Emerging Options for Transcatheter Mitral Valve Treatment

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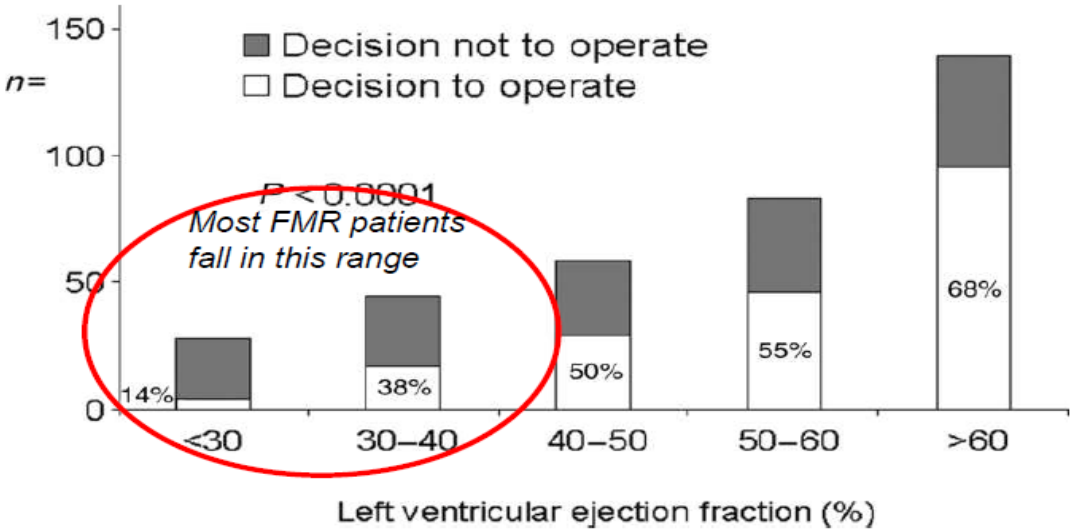
Surgery is rare if EF < 40%



Mirabel Eur H Journal 2007

Percutaneous Transcatheter Mitral Valve Repair

- Less invasive approaches
- Significant proportion of patients
- Elderly persons or those with significant comorbidities or severe left ventricular (LV) dysfunction, are high risk for surgery

Various technologies for TMVR

- A classification of percutaneous (TMVR) technologies on the basis of functional anatomy
- Groups the devices into those **targeting the leaflets** (percutaneous leaflet plication, percutaneous leaflet coaptation, percutaneous leaflet ablation)
- The **annulus** (indirect: coronary sinus approach or an asymmetrical approach)
- Direct: true percutaneous or a hybrid approach, the chordae (percutaneous chordal implantation), or the LV (percutaneous LV remodeling)
- Percutaneous **MVR** (Mitral Valve Replacement)

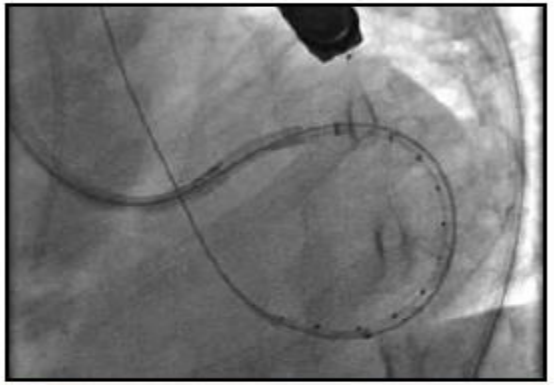
TMVR/ Replacement

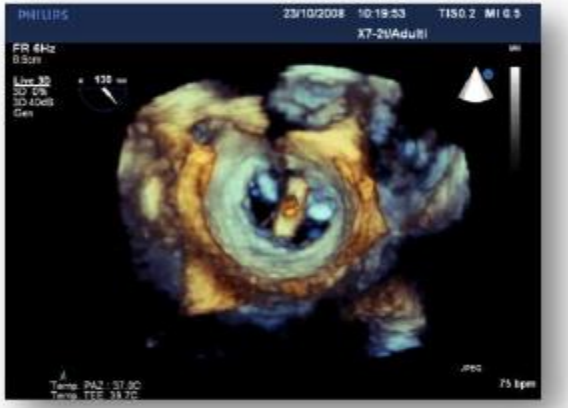
- Mitral valve leaflet repair
  - MitraClip
  - Neochord
- Mitral valve annular repair
  - Coronary sinus approach: Monarc, Viacor, Carillon
  - Direct: Accucinch, Mitralign
  - Other: Recor, BACE
- Mitral valve replacement
  - Valve in valve
  - Valve in ring

Transcatheter MitralValve Repair Outcomes

2012 Challenges of transcatheter MV interventions

- Variability of mitral valve disease
  - Multiple devices
  - Multiple techniques
- Anatomical complexity
  - Most techniques are different from a "stent-based" approach
- Image guidance is more sophisticated
  - Echocardiography is the leading image guidance method



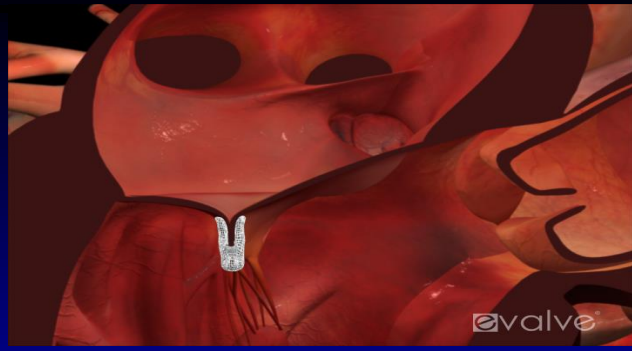


MitraClip
Neochord
Harpoon
Chordart
....

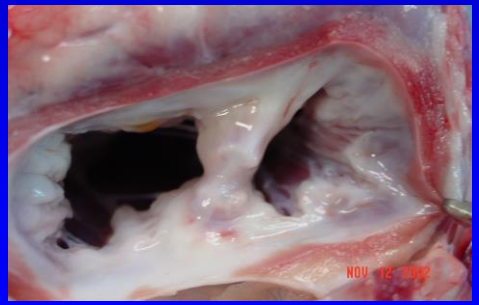
Cardioband
Mitralign
Carillon
Millipede
....

Tendyne
Neovasc
CardiaQ
Twelve
.....

Edge to Edge & MitraClip Concepts



- Facilitates proper leaflet coaptation
  - Degenerative - Anchor flail and prolapsed leaflets
  - Functional - Coapt tethered leaflets to reduce time and force required to close valve
  - Reduces LV volume overload by reducing MR
- Creates tissue bridge
  - May limit dilatation of annulus
    - Septal-lateral (A-P) dimension
  - Supports durability of repair
- Restrains LV wall
  - Limits LV dilatation



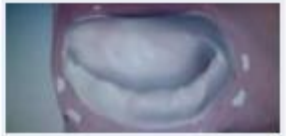
Porcine model, 6M

EVEREST Initial FMR Cohort Conclusions

Percutaneous mitral repair with the MitraClip:

- Effective in reducing MR with a low MAE rate
- Significant reverse LV remodeling at 1-year
- Clinical improvement with 58% of patients NYHA Class I at 1-year
- 79% freedom from death, surgery for valve dysfunction and MR > 2+ at 1-year
- Surgical options preserved in majority of patients
- MitraClip facilitates leaflet coaptation reducing MR in functional patients

CE marked therapies

Company	Abbott	NeoChord	CardiacDim	ValTech	Mitralign
Name	MitraClip	DS1000	Carillon	CardioBand TA and TF	Bident and Tricuspid
					
Description	Alfieri technique	Neochordal implant from the TA approach	Coronary sinus cinching	Surgical ring implanted percutaneously	Plication device
Strengths	• Minimal invsivenes	• Strong surgical background	simplicity	• Strong surgical background • Atrial delivery	• simplicity
Weaknesses	• Lack of annuloplasty	• TA approach • Lack of annuloplasty	• Limited efficacy	• Complexity • imaging	• Efficacy limited in mitral position • Ventricular delivery
Status	• >35000	• >300 pts	• 500 pts	• 100 pts	• 100 pts

ABBOTT SPONSORED CLINICAL TRIAL OVERVIEW

Enrollment Complete

EVEREST Program - US

- EVEREST I – Feasibility Study
- EVEREST II Randomized Controlled Trial
- EVEREST II High Risk Registry
- REALISM Continued Access Study
  - High Risk Arm
  - Non-High Risk Arm

EUROPE

- ACCESS-EU Phase I
- ACCESS-EU Phase II

Enrolling

Randomized HF with FMR - US

- COAPT Trial

Post-Approval Studies

- PAS 1
- PAS 2

Japan

- MitraClip Japan Study

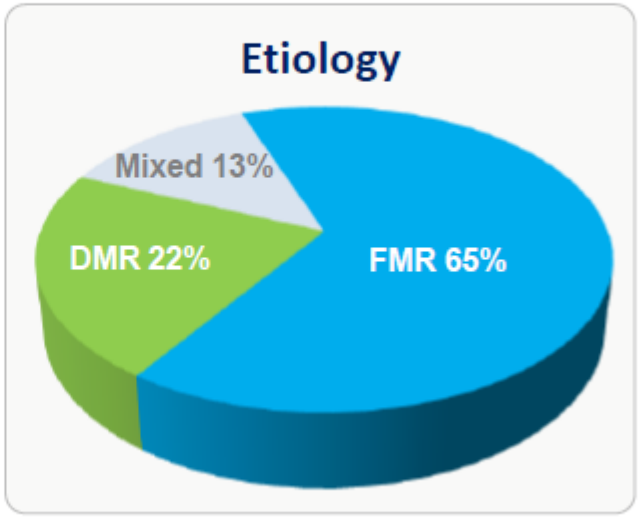
Study	Population	Status	N
EVEREST I (Feasibility)	Feasibility patients	Closed	55
EVEREST II (Pivotal)	Pre-randomized patients	Closed	60
EVEREST II (Pivotal)	Non-randomized patients (High Risk Study)	Closed	78
EVEREST II (Pivotal)	Randomized patients (2:1 Clip to Surgery)	Closed	279 184 Clip 95 Surgery
REALISM (Continued Access)	Non-randomized patients	Enrollment Complete. Follow-up ongoing	899
Compassionate/Emergency Use	Non-randomized patients	Enrollment Complete. Follow-up ongoing	66
ACCESS Europe Phase I	Non-randomized patients	Closed	567
ACCESS Europe Phase II	Non-randomized patients	Closed	286
Post-Approval Study 1 (PAS1)	Commercial patients	Enrolling	1583 §
Post-Approval Study 2 (PAS2)	Commercial patients	Enrollment to start Q1'16	n/a
COAPT Trial	Randomized patients (1:1 Clip to Medical Therapy)	Enrolling	47 Roll-Ins* 317 Randomized*
MitraClip Japan	Non-randomized patients	Enrolling	10
Commercial Use	Commercial patients	Ongoing	Over 25000*
Total			**Over 28000 +95 surgery**

