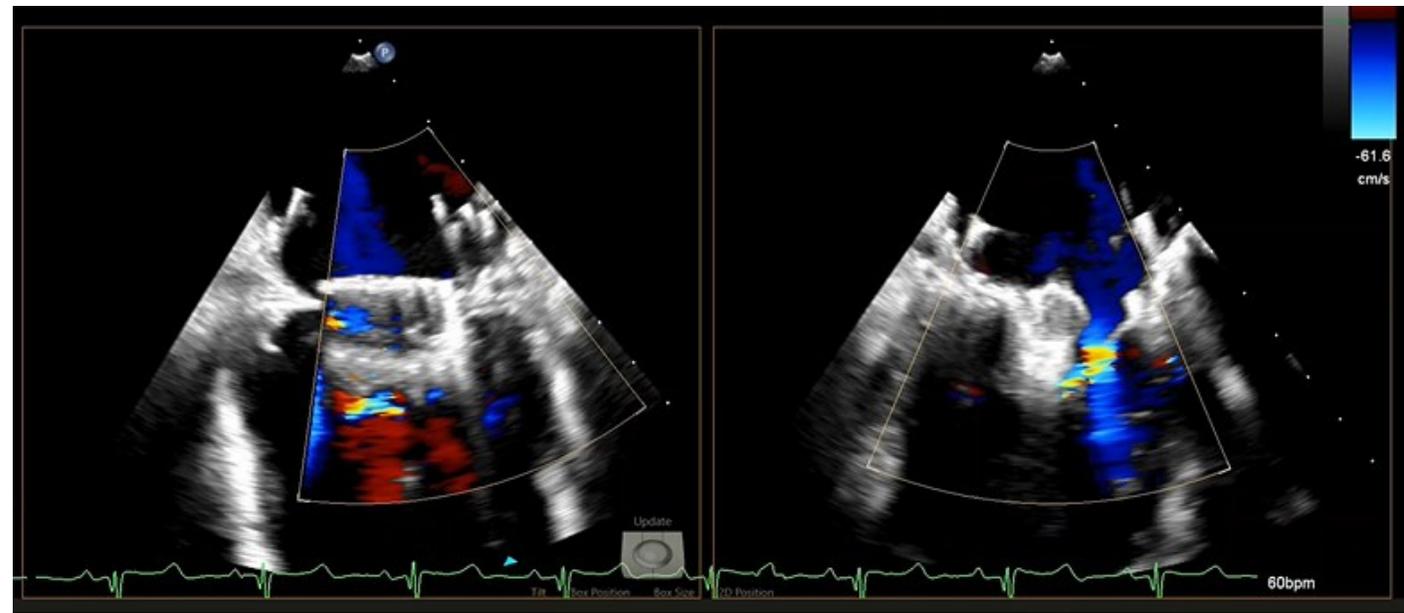
HALF MOON - COAPTATION AUGMENTATION DEVICE*

Post-Implant Results

Pre-implant



Post-implant



Firas Zahr, MD, TCT2021



IS TMVR READY FOR PRIME TIME ?

What remains to be done in MR

- Longterm results of transcatheter interventions
- Indications for transcatheter interventions in patients with severe primary MR at lower surgical risk

My answer is No !

Remaining Knowledge Gaps

- Selection of criteria to identify responders to TEER for secondary MR (severity criteria, concept of „disproportional MR“)
- The role of newer transcatheter treatment options (annuloplasty, combined repair techniques, valve replacement)

Mitral – Where We Are After 15 Years?

THE FUSION AND AQUISITION FRENZY: (MARKET EXPECTATIONS)

Produkt	Wert (Mio)
PVT	+ Milestones
MitraClip	\$455
CoreValve	+ Milestones
Ventor	\$325
Sadra	\$450



Around \$ 50 Mio USD per Patient for Transcatheter Mitral Valve Therapy

THE TMVR² WARS

REPAIR VS. REPLACEMENT



Competitive or Complementary?

The MV repair issues

- The TMV repair landscape is rapidly changing. Devices are relatively safe but efficacy and user friendliness have to be improved
 - complex, time consuming and require training
 - efficacy???
 - not ideal for early symptomatic patients
- The results so far have been disappointing.
- Real milestone has only been achieved by the Edge-to-Edge Techniques which however has its own limitations.
- In the near future the number of TEER will increase but other innovative solutions will emerge

Why is TMVR still an unsolved issue ?

- In 2015, 3 TMVR technologies for trans-apical delivery acquired for \$1+Bn
- In 2016, the cardiology community concluded “future of TMVR is trans-septal”
- In 2021, limitations remain important
 - Current devices still have one or several of the following shortcomings:
 - Pure trans-apical applicability
 - When trans-septal, large French size
 - -> need for ASD closure and surgical cut-down/repair to the femoral vein
 - Persistent peri-valvular leaks
 - Valve/Leaflet thrombosis
 - Difficulty in achieving an adequate position consistently
 - Cannot accommodate for large anatomies
 - Cannot treat LVOTO risk patients
 - Current clinical studies still have to identify the ideal patient population

So why did we still migrate to valve replacement?

For multiple reasons:

- Repair Is a longer and more complex procedure with technology that was developed slowly
- We enjoyed being in a “comfort zone” of doing TAVR in 45 minutes - so why not to replicate it in Mitral?
- The Industry also resented to move from the “comfort zone” of making TAVR devices
- We are holding until MR becomes severe to treat these patients
- No alternative drug therapy exist to date so the gold standard remain surgery

The Result:

After 15 years we still don't have a TMVR device that is ready for prime time...