Data as of : §March 2015 , *December 10, 2015
Source: Abbott Vascular

WORLDWIDE COMMERCIAL IMPLANT EXPERIENCE

>35,000 Patients

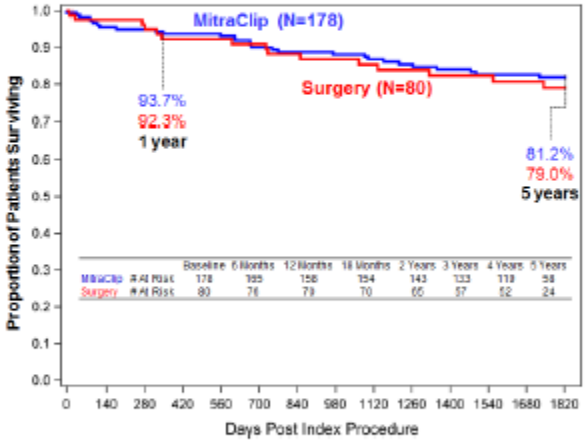
Implant Rate: 96%



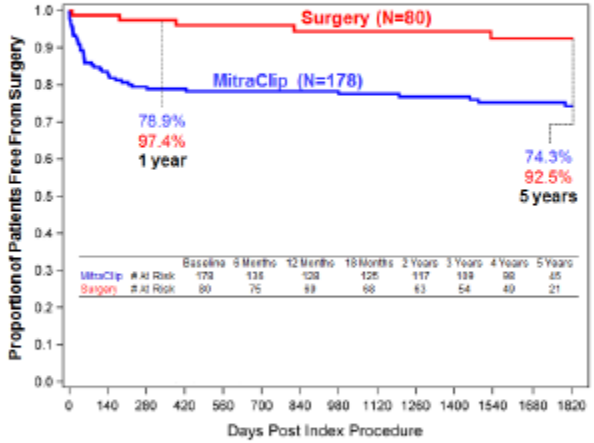
Data as of Sept 2015. Source: Abbott Vascular

EVEREST II RANDOMIZED CONTROLLED TRIAL
FREEDOM FROM MORTALITY AND SURGERY/RE-OP

Kaplan-Meier Freedom From Mortality



Kaplan-Meier Freedom From Mitral Valve Surgery/Re-operation

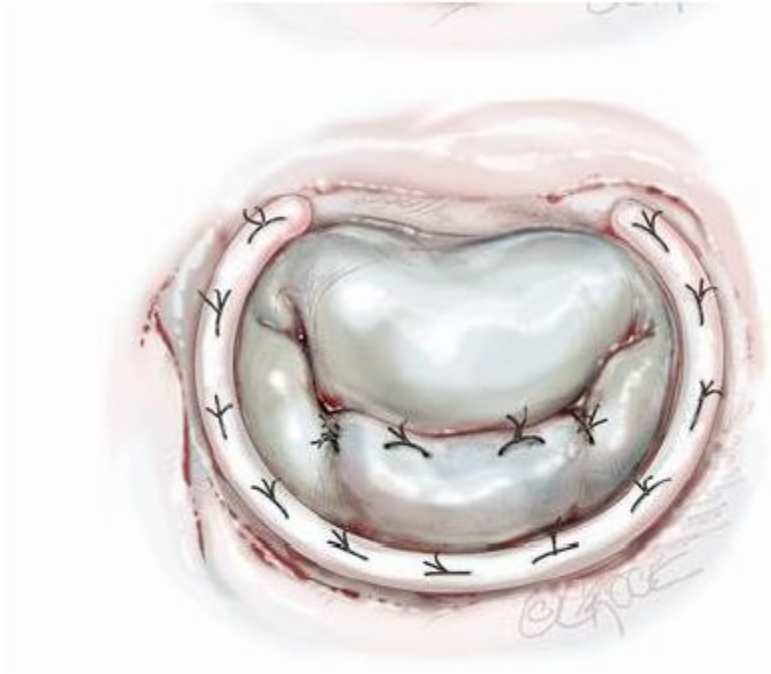


Feldman T, et al. Final results of the EVEREST II RCT of percutaneous and surgical reduction of mitral regurgitation. J. Am. Coll. Cardiol. 2014;63:A1682. .

University Hospital Zurich

ACC Middle East Conference 2016

CLINICAL EXPERIENCE WITH DIRECT AND INDIRECT ANNULOPLASTY IS INCREASING



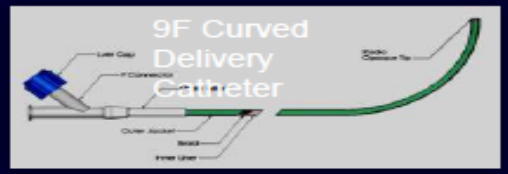
- **CARILLON**
  - ABOUT 500 PTS
- **CARDIOBAND**
  - ABOUT 100 PTS
- **MITRALIGN**
  - ABOUT 80 PTS
- **ARTO**
  - ABOUT 20 PTS
- **VALCARE**
  - FIM TA
- **MILLIPEDE**
  - FIM SURGICAL

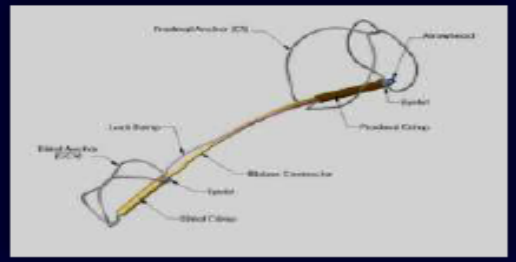
Coronary sinus approach for mitral annuloplasty

- The coronary sinus provides the simplest and least invasive approach for percutaneous annuloplasty
- Its main limitations are the indirect relationship of the coronary sinus to the mitral annulus and the potential for coronary artery compression.
- These anatomical hurdles limit the number of patients suitable for this approach
- Device fracture has been problematic, and so development of 2 out of 3 of the devices was discontinued after early experience in humans
- Early clinical results with this approach have demonstrated reductions of MR, and clinical benefit and further investigation of the Carillon device is ongoing

CARILLON Mitral Contour System

Advanced Delivery System





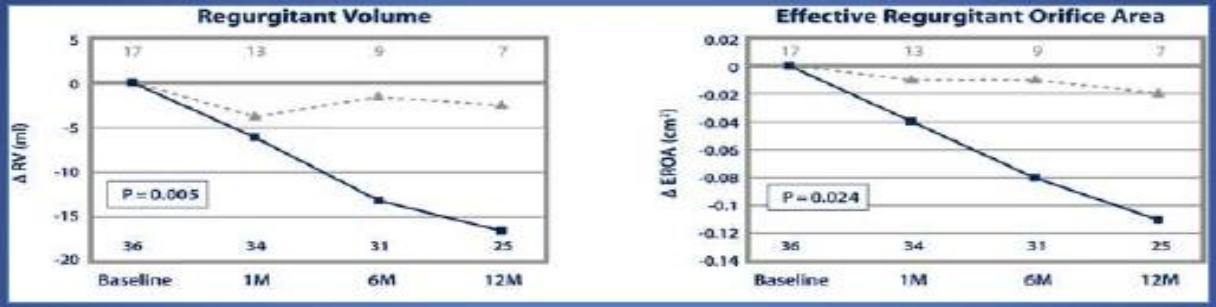
- **Anchor Architecture in CS**
  - Preserves treatment options (eg, LV lead)
  - Designed to maintain position within the CS
- **Adjustable**
  - Addresses variable anatomy
  - Optimize MR reduction
- **Straightforward Access in CS**
  - Designed for rapid deployment
  - No trans-septal puncture

60, 70, 80 mm
DA: 7-14 mm
PA: 12-20 mm

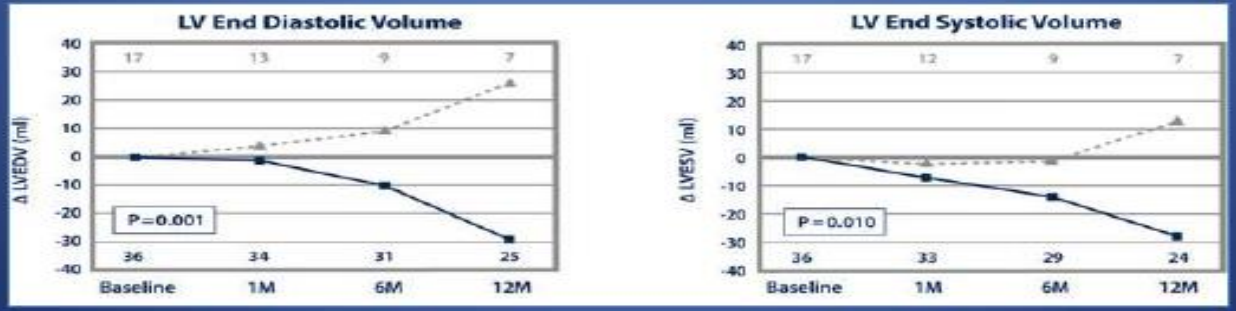
- **Recapture Feature**
  - Assess and avoid coronary compression
  - Enables repositioning

TITAN Trial

Reduction in Mitral Regurgitation



Reverse Remodeling



Between groups comparison of paired absolute differences from baseline

Hoppe UC, Siminiak T, Haude M, et.al., European Heart J 2010:31;160-1.

Direct Annuloplasty by Cardioband

Trans-femoral venous access (transeptal) – best for safety

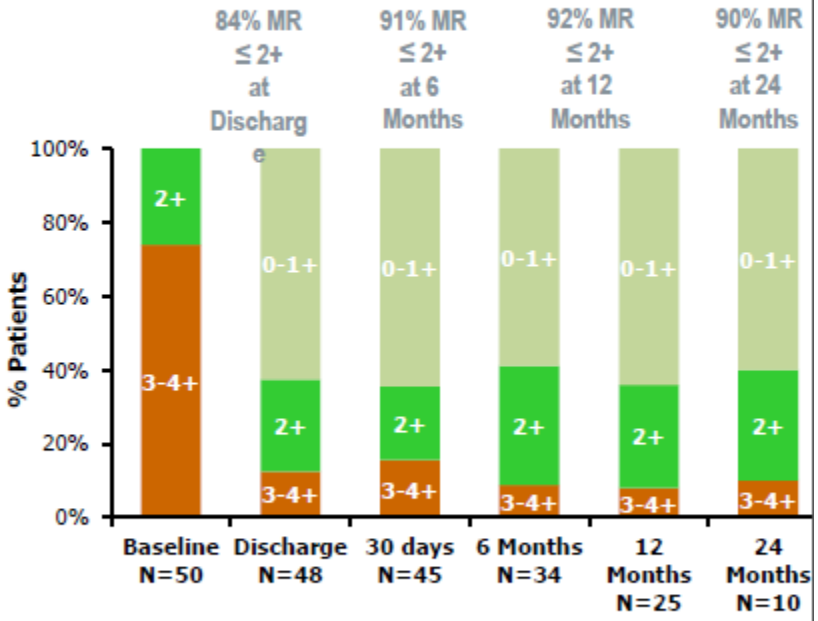
- **Supraannular fixation** like in surgery
- **Significant Reduction of Annular dimensions –** device enables reduction of up to size 28 surgical ring
- Preserves the native anatomy – **keeps future options open**

Study Demographics (N=50)

Variable	No. (%) or Mean
Age (years)	71 ± 8
Gender	Male 39 Female 11
Euroscore II (%)	7.5
Baseline NYHA Class of III or IV (%)	84
Ischemic Non Ischemic	31 19
LVEDD (mm) Avg±SD	61 ± 6
EF (%) Avg±SD	33 ± 11
Prev CABG COPD Moderate to Severe Renal Failure Severe Pulmonary Hypertension Afib	16 (32%) 11 (22%) 38 (76%) 12(24%) 39 (78%)

30 Day Events*	Patients Experiencing Event, # (%)
Death	2 (4%)
Hemorrhagic Stroke**	1 (2%)
Need for elective Mitral Operation**	1 (2%)
Ischemic attack	1 (2%)
Major Bleeding Complications	1 (2%)
Renal Failure	2 (4%)
Myocardial Infarction	0 (0%)
Respiratory Failure	0 (0%)
Cardiac Tamponade	1 (2%)

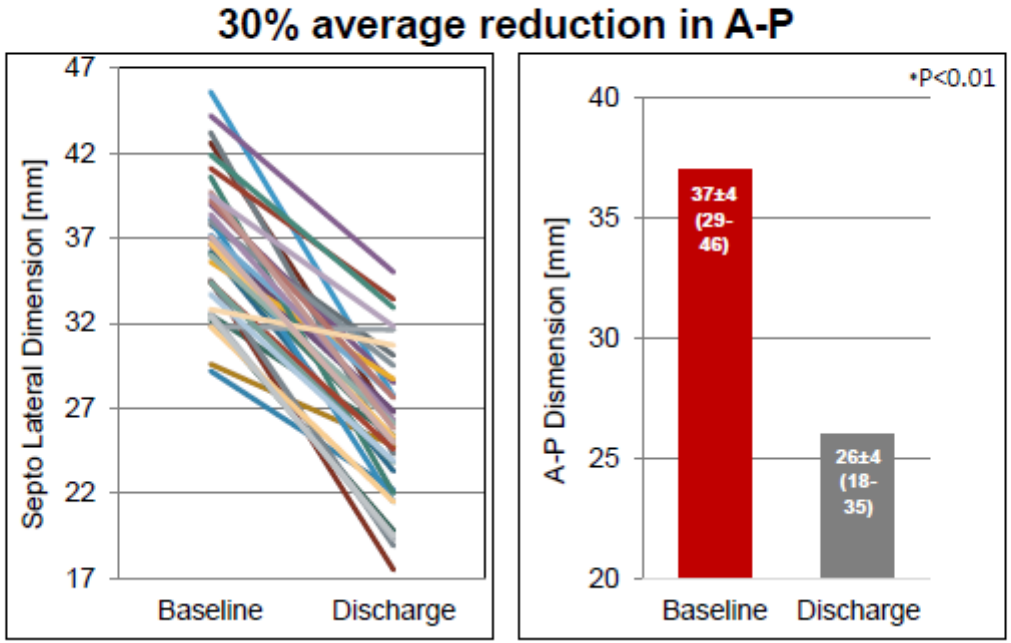
* VARC Guidelines (European Heart Journal, 2012, 33:2403-2414)
** Part of the Death case
One additional death case per ITT - compassionate



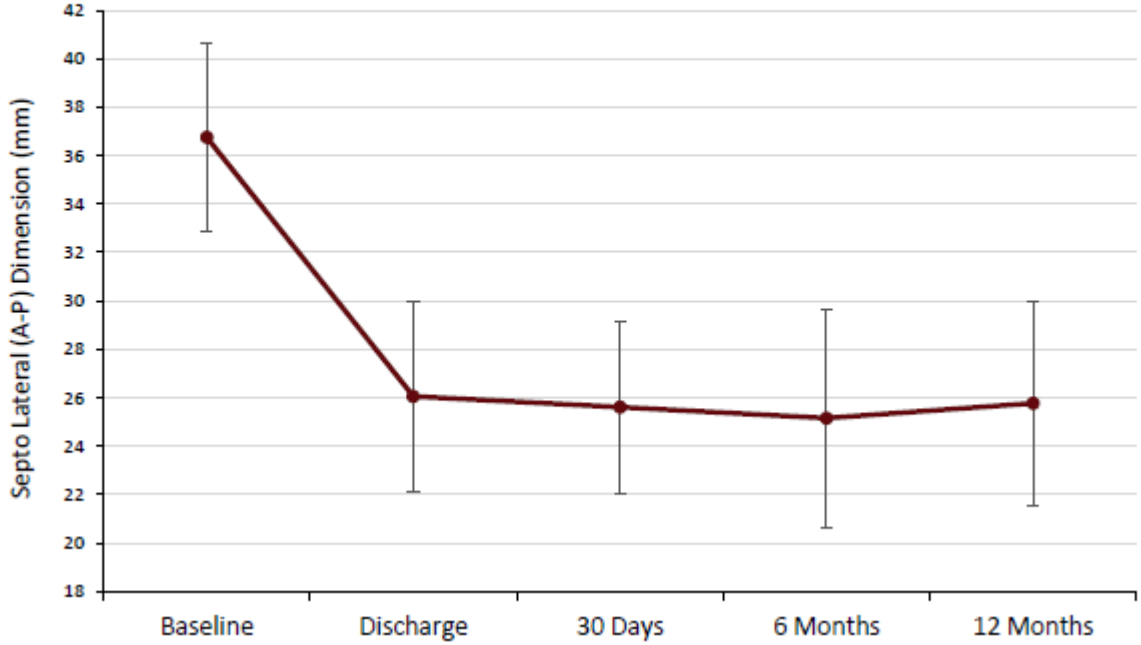
*Dr. Paul Grayburn – Baylor University

UniversityHospital Zurich

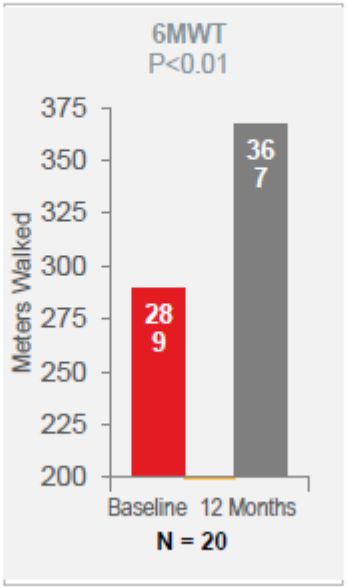
Annular Reconstruction by Significant Reduction in Sept

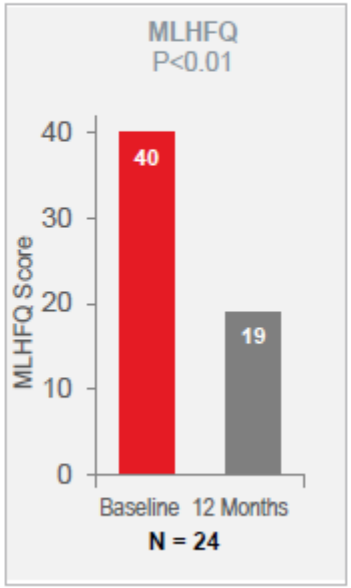


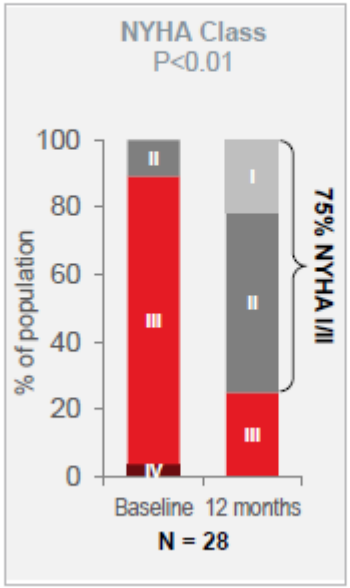
Septo Lateral (A-P) Dimension (mm) over time



Functional Improvement at 12 Months







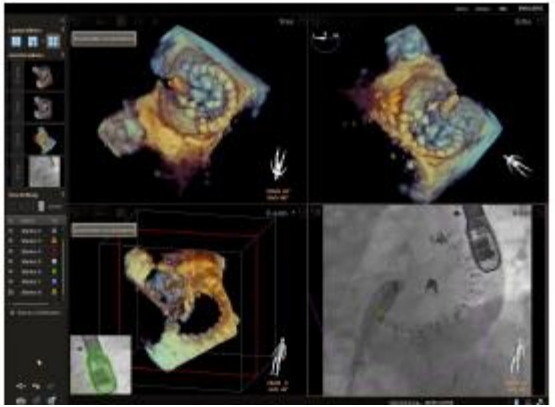
Cardioband is a Surgical Annuloplasty Through A Catheter

Transcatheter surgical annuloplasty is feasible.

Significant and consistent reduction in SL dimension and MR

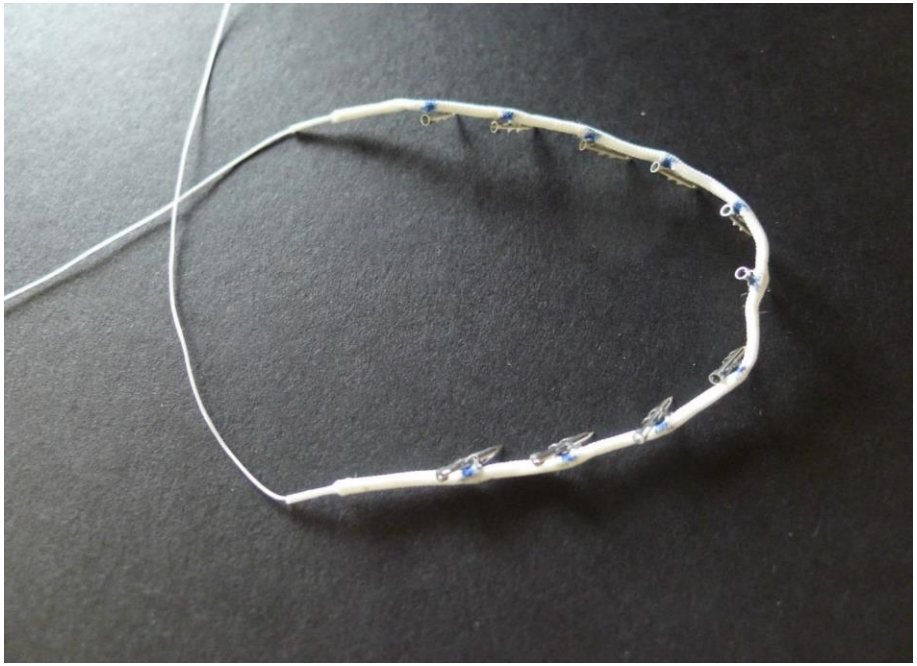
Options remain open for future interventions