TREATMENT OF SEVERE MR IN 2021:

Making a case for the development of catheter-based therapies

- Surgery is the standard of care for patients with severe symptomatic MR
- TEER has demonstrated beneficial outcomes in prohibitive/high risk **Primary MR** and selected (COAPT eligible) **Secondary MR patients**
 - Other important (and more frequent) MR patient categories have not been studied and optimal MR reduction with TEER remains challenging in patients with complex anatomies
- The High Risk MR population therefore represents a big opportunity for catheter based innovations.
- Severe MR+HF in the elderly is:
 - Highly prevalent
 - Frequently rejected from surgery
 - Not represented in surgical trials and
 - Frequently re.hospitalized

CATHETER-BASED TECHNOLOGIES MAY IMPROVE PROCEDURAL OUTCOMES IN THESE HIGH-RISK PATIENTS

Less Invasive mitral valve intervention may be performed with fewer peri-operative complications



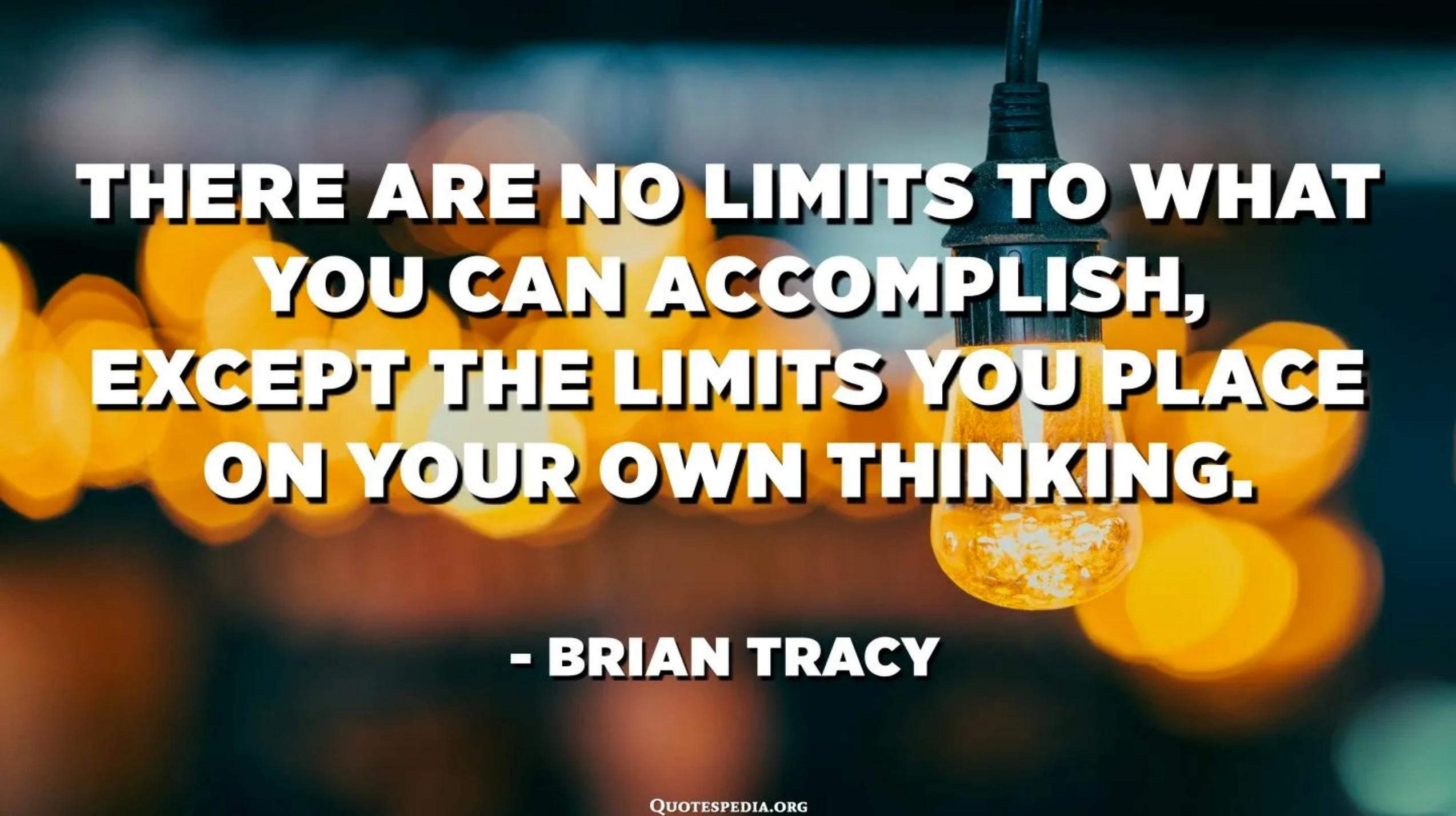
Progression towards minimally invasive interventions impact clinical outcomes, QoL and health care cost

A CALL FROM THE BATTLEFIELD:

To further understand all aspects of the mitral disease and its needs, we have to get **OUT OF THE BOX** and out of the **ZONE OF COMFORT**, to become creative in identifying and implementing new approaches and better solutions to this unmet clinical challenge for low risk patients



To war - men of God!

A glowing lightbulb hangs from a cord, positioned on the right side of the frame. The background is filled with soft, out-of-focus bokeh lights in shades of yellow and orange, creating a warm and inspiring atmosphere. The text is overlaid in the center-left area.

**THERE ARE NO LIMITS TO WHAT
YOU CAN ACCOMPLISH,
EXCEPT THE LIMITS YOU PLACE
ON YOUR OWN THINKING.**

- BRIAN TRACY

Thank you for your kind attention!