Opens the perspective for “surgical Standard” transcatheter repair



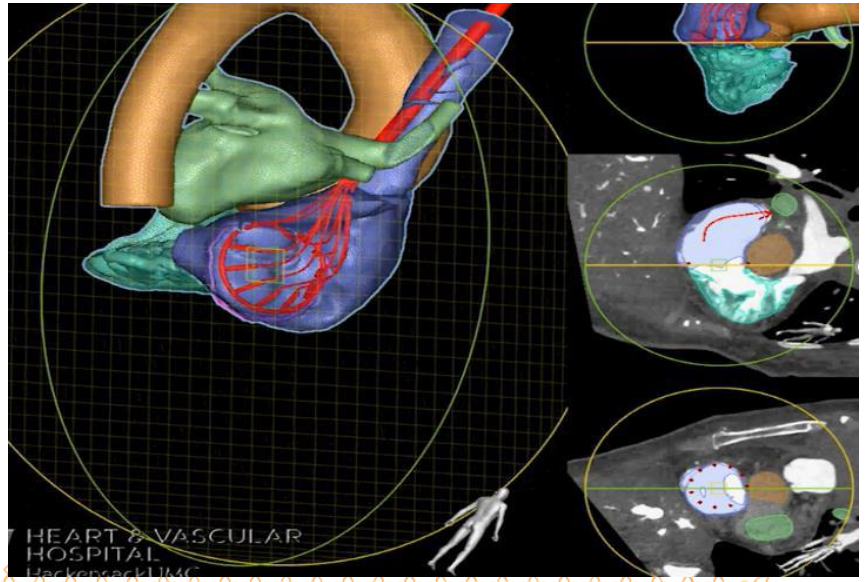
Percutaneous Complete Ring Delivery for Adjustable Atrioventricular Valve AnnuloplastyThe Cardiac Implants Approach

Adjustable Fabric Covered Ring Implant

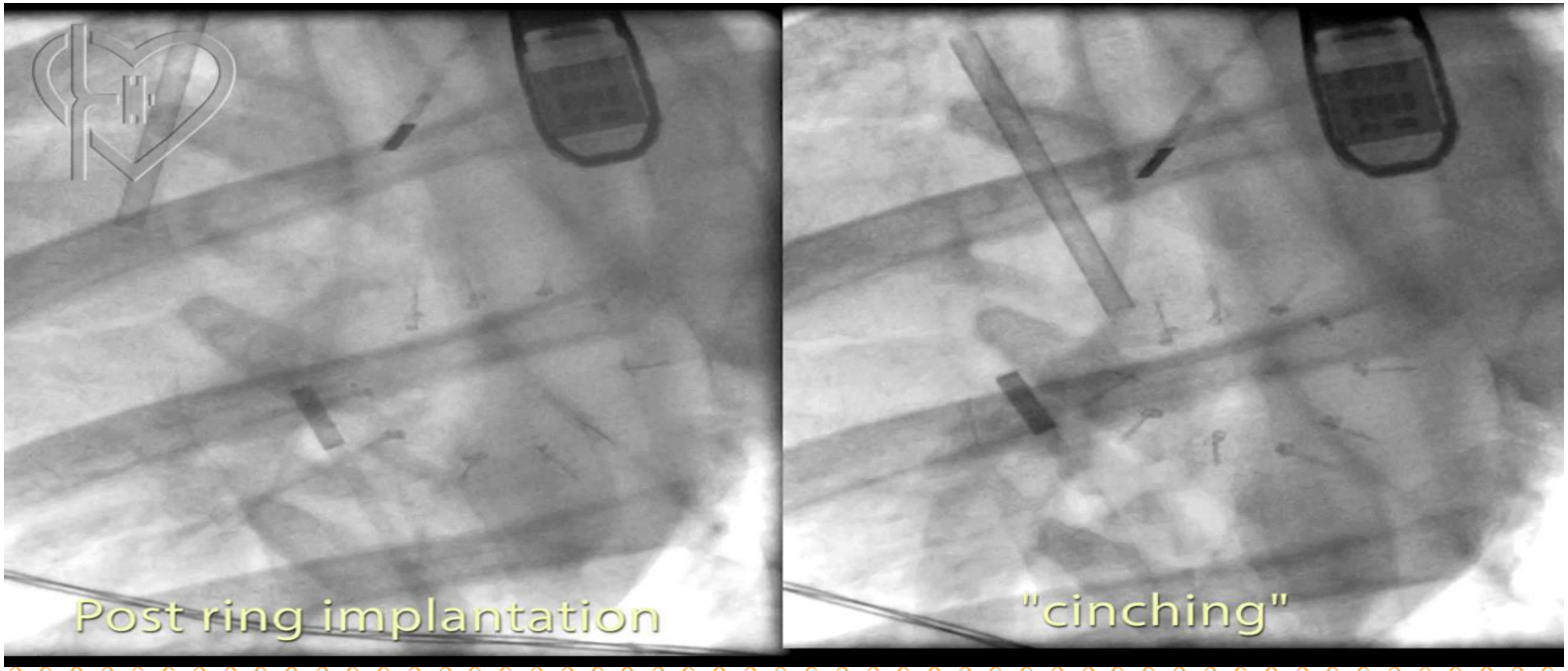


Ring Delivery Scaffold

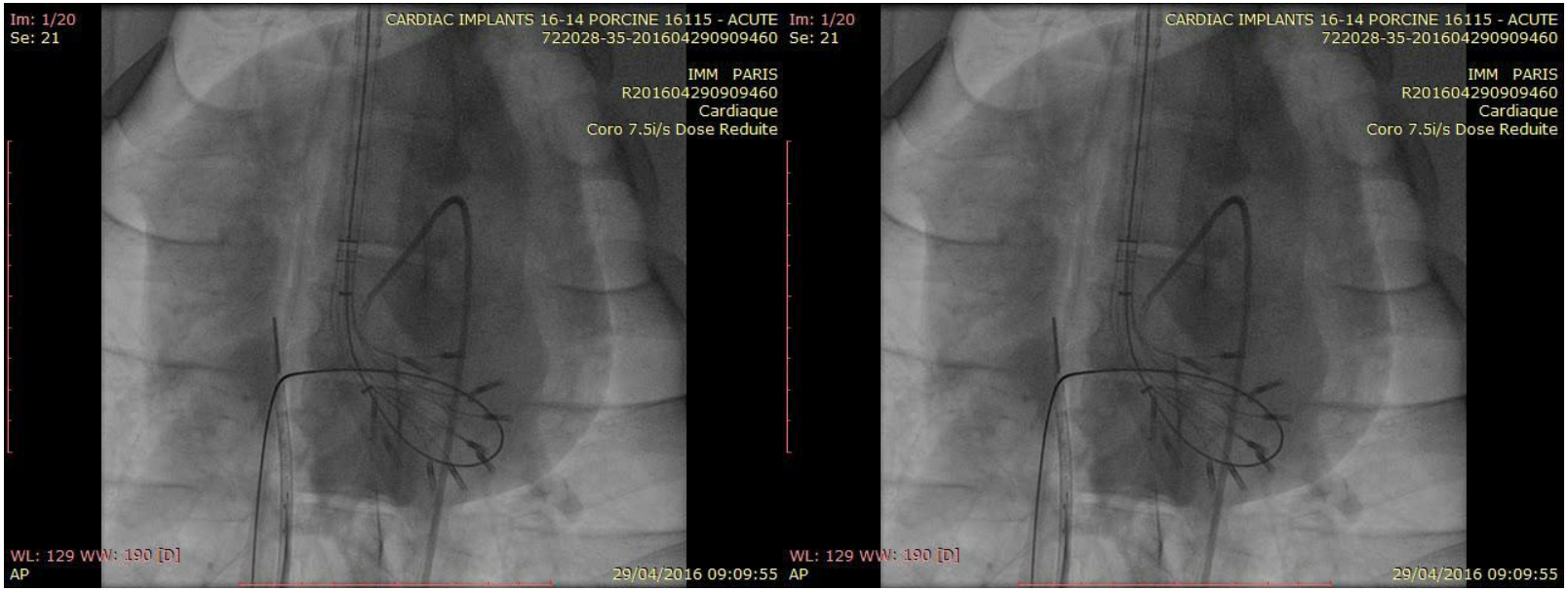
CT Planning



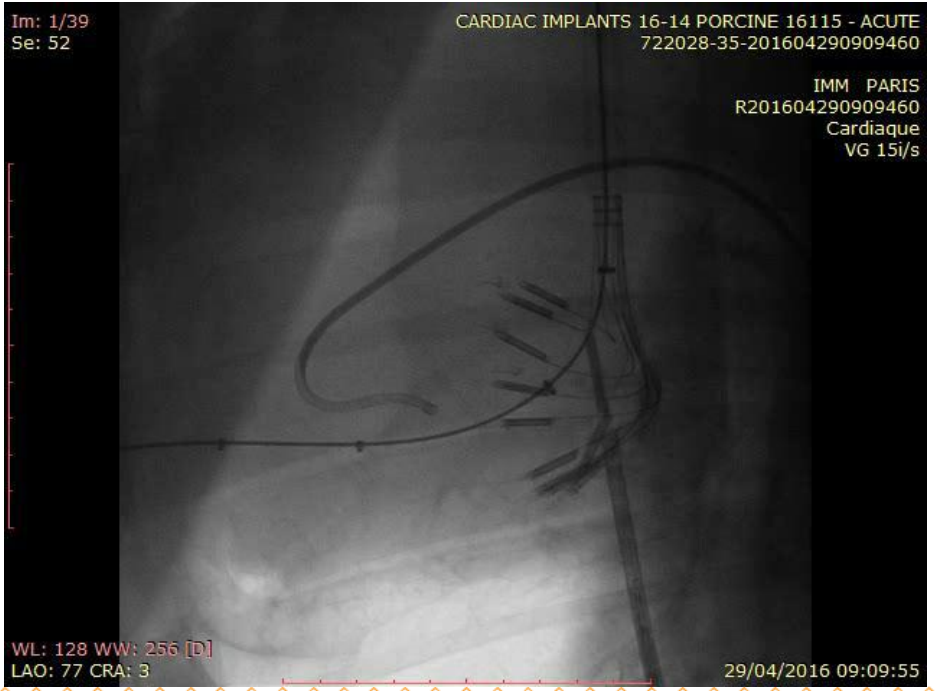
Ring Implant: Complete Control over Cinching



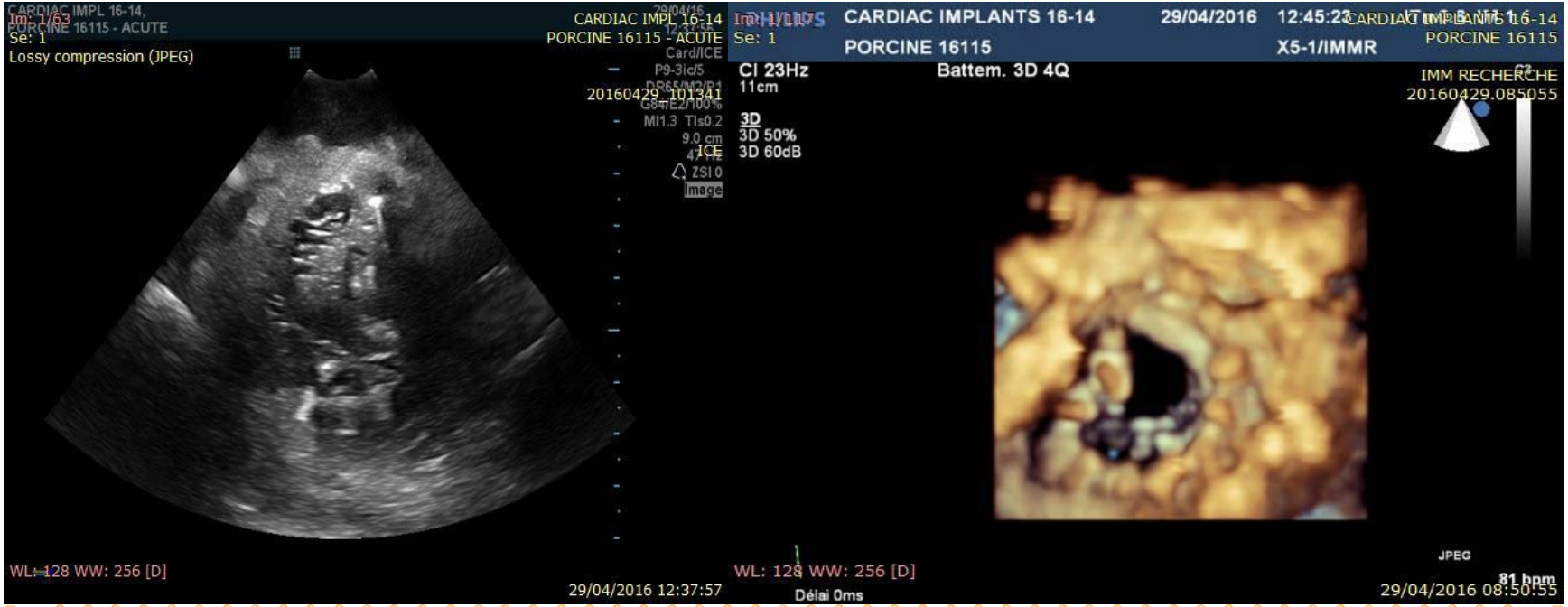
RDS Acute Study: Mitral (Porcine)
Deployment of Mitral Ring in Porcine Model



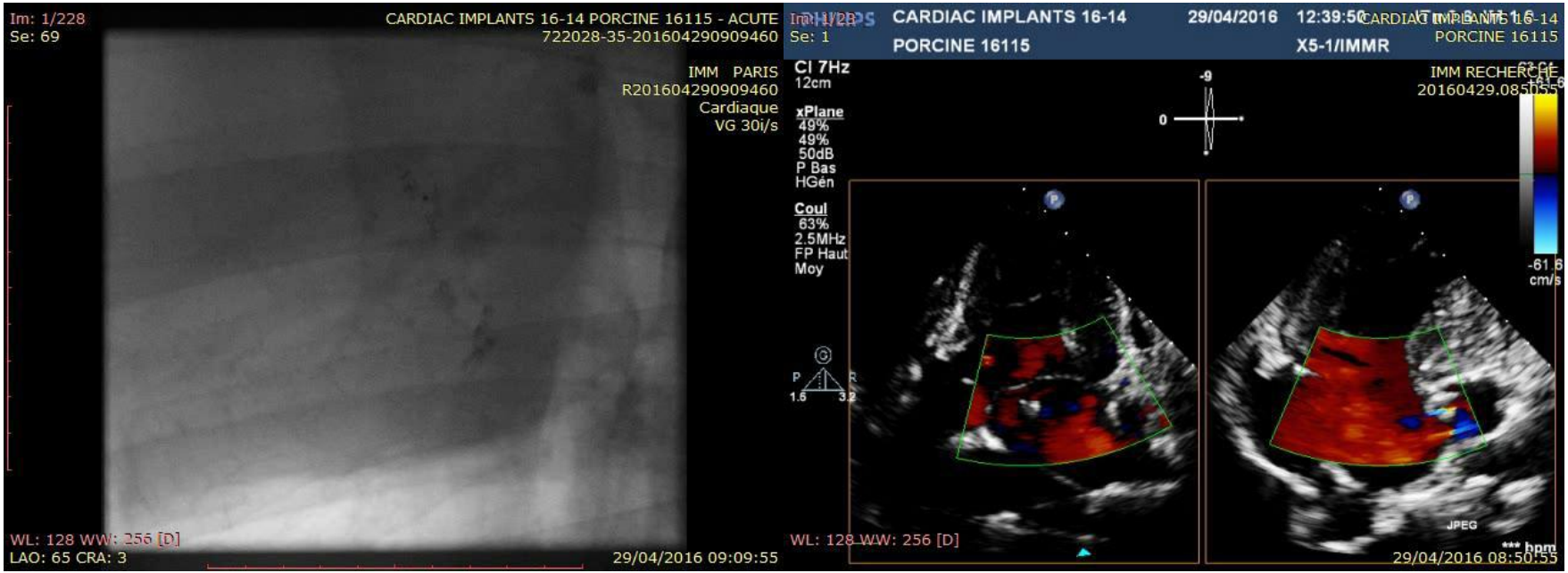
Post Deployment of Ring
RDS Acute Study: Mitral (Porcine)



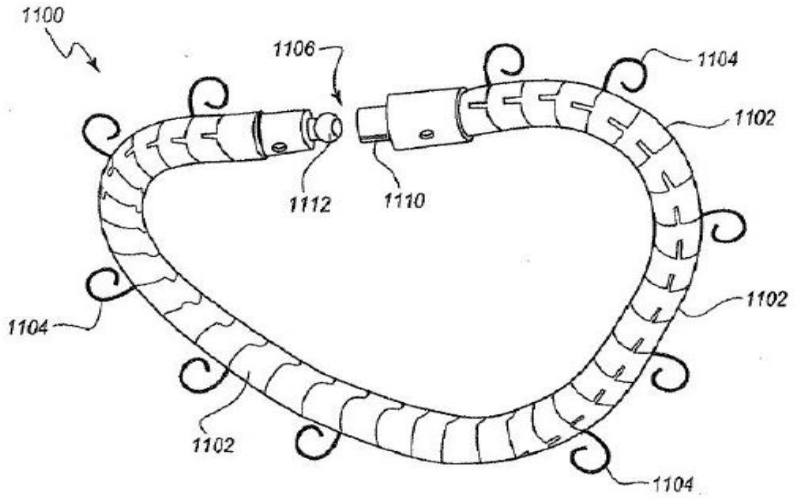
Percutaneous RDS Acute Study: Mitral Final Result



Percutaneous RDS Acute Study: Mitral Final Result



Percutaneous MiCardia (VALCARE)



(19) **United States**

(12) **Patent Application Publication**

Buchbinder et al.

(10) **Pub. No.: US 2012/0310330 A1**

(43) **Pub. Date: Dec. 6, 2012**

(54) **PERCUTANEOUS TRANSCATHETER REPAIR OF HEART VALVES VIA TRANS-APICAL ACCESS**

(75) Inventors: **Maurice Buchbinder**, La Jolla, CA (US); **Samuel M. Shaolian**, Newport Beach, CA (US)

(73) Assignee: **MICARDIA CORPORATION**, Irvine, CA (US)

(21) Appl. No.: **13/397,545**

(22) Filed: **Feb. 15, 2012**

Related U.S. Application Data

(60) Provisional application No. 61/492,279, filed on Jun. 1, 2011.

Publication Classification

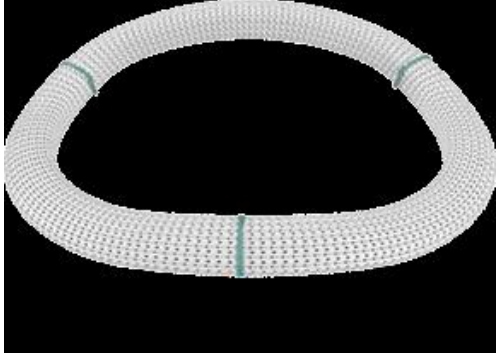
(51) **Int. Cl.**
A61F 2/24 (2006.01)

(52) **U.S. Cl.** **623/2.11**

(57) **ABSTRACT**

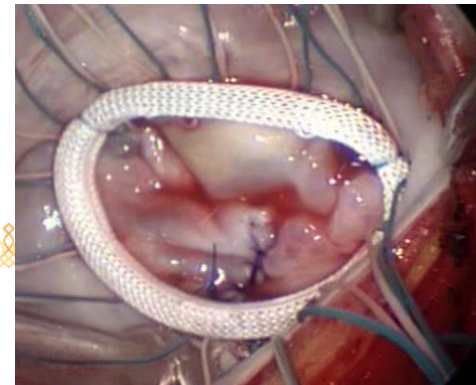
Apparatus, systems, and methods are provided for repairing heart valves through percutaneous transcatheter delivery and fixation of annuloplasty rings to heart valves via a trans-apical approach to accessing the heart. A guiding sheath may be introduced into a ventricle of the heart through an access site at an apex of the heart. A distal end of the guiding sheath can be positioned retrograde through the target valve. An annuloplasty ring arranged in a compressed delivery geometry is advanced through the guiding sheath and into a distal portion of the guiding sheath positioned within the atrium of the heart. The distal end of the guiding sheath is retracted, thereby exposing the annuloplasty ring. The annuloplasty ring may be expanded from the delivery geometry to an operable geometry. Anchors on the annuloplasty ring may be deployed to press into and engage tissue of the annulus of the target valve.

Concept



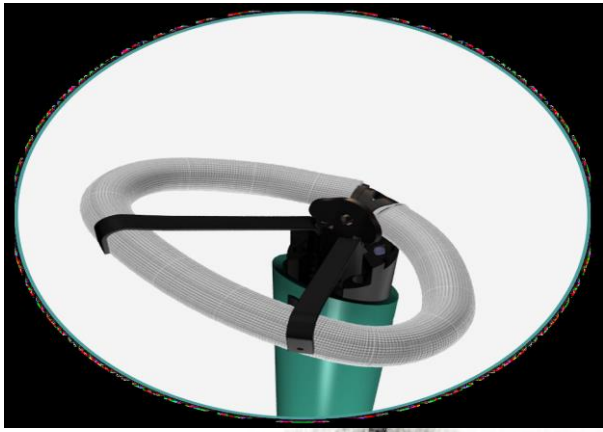
- VALCARE™ system is designed to emulate current semi ridged complete D-shaped annuloplastyrings like MiCardiaand others used as for surgical repair

- Unlike surgical annuloplastyrings the VALCARE system is designed for percutaneous, Trans-catheter delivery



VALCARE System is composed of

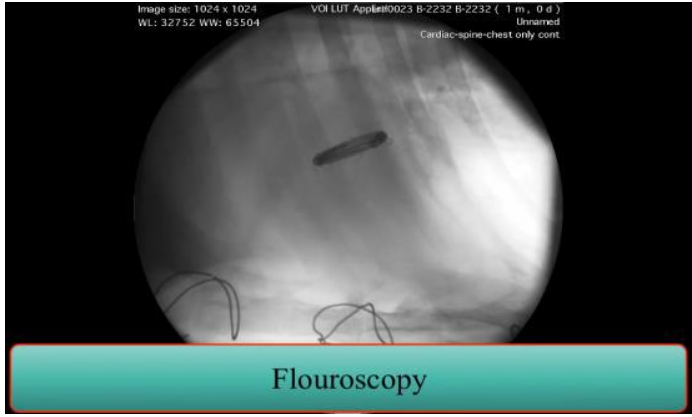
- Proprietary Ring
- •Special delivery device
- •Stabilizing tool
- •Anchoring system



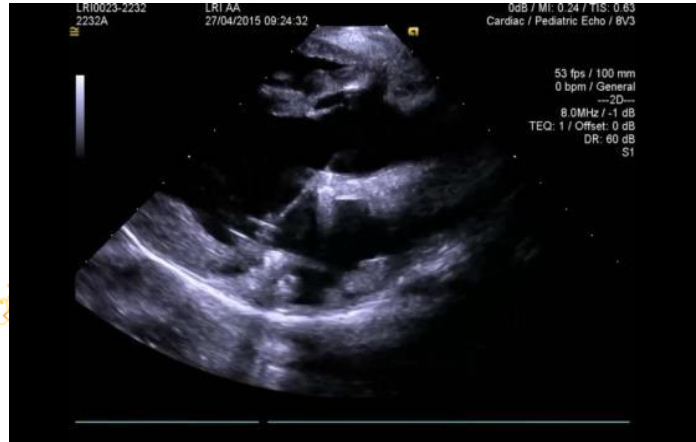
The ProcedureTransapicalApproach to LA

- Chronic porcine studieshave shown
- **Stable Implant**
- **–No Rocking**
- **–No Dehiscence**
- **•Good Hemodynamics**
- **•Good encapsulation and integration into the annulus**
- **•Perfectly maintained structural integrity of Implant**

30 Days



3 Months



Next Step

- First in Man
- –Transapicalapproach for MV repair
- –To date 2 patients have been treated in Prague
- •Detailed presentation of outcomes planned for TCT 2016!!

Valve in Valve (Trans-septal and Transapical)

Patient-Presentation:

-81-year old female patient with two prior cardiac surgeries

- 1984: open commissurotomy of the mitral valve (mitral valve stenosis)

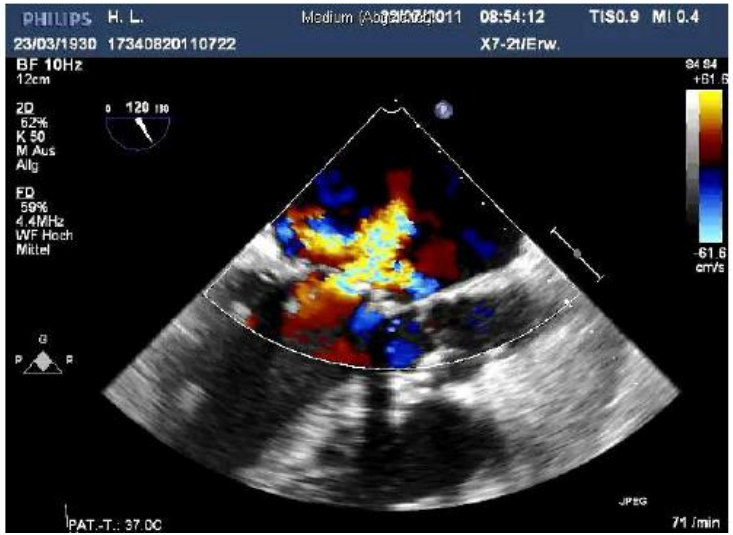
- 2004: Mitral valve replacement with a 27mm Epic™ stented biological prosthesis (mitral valve endocarditis)

-Pulmonary hypertension; renal failure; severely reduced lung capacity

Patient-Presentation:

Logistic EuroScore 48%

STS score 19%



Procedure:

-transfemoral antegrade implantation of a 26mm Edwards Sapien^{XT}-valve

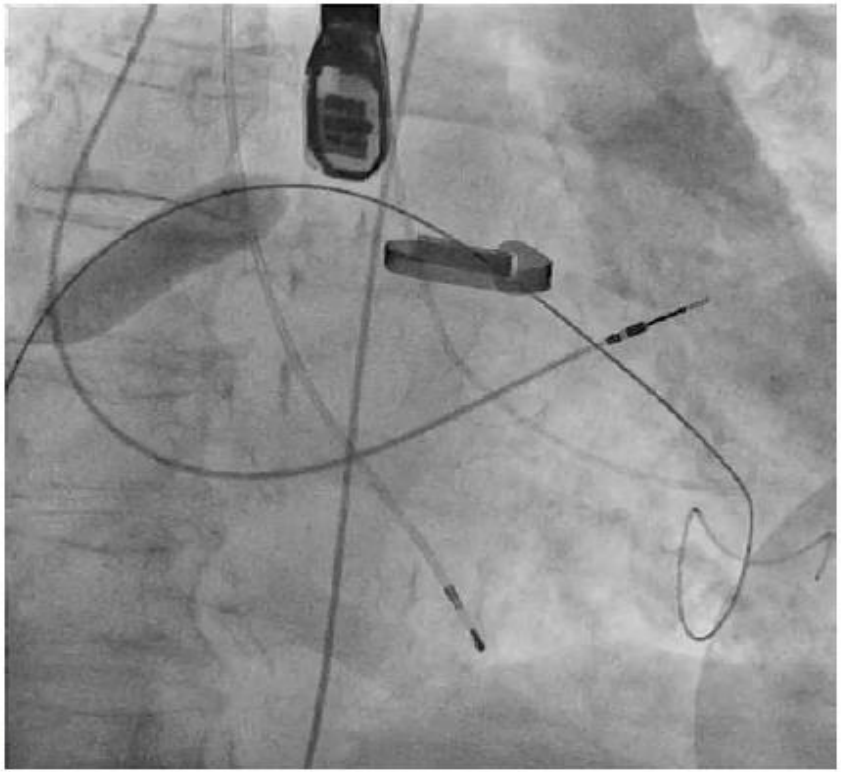
-General anesthesia

-Puncture of the femoral vein

-Transseptal puncture

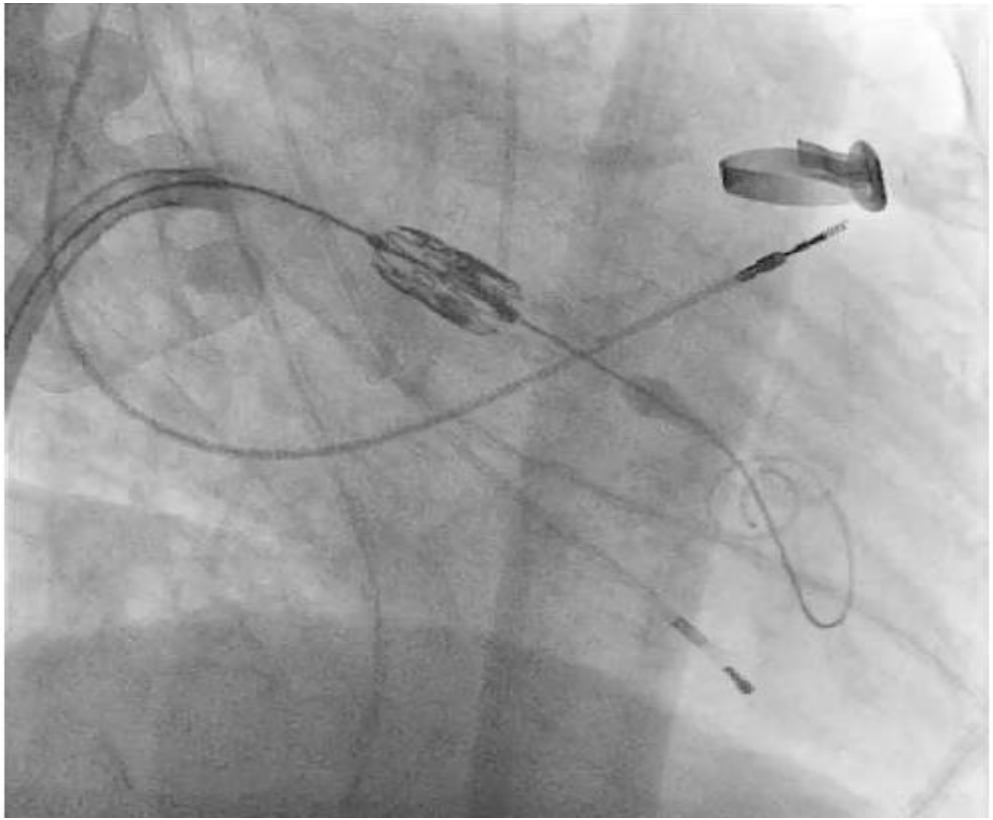
-Placement of a super stiff wire into the left ventricle

-Dilatatation of the septum with a 10mm and 14mm balloon



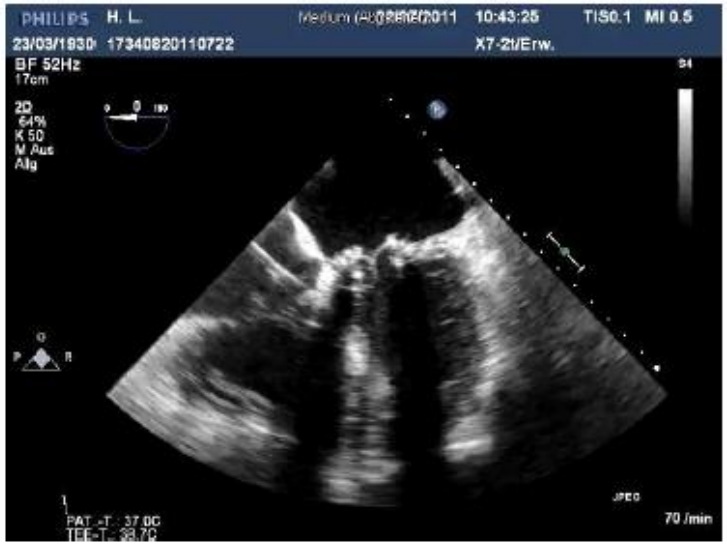
Procedure:

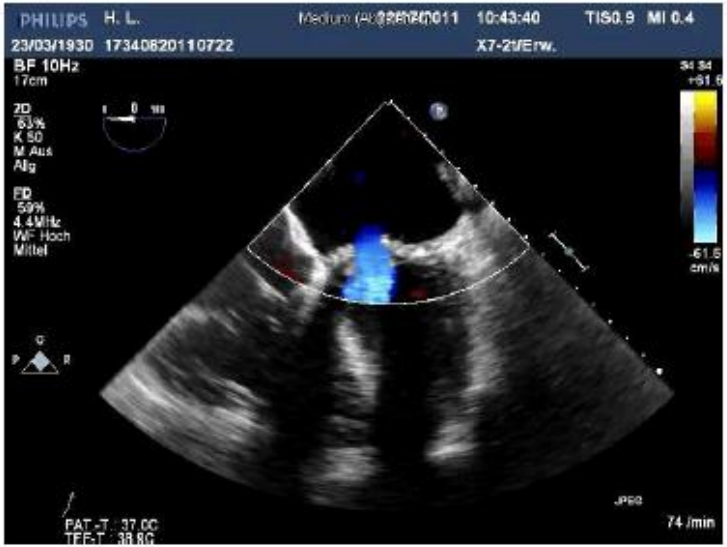
-Slow inflation under rapid pacing



Result:

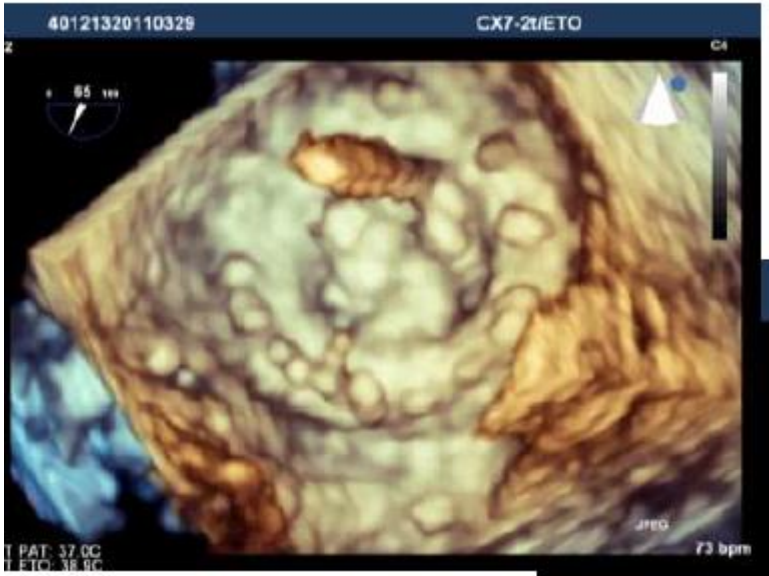
Reduction of mitral regurgitation from severe to none

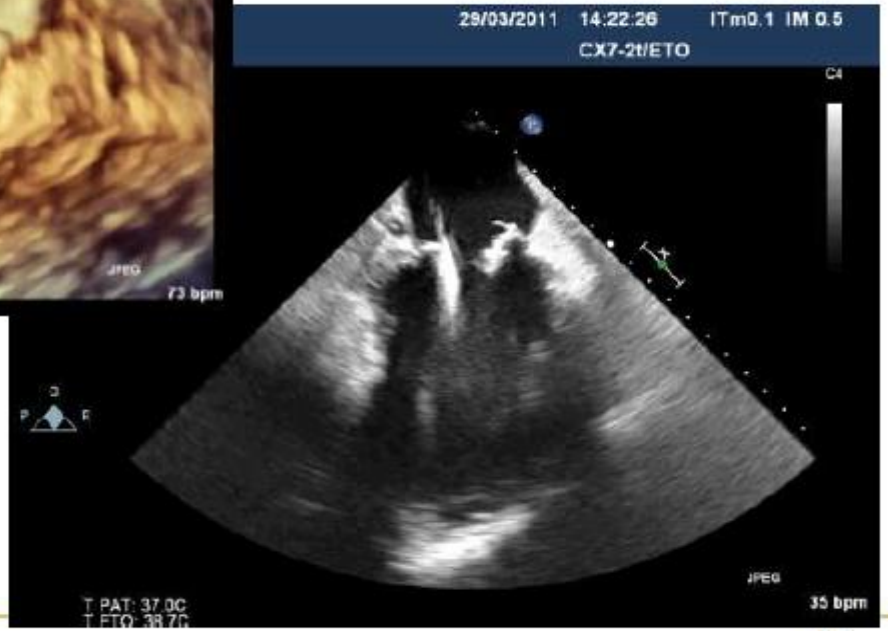




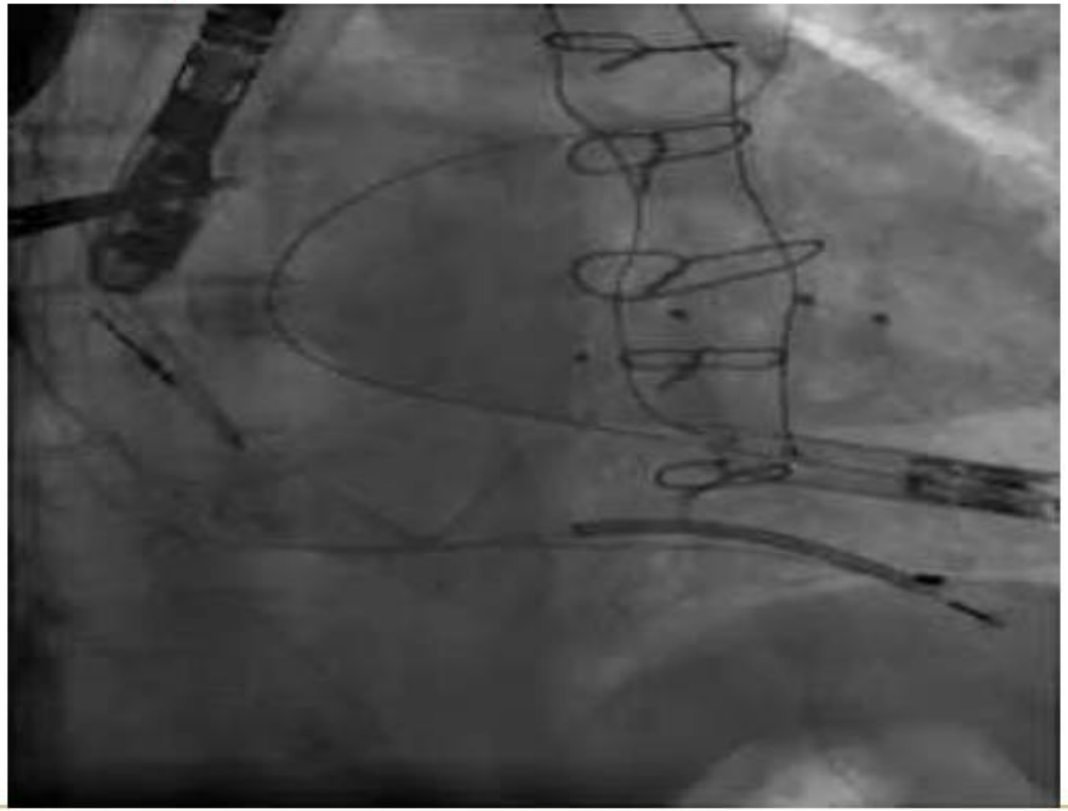
- 84 year old man
- in 1997
  - Coronary grafts (Right mammary on LAD, Left mammary on marginal, Radial on PDA)
  - Post operative myocardial infarction with ischemic mitral insufficiency
  - Mitral valve replacement : bioprosthesis (Medtronic INTACT 29mm)

Wire through the bioprothesis

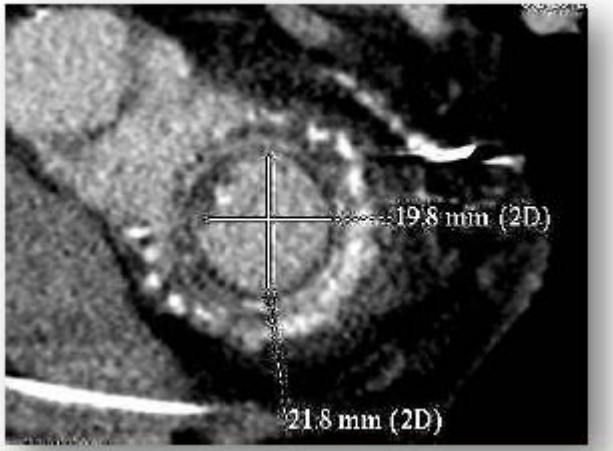


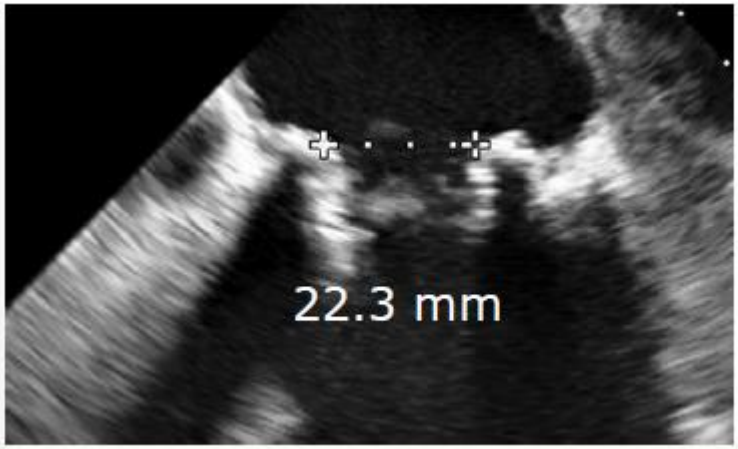


Bioprothesis introduction

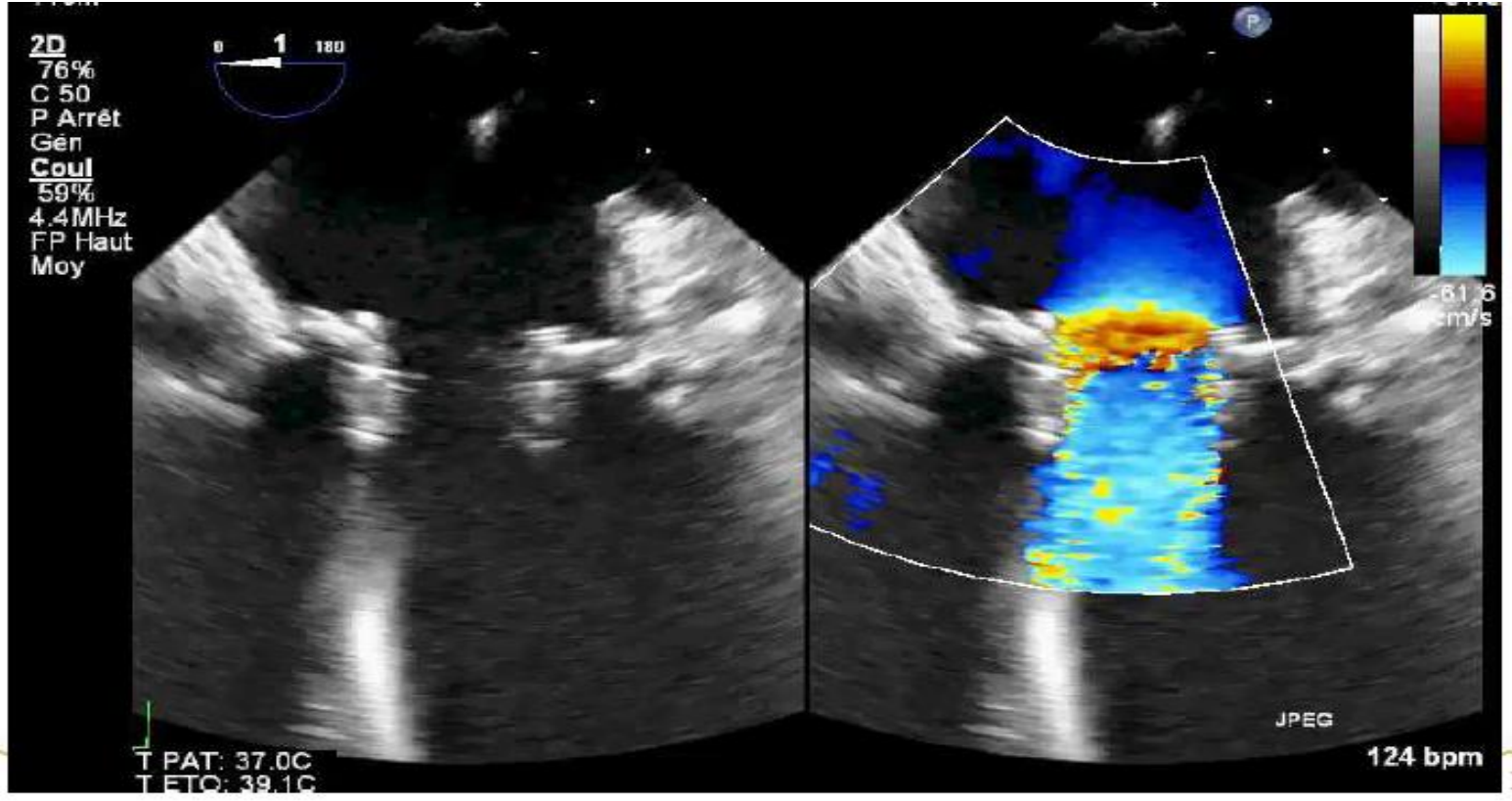


26 mm Sapien-Edwards aortic valve implantation in the bioprosthesis by transapical route





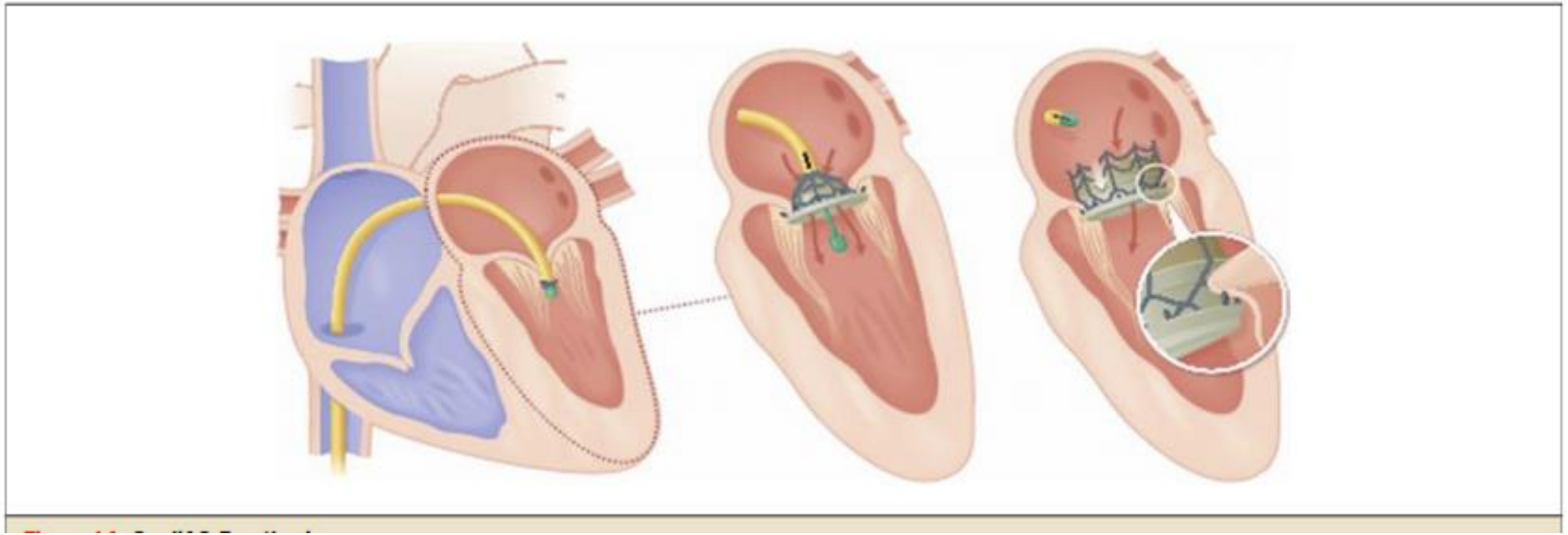
No Mitral Regurgitation



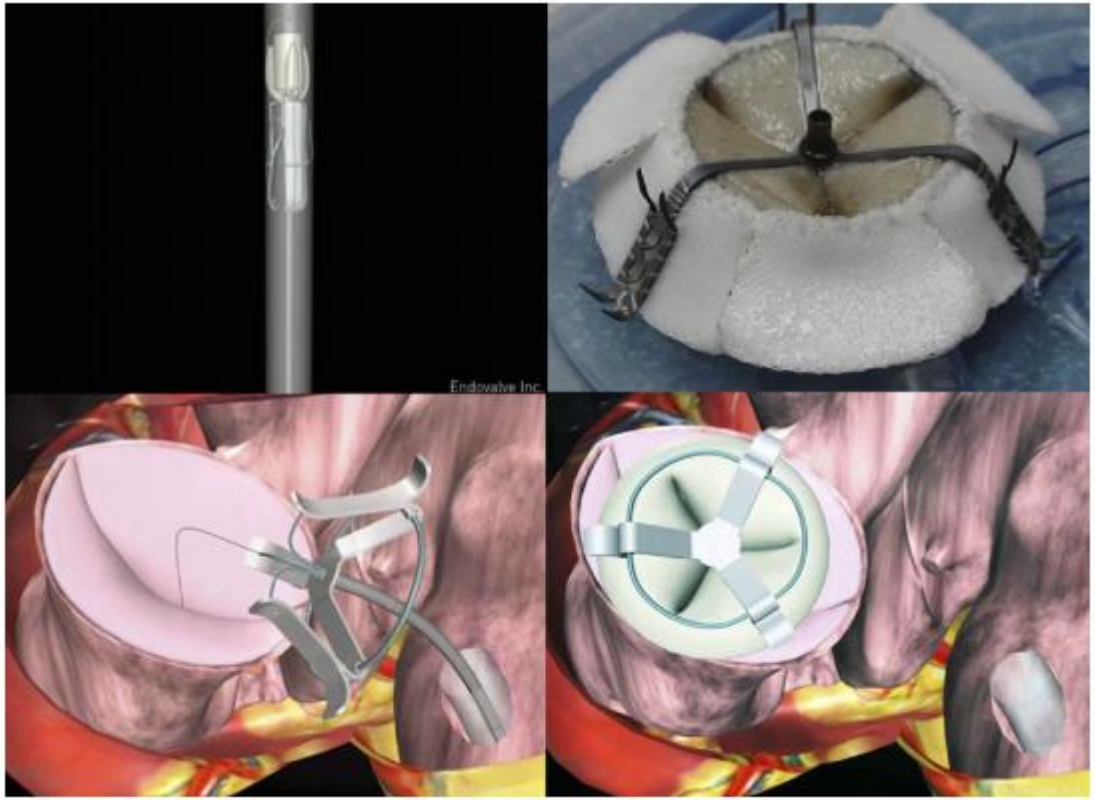
Percutaneous MVR

- The EndovalveHerrmann prosthesis (Endovalve Inc., Princeton, New Jersey) is implanted from the LA side via a right mini-thoracotomy on a beating heart
- The Lutter prosthesis, a nitinol stent-valve, has been implanted transapically in porcine models
- The CardiAQ (CardiAQ Valve Technologies, Inc., Winchester, Massachusetts) prosthesis is in pre-clinical development and is delivered transseptally

The **CardiAQ** (CardiAQ Valve Technologies, Inc., Winchester, Massachusetts) prosthesis; this device is delivered transseptally

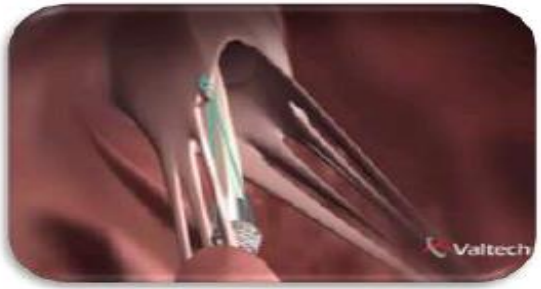


Endovalve-Herrmann Prosthesis

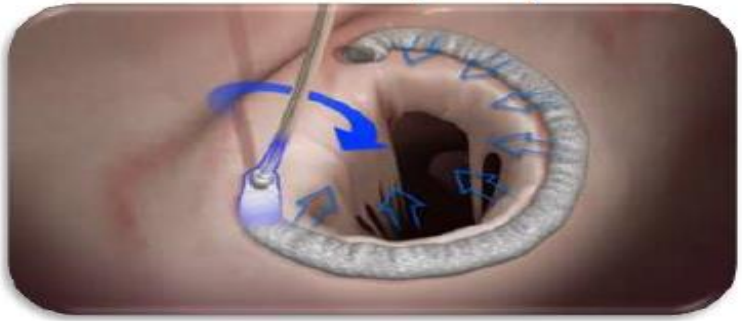


euro PCR 2012

Percutaneous Leaflet repair



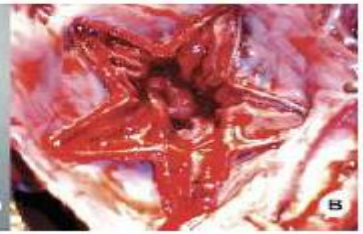
Percutaneous Annuloplasty

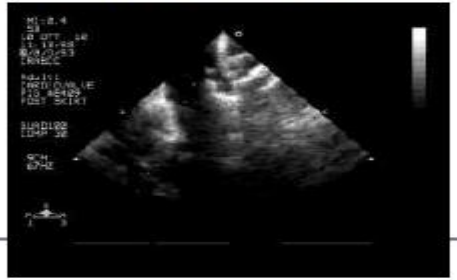


Fully Percutaneous Mitral Repair

Transcatheter MVR: the challenges

- Large anatomy
- Anchoring
  - Cannot use radial force
  - Landing zone is dynamic and fragile
- Asymmetric anatomy
- Interaction with the aortic valve and LVOT
- PVL more problematic





Conclusion

- The percutaneous edge-to-edge repair technology Mitral Clip has been shown to be noninferior to open repair in a randomized clinical trial
- Several other technologies employing the concepts of direct and indirect annuloplasty and LV remodeling have achieved first-in-man results.
- Most likely a combination of these technologies will be required for satisfactory TMVR
- In the future, the novel technology of percutaneous MVR might become a possible alternative in a selected group of patients with a low probability of successful repair
- However, TMVR is not possible for many patients, and MVR will be required.